The 16th Annual Neuroscience Retreat

#FBIRetreat24

ABSTRACTS

MORNING POSTER SESSION - 11:20 am – 12:20 pm

#1 Shereen Abdel-Raheim
#2 Faith Adams
#3 Kelsey Aguirre
#4 Carlos Alcocer
#5 Samuel Allen
#6 Johana Alvarez
#7 Srinivasan Anantha Ramakrishnan
#8 Bergan Babrowicz
#9 Austin Baggetta
#10 Jacqueline Beltran
#11 Natalia Biscola
#12 Clementine Blaschke
#13 Sarah Boukezzi
#14 Samantha Brown
#15 Eduardo Butelman
#16 Grace Butler
#17 Jamie Carty
#18 Kenny Chan
#19 Ting-Jiun Chen
#20 Yuan Cheng
#21 Gabriela Chiarotto
#22 Alexandra Chisholm
#23 Anjalika Chongtham
#24 Linh Chu
#25 Mason Dallegge
#26 Pamela Del Valle
#27 Emma Dereskewicz
#28 Aashna Desai
#29 Lauren Dierdorff
#30 Jonadab Dos Santos Silva
#31 Tory Drescher
#32 Catherine Elorette
#33 Rachel Fisher-Foye
#34 Davide Folloni
#35 ATSUSHI FUJIMOTO
#36 Daniel Garcia
#37 Heidy Gonzales
#38 Manuel Gonzalez Rodriguez
#39 Alejandro Borja Grau Perales
#40 Swati Gupta
#41 Trevonn Gyles
#42 Natalie Hackman
#43 Hannah Hao
#44 Emma Hays
#45 Xueming Hu
#46 Yuefeng Huang
#47 Brandon Hughes
#48 Elley Ishikawa
#49 Mohammad Jodeiri Farshbaf
#50 Ayako Kawatake-Kuno
#51 Annie Khamhoung
#52 Alvi Khan
#53 Michelle Kim
#54 Sarah King
#55 BumJin Ko
#56 Cassidy Kohler
#57 Moussa Konde
#58 Qixiu Fu
#59 Francesco La Rosa
#60 Anthony Lacagnina
#61 Michelle Lee
#62 Sanutha Shetty

AFTERNOON POSTER SESSION - 2:25 – 3:25 pm

#1 Alexa LaBanca
#2 You-Kyung Lee
#3 Hyo Lee
#4 Xingjian Li
#5 Mu Li
#6 Jing Li
#7 Marianna Liang
#8 Michelle Lu
#9 Jeronimo Lukin
#10 Alexandra Magee
#11 Maxine Marchidan
#12 Taelor Matos
#13 Natalie McClain
#14 Alec McKendell
#15 Christabel Mclain
#16 Amber McLaughlin
#17 Adriana Mendez
#18 Charles Mobbs
#19 Raymon Morillo
#20 Irena Muffels
#21 Alexandra Munch
#22 Sanjana Murthy
#23 Lailun Nahar
#24 April Serratelli
#25 Tadaaki Nishioka
#26 David O'Connor
#27 Tracy Okine
#28 Dorothy Otto
#29 Jacqueline Overton
#30 Lyonna Parise
#31 Siddhartha Peri
#32 Sarah Philippi
#33 Graeme Preston
#34 Marco Rizzo
#35 Carmen Romero Molina
#36 Danielle Russo
#37 Sita Sadia
#38 Victoria Samojedny
#39 Marcos Schaan Profes
#40 Grace Selecky
#41 Rameen Shah
#42 Riaz Shaik
#43 Jeremy Sherman
#44 Ha Neul Song
#45 Tessa Spangler
#46 Brian Sweis
#47 Arman Tavallaei
#48 Emily Teichman
#49 Rachel Tejiram
#50 Adam Tengolics
#51 Alexander Tielemans
#52 Jasper van Oort
#53 Yolanda Whitaker
#54 Sarah Williams
#55 Kion Winston
#56 Marjorie Xie
#57 Zili Xie
#58 Elisa Xu
#59 Abi Yates
#60 Kohei Yoshitake
#61 Alessandra Yu
#62 Yosif Zaki
#63 Madeline Bacon

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2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Aashna Desai
Job Title	Master's Student
Lab	Waters Lab
Department	Center for Advanced Therapeutics

Examination of Cortical Excitability as a Treatment Response Biomarker in Deep Brain Stimulation for Treatment-Resistant Depression

Aashna Desai, Elisa Xu, Mason Delegge, Jake Dahill-Fuchel, Tanya Nauvel, Sankar Alagapan, Martijn Figee, Patricio Riva-Posse, Chris Rozell, Ki Sueng Choi, Helen Mayberg, Allison C. Waters

Background: Treatment Resistant Depression (TRD) is a global public health concern correlated with high fatality rates. Deep brain stimulation (DBS) to the subcallocal cingulate has emerged as a promising treatment. While DBS shows immediate responses for motor conditions, psychiatric symptom responses to DBS can take months to show. We hypothesize that changes in cortical excitability over time can serve as a reliable biomarker for DBS success, indicative of enhanced white matter and functional connectivity.

Methods: We measured cortical excitability using stimulation evoked potentials (EPs), which reflected immediate cortical response to DBS in the SCC in 13 TRD patients. Utilizing 256-channel EEG data, we generated a whole-brain source model depicting spatiotemporal patterns of voltage fluctuations at specific time points. We compared these source models at baseline, 3 months, and 6 months post-DBS to understand the patterns of cortical excitability in different brain regions over treatment.

Results: Through longitudinal assessment of cortical excitability to DBS in TRD, we observed striking retest-reliability within patients (ICI .69-97). One-third of samples showed an increase in cortical excitability that changed over time, correlating with treatment response. Approximately half showed no change in pre-specified regions. Post-hoc analyses provide insight into the causal effects of DBS and facilitate identification of novel changes in excitability associated with treatment response.

Conclusions: The development of a SCC DBS treatment response biomarker holds significant promise for improving treatment outcomes and advancing research. By elucidating changes in cortical excitability using source modeling and EEG, we can enhance the precision and efficacy of DBS for TRD patients, offering a life-changing treatment option.

