UCONN HEALTH

The Kroc Family Fund
DEPARTMENT OF NEUROSCIENCE
ANNUAL RETREAT

PROGRAM & AGENDA

Thursday, May 14, 2026

8:00 am – 5:00 pm

Registration begins at 8:00 am

UConn Health Academic Rotunda
263 Farmington Avenue
Farmington, CT

UCONN HEALTH

May 14, 2026

Dear UConn Neuroscience Community,

Welcome to the 2026 Annual Neuroscience Program Retreat! We are thrilled to hold the retreat at the UConn Health Academic Rotunda this year.

We would like to draw your attention to a few important things:

1. **You must bring your university I.D.** as this is a registered event.

2. The facility is air-conditioned. You might want to bring a sweater or light jacket in case you find the temperature unpleasant.

3. **Please print or carry an electronic copy of the program brochure with you to the meeting**. Only a printed agenda for the day is available at the check-in desk.

Oral presentations: Oral presentations will be held in the rotunda. Speakers **must** upload their files before the session by May . Detailed information has been sent to the oral presenters.

Poster presentations: There will be two poster sessions. Session 1 will be before lunch, Session 2 immediately after. Posters will be displayed along the hallway in the ramp of the Academic Rotunda for **the entire duration of the retreat. Each presenter is required to stand by their poster during only one preassigned session.** If you are a poster presenter, please check which session you have been assigned to.

Presentation awards: Presentations by students and postdocs will be judged for awards. You will be evaluated on the quality of your work, clarity of presentation, knowledge of the subject, and responses to questions. Winners will be announced immediately before the closing remarks.

If you have any suggestions for improving the event for next year, please let us know. We hope you will enjoy the day.

Sincerely,

Byoung-Il Bae, Ph.D.
Assistant Professor

Alice Burghard, Ph.D.
Assistant Professor

Akihiro Ishii, Ph.D.
Assistant Professor

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2026 UConn Neuroscience Retreat Program

Date: Thursday May 14, 2026

Location: Academic Rotunda, UConn Health, Farmington, CT 06032)

Starts	Ends	Event	Location
8:00 AM	8:45 AM	Registration	Academic Rotunda
8:45 AM	9:00 AM	Welcome address	Academic Rotunda
9:00 AM	10:00 AM	**Symposium A** *Moderator: Dr. Akihiro Ishii*	Academic Rotunda
10:00 AM	10:15 AM	Coffee break	Academic Rotunda
10:15 AM	11:30 AM	**Poster Session A**	Rotunda Hall
11:30 AM	12:45 PM	Lunch / Elevator Pitch!	Academic Rotunda
12:45 PM	2:00 PM	**Poster session B**	Rotunda Hall
2:00 PM	2:15 PM	Vendor recognition presentation	Academic Rotunda
2:15 PM	3:15 PM	**Symposium B** *Moderator: Dr. Sebnem Tuncdemir*	Academic Rotunda
3:15 PM	3:25 PM	Group picture	Academic Entrance
3:45 PM	4:45 PM	**Keynote address** **Jeff W. Lichtman, MD/PhD** Harvard University "*Relating the Structure to the Function of the Nervous System: Does Connectomics Help or Hurt?*"	Academic Rotunda
4:45 PM	5:00 PM	Presentation of awards and closing remarks	Academic Rotunda

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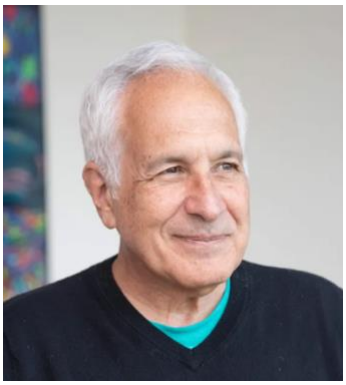
KEYNOTE SPEAKER

“Relating the Structure to the Function of the Nervous System: Does Connectomics Help or Hurt?”



Jeff W. Lichtman, M.D., Ph.D.

Jeremy R. Knowles Professor of Molecular and Cellular Biology
Santiago Ramón y Cajal Professor of Arts and Sciences
Harvard University

Jeff Lichtman is a developmental neurobiologist whose work has helped define the modern field of connectomics, the study of neural circuits at synaptic resolution. His research focuses on how mammalian brain circuits are shaped by experience, especially during the extensive synaptic remodeling that occurs early in postnatal development.

His laboratory has shown how competition between neurons innervating the same target cell can drive synaptic pruning and strengthening, providing a mechanistic basis for how experience leaves lasting traces in the nervous system. His group also developed powerful imaging approaches for studying these processes, including Brainbow, a transgenic labeling strategy that uses fluorescent proteins to distinguish neighboring neurons in densely packed tissue, and automated serial-section electron microscopy methods such as the Automatic Tape-Collecting Lathe Ultramicrotome or ATLUM. In 2024, the Lichtman lab published a large-scale reconstruction of a cubic millimeter-sized sample of human temporal cortex, revealing previously unseen circuit features and advancing connectomic analysis of human tissue.

The lab is now applying these tools to inhibitory interneuron circuits in the prefrontal cortex, with the goal of understanding whether neuropsychiatric disorders such as autism and schizophrenia may reflect “connectopathies,” or disorders of miswiring.

Dr. Lichtman received his A.B. from Bowdoin College in 1973 and his M.D. and Ph.D. from Washington University in St. Louis in 1980, where he trained with Dale Purves. After postdoctoral work at Harvard Medical School, he joined the faculty at Washington University, where he remained for thirty years before moving to Harvard in 2004. He was named the inaugural Santiago Ramón y Cajal Professor of Arts and Sciences in 2013 and was appointed Divisional Dean of Science in 2024. He is a member of the National Academy of Sciences and a faculty director of the Harvard Center for Biological Imaging.

Lab homepage: https://lichtmanlab.fas.harvard.edu/

Symposium A / Talk No. 1

Mapping the contributions of quiescent granule cell progenitors in cerebellar hemisphere expansion

Martina Miranda[1], Qiuxia Guo[1], Kerry Morgan[1], Thomas Perry[1], James Y.H. Li[1,2]

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Cerebellar granule cells (GCs) constitute the most abundant neuronal population in the mammalian brain, produced by the massive amplification of granule cell progenitors (GCPs) and their subsequent differentiation after birth. GCPs are susceptible to developmental insults, indicating a high level of temporal coordination occurring between cell state transitions during this narrow window. While disturbances in GCP cell state transitions result in increased risk of behavioral and cognitive impairments, the mechanisms puppeteering these cell state transitions remain scarcely understood. Therefore, greater understanding of GCP cell states will expand the framework for treating cerebellum-related disorders. GCP proliferation is traditionally thought to be sustained by Purkinje cell (PC)-secreted Sonic hedgehog (Shh) signals, due in part to the treatment of GCPs as a homogeneous population. Through single-cell RNA sequencing and immunohistochemical validations, we have identified a non-Shh-responding population of quiescent GCPs (GCP.Qsc) confined to the TLX3+ region of the posterolateral hemispheres, a markedly expanded region linked to cognition and contains direct projections to the frontal lobe. To understand the contributions of GCP.Qsc in hemisphere growth, we 1) traced the GCP.Qsc lineage, 2) genetically perturbed GCP.Qsc-specific pathways, and 3) genetically ablated GCP.Qsc. Our *in vivo* lineage tracing experiments indicate that GCP.Qsc differentiate into granule neurons much later and preferentially contribute to the hemispheres. Further investigation into GCP.Qsc regulation through MAPK gain- and loss-of-function experiments showed that MAPK effector ETV5 is indispensable to maintain quiescence while acting repressively against Shh. Moreover, we showed that GCP-specific reductions in MAPK activity led to a shrinkage of the hemispheres. Last, genetic ablation of GCP.Qsc phenocopied MAPK loss-of-function cerebella. Therefore, our findings indicate that GCP.Qsc act as a reservoir to fuel the late-onset expansion of the cerebellar hemispheres.

Support: NIH R01 NS106844 and R01 NS120556

Symposium A / Talk No. 2

Recording Voltage and Calcium Transients in Striatal Medium Spiny Neurons: An Ex Vivo Study

Katarina D. Milicevic[1,2], William W. Lytton[3], and Srdjan D. Antic[1,2]

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Striatal spiny projection neurons of the direct (dSPN) and indirect (iSPN) pathways, are the principal input units of the basal ganglia. Their intrinsic electrical properties and dendritic integration are critical for striatal function. Computational models of striatal activity often simplify SPNs as point neurons, neglecting critical aspects of dendritic processing. Experimental data on dendritic voltage dynamics in SPNs remain limited due to the technical difficulty of recording from the distal branches using conventional electrophysiology method. While computational modeling of dSPN and iSPN provides valuable predictions about dendritic responses to synaptic inputs and action potential (AP) backpropagation, these models require validation against experimental data. Here, we expand the experimental characterization of dendritic electrical signaling in SPNs using ex vivo acute brain slices. SPNs are labeled with voltage-sensitive dye (JPW-3028), or calcium-sensitive dye (OGB1-AM), allowing optical imaging from distal dendritic compartments. Labeling is accomplished throuh intracellular loading after establishing whole-cell patch. Because both dyes diffuse slowly into distal dendrites, obtaining reliable optical signals requires significant experimental optimization and time. To date, we have developed and refined techniques to image voltage and calcium dynamics in thin dendritic branches during both synaptic input and AP backpropagation. Voltage imaging demonstrates that AP backpropagate to distal and terminal dendritic segments of SPNs. Complementary Ca^{2+} imaging reveals that, in a subset of distal dendritic branches, AP reliably evokes robust Ca^{2+} transients, indicating AP invasion. Repetative AP firing produces cumulative increases in dendritic Ca^{2+} signals, without any signs of nonlinearity (Ca^{2+} electrogenesis). Increased Ca^{2+} responses in 4-aminopyridine reveal the presence of dendritic A-type K+ channels. Notably, observed properties resemble those of basal dendrites in cortical pyramidal neurons recorded in the same brain slice. In summary, both voltage and Ca^{2+} imaging experiments support AP invasion of distal dendritic branches of SPNs beyond previously reported dendritic distances. This establishes critical empirical support for understanding biophysical properties of SPNs, and serves to constrain and validate future computational models.

Support: This research was funded by the USA National Institute of Neurology and Stroke award NS138991-0; the Connecticut IBACS Grant and Grant #4242 “NIMOCHIP” Science Fund Serbia

Symposium A / Talk No. 3

Subcellular Trafficking of P2X4 Receptors Following Ischemic Stroke

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Acute ischemic stroke (AIS) affects nearly 800,000 individuals annually in the United States and remains a leading cause of death and long-term disability. AIS produces an initial, largely irreversible primary injury from abrupt reduction in cerebral blood flow, followed by a secondary injury phase driven by neuroinflammation that unfolds over hours to days. While thrombolysis and mechanical thrombectomy effectively limit primary injury, eligibility is restricted to 5–15% of patients, underscoring the need for therapies targeting secondary neuroinflammatory cascades. Following stroke, dying cells release damage-associated molecular patterns (DAMPs), including large amounts of adenosine triphosphate (ATP), which activate purinergic P2X4 receptors (P2X4Rs) on myeloid cells (e.g. microglia and macrophages – the immune cells of the brain) and amplify post-ischemic neuroinflammation. Under physiological conditions, P2X4Rs are sequestered in their inactive form within endo-lysosomal compartments. During pathological states such as ischemic stroke and neuropathic pain, surface expression is markedly upregulated, heightening immune cell sensitivity to extracellular ATP and potentiating downstream inflammatory signaling. Previous work from our laboratory has shown that short-term P2X4R inhibition following stroke reduces neuroinflammation and promotes tissue recovery, establishing P2X4R as a promising therapeutic target. However, the subcellular mechanisms governing this redistribution, specifically whether receptor activation drives lysosomal degradation or endo-lysosomal recycling to the plasma membrane, remain unclear. We hypothesize that ischemic conditions promote P2X4R recycling to the plasma membrane, thereby perpetuating P2X4R activation on myeloid cells of the brain. To test this hypothesis, we first characterized P2X4R trafficking in mouse primary bone marrow-derived macrophages (BMDMs) stimulated with extracellular ATP (50 μM). Immunofluorescence and confocal microscopy demonstrated a time-dependent increase in plasma membrane P2X4R localization, accompanied by robust ATP-evoked Ca^{2+} influx indicative of enhanced cell activation, which was inhibited by the P2X4R-specific antagonist NP-1815-PX. Extending these findings to an ischemia-relevant context, BV2 microglial cells and HEK293 cells stably expressing P2X4-pHluorin123, a pH-sensitive construct enabling real-time discrimination of surface versus intracellular receptor pools, were subjected to oxygen-glucose deprivation (OGD) with or without exogenous ATP. Cycloheximide (CHX) chase assay was used to assess receptor turnover independent of new protein synthesis, with MTT-based cell viability assay confirming differential CHX sensitivity between cell lines. Live-cell imaging using lysosomal and plasma membrane dyes revealed an increase in P2X4R surface expression following OGD. Collectively, these findings support a model in which ischemic conditions actively promote P2X4R surface redistribution in immune cells. Ongoing work aims to delineate the molecular regulators of P2X4R trafficking and evaluate functional consequences for inflammatory signaling, with the long-term goal of identifying trafficking-based intervention points for limiting ischemia-induced neuroinflammation.

Support: American Heart Association award 18CDA34110011 and NIH 1R01NS125405

Symposium A Talk / No. 4

Loss of extracellular matrix-interacting receptors on retinal ganglion cells reduces inflammation-promoted axon regeneration in vivo

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Unlike the immature mammalian central nervous system (CNS), neurons in the adult CNS fail to regenerate their axons following injury or disease resulting in neuronal cell death. The mechanisms that govern adult neuronal regeneration are still being explored. One avenue that has been exploited is the interaction of neurons with extracellular matrix (ECM) proteins such as CSPGs, laminins, and fibronectin (Fn1). Recently, we discovered that the RGD domain of Fn1 promotes adult retinal ganglion cell (RGC) axon regeneration in vitro and in vivo when synthesized as a full protein or small peptide. Moreover, we discovered that upon inflammatory stimulation by zymosan, infiltrating CD14+ macrophages secrete fibronectin and support axon regeneration in vivo. To determine the exact mechanism by which Fn1 interacts with RGCs to promote regeneration, our lab developed conditional knockout mice (cKO) to knockout two ECM interacting receptors on RGCs to validate our previous findings. We validated the expression of these receptors on wildtype RGCs by bulk RNA-seq across development and injury by optic nerve crush (ONC). We then validated our knockout of these receptors in RGCs. Finally, we tested the hypothesis that double cKO of these two receptors would result in loss of inflammation associated with axon regeneration. We determined that upon loss of these receptors, zymosan failed to induce axon regeneration or enhance neuronal survival 2 weeks after ONC injury.

Support: R01-EY029739 and R01-EY038322

Symposium B Talk / No. 5

Evaluate Dyadic Interactions and Predictors of Success on a Novel Observational Learning Task Using a Software-Based Approach

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Observational learning is a mechanism by which a learner watches an actor and enacts a behavioral change due to their observations. In a novel observational learning task, “observer” rats were trained to obtain reward by selecting the correct response (Left/Right Nosepoke Apparatus) in forced choice trials. The observational learning task consists of two conditions (“Social” and “Non-Social”). In both conditions, the correct choice for each trial is indicated on the “teacher side” of the operant chamber. Rats placed on the “observer side” are separated from teachers by a clear, perforated, 1cm thick plexiglass barrier. In the “social” condition, the correct response is selected via nose poke by another F344 “teacher” rat. As for the “non-social” condition, the correct response is instead reflected across the perforated barrier via upright reflector. We sought to characterize additional behaviors underlying teacher/observer interactions during the observational learning task and assess whether such behaviors adequately explain differences in performance. Our analysis focused on how nuanced interactions predict task success, and refining our DeepLabCut tracking protocol (Mathis et al., 2018) to reduce error, allowing real-time tracking and accurate classification of dyadic interactions.
Preliminary results indicate that our software-based approach correlated significantly with human ratings on the same footage and produced identical behavioral trends. Still, much of the interactions between teacher and observer were left un-measured and, in some cases, data quality was unreliable and noisy. To overcome this limitation, we implemented additional filtering and preprocessing methods to reduce the incidence of noise, while removing as little data as possible, improving subsequent behavioral classification reliability.

Support: Institute of Brain and Cognitive Sciences Summer Fellowship, 2026

Symposium B Talk / No. 6

Locus coeruleus transforms cortical taste representations

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Noradrenergic neurons in the locus coeruleus (LC) modulate sensory responses throughout the brain, yet how these effects reshape population representations of sensory attributes remains unclear. To address this question, we examined the influence of LC activation on the primary gustatory cortex (GC), a system largely unexplored in the neuromodulation literature. By combining GC miniscope imaging with optogenetic LC activation in awake mice, we tested how phasic and tonic LC activity affect the encoding of three taste attributes: palatability, mixture ratio, and concentration. Phasic LC activation enhanced the correlation between neuronal responses and tastant palatability and increased the dynamic range of basic taste representations along a palatability-relevant axis. Notably, this stretching was driven by an aversive shift in the representation of all tastants except the most palatable stimulus, sucrose. For tastants varying in mixture ratio and concentration, LC activation produced both stretching and rotation of the attribute-relevant axis, potentially reflecting dependencies between these attributes and palatability. These population-level transformations may arise from combinations of multiplicative gain modulation and flexible changes in neuronal tuning. In contrast to phasic activation, sustained tonic LC activation modulated a smaller proportion of GC neurons and did not induce stretching along any attribute axis. Together, our findings suggest that phasic LC activation—a pattern observed in many taste-related contexts—reshapes GC population activity to enhance palatability encoding, potentially contributing to adaptive regulation of feeding behavior.

Support: NIDDK (R00 DK119568 to NRS), Brain Research Foundation seed grant (to NRS), and the UConn Startup fund.

Symposium B Talk / No. 7

Altered Hippocampal Excitability and Coupling to Arousal State in a Mouse Model of Alzheimer's Disease

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Alzheimer's disease (AD) is characterized by profound learning and spatial memory deficits, which aligns with the severe synaptic and neuronal loss occurring in hippocampal areas. The hippocampus is critical for spatial learning and memory, both during experience and subsequent sharp wave-ripple (SWR)-mediated memory consolidation. Stimulus-specific changes in hippocampal activity before versus after learning are considered a paradigmatic substrate of memory. However, learning is also associated with non-specific changes, including changes in SWR-coupled arousal dynamics from before to after learning. These relationships are poorly understood but represent a potential mechanism underlying the memory deficits seen in AD. In fact, the earliest cellular pathology in AD occurs in locus coeruleus (LC), a key noradrenergic brainstem nucleus controlling cortical arousal. However, the contribution of subsequent LC dysfunction to cognitive deficits remains understudied. LC norepinephrine (LC-NE) activity is highly correlated with pupil diameter under stable light conditions. Thus, pupillometry can be used as a non-invasive measure of LC-related arousal dynamics. Using combined pupillometry, electrophysiology, and two-photon imaging of hippocampal neurons before, during, and after a spatial learning task, we investigated arousal dynamics related to spatial learning in the APP mouse model of AD. Our preliminary data show that APP mice display early learning-dependent neuronal hyperexcitability in hippocampal networks and changes in pupil-linked arousal dynamics during the memory-consolidation linked hippocampal population synchrony events (SWRs). However, the mechanistic link between the brain circuits which control arousal and memory deficits is unknown. In ongoing work, we are using simultaneous pupillometry, electrophysiology, and fiber photometry with the $GRAB_{NE2h}$ sensor to monitor LC-NE activity directly in the hippocampus before, during, and after spatial learning across multiple timepoints. Together, this approach will reveal how hippocampal coupling to arousal state during spatial learning and memory consolidation changes across AD disease progression, potentially leading to new therapeutic avenues for AD treatment.

Support: UConn Health Startup

Symposium B Talk / No. 8

RGS12 Modulates THC-Induced Behavior, Physiology and Withdrawal in Mice

A. Matt Reck[1], David P. Siderovski[2], & Steven G. Kinsey[1]

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The Regulator of G-protein Signaling (RGS) superfamily is composed of various proteins that negatively regulate the intracellular signal cascade initiated following G-protein coupled receptor (GPCR) stimulation. RGS12 is a RGS superfamily member that has previously been shown to modulate the analgesic effects of kappa-opioid drugs through its negative regulation of GPCR Gα proteins. Cannabinoid receptors are GPCRs that selectively signal through $G\alpha_{i/o}$ proteins, with which RGS12 preferentially interacts. This study aimed to determine whether RGS12 expression or deletion modulates the behavioral, physiological, and abuse-liability effects of Δ^9-tetrahydrocannabinol (THC) in mice. To this end, we compared THC-induced acute tetrad effects, drug tolerance, and rimonabant-precipitated withdrawal behaviors in *RGS12* knockout or wildtype mice. Adult male and female RGS12 (C57BL/6J background) knockout (-/-) or wildtype (+/+) littermates were administered THC (up to 100 mg/kg, s.c. in 1:1:18 parts kolliphor:ethanol:saline) cumulatively, 50 min before tetrad testing (i.e., antinociception, hypothermia, and spontaneous locomotion). A separate group of RGS12 (-/-) or (+/+) littermates received THC (30 mg/kg, s.c. BID x6 days) with tetrad testing 50 min after each AM injection (~0800) to assess tolerance development. To precipitate withdrawal, all mice were injected with the cannabinoid receptor antagonist rimonabant (3 mg/kg, i.p.) 30 min after the final morning THC injection on day 6 and subsequently scored for somatic signs of withdrawal during a 1 hr observation. THC dose-dependently induced hypothermia (≥10 mg/kg), catalepsy (≥30 mg/kg), and antinociception (≥1 mg/kg) in both genotypes. RGS12 (-/-) mice exhibited potentiated THC effects for antinociception (30 mg/kg) and hypothermia (30 mg/kg). RGS12 genotype did not affect the rate of tolerance development to THC. However, RGS12 deletion increased precipitated THC (30 mg/kg) withdrawal-induced paw tremors and head twitches. In conclusion, RGS12 negatively modulates acute THC-induced antinociception and hypothermia. Additionally, RGS12 deletion potentiates the frequency of somatic withdrawal behavior following repeated THC administration. These data support the role of RGS12 in modulating the effects of a cannabinoid receptor agonist. Notably, increased withdrawal behavior after RGS12 deletion suggests its expression influences the abuse liability of THC. Future work is ongoing to determine potential mechanistic explanations for this phenomenon and to explore other cannabinoid drugs in relation to RGS12 expression.

Support: NIH R01 DA048153 and the UConn Center for Advancement in Managing Pain.

Poster Session 1 / No. 1

Proteomic Analysis of ASPM-Dependent Centrosomal Assembly

Haley Tallman and Byoung-il Bae

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The cerebral cortex is the largest part of the human brain and is responsible for higher-order cognitive functions. Disrupted cortical development leads to neurodevelopmental disorders, including autism spectrum disorder, intellectual disability, and attention-deficit/hyperactivity disorder. Impaired proliferation of neural progenitors can result in microcephaly, a condition characterized by reduced brain size. Mutations in *ASPM* (assembly factor for spindle microtubules), a centrosomal protein expressed in proliferating cells, represent the most common cause of primary microcephaly (MCPH). Notably, many MCPH-associated genes encode centrosomal proteins, underscoring the importance of centrosome assembly and function during neurodevelopment. However, it is unknown how loss of *ASPM* reduces the size of the cerebral cortex with species specificity (more severe microcephaly in animals with a large and folded cortex, such as humans, non-human primates, and ferrets, but less severe microcephaly in those with a small and smooth cortex, such as mice) and tissue specificity (only the cortical size, but not the size of other organs, is affected). Protein-protein interactions mediate the function of a protein. Previous studies have shown that loss of ASPM disrupts recruitment of the CPAP/CENPJ/SASS4 complex to the centrosome, suggesting that ASPM functions as a key scaffold for centrosome assembly. To investigate how the presence or absence of ASPM remodels the centrosome proteome, I sought to define both the ASPM interactome and the centrosome proteome in its presence and absence. Using molecular cloning and CRISPR/Cas9 genome engineering in HEK293T/17 cells, I generated a TurboID-based proximity labeling system incorporating a GFP nanobody (NbGFP) targeted to the AAVS1 safe-harbor locus under control of the PGK1 promoter. EGFP-tagged ASPM enabled selective labeling of proximal and transient interactors, which were identified by mass spectrometry, significantly expanding the known ASPM interactome. In parallel, centrosomal affinity purification (CAPture) was performed in wild-type and *ASPM* knockout HAP1 cells to define changes in the centrosome proteome. Loss of ASPM resulted in reduced abundance of key centrosomal proteins, including NIN, CDK5RAP2, and CEP250. These findings support a model in which ASPM functions as a scaffold required for proper centrosome assembly and demonstrate that its loss remodels the centrosome proteome in ways that may disrupt cortical development. Future studies will extend these approaches to more physiologically relevant systems, including human cortical organoids, as well as mouse and ferret cortex, to further elucidate the species-specific and tissue-specific roles of ASPM during cortical development.