2024 Neuroscience Retreat

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Full Name	Abi Yates
Job Title	Postdoctoral Fellow
Lab	McAlpine
Department	Cardiovascular Research Institute

Astrocytic interleukin-3 instructs microglial synaptic pruning during neurodevelopment

Abi G. Yates, Annie Khamhoung, Lena Gaebel, Susana I. Ramos, Máté Kiss, Pacific Huynh, Teresa Gerhardt, Scott Russo, Nadejda M. Tsankova, & Cameron S. McAlpine

Background: Interleukin-3 (IL-3) is a multifunctional cytokine recently implicated as a critical mediator of glial communication and function in neurodegenerative diseases. Surprisingly, our work revealed that IL-3 and its receptor, IL-3Rα, are constitutively expressed by astrocytes and microglia, respectively, under healthy conditions, suggesting that IL-3 may play a role in brain homeostasis or development. Indeed, IL-3 has been linked to neurogenesis and cortical volume in humans. Here, we aimed to investigate IL-3-mediated glial cell crosstalk and evaluate its contribution to neurodevelopment.

Methods, results: First, we characterized IL-3 signaling in the brain. Using flow cytometry, we found that IL-3 expression in astrocytes was greatest at postnatal day 3 (P3) and diminished into adulthood. Consistent with this, snRNAseq of human brains revealed that expression of microglial IL3RA is greatest during the third trimester. To explore the impact of IL-3 on brain architecture, we used global Il3 and Il3ra knockout mice and performed Golgi staining. We observed increased neuronal complexity and spine density in mice lacking IL-3 signaling, compared to controls, suggesting a reduction in synaptic pruning during the postnatal period. This was confirmed with a functional engulfment assay where the volume of engulfed synapses in microglia was reduced in Il3-/- mice. Microglial pruning is a critical step in healthy brain development, impairment in which has been associated with neurodevelopment disorders. Indeed, we found that global Il3 and Il3ra knockout mice exhibited increased anxiety, decreased social interaction, and elevated compulsive behavior, compared to controls.

Conclusions: Our data suggest that astrocyte-derived IL-3 instructs microglial pruning of neurons during a critical neurodevelopmental window to establish proper synaptic connectivity and social behaviors.

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Full Name	Adam Tengolics
Job Title	Postdoctoral Fellow
Lab	Slesinger Lab
Department	Neurosciences

Title: Investigating the Impact of Polygenic Risk Scores for AUD in NMDA-R Dependent Neuronal Activity

Authors: Adam J. Tengolics, Isabel Gameiro-Ros, Iya Prytkova, Katherine Jacobs, Alison Goate, and Paul A. Slesinger

Background: Alcohol use disorder (AUD) is one of the major substance use disorders, with 11.2% of adults aged 18 years or older affected in 2021 according to the National Survey on Drug Use and Health. This highlights the need for a better understanding of the condition and the development of novel drug therapies. The Collaborative Studies on the Genetics of Alcoholism (COGA) computed a polygenic risk score (PRS) to categorize patient involvement in AUD (low - high PRS). We investigate possible differences in glutamate neuronal activity between the high and low PRS groups, focusing on N-methyl-D-aspartate receptors (NMDA-Rs).

Methods: Twelve individuals (6 high and 6 low PRS) were selected from the COGA participants, and their induced pluripotent stem cells were differentiated into glutamatergic neurons (Neurogenin-2 protocol/NGN2). Neurons were exposed to chronic intermittent ethanol (CIE). We then measured population neuronal activity (using calcium-imaging and GCaMP8f expression) and single-cell activity (patch clamp electrophysiology, cell attached, whole-cell configuration, I0 current clamp mode).

Results: In the Ca2+-imaging experiments, CIE exposure increased α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R) and decreased NMDA-R related activity, while increased physiological spontaneous activity in high PRS neurons and decreased in low PRS. We observed a general activity increase in magnesium-free artificial cerebrospinal fluid (ACSF), in both patch and Ca2+-imaging techniques. Electrophysiology studies showed that the individual differences between the selected lines were consistent to the Ca2+-imaging results.

Conclusion: Our results demonstrate that neurons derived from severe cases of AUD patients are more sensitive to chronic ethanol treatment. The consistency of these findings across experimental designs strongly suggests that synaptic events underlie the changes in population activity measured with Ca2+-imaging.

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Full Name	Adriana Mendez
Job Title	Graduate Student
Lab	Ables Lab
Department	Neuroscience

Elucidating the Role of the Extracellular Matrix in Behavioral Dysregulation in Hyperglycemia

Adriana Mendez1, Mohammad Jodeiri Farshbaf2, Jake Tetenman2,3, Zim Kahn4, Hridika Tasnim4, Jessica L. Ables1,2

1Department of Neuroscience, 2Department of Psychiatry, Icahn School of Medicine at Mount Sinai, 3 Washington University, 4Hunter College

Diabetes (DM) is highly comorbid with neuropsychiatric disorders such as depression. Yet, little research has been focused on understanding the mechanisms by which DM is able to inflict changes on the brain to alter reward behavior. To investigate this, we injected mice with streptozocin (STZ), a chemical compound that destroys pancreatic beta cells, and models type-1 DM. We then performed targeted purification of polysomal mRNA (TRAP-Seq) in cholinergic neurons of the medial habenula (mHb) in diabetic and non-diabetic mice. We collected tissue from the mHb as cholinergic neurons from the mHb that project to the interpeduncular nucleus (IPN) have been shown to be involved in the regulation of both reward-related behavior and blood glucose. We found that several pathways involved in the regulation of the extracellular matrix (ECM) such as the activation of matrix metalloproteinases and ECM organization were upregulated in mice with DM. Thus, we wanted to explore the ECM as a possible mechanism linking neuropsychiatric disorders and DM. To investigate this, we used biotinylated lectins to visualize the effects of DM on the ECM of the mHb and IPN. We found that the area, total length, branch points, and endpoints of the ECM of the IPN, but not the mHb, were significantly decreased after chronic diabetes, but not subchronic diabetes. Together, our data suggests that DM causes time and region-specific changes to the ECM in reward regions of the brain. Together, these findings identify the ECM as a novel therapeutic target to prevent incidences of neuropsychiatric disorders in individuals with DM.