Support: Grants from the NIH/NINDS, Eagles Autism Foundation, and Brain Research Foundation

Poster Session 1 / No. 2

How *ASPM*-Mediated Microcephaly and Macrocephaly Cause Distinct and Similar Behavioral Deficits in Mice

Krystina Jorgensen[1], Gayle Edelstein[2], Jenelle Miller[2], Alev Ecevitoglu[2], Renee Chasse[2], Hyopil Kim[1,3], R. Holly Fitch[2], John Salamone[2], Timothy Spellman[1], Byoung-Il Bae[1]

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Dysregulated proliferation of cerebral cortical progenitor cells during embryogenesis causes multiple neurodevelopmental disorders (NDDs) with distinct yet overlapping phenotypes. Insufficient progenitor proliferation results in microcephaly (small head circumference), which is associated with attention-deficit/hyperactivity disorder (ADHD). In contrast, excessive progenitor proliferation results in macrocephaly (large head circumference), which is associated with autism spectrum disorder (ASD). Intriguingly, ADHD and ASD show significant comorbidities, including obsessive-compulsive disorder (OCD)-like symptoms. However, the mechanism by which insufficient and excessive progenitor proliferation cause these distinct, yet paradoxically similar phenotypes remain unknown. To address this, the Bae lab developed paired mouse models of microcephaly and macrocephaly by utilizing loss-of-function (LOF) and gain-of-function (GOF) mutations in the *ASPM* (abnormal spindle-like microcephaly-associated) gene. *ASPM* encodes a centrosomal protein essential for mitotic spindle orientation and neurogenesis; LOF mutations are the most common cause of primary microcephaly and intellectual disability. Conversely, we identified an ASD-associated variant (p.Ala1877Thr) as a robust GOF mutation that increases ASPM protein levels. We generated knock-in mice carrying the orthologous mutation, which exhibit excessive embryonic neurogenesis and macrocephaly. To investigate how bidirectional disruption of *Aspm* leads to distinct and shared behavioral abnormalities, I analyzed *Aspm* LOF and GOF mice across multiple domains: social behavior, anxiety, repetitive behavior, and sensory processing. Our ongoing analysis shows that *Aspm* GOF mice exhibit abnormal attachment to familiar rather than novel conspecifics, increased anxiety and sociability, and hypersensitivity to auditory and nociceptive stimuli. In contrast, *Aspm* LOF mice show an increased interest in toys (inanimate objects) over conspecifics, decreased anxiety, repetitive behavior, and sex-specific alterations in vocal communication (males show longer, simpler calls, while females show shorter calls than WT). Interestingly, both GOF and LOF mice exhibit increased repetitive behavior and enhanced pitch discrimination, suggesting sensory hypersensitivity. Through further behavioral analysis, combined with calcium imaging and the Developmental Activation Timing-based Longitudinal Acquisition System (DevATLAS), I will reveal how dysregulated progenitor dynamics elicit these distinct yet paradoxically similar functional deficits.

Support: NIH R21HD108696, Eagles Autism Foundation, IBACS Seed Grant

Poster Session 1 / No. 3

Elucidating the Role of *GABRB3* in Dup15q Syndrome Neuronal Phenotypes

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Dup15q syndrome (Dup15q) is a rare neurodevelopmental disorder caused by duplication or triplication of maternal chromosome 15q11-q13 region. It is characterized by seizures, intellectual disability, and autism. Of the many duplicated genes in this region, *UBE3A,* a gene that encodes for a ubiquitin ligase, is solely expressed from the maternal allele and silenced by genomic imprinting on the paternal allele in neurons. While *UBE3A* has been hypothesized to be the main driver for Dup15q phenotypes, the role of other genes remains unknown. Because current mouse models only address overexpression of *UBE3A*, we have utilized patient specific neurons derived from induced pluripotent stem cell lines and isogenic CRISPR corrected control lines to formulate a better understanding of the role of non-imprinted genes in the pathology of Dup15q. Using the whole cell patch clamp technique to record electrophysiological parameters from 10-15 week old neurons, we have found that Dup15q neurons exhibit a hyperexcitability phenotype characterized by increased action potential firing frequency and decreased potassium current density compared to isogenic control neurons. Additionally, at these developmental timepoints, the frequency of active GABAergic synaptic inputs is significantly higher in the Dup15q neurons compared to isogenic control neurons. Of the non-imprinted genes that are duplicated in this region, we focused on normalizing the expression of *GABRB3*, a gene that encodes for the β_3 subunit of the $GABA_A$ receptor, because there is an increased percentage of Dup15q cells receiving GABAergic inputs. This subunit is highly expressed in the developing forebrain cortex and gain of function mutations in this subunit have been implicated in epilepsy. To normalize the expression of this gene early in development, we utilized specific antisense oligonucleotides and assessed electrophysiological parameters in 10-15 week old neurons. We found that normalizing the expression of this gene prevented the development of increased GABAergic transmission phenotype but did not affect the increased action potential firing frequency and decreased potassium current density in Dup15q neurons. These data suggest that overexpression of *GABRB3* contributes to the synaptic phenotypes in Dup15q neurons. Understanding the role played by non-imprinted genes in addition to *UBE3A* will be crucial in not only identifying targets to develop more effective therapies, but to also develop improved mouse models for Dup15q.

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Poster Session 1 / No. 4

Distinct and Shared Electrophysiological Phenotypes in Chromosome 15q11-q13 Deletion and *UBE3A*-Knockout Models of Angelman Syndrome

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Angelman syndrome (AS) is a severe neurodevelopmental disorder caused by loss of function of the maternal *UBE3A* gene, which encodes an E3 ubiquitin ligase responsible for targeting specific proteins for proteasomal degradation. While some patients have mutations only affecting *UBE3A*, most cases of AS arise from deletions of the 15q11-q13 region that remove *UBE3A* along with neighboring genes, including $GABA_A$ receptor subunits. Patients with the full deletion exhibit more severe characteristics, such as microcephaly and increased seizure susceptibility, compared to those with *UBE3A* mutations alone. The extent to which neighboring gene loss contributes to phenotypes beyond *UBE3A* deficiency remains incompletely understood. To parse *UBE3A*-specific contributions from broader deletion effects, I performed an electrophysiological characterization of three isogenic H9 human embryonic stem cell-derived neuronal lines: wild-type control, a CRISPR-mediated maternal *UBE3A*-specific knockout, and a CRISPR-mediated deletion of the full 15q11-q13 region (AS deletion). Recordings were conducted at two developmental windows, weeks 7-8 and weeks 9-10 *in vitro*, using whole-cell patch clamp to assess intrinsic membrane properties, action potential firing, and spontaneous synaptic transmission. Both the *UBE3A*-specific knockout and AS deletion lines exhibited increased membrane capacitance, suggesting larger cell size, with no differences in input resistance or resting membrane potential when compared to controls. Voltage-clamp recordings revealed significantly reduced inward and outward current densities in the *UBE3A*-specific knockout and AS deletion lines at weeks 9-10 compared to controls, consistent with a failure to scale channel expression in proportion to membrane area. Both the *UBE3A*-specific knockout and AS deletion lines showed a higher proportion of immature or non-firing cells at weeks 7-8, though this maturational delay was more severe in the AS deletion line. In the subset of neurons that achieved mature firing, action potential threshold, amplitude, and half-width were not significantly different between cell lines at either time window. Recordings of GABAergic synaptic currents revealed that both the *UBE3A*-specific knockout and AS deletions lines had a lower percentage of cells with activity at weeks 7-8 compared with controls. At weeks 9-10, the *UBE3A*-specific knockout reached levels comparable to controls, whereas the AS deletion line continued to show reduced synaptic activity. Among active cells, the *UBE3A*-specific knockout and AS deletion lines exhibited reduced event amplitude and prolonged decay kinetics compared to controls. These findings indicate that *UBE3A* loss drives deficits in neuronal maturation and channel expression, while the additional loss of neighboring genes in the 15q11-q13 region exacerbates developmental delay and impairs synaptic recruitment.

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Poster Session 1 / No. 5

Exploring the therapeutic potential of CX3CL1-derived peptide in Alzheimer's disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-β (Aβ) plaques, neurofibrillary tau tangles, neuronal loss, and cognitive decline. Although recently approved anti-amyloid therapies reduce Aβ burden, they provide limited benefit for neuronal survival. Thus, there remains a critical need for neuroprotective strategies that preserve neurons, as neuronal loss correlates most strongly with cognitive impairment in AD patients. Our laboratory addressed this gap by identifying a non-canonical neuroprotective mechanism of CX3CL1 (fractalkine). CX3CL1 is a membrane-anchored chemokine known for regulating neuron-glia crosstalk via CX3CR1 receptors. However, we found that CX3CL1 is also sequentially cleaved by α-, β-, and γ- secretase to release an intracellular domain (CX3CL1-ICD) that translocates to the nucleus and upregulates pro-survival signaling pathways, such as TGF-β/Smad and insulin/IGF-1. In our prior studies, neuronal overexpression of CX3CL1-ICD in AD mice enhanced neuronal survival, promoted neurogenesis, reduced pathology, and improved cognitive function. To translate this mechanism therapeutically, we developed Tet34, a synthetic peptide derived from CX3CL1-ICD, and Alexa-488-Tet34 (Alexa-Tet34), a fluorescently labeled variant for tracking cellular uptake and localization. Our previous *in-vitro* studies demonstrated that Alexa-Tet34 is taken up by neuroblastoma cells, with a detectable intracellular signal at 24-48 hours. Functionally, Tet34 promoted neuronal survival and proliferation while activating neurogenic signaling pathways similar to the CX3CL1-ICD. These findings support Tet34 as a pharmacologic mimic of CX3CL1-ICD, and our overall aim is to test its therapeutic potential *in vivo*. A major challenge in CNS drug delivery is poor blood-brain barrier (BBB) penetration. To circumvent this, we plan to utilize intranasal (IN) delivery, as small peptides may not cross the BBB. This approach also provides direct nose-to-brain transport with minimal systemic exposure. We tested the feasibility of intranasal delivery of Alexa-Tet34 in mice, and our preliminary studies demonstrate that Alexa-Tet34 reaches the olfactory bulb within 2 hours and distributes to the cortex, hippocampus, and cerebellum by 8-24 hours, supporting a rapid and widespread nose-to-brain delivery. Since Alzheimer's disease pathology affects multiple brain regions, including the entorhinal cortex, hippocampus, and association cortices, achieving broad brain distribution is important for therapeutic efficacy. Therefore, based on this preliminary data, intranasal delivery appears to be a promising approach. Next, we plan to establish the pharmacokinetic and safety profile of Tet34 in wild-type mice using LC-MS/MS, signaling pathway analysis, and histological assessment of nasal and CNS tissues. Following dose and safety optimization, we will test the therapeutic efficacy of Tet34 in two AD mouse models (5xFAD (amyloid-driven) and PS19 (tauopathy)) using

early- and late-intervention strategies. We will evaluate effects on neuropathology, neuronal survival, synaptic integrity, neurogenesis, and cognitive function using molecular, electrophysiological, and behavioral assays. Furthermore, we will use proteomics to identify Tet34-induced neuroprotective pathways and compare them with the human AD dataset to assess translational relevance.

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Poster Session 1 / No. 6

Investigating the role of microglial KLF2 in Alzheimer's Disease

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Alzheimer's Disease (AD) is the leading cause of dementia in the population. Accumulation of extracellular amyloid plaques and intracellular tau tangles are the classic hallmarks of the disease resulting in neurodegeneration and cognitive decline. Microglia, resident immune cells of the brain, are primarily responsible for reducing the plaque load. However, as the pathology worsens, they turn dysfunctional leading to engulfment of healthy synapses, neuronal loss, impaired memory and neuroinflammation. Several single cell sequencing studies have reported different microglial states, sin both diseased and non-diseased brains, providing evidence of their dynamic nature. Most of them tend to possess a homeostatic transcriptomic profile in a healthy brain, however, the transcriptomic signature shifts towards a more disease associated microglia (DAM) state due to activation in response to AD pathology. Our previous work has identified an intermediate transition state, in AD patients and 5XFAD mice, which exhibited upregulation of **Kruppel-like factor-2 (KLF2)**, a zinc finger transcription factor, compared to other states, making it a promising characteristic feature for transition state. KLF2 has been widely studied in peripheral immune cells and brain endothelium but the amount of research done in microglia is limited.

Here, we aimed to explore the effect of KLF2 levels on cellular functions such as phagocytosis. BV2, mouse microglial cell line, is used to generate a stable cell line for over-expressing KLF2 in a doxycycline inducible manner. Enhanced expression of KLF2 has shown to improve phagocytic efficiency of the cells and to promote the proteolytic and lysosomal-autophagosomal pathway. Additionally, we have used fluorescence in-situ hybridization (FISH) and a combination of FISH and immunohistochemistry (IHC) to locate KLF2 expressing microglial cells in 3-month-old and 10-month-old 5XFAD brain slices as a part of characterizing the levels and nature of the sub-population. For in-vivo studies, we have developed a microglial- specific KLF2 overexpression model using FLEx (flip-excision) approach by crossing Tmem119-Cre^{ERT2} and KLF2 mice in WT and 5XFAD background which is being used for IHC, FISH, and single -cell RNAseq to further understand KLF2 driven functional pathways, its role in driving microglial states and its impact on different aspects of the disease pathology. Behavioral experiments on these mice will allow us to determine the effect on cognitive functions as well.

Together, we aim to address the unknown in the field and investigate the potential of KLF2 to ameliorate the disease pathology. Future studies and more work will need to be done in developing therapies against various microglial targets regulated by KLF2 or KLF2 itself to treat AD patients.

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Poster Session 1 / No. 7

Studying the impact of microglial KLF2 in Alzheimer's disease using hiPSC-derived models

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Alzheimer's Disease (AD) is one of the most common neurodegenerative disorders and dementias. It is a multifactorial disease characterized by the accumulation of extracellular amyloid-beta (Aβ), tau neurofibrillary tangles (NTFs), and neuroinflammation. In the context of AD, microglia play a crucial role in disease pathogenesis and progression. Previous studies have shown that microglia play an early neuroprotective role by attempting to clear Aβ accumulation. However, in aging or neurodegenerative diseases such as in AD, microglia can become overly active and can transition to a Disease Associated Microglial (DAM) state, leading to altered Aβ clearance either positively via enhanced phagocytosis or negatively by exacerbating AD pathology. Previous transcriptomic studies, done in our lab, identified elevated Kruppel-like factor-2 (KLF2), levels in transition state microglia. KLF2, is a zinc finger transcription factor that has been extensively studied in other disease contexts such as stroke and cancer, particularly in endothelial cells. Recent studies have implicated that KLF2 may play a role in neuroinflammation and neurodegenerative diseases. However, the role of KLF2 in microglia and under AD conditions is poorly understood, highlighting an unmet need in the field. In order to understand the function of KLF2 in microglia, future experiments will utilize CRISPR-Cas9 to knock-out (KO) KLF2 in hiPSC-derived microglia. For this project, we will utilize the CLYBL 6-TF-iMG KI1/KI2 TF-driven microglia line of which we have done preliminary characterization. We will then use qPCR and western blot to assess expression levels, phagocytosis assay to investigate the functional output and chemokine arrays to monitor immune response after Aβ oligomer or LPS exposure. Additionally, rescue experiments will be performed by reintroducing functional KLF2 to assess the specificity of the observed phenotypes. We will then study the effect of KLF2 KO in microglia-neuronal crosstalk utilizing conditioned media experiments and implement cultured adhesion brain organoid models (ABO) to recapitulate a 3D human-like neural microenvironment and assess how KO of KLF2 affects and shapes microglia behavior and interactions in contact-dependent mechanisms. Together, this work will provide further insights into the role of microglial KLF2 and its potential implications for AD.

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Poster Session 1 / No. 8

Targeting Microglial BACE1 for Mitigating Tauopathy pathology.

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Alzheimer's disease and related tauopathies are characterized by progressive tau accumulation, neuroinflammation, and loss of neuronal homeostasis, with microglia emerging as key regulators of disease progression and cognitive resilience. In this study, we investigated whether microglial BACE1 contributes to tau pathology and whether its deletion could mitigate disease-associated changes in a tauopathy model. Using PS19 mice expressing human P301S tau, we examined the effects of constitutive and microglia-specific Bace1 deletion on microglial states, tau pathology, and lysosomal/autophagy-related pathways. Immune-sorted microglia were analyzed by single-cell RNA sequencing, and brain tissues were assessed by immunostaining and western blotting. The data showed that loss of Bace1 altered microglial clustering and shifted microglial signatures away from a disease-associated state, with changes in homeostatic and disease-associated microglia (DAM) related marker expression. Bace1 deletion also reduced phosphorylated tau levels, improved axonal structure, and was associated with upregulation of lysosomal and autophagy-related pathways, including Lamp1 and other lysosomal genes, while NF-κB related inflammatory signaling was reduced. In inducible microglia-specific Bace1 conditional knockout mice, tamoxifen-mediated deletion similarly increased the homeostatic microglial population and significantly decreased phosphorylated tau at 9 months. Together, these findings suggest that microglial BACE1 promotes maladaptive microglial responses and tau pathological progression, and that targeting BACE1 in microglia may represent a therapeutic strategy to alleviate tauopathy by enhancing lysosomal-autophagic function and dampening inflammatory signaling.

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Poster Session 1 / No. 9

Targeting Non-Canonical HSF1 Functions to Treat Early Alzheimer's Disease

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Alzheimer's disease (AD) begins with the accumulation of misfolded intracellular amyloid-beta (Aβ) oligomers well before the formation of extracellular Aβ plaques and cognitive decline. This early phase is marked by subtle but progressive cellular stress, including impaired proteostasis (the system for regulating protein folding, degradation, and clearance), mitochondrial dysfunction, and shifts in metabolic gene expression, yet current therapeutic interventions exclusively target later pathology, after irreversible damage has occurred. Identifying endogenous protective mechanisms that could act during this early phase will be critical for developing preventative therapies for AD. One candidate is Heat Shock Factor 1 (HSF1), a master regulator of transcriptional responses to cellular stress. While classically known for its role as a transcription factor, in vitro studies suggest HSF1 may also act outside the nucleus to promote cell survival, potentially through the modulation of proteostasis and other cytoplasmic functions. These non-transcriptional functions have not been tested in vivo. To explore this, we developed a novel mouse model, Hsf1$^{\Delta HRab}$, which contains a targeted deletion of HSF1's oligomerization domains, preventing trimerization and DNA binding while preserving domains thought to mediate cytoplasmic activity. We have experimentally confirmed that HSF1$^{\Delta HRab}$ protein is expressed in cortex and hippocampus but does not form trimers. We hypothesize that HSF1$^{\Delta HRab}$ will retain its cytoplasmic neuroprotective functions to alleviate Aβ toxicity. However, we also propose a second hypothesis: that the beneficial effects of cytoplasmic HSF1 activity may be insufficient under chronic stress, reflecting the known decline in HSF1 transcriptional activity in AD brains. Supporting this, we observe down-regulation of key survival genes like Bcl2 and Pgc1a, synaptic maintenance gene PSD95, and upregulation of poly-ubiquitinated misfolded proteins in adult Hsf1$^{\Delta HRab}$ mouse hippocampus. Bulk RNA-seq revealed the upregulation of the immunoglobulin kappa constant (IGKC) transcript, a rare stress response that may stimulate neuronal growth, synaptic maintenance, and circuit reorganization, a potential attempt at compensation. These findings suggest that the hippocampus is especially vulnerable to transcriptionally-insufficient HSF1 over time, potentially highlighting HSF1 polymorphisms as predictive markers for chronic cell stress. Together, this work aims to define both the therapeutic potential and limits of HSF1's cytoplasmic functions in AD, particularly their role in regulating intracellular Aβ oligomers. Understanding this balance will allow us to determine whether modulating HSF1 is a viable strategy for early intervention in AD.

Support:

Poster Session 1 / No. 10

Probing Early Alzheimer's Disease Physiology with Dual Glutamate-Voltage Imaging the Same Brain Slice

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Early-stage physiological alterations preceding amyloid plaque deposition in Alzheimer's disease (AD) remain incompletely characterized. Here, we investigated candidate physiological determinants of prodromal AD using ex vivo approaches in a transgenic mouse model. Acute cortical slices were prepared from APP^NLGF mice and littermate controls at two early time points: postnatal day 50 (P50 ± 7; prodromal stage 1) and P100 (P100 ± 7; prodromal stage 2). Synaptically evoked cortical responses were quantified across increasing stimulus intensities using two complementary optical modalities: glutamate imaging with iGluSnFR, and voltage imaging with the voltage-sensitive dye EF-630. At P50, but not P100, stimulus-evoked signal amplitudes (ΔF/F) were significantly elevated in NLGF mice relative to controls across both modalities. However, normalization to maximal response amplitude abolished these differences, and no genotype-dependent changes in stimulus-response relationships were observed. Responses increased monotonically and approximately linearly with stimulus intensity, with no evidence of nonlinear scaling. Kinetic analyses revealed no significant genotype-dependent differences in rise or decay times across modalities or ages, indicating preserved temporal dynamics of cortical responses. Pharmacological disinhibition with 4-aminopyridine (4-AP) produced a greater increase in glutamate signal amplitude at P50 compared to P100, suggesting age-dependent differences in cortical excitability rather than AD-specific effects. Complementary UPLC-MS proteomic analyses identified AD-associated protein alterations across three time points (P50, P100, and P200). At P50, inflammatory markers were already upregulated, while several neuronal proteins (e.g., tetraspanin-3, synaptotagmin) were downregulated. By P200, proteins associated with immune function (complement C4-B, tumor necrosis factor-α), lysosomal pathways (progranulin), and amyloid/lipid metabolism (clusterin, apolipoprotein E) were upregulated, whereas proteins involved in dopamine transport, intracellular calcium regulation (neurogranin), and synaptic transmission (synaptophysin) were reduced. Notably, inflammatory markers (CD180 and ISG15) were elevated at both P50 and P200, indicating sustained immune activation. Collectively, these findings demonstrate that early prodromal AD is characterized by increased cortical response amplitudes without accompanying changes in response kinetics or input-output transformations. Concordant results across glutamate and voltage imaging support a physiological, rather than methodological, basis for enhanced synaptic responses. Increased sensitivity to disinhibition at P50 further suggests elevated network excitability at earlier stages. Proteomic alterations in immune-related pathways may represent early molecular signatures of disease progression, preceding later synaptic dysfunction.

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Poster Session 1 / No. 11

Retrograde Transport of β-Glucocerebrosidase (GCase) in Parkinson's Disease

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Parkinson's disease (PD) is the second most common neurodegenerative disease, however, there is currently no curative treatment. Mutations in *GBA1*, encoding the lysosomal enzyme β-Glucocerebrosidase (GCase), are the most common genetic risk factor for PD. Despite this well-established link, the mechanisms of how these mutations contribute to the disease are unknown. Proper membrane trafficking is vital to GCase function. GCase is synthesized in the endoplasmic reticulum (ER), transported to the Golgi, then moved to the lysosome where it is mature and active. Mutations in *GBA1* result in misfolded GCase that becomes retained in the ER, leading to loss of its function and accumulation of its substrates in the lysosome. Throughout the trafficking process, glycosylation modifications occur on GCase which are crucial for its function, resulting in various-sized forms of GCase occurring at different subcellular locations. To identify candidates for modifiers of GCase, we performed an unbiased siRNA knockdown screening. Alterations in genes implicated in retrograde transport were consistently found to shift GCase size. Further immunoprecipitation experiments revealed binding of the corresponding protein complex to GCase. Despite the important role of membrane trafficking in GCase function, little is known about its retrograde transport. As alterations in machinery required for this transport alter GCase modifications, our data suggests that GCase may undergo transport beyond its canonical anterograde processing. It is possible that this process is implicated in the ER retention of GCase, ER stress, and decrease in GCase activity found in PD. This work further suggests protein interactions that have not yet been characterized. In future research, we will investigate the physical interaction of GCase and this complex, how GCase localization and function are affected by alterations to these proteins, and how these processes are implicated in PD pathogenesis.

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Poster Session 1 / No. 12

Microglia lipid metabolism as a bridge between brain aging and glioblastoma progression

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Glioblastoma (GBM) remains the most lethal primary brain malignancy, with median survival under 15 months despite aggressive multimodal therapy. Its incidence peaks at 75 years and prognosis worsens with age, yet the mechanistic link between aging and GBM lethality remains unexplored. In the aging brain, progressive white matter degeneration generates excessive myelin debris that overwhelms microglial (MG) phagocytic capacity, resulting in chronic lipid accumulation within aged MG. To manage this overload, aged lipid-droplet accumulating MG (LDAM) upregulate cholesterol efflux pathways to help offload their lipid burden. Interestingly, macrophages and MG comprise up to 50% of GBM tumor mass but adopt dysfunctional phenotypes rather than mounting anti-tumor responses. Tumor-associated macrophages (TAMs) that phagocytose myelin debris strikingly acquire similar lipid-laden phenotypes and exploit the same cholesterol efflux pathways to transfer myelin-derived lipids to GBM cells, fueling proliferation and invasion. This raises the unexplored possibility that LDAMs represent “pre-loaded” versions of tumor-fueling TAMs, where they predispose the brain to GBM progression by supplying essential metabolic fuel to the tumor. To test our hypothesis, we are leveraging induced pluripotent stem cell (iPSC)-derived MG (iMG) and patient-derived glioma stem cells (GSCs) to mechanistically dissect age-related metabolic fueling. Our work shows that iMG recapitulate critical LDAM phenotypes when exposed to myelin debris *in vitro*, including scavenging of myelin debris and formation of lipid droplets. Metabolic coupling of LDAM with GSCs will transform our understanding of age as an active driver of GBM lethality and establish a shift toward metabolic-based therapies that exploit age-specific vulnerabilities in the tumor microenvironment. By targeting the fuel supply rather than the tumor directly, this approach offers new hope for elderly GBM patients, who currently face the worst outcomes with existing therapies.