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Full Name	Alberto Corona
Job Title	Postdoctoral fellow
Lab	Kenny
Department	Neuroscience

Stress-sensing microglia and habenular function
Alberto Corona, Masago Ishikawa, Lauren Wills, Victor Mathis, Junshi Wang, Paul J. Kenny
BACKGROUND: Stress-induced maladaptive changes in lateral habenula (LHb) neuron activity contribute to negative behavioral states, yet the underlying mechanisms remain elusive. Stress enhances norepinephrinergic (NE) transmission throughout the brain. Microglia express β2 adrenergic receptors (β2ARs) and are directly regulated by NE. Here, we will test the hypothesis that stress engages NE signaling in microglia in the LHb, which promotes burst-firing of LHb neurons to precipitate stress-related behavioral deficits.
METHODS: Single-cell RNA sequencing (scRNA-seq) was performed using the 10x Genomics Chromium and Illumina NovaSeq 6000 platforms. Norepinephrinergic (NE) transmission in the LHb was monitored using the GRABNE sensor and fiber photometry. Microglia were depleted from the brain of mice for electrophysiology and fiber photometry recordings. Intrinsic activity patterns of LHb neurons were characterized using whole-cell current-clamp recordings. Calcium activity in microglia was monitored on brain slices using a fluorescent microscope.
RESULTS: Using whole-cell recordings in LHb-containing brain slices, microglia depletion in mice led to a stress-like increase in LHb neuron burst-firing. Fiber photometry in GCaMP6s-expressing LHb neurons showed microglia regulation of LHb activity in vivo, with aversive foot shocks inducing prolonged calcium responses in microglia-depleted mice. scRNA-seq revealed β2AR gene expression predominantly in LHb microglia. Stressors promoting LHb neuron burst-firing elicited synchronized changes in NE transmission, as observed using the GRABNE sensor and in vivo fiber photometry. Using LHb containing slices, we observed that ATP-induced Ca2+ transients in GCaMP-expressing LHb microglia were diminished by NE.
CONCLUSIONS: Our findings suggest that stress enhances norepinephrine (NE) transmission in the LHb, acting on microglia via β2ARs, which modulate LHb neuron activity, potentially contributing to stress-induced behavioral abnormalities. This highlights the critical role of microglia in stress adaptation within the LHb due to their exclusive β2AR expression.

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Full Name	Alec McKendell
Job Title	PhD Graduate Student
Lab	Merina Varghese / Patrick Hof
Department	Neuroscience

Glial and vascular contributors to neocortical vulnerability in Alzheimer's disease

Alec K. McKendell, Carmen Freire-Cobo, Aurélien M. Badina, Ava Pellagrini, Elizabeth McDonough, Lisa Lowery, Benjamin B. Tournier, Dan E. Meyer, Patrick R. Hof, Merina Varghese

BACKGROUND: In Alzheimer’s disease (AD), specific neocortical neurons become vulnerable to pathology and neurodegeneration while others remain resistant. Spatial information from novel imaging methods, like highly multiplexed immunofluorescence (MxIF), combined with computational analysis can address questions of cellular contributors to this regional vulnerability.

METHODS: We performed MxIF staining for 26 markers on postmortem human samples from an AD-susceptible brain area, the prefrontal cortex (PFC) and an AD-resistant brain area, the primary visual cortex (V1). Subjects included AD (n = 3, clinical dementia rating CDR 3, Thal stages 3-4, Braak stages V-VI), mild cognitive impairment (n = 4, CDR 0.5, Thal 1-3, Braak I-V), and age-matched healthy controls (n = 5, CDR 0, Thal 0-1, Braak I-II), both females and males. Using QuPath and a custom Fiji plugin, these images were segmented and classified to measure cell-type densities, states, and interactions across neocortical layers and brain regions.

RESULTS: Neuronal density showed a downward trend from CDR 0 to 3, with a significant decrease in CDR 0.5 compared to CDR 0 specifically in PFC layer 5. In PFC layers 4-5, we observed an upward trend for juxtavascular microglia in CDR 3 compared to CDR 0.5. Finally, reactive astrocytes in the PFC showed increased proximity to vasculature with worsening CDR, however their proximity to amyloid-β plaques only increased significantly with CDR in the V1.

CONCLUSIONS: These preliminary results suggest a regional inflammatory response in glia proximal to vasculature and pathological protein deposits in areas with selective neurodegeneration. Further investigation into markers of cell state in situ will provide information on cellular interactions contributing to neuronal vulnerability in AD.

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Full Name	Alejandro Borja Grau Perales
Job Title	Postdoctoral Fellow
Lab	Castellano Lab
Department	Neuroscience

YOUTH-ASSOCIATED BLOOD-BORNE PROTEIN TIMP2 REGULATES ALZHEIMER'S PATHOLOGY IN MULTIPLE MODELS OF BETA-AMYLOIDOSIS

Alejandro Grau-Perales, Ana Catarina Ferreira, Jacob L. Rosenstadt, Suhani Yerapathi1, Joseph M. Castellano,*

Accumulating evidence supports the concept that processes dysregulated in aging and AD brain are responsive to signals in the periphery across lifespan. Though we previously showed that the youth-associated blood-borne protein, tissue inhibitor of metalloproteinases-2 (TIMP2), revitalizes hippocampal function in aged mice, the mechanisms for this regulation have remained unclear. We hypothesize that TIMP2 and other blood-borne factors regulate synaptic plasticity processes and amyloid-beta metabolism in the hippocampus. Using behavioral assessments and super-resolution confocal microscopy in TIMP2 deletion models, including a conditional deletion model, we recently showed how TIMP2 regulates adult neurogenesis, dendritic complexity, and hippocampus-dependent memory. We deleted TIMP2 in several mouse models of AD pathology and examine perturbations in amyloid-beta metabolism and markers of the neurovascular unit. We address rescue of TIMP2 in these models using viral-mediated overexpression strategies to examine behavioral improvements. We recently reported that TIMP2 regulates adult neurogenesis and dendritic complexity with concomitant accumulation of extracellular matrix components. Removing this accumulation via intrahippocampal targeting of ECM HSPGs results in rescue, arguing that TIMP2 acts through the extracellular matrix to facilitate synaptic plasticity. In APP-knockin and 5XFAD models of beta-amyloidosis, we find that loss of TIMP2 increases astrogliosis and disrupts the neurovascular unit, while exacerbating amyloid-beta plaque deposition in several brain regions, all of which may be mediated by excessive ECM accumulation. TIMP2 regulates a diverse set of phenotypes across normal hippocampal physiology and in the context of AD pathology, including in processes that depend on flexibility to remove pathological debris. Together our results argue that age-relevant factors in the systemic environment have long-range roles in shaping hippocampal function, including neurodegenerative processes that depend on the dynamics of extracellular matrix homeostasis.