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Poster Session 1 / No. 13

Spatial transcriptomic analysis reveals disease-specific developmental changes in a mouse model of globoid cell leukodystrophy

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Globoid cell leukodystrophy (GLD) is a rare and fatal autosomal-recessive disease that results in the supraphysiological accumulation of the sphingosine-based lipid, psychosine, throughout the CNS. There is no known cure for this disease. Our lab has previously demonstrated that $CD8^+$ T-cells play a significant role in driving the neuroinflammation and CNS destruction seen in GLD. Transcriptomic analyses revealed that $CD8^+$ T-cells in a mouse model of GLD called twitcher ("twi") exhibit a cytotoxic T lymphocyte (CTL) phenotype. Prior work also determined that t cell populations in twi mice do not exhibit clonal expansion, and recent ex vivo experiments indicate that the activation of twi t cells is not dependent upon MHC-mediated antigen presentation. These findings suggest that these disease-associated CD8+ t cells are not a classic antigen-driven CD8+ t population but instead are consistent with the phenotype of embryonically derived $CD8^+$ T-cells which are distinct from adult born CD8 t cells. Embryonically derived $CD8^+$ T-cells begin to undergo differentiation from their hematopoietic progenitors in the thymus during embryonic development, specifically at embryonic day (E) 13.5. Therefore, we hypothesized that if pathogenic CD8+ t cells in twi are of embryonic origin, then there may be developmental imbalances within the developing twi mouse that would be detectable during embryonic development. To test this hypothesis, we collected E13.5 twi and wildtype (wt) littermate embryos to evaluate gross developmental differences, and performed spatial transcriptomic analyses using the 10x Genomics Xenium *In-Situ* platform to examine and characterize any potential changes in gene expression in these wt and twi mouse embryos. This 10x Xenium spatial platform is a probe and imaging-based approach that uses multiple rounds of replication and fluorescent probe labeling to identify and decode transcripts and simultaneously map them to an individual cell, thus providing single-cell resolution of all probed transcripts. Our preliminary analysis of these data has identified numerous genotype-based differences in gene expression. For example, there was a notable dense region of *sox17* expression in the developing thymus of the *twi* embryo, which was not observed in the WT embryo. This finding was of particular interest because prior studies by others have determined that embryonically derived $CD8^+$ T-cells cells require the transcription factor *Sox17*, which is not expressed in adult-derived $CD8^+$ T-cells. There are no major histomorphological differences between the two embryo genotypes, which is also consistent with children born with GLD to appear healthy, which clinically may contribute to delaying diagnoses. Our ongoing studies will use interrogate and validate these spatial datasets that will support future *in-vivo* and *in-vitro* studies into whether these very early differences portend immunological changes associated with GLD disease pathophysiology.

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Poster Session 1 / No. 14

Regulation of gap junctions by stomatin-like proteins in *C. elegans*

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Gap junctions are intercellular channels that play important roles in neurons and muscle cells. Neuronal gap junctions are commonly referred to as electrical synapses. Connexins and innexins are the building blocks of vertebrate and invertebrate gap junctions, respectively. Increasing evidence indicates that regulatory proteins can crucially influence gap junction function, but much remains unknown about their identities and molecular mechanisms.

In *C. elegans*, loss-of-function mutations in two innexin genes (*unc-7* and *unc-9*) and two stomatin-like genes (*unc-1* and *unc-24*) produce similar phenotypes—*Kinker* motion, hypersensitivity to volatile anesthetics, and gap junction dysfunction—without additive effects in double mutants. It is not entirely clear why *unc-1* and *unc-24* mutations phenocopy *unc-7* and *unc-9*. Our previous study (Chen et al., *Curr Biol* 2007) showed that loss-of-function mutations in *unc-1* inhibited electrical coupling of body-wall muscle cells similarly to *unc-9* mutations, with no additive effect in *unc-9;unc-1* double mutant, suggesting that UNC-1 is required for UNC-9 gap junction function. However, it remains unclear how UNC-1 plays this role, whether UNC-24 also regulates UNC-9 gap junctions, and whether UNC-1 and UNC-24 regulate UNC-7 gap junctions. Importantly, the potential roles of UNC-1 and UNC-24 with respect to neuronal UNC-7 and UNC-9 gap junctions—which are crucial for neural circuit function—remain unexplored.

I began addressing these important questions by testing the effects of UNC-1 and UNC-24 on biophysical properties of UNC-7 and UNC-9 homotypic gap junctions (formed by UNC-7 or UNC-9 alone) using the *Xenopus* oocyte heterologous expression system. Key procedures include oocyte isolation, complementary RNA injection, pairing oocyte culture to allow gap junction formation, and electrophysiological recording of junctional currents. My preliminary data showed that coexpression of UNC-1 with UNC-7 substantially increased the amplitudes of junctional currents, while coexpression of UNC-24 with UNC-9 altered junctional voltage dependence and slowed gap junction deactivation. These observations suggest that UNC-1 and UNC-24 can modulate gap junction function, laying the foundation for further investigations.

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Poster Session 1 / No. 15

Investigating Early Life Factors Contributing to the Integration of Developmentally-Specified Hippocampal Neurons

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Early life experiences (ELE) are crucial to mammalian brain development, particularly in the hippocampus, a region key in memory encoding and consolidation. The dentate gyrus (DG) subfield regulates cortical input propagation to hippocampal region CA3, influencing neural plasticity and the formation of spatial and episodic memories. Unlike most brain regions, where neurogenesis is restricted to embryogenesis, DG granule cells (GCs) are generated across three neurogenic waves spanning embryonic, neonatal, and adult stages. Despite their shared lineage, GCs exhibit substantial heterogeneity in laminar positioning, morphology, and connectivity, but whether these distinctions translate into subtype-specific functioning roles in memory-guided behaviors remains unclear. Much research in the field focuses on adult-born GCs (abGCs), however, adult neurogenesis only constitutes a small minority of the total GC population. Our study therefore aims to first develop novel transgenic and viral-mediated methods to differentially target embryonically and neonatally-born GCs (eGCs and nGCs respectively), and then investigate the effects of early life exercise and social isolation on these developmentally-specified populations. To label eGCs, we performed P1 transverse sinus injections (TSI) on Dock10^{Cre} mice with ~350 µL of undiluted AAV9-CAG-Flex-TdTom. To label nGCs, we performed intragastric tamoxifen (TMX) injections on Ascl^{CreER} mice at different postnatal timepoints. Results showed that the Dock10^{Cre} x TSI and Ascl^{CreER} x TMX methods allow us to distinguish between eGCs and nGCs in the developing hippocampus, however, presumed glial expression in the Ascl^{CreER} line reduces reliability of nGC labeling. Given these limitations, we focused on investigating the effects of ELE between P21-P53 on eGCs only. We looked at cell density and fluorescent intensity of eGCs, parvalbumin interneurons (PV-INs), and abGCs. Preliminary data indicates no statistically significant effects of our ELE model on TdTom+ eGCs or Doublecortin+ abGCs at the populational level. This may suggest that our peri-adolescent manipulation missed the eGC critical maturation window and that there may be developmental-stage specificity in adult neurogenesis. PV-INs exhibit subtle changes in the DG and CA3, which may point to a unique role of mediating DG excitability when exposed to adversity compared to exercise. Together, with future experiments investigating the effects of ELE on nGCs, our work will pave the way in understanding how these populations contribute to hippocampal function in response to positive and negative ELE, while informing therapeutic approaches for neurodevelopmental disorders.

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Poster Session 1 / No. 16

A histological analysis of volumetric differences in the dentate gyrus of male Shank3B knockout mice versus wild types.

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Autism Spectrum Disorder (ASD) is a polygenic neurodevelopmental disorder characterized by restricted and repetitive behaviors, as well as deficits in social communication. SHANK3 is a synaptic scaffolding protein that plays a key role in both synaptic development and plasticity. Shank3B, one mouse allele of the gene, is a well-established knockout to model an ASD-like phenotype in mice. Rodents with a knockout of the Shank3B gene present with compulsive, repetitive behaviors and impaired social function, as well as heightened aggression in some models. These behaviors are consistent with the profile of ASD. The dentate gyrus is critically involved in memory encoding as well as emotional regulation. As one of the few sites of adult neurogenesis in both humans and rodents, it is particularly susceptible to genetic abnormalities impacting synaptic development. Previous studies have shown that ASD-linked genes have a wide range of impacts on the development and function of the dentate gyrus. This study examines whether there is a difference in the volume of the molecular, granule, and polymorph layers of the dorsal dentate gyrus in Shank3B knockout (KO) (n=4) mice versus wild types (WT) (n=4). Results show a significant increase in volume of the left dental gyrus, suggesting lateralization of the dorsal dentate gyrus in mice, and a unique hypertrophy in the left hemisphere present in the KO mice. These preliminary results implicate the dentate gyrus in the ASD-like phenotype present in the Shank3B KO mice.

Support: N/A

Poster Session 1 / No. 17

Age-related Shifts in Endocannabinoid and BDNF Regulation of Hippocampal Long-term Depression

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Background: While Group I metabotropic glutamate receptor-dependent LTD (mGluR-LTD) is a primary model of synaptic plasticity, its induction requirements and regulatory mechanisms across the lifespan remain controversial. While often considered a developmentally restricted phenomenon, the degree to which age-related shifts in endocannabinoid (eCB) and brain-derived neurotrophic factor (BDNF) signaling regulate this plasticity is not well understood. Objective: This study examined mGluR-induced LTD under varying ionic conditions across the murine lifespan to explore how CB1 and TrkB receptor signaling differentially regulate its expression from weaning to senescence.
Methods: Electrophysiological recordings of evoked field excitatory postsynaptic potentials (fEPSPs) were conducted in hippocampal slices (CA3 → CA1) from mice aged 2-4 weeks, 2-4 months, 10-12 months, and 22-24 months. LTD was induced using Group I mGluR agonist: (S)-3,5-dihydroxyphenylglycine (DHPG), under varying Ca/Mg ratios, with a focus on the regulatory roles of CB1 and TrkB receptors.
Results: In standard physiological media (2 mM Ca / 1.3 mM Mg), DHPG-LTD was largely absent across all ages. Reducing Mg to 0.05 mM (maintaining 2mM Ca) permitted robust LTD only in young mice (2-4 weeks). However, a 5:1 Ca/Mg ratio unmasked DHPG-LTD across all age groups. A distinct age-dependent shift emerged in both amplitude (decreasing with age) and mechanism: (i) Developmental Stage (2–4 weeks): LTD expression was independent of eCBs and TrkB signaling; (ii) Adult Stages (2–12 months): TrkB signaling became essential, while eCBs remained uninvolved; (iii) Senescence (22–24 months): A unique signaling reversal occurred. In the aged brain, both eCBs and TrkB receptor antagonists significantly enhanced DHPG-LTD, indicating a shift where these pathways transition from permissive or neutral roles to actively limiting synaptic plasticity.
Conclusion: Our findings demonstrate that mGluR-LTD is a lifelong capacity whose expression is gated by the Ca/Mg ratio. Crucially, the transition from adulthood to senescence involves a fundamental reorganization of regulatory signaling, where BDNF and eCBs shift to an inhibitory role that constrains plasticity in the aging hippocampus.

Summary of Key Findings (Ca/Mg Ratio: 5:1):

Age Group	LTD Amplitude	CB1 Blockade Effect	TrkB Blockade Effect
2–4 Weeks	Robust	No Effect	No Effect
2–4 Months	Robust (Similar to young)	No Effect	Impairs LTD
10–12 Months	Moderate	No Effect	Impairs LTD
22–24 Months	Reduced	Enhances LTD	Enhances LTD

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Poster Session 1 / No. 18

The Behavioral and Anatomical Characterization of Prefrontal Cortex Neurons in Cognitive Flexibility

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Cognitive flexibility is a process that involves dynamically adapting behavior to obtain a desired series of outcomes during continuously changing stimulus-response-reward associations. This process is impaired in many neuropsychiatric disorders including schizophrenia, Alzheimer's disease, depression, and anxiety. Current psychiatric treatments struggle to target deficits in executive function, and the neural mechanisms of cognitive flexibility are unclear. Previous research has found the role of the medial prefrontal cortex in feedback monitoring and outcome encoding during attentional set-shifting. To further investigate its role in decision-making during uncertainty, we used optogenetics in a rodent probabilistic cognitive flexibility task, the 2-armed bandit, to silence pyramidal cells in the medial prefrontal cortex. The 2-armed bandit is a head-fixed probabilistic reversal learning task in which animals must shift their behavioral strategy during a period of uncertainty. Consistent with prior studies leveraging uncertainty-based decision-making models, our results suggest that the prefrontal cortex plays a larger role in probabilistic decision-making than deterministic decision-making, with prefrontal engagement scaling with uncertainty. Specifically, mPFC suppression during rule switching, but not during rule execution, appears to have a negative effect on task performance. Furthermore, previous research suggests that layer VI of the prefrontal cortex is involved in feedback monitoring to guide adaptive behavior. Thus, using immunohistochemistry and anatomical tracing via retrobeads signaling, we have found shared populations of PFC-RE (nucleus reuniens) and PFC-MDT (mediodorsal thalamus) projections. Our future research will combine our knowledge of the mapping of these projection neurons with the two-armed bandit to fully understand the broader circuitry of probabilistic decision-making *in vivo.*

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Poster Session 1 / No. 19

An Appetite for Discovery: Feed Your Curiosity in the Fortin Lab

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The Fortin Lab at UConn Health is a newly established and growing research group focused on understanding how the brain regulates behavior and physiology. Our work sits at the intersection of behavioral neuroscience, metabolism, and neural circuit dissection. We use a multidisciplinary approach in rodent models to **[1.]** interrogate nuclei- and cell-type-specific receptor populations and circuits within the brain that control physiology and behavior; **[2.]** explore novel drug targets for obesity pharmacotherapies; **[3.]** correlate neural responses with physiological measurements and behavioral events in awake animals; and **[4.]** determine the cellular mechanisms behind complex ingestive behaviors and physiological regulation of energy balance control. We are currently focused on how discrete nuclei of the brain coordinate responses to maintain energy balance control.