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Full Name	Alessandra Yu
Job Title	PhD Candidate
Lab	Schiller & Fiore Labs, Center for Computational Psychiatry
Department	Neuroscience

Investigating Agentive Perspective and Environmental Feedback

Alessandra Yu, Vincenzo Fiore, & Daniela Schiller

In making decisions, we rely on both internal and external information. Context—both outside and within—is crucial in integrating information from these sources to make decisions. For example, sometimes, your environment can offer stimuli with explicit relevance (e.g., rewards). Other times, relevance is implicit, like making decisions based on sensory aspect (e.g., color). Meanwhile, how we process those stimuli can depend on our internal orientation (such as whether we're active, like when driving, or passive, when we're the passenger instead). We present two converging lines of research: external context and internal orientation. For external context, existing human fMRI work shows that, when processing of explicit rewards from slot machines, the mPFC and amygdala inform the aHPC. However, the opposite is true when guessing which pond certain fish came from. We are investigating neurocomputational dynamics using intracranial EEG in epileptic patients. On the other hand, prior work has shown that agency can influence both time perception and valuation. These illusions, while healthy in moderation, are aberrant in agency-related disorders (e.g., heightened in schizophrenia, while dampened in depression). We are, therefore, piloting tasks where participants are primed with agentive and unagentive linguistic stimuli (e.g., active and passive voice sentences), then asked to estimate the delay of feedback after button press. We hope to characterize a gradient of how perception can be influenced by internal agentive shifts. Given the limited cognitive research on manipulating both internal orientation and external outcomes, we aim to use this agentivity manipulation in the slot machine and perceptual fish tasks to study the potential interaction between internal and external contexts in decision-making. Ultimately, we hope these converging lines of research ground future work manipulating internal agentivity and external outcomes in disorders of agency.

2024 Neuroscience Retreat

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Full Name	Alexa LaBanca
Job Title	PhD Student
Lab	Nestler
Department	Neuroscience

Title: Ensembles encoding drug memories in the nucleus accumbens mediate drug-seeking after chronic stress

Authors: Alexa R. LaBanca, Rita Futamura, Angelica Minier-Toribio, Arthur Godino, Veronika Kondev, Tamara Markovic, Caleb J. Browne, Leanne Holt, Eric M. Parise, Marine Salery, Eric J. Nestler

Background: Several overlapping environmental factors such as chronic stress and adverse life events dramatically increase the risk of developing both substance use- and stress-related psychiatric disorders in the human population. However, the neurobiological mechanisms underlying this comorbidity have yet to be fully characterized. Here, we explored the contribution of nucleus accumbens (NAc) neuronal ensembles, or sparse populations of cells, in the encoding of cocaine-related memories and assessed the impact of stress on ensemble recruitment to elucidate the correlates supporting stress-induced precipitated drug responses.

Methods: Capitalizing on the Arc-CreERT2 transgenic mice, a tamoxifen-inducible system that allows for activity-dependent tagging of neuronal populations, we captured cells recruited at different stages of drug exposure. Using a cocaine conditioned place preference (CPP) procedure, we permanently tagged neurons recruited during the expression of a previously acquired place preference (test 1). Subsequently, mice underwent chronic stress before assessing place preference for a second time (test 2) in order to observe the impact of stress on drug associative memory recall.

Results: We show an increase in CPP at test 2 in animals that experienced chronic stress between test 1 and test 2, suggesting stress has the ability to potentiate drug memory consolidation. Additionally, we show that stress exposure increased the reactivation of NAc ensembles during test 2 that were previously recruited on test 1.

Conclusions: These findings uncover a mechanism by which stress could potentiate drug responses via the modulation of drug-context associative memories through ensemble reactivation and could further contribute to our understanding of how stress and drug cross-sensitization may be encoded in the brain.

2024 Neuroscience Retreat

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Full Name	Alexander Tielemans
Job Title	PhD Student
Lab	Benson & Huntley Lab
Department	Neuroscience

Temporal and Cellular Specificity in Subcellular Localization of Phosphorylated Rab8 in Striatal Spiny Projection Neurons

Alexander Tielemans, Swati Gupta, George W. Huntley, Deanna L. Benson

[Background]
Kinase enhancing mutations in Leucine-Rich Repeat Kinase 2 (LRRK2) are associated with Parkinson's. The small GTPase Rab8 is a phosphorylation target of LRRK2. Prior studies in hippocampal neurons show Rab8 is important for AMPAR subunit trafficking. However, it is unknown if Rab8 functions similarly in striatal spiny projection neurons (SPNs) and how phosphorylation may modulate Rab8 activity and localization. As an initial step in understanding Rab8's function in striatal circuits, we are characterizing cellular and subcellular localization of Rab8 and phosphorylated Rab8 (pRab8) in wildtype (WT) and LRRK2G2019S knock-in mice.

[METHODS]
Immunofluorescent staining was performed on striatal brain slices from aldehyde-perfused WT and Lrrk2G2019S mice aged P0, P21, or P60-90. Primary cortico-striatal neuron co-cultures were generated from mice expressing tdTomato in D1R SPNs and used for immunofluorescence. ImageJ was used for quantifying colocalization.

[Results]
Quantitative analyses in p60-90 slices showed pRab8 was more abundant in LRRK2G2019S SPNs and in both genotypes, was similarly distributed between D1R and D2R SPNs. In both genotypes, Rab8 and pRab8 displayed distinct subcellular distributions in SPNs; pRab8 localized to the cis Golgi whereas Rab8 was diffusely localized. In contrast, pRab8 was not localized to the cis Golgi in cultured SPNs, suggesting a developmental redistribution. Consistent with this, pRab8 localization in slices from young mice resembled cultured neurons.

[Conclusion]
The distribution of pRab8 in SPNs is dependent on developmental age, implying a diversity in functional roles as SPNs mature.

2024 Neuroscience Retreat

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Full Name	Alexandra Chisholm
Job Title	Postdoc
Lab	Hurd
Department	Psychiatry

Neurobiological Underpinnings of Cannabidiol's Action in Attenuating Opioid Relapse

Alexandra Chisholm, Joseph Landry, James Callens, Jacqueline Ferland, and Yasmin L. Hurd

Background: Drug addiction is a chronic relapsing disorder characterized by periods of compulsive drug use, abstinence, and relapse. Cannabidiol (CBD), a non-intoxicating cannabinoid, is currently under investigation as an anti-relapse treatment. Our laboratory has demonstrated that CBD attenuates cue-induced heroin-seeking in an animal model of relapse. Clinically, we showed that CBD attenuates craving and anxiety induced by drug-associated cues in abstinent individuals with heroin use disorder. The exact mechanisms by which CBD exerts its anti-relapse effects are poorly understood. The objective of the current study was to assess the effects of CBD treatment on heroin-seeking in conjunction with transcriptomic profiling of the basolateral amygdala (BLA).

Methods: Male rats were trained to intravenously self-administer heroin over 15 days followed by 14 days of forced abstinence. Rats were acutely administered either vehicle or CBD (5 or 10 mg/kg, i.p) 24 hours before a drug-seeking session. Blood was collected 1 hr after the CBD administration, and brains extracted 1.5 hours following the drug-seeking session. Plasma was used to measure endocannabinoid and CBD levels. BLA tissue was dissected and bulk RNA sequencing performed.

Results: CBD attenuated heroin-seeking compared to controls. CBD administration increased the levels of CBD, 7-OH-CBD, anandamide, and arachidonic acid. The BLA differential gene expression signature observed with heroin-seeking was normalized by CBD, particularly in processes relevant to morphine addiction, chemical synaptic transmission, and neuronal projection. Interestingly, a known CBD target, TRPV1, was amongst the normalized genes and correlated with active lever responding at the test. Ingenuity pathway analysis revealed that CBD reversed canonical pathway alterations and upstream regulators induced by heroin.

Conclusions: These findings suggest that CBD reduces cue-induced drug-seeking behavior associated with normalizing BLA biological pathways impacted by heroin.

2024 Neuroscience Retreat

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Full Name	Alexandra Magee
Job Title	Graduate Student
Lab	Benson/Huntley
Department	Neuroscience

Investigating the cholinergic basis of cognitive deficits in Lrrk2G2019S mice

Alexandra Magee, Deanna L. Benson, George W. Huntley

Early Mild Cognitive impairment (MCI) is prevalent in idiopathic and hereditary Parkinson's. Young adult male mice carrying the kinase-enhancing G2019S mutation of Leucine-Rich Repeat Kinase 2 (Lrrk2), a prevalent mutation in hereditary and sporadic Parkinson's, exhibit attention deficits and other cognitive changes, which may reflect deficient cholinergic innervation of the mPFC that we have shown in males previously. The G2019S mutation can impair primary cilia formation, which may disrupt trophic signaling. We hypothesize that G2019S-mediated disruption of primary cilia leads to deficient NGF-mediated trophic support that in turn underlies altered cholinergic innervation. As a first step, we sought to characterize sex-specific changes in cholinergic innervation of mPFC and to examine quantitatively the cilia of NGF-releasing GABA cells.

Immunofluorescent labeling for vesicular acetylcholine transporter (VAChT), a marker of cholinergic terminal fibers, in mPFC tissue from wildtype (WT) and Lrrk2G2019S (GS) mice allowed quantification of cholinergic innervation density in confocal images. Staining for GABAergic neurons, the primary NGF-releasing cells, and cilia markers allowed us to assess primary cilia formation and morphology.

Results showed that male Lrrk2G2019S mice display overall sparser fiber density while female Lrrk2G2019S mice show denser fiber density in the mPFC compared to wildtypes. Analysis of cilia on GABAergic neurons revealed no changes in overall percent ciliation, but interestingly, longer primary cilia only in male Lrrk2G2019S mice.

The G2019S mutation leads to sex-specific alterations in cholinergic innervation and primary cilia morphology in the mPFC. The change in primary cilia length in Lrrk2G2019S males does not disprove our hypothesis that deficient trophic support underlies altered cholinergic innervation of mPFC, but more work is needed to understand the sexually dimorphic mechanisms driving these differences and how they influence early cognitive impairment in Parkinson's.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Alexandra Munch
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Department	Neuroscience

Title: Uncovering the role of the MS4A gene family in Alzheimer's Disease

Authors: Alexandra Münch, Anastasia Efthymiou, Grace Peppler, Edoardo Marcora, Anne Schaefer, Alison Goate

Background: Accumulating evidence from genome wide association studies posit that the brain's innate immune system plays a central role in Alzheimer's Disease (AD) etiology. As the central nervous system's resident immune cells, microglia have emerged as attractive cells to target therapeutically. Such drug targets may lie within the MS4A locus, a region associated with AD risk, age-at-onset, and the primary locus associated with CSF levels of soluble TREM2, a biomarker of microglial activity. This region contains multiple genes within the MS4A gene cluster, which encode structurally related transmembrane proteins primarily expressed by immune cells whose functions are not yet understood. We previously nominated a causal variant within this locus, rs636317, whose risk allele is predicted to disrupt an anchor binding site for the chromatin remodeling protein CTCF and is associated with increased expression of MS4A4A and MS4A6A in myeloid cells.

Methods: Using CRISPR-edited iPSC-derived microglia (iMGLs) we directly test the hypothesis that candidate functional variant rs636317 mediates its effect by modulating MS4A4A and MS4A6A expression via differential CTCF binding. We perform targeted functional assays related to immune signaling in MS4A knockout and rs636317-edited isogenic iMGLs. We then employ a xenotransplantation model to evaluate the effect of this variant on cell function in the context of disease using 5xFAD chimeric mice. In parallel, we generated macrophage-specific conditional knockout mouse lines for orthologs Ms4a4a and Ms4a6d.

Results: As predicted, we observe decreased CTCF binding and increased MS4A4A and MS4A6A expression in iMGLs homozygous for the rs636317 risk alleles.