Ongoing and planned studies in the lab involve rodent behavioral paradigms designed to measure feeding, motivation, and stress-related behaviors, alongside neural recording and manipulation methods such as fiber photometry and optogenetics. These approaches allow us to monitor and control neural activity in real time as animals engage in complex behaviors. In parallel, we use molecular techniques like immunohistochemistry, RNAscope, and neural tracing methods to phenotype and map the neural circuits underlying these processes.

We are actively recruiting! Joining the lab provides a unique opportunity to contribute meaningfully to the development of research projects from the ground up. Trainees will gain hands-on experience across a wide range of techniques, including animal handling, behavioral testing, stereotaxic surgery, neural recording, and histological analysis. Just as importantly, students will be mentored in experimental design, data analysis, and scientific communication, with the goal of fostering independence and preparing them for careers in neuroscience, medicine, and related fields. Individuals interested in behavioral neuroscience, neural circuits, and the biological basis of behavior are encouraged to inquire about joining our growing team.

Poster Session 2 / No. 1

A Corticothalamic Circuit for Valence Feedback Modulation

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Prefrontal corticothalamic loops are fundamental to executive function but remain poorly characterized. The principal pathway connecting the cortex with the thalamus originates from layer 6 corticothalamic (L6CT) neurons. In sensory and motor cortices, L6CT neurons form local circuits with inhibitory interneurons to regulate deep and superficial layered neurons. Using slice electrophysiology, optogenetics, *in vivo* 2-photon calcium imaging, and behavioral experiments, we tested the hypothesis that prefrontal L6CT neurons regulate higher-order task representations through excitation of cortical inhibitory interneurons. Head-restrained mice were trained to perform a cognitive flexibility task that demanded selective attention to one sensory modality (e.g., odor) while ignoring another (e.g., whisker vibrations). The task rule switched periodically, requiring the animal to shift attention to the previously irrelevant sensory modality. First, we used 2-Photon calcium imaging to show that L6CT neurons preferentially dissociated between rewarded and unrewarded trials (trial outcome) during the post-trial epoch, which contrasted with neighboring L5CT neurons. Compared to correct (rewarded) trials, L6CT neurons more commonly preferred to fire following error (unrewarded) trials. Following this discovery, we used optogenetics to stimulate L6CT neurons immediately after trial completion, consistent with their preferential engagement for encoding trial outcomes. We suspected that stimulation of L6CT neurons would suppress neighboring cortical neurons, however, we instead observed both excitatory and inhibitory effects across multiple mPFC laminae. Neurons excited by L6CT stimulation showed enhanced predictability of trial-outcomes, driven by improved error-coding. Notably, error-coding neurons were suppressed at a lower rate than correct-coding neurons, whereby correct-coding neuronal populations maintained outcome representations at a reduced response amplitude (i.e., gain modulation). To determine whether L6CT neurons regulate neighboring populations through local circuitry, we performed slice electrophysiology paired with optogenetics. Stimulation of L6CT neurons weakly excited a small subset of L2/3 and L5 neurons, but elicited modest post-synaptic potentials in neighboring L6 pyramids and interneurons. Together, these experiments show that L6CT neurons engage local circuits to modulate mPFC representations of post-choice valence.

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Poster Session 2 / No. 2

Adult-Born Granule Cells and Beyond: Subtype-Specific Control of Fear Generalization in the Dentate Gyrus

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A defining feature of episodic memory is the ability to discriminate between similar experiences. Impairments in this function have been linked with overgeneralization of fear responses to neutral contexts, a core symptom of psychiatric disorders such as post-traumatic stress disorder (PTSD). Converging evidence implicates dysfunction within the hippocampal dentate gyrus (DG), a key structure for pattern separation and contextual encoding in regulating this process. However, the contributions of distinct DG neuronal populations to memory discrimination remain incompletely understood.

Using contextual fear conditioning (cFC), we investigated the role of adult-born granule cells (abGCs) in regulating fear generalization. In the first experiment, mice were fear conditioned in context A (Day 0) and abGCs were chemogenetically silenced during repeated exposures to both the conditioned context (A) and a neutral context (B) on Days 14–17. Silencing abGCs resulted in increased freezing in the neutral context, indicating impaired discrimination and enhanced fear generalization. In a second experiment, mice received corticosterone (CORT) or vehicle at the time of conditioning (Day 0), and abGCs were silenced during retrieval (Day 14). Under elevated stress, silencing abGCs did not further effect contextual discrimination, suggesting that elevated stress may limit the dynamic range of abGC-dependent modulation. Given that adult neurogenesis is rare in primates and contributes to less than 5% of granule cell population in rodents, these findings suggest that abGCs are one component of a broader, developmentally defined population of granule cells regulating contextual specificity. This motivates examining how granule cell populations generated across developmental time contribute to memory precision within DG circuits. Complementary work from our group demonstrates that sensory features of contextual memory are encoded by largely non-overlapping neuronal ensembles in mature DG granule cells, supporting a circuit architecture that enables flexible remapping of sensory cues across contexts.

To determine how stress alters the neural representation of sensory cues, we developed an olfaction-based paradigm in head-fixed mice, using pupil dynamics as a quantitative proxy for arousal analogous to freezing. Elevated stress via systemic CORT injections prior to conditioning induced lasting alterations in odor-evoked responses. Fourteen days after conditioning, CORT-treated animals exhibited increased pupil dilation to conditioned (banana; $p < 0.01$), neutral (lemon; $p < 0.05$), and novel (apple; $p < 0.001$) odors, consistent with persistent fear generalization. In contrast, control animals showed attenuation of pupil responses over time, while non-CORT conditioning animals exhibited selective and more restricted responses, with increased pupil dilation primarily to the conditioned cue (banana; $p<0.05$) and delayed responses to novel stimuli. Together, these results indicate that stress broadens sensory tuning

and reduces discrimination, suggesting a shift toward more generalized responses to fear-relevant stimuli.

Our ongoing studies combine neurogenesis-based labeling with intersectional circuit-targeting to monitor and manipulate embryonic and postnatal GC subtypes. Using single-cell-resolution two-photon imaging, we will examine how distinct DG granule cell subtypes underlie context representation and contribute to maladaptive fear generalization. Together, this work aims to link circuit dynamics to behavior, towards understanding memory precision and informing targeted interventions for trauma-related disorders.

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Poster Session 2 / No. 3

Dissecting stress-dependent modulation of entorhinal and hypothalamic inputs to dentate gyrus

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Post-traumatic stress disorder (PTSD) is characterized by experiencing distress in the absence of a dangerous event following a traumatic experience, resulting in generalized fear due to context discrimination deficits. The retrieval of a memory encoded under stress is poorly understood, preventing the discovery of precise therapeutic and medical treatments. The dentate gyrus (DG) of the hippocampus is the primary input region whose function is disrupted by stress. The intrinsic DG changes in response to stress have been studied; however, the changes in long-range input dynamics following stressful conditions remain unknown. By obtaining a circuit-level approach to the input-regulated discrimination function of DG, we can have a better understanding of the generalized fear, a hallmark of PTSD. Contextual fear conditioning (CFC) is a widely used animal model of PTSD pathology in rodents and has been adapted to assess fear generalization by the addition of a fear-associated and neutral context discrimination. We have shown that stress enhancement via intraperitoneal corticosterone injection before fear acquisition disrupts discrimination between a fearful and a neutral context in adult mice of both sexes. This manipulation induces freezing in both the shock-paired and a novel, non-shock context during discrimination, in contrast to control mice that freeze selectively in the conditioned context. Preliminary analysis of cFos expression, a marker for neuronal activity, revealed that mice with discrimination deficits show spatially biased activation in the DG and LEC during retrieval, accompanied by a decrease in SuM. Furthermore, the *in vivo* 2-photon calcium imaging of the LEC synapsing at DG and DG soma during a cue-based spatial navigation task shows higher calcium activity at the position where the animal is presented with an olfactory cue. On the other hand, the SuM axons with monosynaptic projections to DG show the peak calcium activity at a novel location following a cue-location shift using a similar task. The results indicate that the LEC is a driver of the DG activity, providing the content information, while the SuM activity is correlated with the novelty signaling. The differential cFos expression in the LEC and SuM during the context discrimination task indicates an activational imbalance accompanied by fear generalization. By studying the influence of stress on the hippocampus and its inputs, we can generate novel target-specific interventions for anxiety disorders, including PTSD.

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Poster Session 2 / No. 4

A role for medial prefrontal cortex in the evaluation of uncertainty in a head-fixed 2-armed bandit task

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Animals face complex decisions in a series of ever-evolving contexts. We define this process of identifying subtle changes in context and shifting behavior accordingly as “Cognitive Flexibility”. Impairments to cognitive flexibility are a hallmark of many neuropsychiatric diseases, and represent a significant burden on patients, caregivers, and the healthcare system, yet its underlying neurobiology is not fully understood. The medial prefrontal cortex (mPFC) is a region of the brain implicated in higher-order cognitive functions, including cognitive flexibility, and therefore represents a locus of research on cognitive flexibility. Work in several complex tasks for rodents, including attentional set-shifting and competitive mixed strategy games, has implicated the mPFC. But the exact computations performed by these neurons in different asks remains a topic of energetic debate.

We approach cognitive flexibility with a head-fixed variant of the two-armed bandit (2AB) for mice. We trained the mice on the task and had them perform it under differing levels of environmental uncertainty. Simultaneous two-photon calcium recordings from mPFC, specifically using the viral vector pAAV9.Syn.GCaMP6f.WPRE.SV40, were generated as the animals performed the task. The activities of these neurons were then aligned to specific features of the task. We found that our animals would adjust their behavior to fit different probabilistic contexts in a 2AB task. We hypothesized that only a subset of mPFC neurons is active and modulated by features of the task, and that distinct populations would be active in high and low uncertainty variants of the task. We also found that different groups of neurons are active both at the time of the delivery of the reward as well as some that persist in activity after the conclusion of the trial. These findings together show a role for the mPFC in evaluating environmental uncertainty and paint a clearer picture of the mPFC’s role in complex decision-making in uncertain environments.

Support: UConn Health startup

Poster Session 2 / No. 5

Impact of Somatostatin-Expressing Inhibitory Neuron Specific BACE1 Deletion in Synaptic plasticity

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BACE1, an enzyme involved in APP processing, is a prime therapeutic target for treating Alzheimer's disease. Inhibitory interneurons make up around 15–20% of the total neuron population in the cerebral cortex. It is generally understood that there are three distinct and non-overlapping interneuron classes in the mouse neocortex, namely, parvalbumin (PV) -expressing, 5-HT_{3A} receptor-expressing and somatostatin (Sst)-expressing interneuron classes. PV and Sst interneuron dysfunctions have been implicated in AD models. Here, we prepared the conditional BACE1 deletion in Sst-expressing cells by crossing the BACE1 flox/flox mice with Sst-IRES-Cre mice, obtaining mice homozygous for BACE1 floxed allele and heterozygous for the Sst-IRES-Cre allele (BACE1 fl/fl;Sst_IRES-Cre +/WT, or Sst-BACE1-KO mice). We found that the field excitatory post synaptic potentials (fEPSPs) have been significantly inhibited in these Sst-BACE1-KO mice when compared with the control (BACE1 fl/fl mice). Fear Conditioning Behavior data showed a significant decrease in freezing time during time component (s) by Sst-BACE1-KO mouse when compared with the control (BACE1 fl/fl) on day 3rd Cue. No change was observed in open field and y-maze behavior between the groups. EEG recording indicates no seizure activity in Sst-BACE1-KO mice when compared with control (BACE1 fl/fl mice). These data suggest the important role of inhibitory BACE1 in synaptic plasticity and function. Future directions include the measurement of intrinsic membrane properties, miniature inhibitory post-synaptic currents (IPSCs) and evoked IPSCs.

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Poster Session 2 / No. 6

MT_1 melatonin receptor-dependent BK channel function in neurotransmitter release, synaptic plasticity, and learning/memory

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The BK channel (Slo1) is a large-conductance, Ca^{2+}/voltage-gated K^+ channel ubiquitously expressed in the brain and highly enriched at presynaptic sites. While BK channels clearly downregulate neurotransmitter release in *C. elegans*, their role in mammalian neurons remain unclear. Our previous work with *C. elegans* showed that BK channel function *in vivo* depends on melatonin and a specific melatonin receptor (Niu et al., *PNAS* 2020). More recently, we found that melatonin promotes sleep in melatonin-proficient CBA/CaJ mice by activating BK channels in the suprachiasmatic nucleus (Vedantham, Ahmad, Niu, et al., *Adv Sci*, under revision). Given that most labs use melatonin-deficient C57BL/6 mice, we hypothesize that BK channels do regulate neurotransmitter release in mammalian brain, but this function is only detectable in mice capable of melatonin synthesis.

My project examines putative melatonin- and MT_1-dependent roles of BK channels in neurotransmitter release and synaptic plasticity using hippocampal slice electrophysiology in CBA/CaJ mice (wild-type, and MT_1 knockout, and Slo1 knockout). I will also test whether learning and memory behaviors depend on the MT_1-BK channel molecular pathway. Preliminary data from our lab show that in Slo1 knockout mice, paired-pulse ratio of field excitatory postsynaptic potentials (fEPSPs) is decreased while the fEPSP slope is increased, compared to littermate controls. These findings are consistent with an inhibitory role for BK channels in neurotransmitter release in wild-type mice.

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Poster Session 2 / No. 7

Locus Coeruleus Iron Homeostasis in Western Diet-Induced Metabolic Dysfunction

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Disruption of iron homeostasis, a process essential for neuronal health and function, has been implicated in metabolic diseases, including obesity and type-2 diabetes. Increases in intracellular iron storage can lead to production of reactive oxygen species (ROS) and even ferroptosis, a form of non-apoptotic regulated cell death. Iron dysregulation in the brain has been explored primarily in hypothalamic and hindbrain circuits due to their roles in regulation of feeding and energy balance. While it has been shown that cognitive deficits accompany iron dysfunction, as well as metabolic disease, the central sites of action mediating these effects are unknown. The locus coeruleus (LC), the brain's primary source of norepinephrine, plays an integral role in regulation of attention, arousal, stress responsiveness, and cognitive flexibility, all cognitive processes associated with metabolic disease. LC neurons may be particularly susceptible to disruptions in iron homeostasis due to their vulnerability to lipid peroxidation, reliance on mitochondrial metabolism, and oxidation processes resulting from catecholamine synthesis. However, research has not been conducted to examine the impact of iron dysregulation in the LC. To dissect this mechanism, we are using western-diet to induce metabolic disease in mice. Western-diet fed mice are obese, glucose intolerant, and insulin resistant, compared to chow-fed control mice. Ongoing studies are aimed at evaluating iron deposits using Perls+DAB histochemistry together with immunofluorescence and RNAscope to identify LC cell types (e.g. neurons, glia) in which iron accumulates, and iron storage systems (FtL, FTH1) and iron export (ferroportin) is disrupted. To determine the impact of iron dysregulation on cognition, behavioral testing will be conducted before and after intervention with the iron chelator deferiprone. LC tissue will be analyzed to determine if iron chelation rescues metabolic dysfunction-induced changes in LC iron homeostasis. Understanding the mechanisms by which iron dysregulation impacts brain metabolic processes may provide insight to novel therapeutic treatments for metabolic disease.

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Poster Session 2 / No. 8

Effect of encephalomyosynangiosis (EMS) on post stroke recovery in a permanent model of ischemic stroke

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Acute ischemic stroke (AIS) remains a leading cause of disability worldwide. Limited treatments for AIS with thrombolytics are further constrained by narrow therapeutic windows and no neuroprotective effects. Damaged or underdeveloped vasculature and poor angiogenesis after AIS remains a major cause of failed neuroprotective therapy after AIS. There is a critical need for alternative approaches that enhance angiogenesis and neuroprotection to improve post-stroke recovery. Here, we use an indirect intracranial bypass technique via encephalomyosynangiosis (EMS), which involves the transposition of autologous temporalis muscle onto the ischemic cortex to stimulate angiogenesis. EMS has proven effective in moyamoya disease, and we hypothesized that it may provide sustained angiogenesis and functional recovery after AIS. We investigated the therapeutic potential of EMS in a mouse model of cortical ischemia, performed four hours after permanent distal middle cerebral artery occlusion (dMCAo). Forty-two male and female C57BL/6 mice were randomized into sham, dMCAo, and dMCAo+EMS groups. Outcomes were assessed by infarct volume quantification, cerebral perfusion imaging (laser speckle), immunohistochemical analyses of vascular density and inflammatory response, and neurobehavioral testing using open field, rotarod, and novel object recognition tasks. EMS significantly reduced infarct volume at 5 days post-stroke compared to dMCAo controls (28.5 ± 9.9 % vs. 49.3 ± 14.5 %, $p < 0.05$). At 30 days, EMS-treated mice demonstrated improved cerebral perfusion in perilesional regions and increased blood vessel density, accompanied by reduced IBA1+ cell accumulation. While EMS did not significantly reduce long-term cortical atrophy or affect sensorimotor function, but it improved learning and memory performance in novel object recognition tasks. In summary, EMS enhances angiogenesis, cerebral perfusion, and cognitive recovery after AIS in mice. These findings provide proof-of-concept evidence for the first time supporting EMS as a novel surgical strategy for promoting vascular repair and functional recovery following AIS, warranting further translational investigation.

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Poster Session 2 / No. 9

Transcription factor regulation of retinal ganglion cell survival and axon regeneration after optic nerve injury

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Retinal ganglion cells (RGCs) are prototypical central nervous system (CNS) projection neurons which transmit visual information to the brain. As other types of CNS projection neurons, RGCs fail to spontaneously regenerate axons after injury, resulting in permanent loss of vision due to conditions such as trauma, ischemia, and glaucoma. There are currently no approved clinical therapies which induce optic nerve/tract axon regeneration. The neuronal intrinsic factors which contribute to regeneration failure are still not fully understood, and while certain pre-clinical approaches targeting the proclivity of neurons to regenerate have been explored, these generally lead to sparse regeneration from a limited subset of RGCs. Here, we performed single-cell RNA sequencing (scRNA-seq) of RGCs following optic nerve crush (ONC) injury and treatments with knockdown (KD) of developmentally-upregulated experimental transcription factor 1 (Exp1-TF) and overexpression (OE) of developmentally-downregulated experimental transcription factor 2 (Exp2-TF), which we have identified as regulating RGC axon regeneration. Using bioinformatics analysis of the generated scRNA-seq datasets, we were able to determine the RGC subtypes which responded to these treatments. We also analyzed the downstream gene networks that are regulated by these treatments following optic nerve injury. We found partial overlap between the RGCs subtypes that responded to these treatments, and there was also a substantial overlap in the downstream gene networks associated with axon regeneration, which included several genes known to be involved in axon regeneration. Our findings provide new insights into the mechanisms of optic nerve axon regeneration, in an RGC subtype-specific manner.

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Poster Session 2 / No. 10

Understanding the Role of Tacrolimus in Corneal Nitrogen Mustard Injury

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Chemical warfare agents such as sulfur mustards remain a significant global threat and are well known to cause severe and often irreversible ocular injuries, including corneal opacity, neovascularization, inflammation, and damage to sensory innervation. These injuries can lead to long-term vision impairment and decreased quality of life, highlighting an urgent need for effective therapeutics that can be administered on site in scenarios of civilian mass casualties. These strict criteria prompted us to test the efficacy of Tacrolimus (TCM), an FDA-approved immunosuppressive and anti-inflammatory agent in the ocular injury model produced by the vesicant nitrogen mustard (NM), an analog of sulfur mustard. We employed the proteolipid protein 1-enhanced green fluorescent protein (Plp1-eGFP) transgenic mice in our injury studies to afford visualization of corneal Schwann cells (CSCs) in vivo under a fluorescent microscope. A 1% NM solution was applied to the eyes of Plp1-eGFP mice to simulate chemical-induced corneal damage. Mice were divided into two treatment groups: Group A (n=10 mice) received an increasing dose regimen of 0.1% TCM (once daily for the first week, twice daily for the second week, and three times daily for the final two weeks), and Group B (n=10 mice) received a constant dose regimen (twice daily for 28 days). To further validate findings, an additional 28-day study was conducted in wild-type C57Bl6 mice (n=10) using the increasing dose paradigm. Through the clinical trial, corneal mechanosensory function was assessed using a Cochet-Bonnet aesthesiometer to evaluate sensory function, while body weights were monitored to track overall health. Slit lamp imaging of the cornea and eGFP fluorescence was measured weekly to monitor clinical features of corneal pathology and CSCs degeneration/regeneration. Ocular injury severity was graded based on a standardized scoring system ranging from 0 to 5, with higher scores reflecting more severe pathology, including increased opacity, neovascularization, and crust formation. Group B mice showed significant increase in corneal opacity over each week ($P<0.0001$), with neovascularization presenting by week 2. Group A mice at week 2 segregated into two distinct phenotypes: 50% proceeded to fibrosis ($P<0.001$) with remaining 50% of mice further differentiated into two subgroups. Complete resolution (40%) and partial resolution of opacity (60%). Complete loss of mechanosensitivity in group B mice was observed by week 4 ($P<0.001$), whereas only 50% of group A mice lost complete mechanosensitivity. This functional improvement in this distinct cohort of group A mice was supported by immunohistochemical findings, which revealed increased total length of axonal processes providing evidence of nerve regeneration. Non-injured fellow eyes retained corneal clarity and an intact CSC network. Overall, these findings suggest that an increasing dose paradigm of topically administered TCM is effective in promoting corneal healing and sensory nerve regeneration in this model of severe chemical injury, although inherent variability in responses highlights a need for further investigation. Future studies will focus on investigating combination therapies, including the use of tapering doses of tobramycin/dexamethasone (Tobradex), to enhance therapeutic efficacy and increase the proportion of eyes that achieve favorable recovery outcomes.

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Poster Session 2 / No. 11

Cuprizone-Induced Demyelination Impairs Performance in Set-Shifting Paradigms

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The ability to perform complex cognitive tasks relies on coordinated neural activity. Disruptions to these systems, such as what is considered to occur in multiple sclerosis (MS) – a neurodegenerative, autoimmune disorder of the central nervous system (CNS) – can result in cognitive impairment. One feature of cognitive function notably affected in MS patients is cognitive flexibility, an executive function of the prefrontal cortex (PFC) which enables individuals to adapt behaviors and shift attention in response to changing environmental demands. However, it is not known if, and to what degree, higher-order cognitive tasks, such as cognitive flexibility, are affected in the cognate models of MS. To address this, we sought to investigate how demyelination and remyelination influence a mouse's performance in a set-shifting behavioral paradigm. To test this, in this trial study, we treated cohorts of mice (both male and female, aged 16 weeks old at initiation of study, N=3-4 per group) for four consecutive weeks with cuprizone (CPZ), a copper chelator known to induce widespread, immune-independent CNS demyelination. In these mice, we measured cognitive flexibility at three distinct phases of treatment: before demyelination (baseline), at the peak of demyelination (injury), and again a month following withdrawal of CPZ, which results in significant remyelination (recovery). Animals were trained on a set-shifting task, the serial extradimensional shift task (SEDS), to proficiency before initiating cuprizone treatment. Proficiency was defined as completing a minimum of two blocks of trials with 80% accuracy. Animals were fed CPZ for four weeks to stimulate CNS demyelination, and after four weeks of treatment, CPZ was withdrawn to allow for spontaneous remyelination. Control groups were fed chow that did not contain CPZ. From injury to recovery, animals were retrained on SEDS and tested for five consecutive days every week for eight consecutive weeks. The objective of this testing paradigm was to determine if demyelination, and subsequent recovery, had a measurable impact on SEDS performance. Our preliminary findings indicate that animals that had been treated with CPZ required more sessions than non-CPZ-treated controls to achieve proficiency at SEDS during this re-training period. We also noted that CPZ-treated mice generally exhibited lower accuracy in performance during the first block of the task compared to the second block. These studies, which are currently based on a small N, are ongoing. Nevertheless, the outcomes to this point suggest that CPZ administration may result in a mild impairment of mouse performance in SEDS. Additional cohorts of mice are in process to evaluate these treatment-related differences in performance, while future directions are also expected to pair behavioral paradigms with 2-photon calcium imaging to identify circuit-level changes in PFC activity in

response to de- and remyelination. Outcomes from this work are expected to provide novel insights into the role of CNS myelination on PFC executive function and connectivity that would also have potential relevance to understanding the basis for cognitive impairment in CNS demyelinating diseases like MS.