Conclusions: We hypothesize that decreased expression of MS4A4A and MS4A6A in human microglia promotes protective microglial responses related to TREM2 signaling, ameliorating amyloid plaque containment and subsequent cognitive decline.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Alvi Khan
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Differences in motivation drive robust leader-follower relationships in a novel cooperative foraging task

Alvi Khan, Yuan Cheng, Herbert Zheng Wu

Background: Cooperative foraging is a common strategy among animals seeking resources, often resulting in the establishment of consistent leader-follower relationships within dyads. However, the influence of physiological motivation, such as hunger or thirst, on these relationships remains an intriguing aspect. Our hypothesis posited that reduced motivation would drive followership, while increased motivation would propel leadership. To investigate this, we manipulated the motivation of pairs of mice and observed their roles in a unique cooperative foraging task.

Methods: Two mice were tasked with initiating a trial and jointly traveling to two out of four active reward zones to receive a water reward. Motivation manipulation involved administering 0.5 mL of water to one mouse in each pair 30 minutes before training, while control pairs received no supplementary water. Weight changes were recorded before and after training for both mice.

Results: Over 14 training sessions, mice with water supplementation consistently assumed the leader role, contrasting with unwatered mice, which predominantly acted as followers. This result deviates from prior findings in stickleback fish studies, in which heightened motivation actually drove leadership. Unwatered mice initiated most trials, while control pairs exhibited inconsistent leader-follower relationships. Notably, unwatered mice experienced greater weight changes compared to their water-supplemented counterparts.

Conclusions: Physiological motivation strongly influences leader-follower dynamics. Contrary to stickleback fish studies, reduced motivation propels leadership, potentially linked to an increased sensitivity to stimuli due to supplementation. Interestingly, despite these findings, followers consumed more water per session, indicating a comprehensive role of such behavior in cooperative foraging. Future investigations employing chemogenetic and optogenetic manipulations in potentially implicated brain regions, such as the medial prefrontal cortex (mPFC), along with calcium imaging, aim to unravel the neural basis of this behavior.

2024 Neuroscience Retreat

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Full Name	Amber McLaughlin
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Department	Neuroscience

Modeling Reversal Learning in Obsessive Compulsive Disorder

Amber McLaughlin, Andrew Smith, Vincenzo Fiore

BACKGROUND: The ability to flexibly adapt to changing conditions is an essential feature of cognition that, when impaired, can manifest as compulsive perseveration in thought or action and is a common symptom of obsessive compulsive disorder (OCD). Reversal learning tasks have historically been used to probe the nature of cognitive flexibility deficits, their neurobiological mechanisms, and test conditions under which they arise.

METHODS: We presented N=12 severe OCD patients (YBOCS >24) with a 2-option reversal learning task while they were in the operating room undergoing neurosurgery for deep brain stimulation (DBS) treatment. We analyzed this group's choice behavior using an array of reinforcement learning (RL) and Bayesian observer models which all performed comparably to one another and revealed no significant difference in comparison to the heuristic (win-stay-lose-shift) model. We compared these results with an unmatched Parkinson's (PD) population N=12 under the same surgical conditions and found comparable behavioral performance between groups.

RESULTS: The parameters fit by each of the standard models showed no significant difference in variation between the two populations. However, we constructed a dynamic Bayesian model which differentiated trials based on choice confidence, allowing us to visualize the relationship between likelihood and prior belief. While both groups show positive correlation between prior confidence and choice likelihood, the model reflects a greater pace of belief updating under low confidence ($p<0.007$) for OCD patients as compared to PD. This model offers insight into confidence-based dynamics that are otherwise undetected, even by the static Bayesian observer model.

CONCLUSIONS: Insights from this dynamic model can be used to help guide the analysis into the single unit recordings from the Globus Pallidus Externus (GPe) in the OCD population as we connect brain activity to the explore/exploit behavior from this task.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Anina Lund
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Establishing the Molecular Foundation of Brain Anatomy in Living Individuals

Anina N Lund, Lora Liharska, Eric Vornholt, Ryan Thompson, Yuyang Luo, Esther Cheng, You Jeong Park, Brian Fennessy, Lillian Wilkins, Deepak Kaji, Hannah Silk, Kimia Ziafat, Alice Hashemi, Eric Schadt, Brian Kopell, Alexander W Charney, Noam D Beckmann

Background: The relationship between brain molecular traits (i.e., gene and protein expression) and brain anatomical features in living individuals, each independently shown to be associated with disease, has yet to be defined. Here, we use neuroimaging linked molecular data, generated from 320 biopsies from the prefrontal cortex from 202 older individuals undergoing the deep brain stimulation electrode implantation procedure to characterize this relationship.

Methods: Gene expression (single-nuclei [snRNAseq], N=31 and bulk RNA-seq, N=289) as well as protein expression (liquid chromatography-mass spectrometry, N=155) data generated as part of the Living Brain Project, were processed, and integrated with structural MRI-derived anatomical features (N=197, cortical thickness, area, and volume) measured in the same individuals. Associations of molecular traits to anatomical features were performed for each imaging feature using linear mixed models. Associations were replicated between-omics and annotated to specific cell type effects using snRNA-seq data.

Results: Molecular signatures of brain anatomical features in living individuals were identified, with multiple features associated with bulk gene expression (19 features with ≥1gene at FDR≤0.05). These associations replicated in protein expression (median absolute Spearman rho=0.13). SnRNAseq replicated gene and protein expression signatures, and annotated them to specific cell types, providing further characterization of these signatures and their pathways (e.g., for medial orbitofrontal thickness, snRNAseq signature in excitatory neurons is correlated to gene [rho=0.22] and protein [rho=0.24] expression).

Conclusion: By associating molecular traits with imaging anatomical features generated from the same individuals, we provide an in-depth characterization of the molecular foundation of brain anatomy in living individuals.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Annie Khamhoung
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Interleukin-3 protects against neurodegeneration in tauopathy

Annie Khamhoung, Lena Gaebel, Abi Yates, Pacific Huynh, Teresa Gerhardt, Andrew Varga, Cameron S. McAlpine

BACKGROUND: The molecular networks that mediate leukocyte and glial cell interactions between brain and periphery in neurodegeneration remain unclear. Previous work from the McAlpine lab has demonstrated that the multifunctional cytokine interleukin-3 (IL-3) protects against a beta-amyloid driven Alzheimer's disease, yet is pathological in multiple sclerosis. IL-3's function in diverse neurodegenerative settings, including tauopathy, needs to be elucidated to advance clinical translation.

METHODS: To investigate the impact of IL-3 signaling on neurofibrillary tau formation and brain atrophy, we analyzed Il3-/-PS19 with PS19 mice. At 10 months of age, memory deficits were evaluated by Barnes maze latency. Brain atrophy was determined through brain volume, ventricular size, hippocampal structure and immunofluorescent p-tau staining. Flow Cytometry was utilized to assess IL-3 producing leukocytes in brain and spleens of PS19 mice and age-matched controls. Lastly, IL-3 production by splenic T cells was assessed after ex vivo stimulation in PS19 mice and age-matched controls.

RESULTS: In the spleen and brain of PS19 mice, we find a higher percentage of IL-3 producing T cells along with increased IL-3 levels in splenic cell culture supernatant after ex vivo stimulation. We have discovered that deletion of Il3 in PS19 mice prolongs Barnes maze latency, indicating deficits in spatial memory. Moreover, Il3-/-PS19 mice show reduced hippocampal volume and increased tau accumulation, relative to PS19 mice, suggesting accelerated brain atrophy and neurodegeneration. Further, microglia of PS19 mice show augmented expression of IL-3's receptor, IL-3Rα.

CONCLUSIONS: Our findings suggest a protective role for IL-3 in tauopathy. Further studies are needed to delineate the mechanisms through which T cell produced IL-3 influences microglia functionality in tau-driven AD and related dementias to ameliorate neurodegeneration.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Impact of social hierarchy on individual difference in cognitive performance in genetically identical mice

Author Name(s): April Serratelli, Tadaaki Nishioka, Samuel Allen, Hirofumi Morishita

Background: The development of cognition in animals results in a variable distribution of performance and ability which is even apparent across genetically identical cohorts. While this individual variability has been observed in behavioral modalities, the processes and experiences that mediate the formation of individuality remain unclear and typically left ignored. Here we examined to what extent social hierarchy is associated with individual differences in cognitive performance in mice.

Methods: Attentional behavior of genetically identical C57/BL6 mice were assessed using 5-choice serial reaction time task, or 5CSRTT). Behavioral performance was analyzed based on the trial history (after correct, incorrect, or omission). We then implemented a social hierarchy test (tube test) to assess if social dominance status (highest, middle, and lowest ranks) could be influencing cognitive behaviors.

Preliminary results: We found individual variability in post-error attentional adjustment where we can cluster the mice into four different groups. We further investigate this clustering and find that there is a post-error difference within cagemates. Taking into consideration social rank, we found that highest socially ranked mice do not belong to the group with lowest cognitive performance. In addition, intermediately socially ranked mice were underrepresented in the largest group.

Conclusion: Overall, our preliminary results suggest that post-error attentional performance is variable among genetically identical mice, and social rank could contribute to the individual differences. These findings suggest that social determinants such as social hierarchy and associated circuits (e.g. dopamine) may play a key role in establishing individual differences in the post-error cognitive control.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Neutrophil elastase promotes stress-susceptibly and is modulated by fluoxetine treatment.

Arman Tavallaei, Lyonna Parise, Kenny Chan, Flurin Cathomas, Romain Durand-de Cuttoli, Antonio V. Aubry, Johana Alvarez, Tory Drescher, Rachel Fisher-Foye, Long Li, Hsiao-Yun Lin, Scott J. Russo.

Background: Peripheral immune dysregulation, including upregulation of pro-inflammatory signaling, is found widely in depression. So far as stress plays a role in the onset of depression, research has also shown that neutrophils are upregulated after chronic stress. Interestingly, using the chronic social defeat stress model we find that neutrophil elastase, a secreted neutrophil serine protease, is upregulated in stress-susceptible mice. The ongoing question remains to what extent this depression-associated peripheral imbalance can be modulated by currently available antidepressants (fluoxetine). Additionally, we tested the functional relevance of directly modulating elastase to either promote or reverse stress susceptibility.

Methods: Mice were expose to 10 days of chronic social defeat stress and then stratified by their interaction ratio (>1=resilient (RES), <1=susceptible (SUS)). SUS mice received chronic fluoxetine (160 mg/L in drinking water) and elastase levels were measured by ELISA after 8 weeks of treatment. A separate cohort of defeated mice were separated by phenotype and instead of fluoxetine, SUS mice were treated with Alvelestat, a neutrophil elastase inhibitor. In parallel, RES mice received chronic recombinant elastase treatment to precipitate a susceptible phenotype.

Results: Mice that received chronic fluoxetine after stress showed a reversal of social avoidance and an attenuation of neutrophil elastase activity. Interestingly, recombinant administration of elastase only modestly facilitated a SUS phenotype in RES mice whereas attenuating elastase activity was sufficient to reverse stress susceptibility, similar to that seen after chronic fluoxetine treatment.

Conclusions: Neutrophil elastase could be a novel peripheral biomarker of stress susceptibility and a viable target for antidepressant treatment. Additionally, neutrophil elastase could be an indicator of positive antidepressant treatment response.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Ashley Cunningham
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Cell Type-Specific Roles of H3 Serotonylation in Postnatal Neurodevelopment

Ashley Cunningham,Eric Nestler,Ian Maze

Background:The serotonergic (5HTergic) system and homeostasis in early life are critical to establishing proper architecture of the developing brain and early life stress (ELS) can alter these precise developmental trajectories, and increase lifetime risk for depression. We now know 5HT not only works through receptors but also forms covalent bonds with histone H3 tail (H3 serotonylation; H3 Ser.) regulating neuroplasticity. However, functional roles for H3 Ser. during postnatal neurodevelopment and impacts of environmental stimuli during early life have largely been unexplored.

Methods:We employed immunosorbent assays to examine 5HT levels across postnatal neurodevelopment with and without ELS in the medial prefrontal cortex (mPFC). To delineate the functional consequences of H3 Ser. during postnatal brain development and in response to ELS, we leveraged FANS-coupled genome-wide analyses (CUT&RUN, RNA-sequencing) in mPFC of male and female mice.