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Poster Session 2 / No. 12

Assessing the Effort-Related Motivational Effects of the Selective Norepinephrine Transport Inhibitor Atomoxetine and the Atypical Dopamine Transport Inhibitor GBR-12909

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Major Depressive Disorder (MDD) is a common mood disorder characterized by low mood, agitation, anxiety-related symptoms, and motivational dysfunctions such as fatigue, anergia, and apathy. These symptoms are highly debilitating and resistant to treatment with commonly prescribed antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). In contrast, compounds that increase extracellular dopamine (DA), such as the dopamine/norepinephrine (NE) transport inhibitor bupropion (Wellbutrin), have shown efficacy in alleviating motivational dysfunction. Current antidepressant treatment is focusing on the development of triple reuptake inhibitors (TRIs), an emerging class of antidepressants that block reuptake of all three monoamine transport proteins (SERT - serotonin transport, DAT - dopamine transport, NET - norepinephrine transport) in roughly the same dose range. The present study assessed the effort-related effects of monoamine transport inhibitors in rats performing on the fixed ratio 5 (FR5)/choice task. Using this task, we can assess monoamine transport inhibitors for their ability to treat motivational dysfunction in male and female rats. With this task, rats choose between exerting more effort to obtain a more preferred reinforcement (high carbohydrate pellets) vs. exerting less effort for a less preferred reinforcement (concurrently available laboratory chow). To model motivational dysfunction, the vesicular monoamine transport inhibitor tetrabenazine (TBZ), which induces depressive symptoms such as fatigue and apathy in humans, is administered to rats, producing a low-effort behavioral bias characterized by decreased lever pressing and increased chow intake. Previous research demonstrated that the TRI diclofensine was inconsistent at reversing the TBZ-induced motivational dysfunction, potentially due to the ability of actions on 5-HT or NE to blunt the impact of DA transmission. The present study investigated whether co-administration of the DAT inhibitor GBR-12909 (vanoxerine) and the selective NET inhibitor atomoxetine could reverse TBZ-induced behavioral deficits. Male and female rats received TBZ combined with GBR-12909 and atomoxetine across multiple doses. Results demonstrated that GBR-12909 significantly reversed TBZ-induced motivational deficits, whereas atomoxetine did not. Furthermore, atomoxetine dose-dependently attenuated the reversal produced by GBR-12909. These findings demonstrate that NET inhibition may counteract dopaminergic mechanisms involved in effort-related motivation and may limit the efficacy of TRIs in treating motivational dysfunction.

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Poster Session 2 / No. 13

Enhancing Endocannabinoid Signaling to Counteract Opioid-Induced Hyperalgesia

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Opioid-induced hyperalgesia (OIH) is results when repeated opioid use increases pain sensitivity, often manifesting as allodynia (i.e., painful perception of innocuous stimuli). OIH treatments are limited, hindered by perceived patient drug-seeking, and promote continued opioid use. The endocannabinoid system, with two accepted receptors, CB_1 and CB_2, their endocannabinoid ligands, and their metabolic enzymes, offers new targets for addressing OIH. For example, CB_1 receptor positive allosteric modulation reduce allodynia in multiple models. Similarly, inhibiting monoacylglycerol lipase (MAGL), the primary catabolic enzyme for the endocannabinoid 2-arachidonoylglycerol, decreases both inflammation (via CB_2 and COX pathways) and central sensitization (via CB_1). We hypothesized that either MAGL inhibition or CB_1 positive allosteric modulation reduces OIH in mice. Male and female C57BL/6J mice (n = 8–10 per group) were delivered morphine by osmotic minipump (64 mg/mL; 1 µL/hour). Mechanical and acetone-induced cold allodynia presented consistently by day 5 of morphine administration. Morphine treatment also induced splenomegaly ($p=0.012$). The acute effects of the MAGL inhibitor JZL184 (40 mg/kg) or the CB_1 PAM ZCZ011 (40 mg/kg) were tested. Next, the effects of repeated JZL184 (0.6, 2.5, 10, 40 mg/kg) were assessed. Finally, the potential cannabinoid receptor mechanism was assessed using the selective CB_2 receptor antagonist SR144528 (3 mg/kg) co-administered daily with JZL184 (40 mg/kg). Acute ZCZ011 reduced mechanical ($p=0.047$) and cold allodynia ($p<0.001$). Repeated, but not acute, JZL184 dose-dependently reduced both mechanical allodynia ($F(12, 123) = 7$, $p<0.001$) and cold allodynia ($F(12,126) = 3$, $p<0.001$) as compared to controls. SR144528 did not block JZL184 anti-allodynia ($p=0.619$), consistent with a CB_2-independent mechanism. Together, these data support the idea that MAGL inhibition has therapeutic potential to attenuate opioid-induced hyperalgesia.

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Poster Session 2 / No. 14

Genetic Modifiers in Behavioral and Cognitive Response to Repetitive Traumatic Brain Injury (rmTBI)

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A repetitive minor traumatic brain injury (rmTBI) results from repeated high velocity head impact. rmTBI can cause cognitive and behavioral changes that can vary by individuals. This study aims to investigate the impact of different genetic profiles on outcomes following rmTBI. We looked at two different strains of mice that received a minor traumatic brain injury (Marmarou weight drop) over five days. We compared behavioral profiles from these mice to mice with a sham injury, as well as to each other. Specifically, the mice then went through various cognitive, spatial, and behavioral tasks. Our goal was to determine the effects of the injury in each individual strain. We found a strong positive correlation among the rmTBI C57Bl6 mice between social dominance (percent wins) versus sociability (duration in the social chamber). In contrast, we found a strong negative correlation for these variables among the rmTBI DBA2J mice. We also found significant strain and rmTBI differences for the C57 mice on social dominance wins, a non-spatial learning task, and number of entries into the open arms of a plus-maze (used to assess anxiety). On the other hand, both strains showed an rmTBI deficit in spatial learning. These findings show significant differences in how genetics impact severity of rmTBIs. Overall findings reveal significant differences in how genetics may impact the behavioral effects of rmTBIs, with implications for potential genetic screening for individuals in high-risk professions and could also be beneficial in examining individualized therapies for those suffering from more severe symptoms of rmTBI.

Poster Session 2 / No. 16

Behavioral and Neurochemical Effects of the Atypical Dopamine Transport Inhibitor Vanoxerine

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Motivational dysfunction symptoms, including fatigue and r
eduction in goal directed behavior, have been linked to disruptions in dopamine (DA) signaling. These symptoms are core features of numerous psychiatric and neurological disorders such as depression. Rodent effort-based decision-making tasks can be used to model these symptoms and to test potential therapeutic treatments. One such task is the fixed ratio (FR)5/ choice task in which rats have a choice between completing a high-effort behavior of lever pressing to receive a highly preferred food reinforcement vs a low-effort behavior of eating concurrently available laboratory chow. Tetrabenazine (TBZ) is used to treat Huntington's Disease and Tardive Dyskinesia but produces depressive-like side effects such as apathy and fatigue in humans. In rats, TBZ shifts behavior away from high-effort lever pressing and towards low-effort chow consumption. Drugs that block the DA transporter (DAT) and increase extracellular DA, such as vanoxerine, have been shown to reverse the behavioral impairments induced by TBZ on the FR5/choice task in male and female rats. To compliment the behavioral findings, ongoing studies using in vivo microdialysis with high-performance liquid chromatography show that the same doses of vanoxerine that reverse the behavioral effects of TBZ significantly increase extracellular DA in the nucleus accumbens. Additionally, these results reveal important sex differences in behavioral and neurochemical response to vanoxerine. Together, these results provide evidence supporting the role of DA in effort-related processes and highlights atypical dopamine transport inhibitors such as vanoxerine as promising candidates for treating motivational symptoms in clinical populations.

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Poster Session 2 / No. 17

Combination of the Serotonin Transport Inhibitor Fluoxetine and the Dopamine Transport Inhibitor GBR12909: Depression-related Motivational Effects in Female Rats

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Major depressive disorder (MDD) affects approximately 16% of Americans, with women being twice as likely to suffer from MDD compared to men. Individuals with MDD show symptoms related to mood, cognitive functioning and dysfunctions in motivation. Motivational dysfunction symptoms are extremely debilitating and can be resistant to commonly prescribed antidepressants (i.e., selective serotonin reuptake inhibitors (SSRIs)). Combining SSRIs with drugs that increase extracellular dopamine (DA) is a strategy used in attempts to attenuate a wider range of MDD symptoms. However, it remains unclear if increasing serotonin neurotransmission will have an additive or inhibitory effect on the pro-motivational effects of increasing extracellular DA. To assess this, a validated rat model of motivational dysfunction, the tetrabenazine (TBZ) model of the fixed ratio 5 (FR5)/choice task, can be used. TBZ, used clinically for Huntington's Disease, produces depressive-like side effects in humans. In rats, TBZ induces a shift in behavior from high-effort lever pressing to low-effort chow intake, mimicking motivational deficits. The present study aims to assess if combining the atypical DA transport inhibitor GBR12909 with the SSRI fluoxetine (FLX) will reverse the behavioral effects induced by TBZ in female rats. Results show that while administration of GBR12909 alone reverses the behavioral effects of TBZ by increasing lever pressing and decreasing chow consumption, the addition of FLX dose-dependently decreased lever pressing, suggesting that FLX may inhibit the pro-motivational effects of GBR12909. Altogether, these results point to the vital role that DA plays in attenuation of motivational dysfunction symptoms.

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Poster Session 2 / No. 18

Learning drives reciprocal causal binding between hindbrain-mediated arousal and hippocampal memory consolidation

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Learning involves the formation of stimulus-specific associations in the brain. In the hippocampus, these associations are expressed as co-active neural ensembles that are largely absent during pre-learning population synchrony events (sharp-wave ripples, SWRs) but reactivate during post-learning SWRs. However, learning is also accompanied by non–stimulus-specific physiological changes, including shifts in states of arousal. These processes may provide a critical backdrop that enables memory-specific activity to become effective by embedding it within the organism's evolving physiological context. Here we examine how hippocampal activity couples to arousal dynamics across learning using a combination of approaches before, during, and after mice learned a virtual reality–based spatial memory task. We find that SWRs, though generated within the hippocampus, are tightly linked to organism-wide fluctuations in arousal, measured via pupillometry and $Grab_{NE2h}$-based fiber photometry. Moreover, this relationship is not static but is systematically reshaped by learning and relates to distinct SWR properties. In turn, these evolving arousal dynamics are associated with shifts in hippocampal memory reactivation regimes measured via two-photon calcium imaging of populations of place cells, suggesting a role in shaping consolidation. To test these relationships causally, we show that PdCO-mediated, hippocampus-specific optogenetic inhibition of locus coeruleus norepinephrinergic terminals alters hippocampal SWR generation. Conversely, closed-loop SWR boosting decreases extracellular concentrations of norepinephrine, while SWR-targeted silencing produces the opposite effect. Together, these findings establish a previously unreported reciprocal loop between hippocampal memory consolidation and hindbrain arousal circuits. This coupling situates memory within the organism's continuously shifting physiological state and provides a new framework for understanding disorders where these systems have been studied in isolation.

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Poster Session 2 / No. 19

Generation of miR-141/200c conditional knockout mice from knockout-first, reporter-tagged parent and functional validation of the floxed allele

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MicroRNAs (miRNAs) of the miR-200 family—specifically miR-141 and miR-200c—regulate neurogenesis, differentiation, and epithelial–mesenchymal transitions in development. Dysregulation of these miRNAs is associated with several diseases including cancer and stroke. The Mirc13tm1Mtm/Mmjax mouse line, which targets the miR-141/200c cluster, was originally generated and described by Park et al. 2012 as a knockout-first, reporter-tagged insertion with conditional potential (conditional-ready) mouse line. To harness the full potential of this mouse line, it would require a two-step breeding process: breed with FLP mice to excise lacZ/neo cassettes followed by breeding with Cre to delete the floxed miRNA cluster (Park, et al. 2012). However, many studies either bypassed removal of the lacZ/Neo cassettes and treated the mouse line as Mirc13 knockouts or bred directly with Cre mouse lines, which could lead to unpredictable recombination and genotypes. In this study, we show that the presence of the Neo cassette influences expression of neighboring genes such as, *ptpn6, phb2* and *atn1* which may affect the phenotype of Mirc13 knockout mice. We demonstrate that it is essential to follow the two-step breeding plan.

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THANK YOU for attending this year's retreat.

Special thanks to all trainees, judges and vendors for their time and contributions to this event.

We hope you enjoyed yourselves!

WE LOOK FORWARD TO SEEING YOU NEXT YEAR!

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