Results:We found mPFC 5HT levels fluctuate during postnatal neurodevelopment of mice and ELS decreases levels of 5HT acutely in adolescence. FANS-coupled genome-wide analyses revealed sex- and developmental-differential binding of H3 Ser. in both neurons and glia. Interestingly, males show pronounced developmental differential binding and ELS shifts H3 Ser. dynamics in both neurons and glia which are associated with changes in gene expression. At adolescence, ELS induces the largest change in H3 Ser. genomic binding with robust increased binding of H3 Ser. at oligodendrocyte-related genes, such as Olig2. Interestingly, Olig2 was also predicted as a top-associated TF and shows increased promoter binding of H3 Ser. in response to ELS in adolescence. These data suggest ELS leads to cell-type specific changes in H3 Ser. and its transcriptional regulation, particularly in oligodendrocytes.

Conclusions:These findings provide novel insight into how H3 serotonylation regulates neurodevelopment and the mechanisms by which disruptions to this PTM cause aberrant pathophysiological states.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Title: Pharmacological modulation of dopamine receptors reveals distinct brain-wide networks for learning and motivation in non-human primates

Authors: Atsushi Fujimoto, Catherine Elorette, Satoka H. Fujimoto, Lazar Fleysher, Peter H. Rudebeck, and Brian E. Russ

Background: The neurotransmitter dopamine (DA) has a multifaceted role in healthy and disordered brains through its action on multiple subtypes of dopaminergic receptors. How modulation of these receptors controls behavior such as learning by altering intrinsic brain-wide networks remains elusive.

Methods: We performed parallel behavioral and resting-state functional MRI experiments after administration of two different DA receptor antagonists in drug-naïve adult macaque monkeys. Subjects were trained in a probabilistic learning instrumental choice task. Behavioral and brain-wide effects of D1 and D2 receptor-selective antagonists, SCH-23390 and haloperidol, were examined. We also asked whether the variability in pharmacologically-induced network alterations were associated with the changes in learning performance and motivation to complete the task.

Results: Systemic administration of SCH-23390 disrupted probabilistic learning when subjects had to learn new stimulus-reward associations and diminished functional connectivity (FC) in cortico-cortical and fronto-striatal connections. By contrast, haloperidol improved learning and broadly enhanced FC in cortical connections. Further comparison between the effect of SCH-23390/haloperidol on behavioral and resting-state FC revealed specific cortical and subcortical networks associated with the cognitive and motivational effects of DA manipulation, respectively.

Conclusions: We provide clear evidence that D1 and D2 receptors play distinct roles in behavior in primates and do so by modulating distinct brain-wide networks.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Austin Baggetta
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How does the brain accumulate cognitive maps?

Austin M. Baggetta, Brian M. Sweis, Denise J. Cai

Background: It has been postulated that the brain uses cognitive maps, or internal neural representations, to enable flexible behavior. Both the engram and spatial navigation literatures have shown that distinct cognitive maps are used to encode two different environments. However, recent work suggests that linking two distinct memories neuronally can enhance memory strength by sharing neural resources. Due to this linking, recall of one memory leads to a higher probability of recalling the other, implying that some aspects of the two cognitive maps have increased in similarity and are no longer distinct. Others have hypothesized that increased similarity between cognitive maps may link experiences across environments and provide a mechanism to increase learning rates. As animals learn multiple environments, it's unclear if each new environment would be represented as a distinct cognitive map (low representational similarity) or share neural resources (high representational similarity) to influence behavior.

Methods: We combined in vivo calcium imaging with miniature microscopes in dorsal CA1 with a novel spatial navigation task consisting of a circular track with eight distinct water reward ports, where two ports gave water and six did not. We built four separate circular tracks, each with distinct visual cues, to study how mice accumulated cognitive maps.

Results: Mice increase their rate of achieving high lick accuracy after switching to each new circular track. We also observed that the number of neurons shared between each new circular track with the previous circular track increased as mice accumulated cognitive maps.

Conclusions: Based off our preliminary data, it's possible that the representational similarity between cognitive maps (measured through neuronal overlap and population vector correlations) increases as mice accumulate cognitive maps, providing a way to increase learning rates in new environments.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Title: Juvenile social isolation dysregulates frontal VIP interneurons to induce social withdrawal

Authors: A Kawatake-Kuno, K Okamura, J Riceberg, A Bansai, A Smith, S Fulton, I Maze, P Kenny, K Hashimoto-Torii, H Morishita

Background: Social isolation during juvenile period is known to dysregulate frontal circuits and social behavior in adulthood. In contrast, adult isolation shows limited effect, suggesting the presence of a sensitive period for social experience-dependent social behavior development. However, the mechanisms that regulate this sensitive period are entirely unknown. Here we aimed to determine what aspect of isolation-induced social behavior deficits is uniquely associated with juvenile isolation, and which frontal cortical cell types mediate the juvenile-specific effect of isolation in mice.

Method: Social behavior was characterized during reciprocal social behavior test in male and female mice that underwent juvenile social isolation (jSI) or adult social isolation (aSI). scRNA-seq and whole-cell patch clump recording were performed to identify frontal cortical cell types. Chemogenetic approach was used to examine the causal contribution of specific frontal cortical cell-type activity to behavioral changes.

Results: We found that social withdrawal significantly increases immediately following jSI, but not after aSI in male mice. The scRNA-seq identified that frontal VIP interneuron is one of the top frontal cortical cell types with aberrant gene expressions in jSI mice. Whole-cell patch clamp recording revealed that frontal VIP interneurons show reduced excitatory inputs selectively by jSI, but not by aSI. Notably, the chemogenetic activation of the frontal VIP neuron activity significantly reduced withdrawal in jSI males.

Discussions: These findings suggest that frontal VIP interneurons are particularly vulnerable to juvenile social isolation and contribute to excessive social withdrawal following isolation. Our findings motivate our future study to determine the molecular mechanisms within frontal VIP interneurons that regulate the juvenile-sensitive period for isolation-induced withdrawal.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Bergan Babrowicz
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TITLE: Genome-wide Association Study of Histopathological Quantification Methods in Primary Age-Related Tauopathy

Authors: Bergan Babrowicz, Kurt Farrell, Gabriel A. Marx, Jamie M. Walker, Timothy E. Richardson, & John F. Crary

BACKGROUND: Tau pathology is prevalent in various neurodegenerative diseases, impacting millions globally. Primary age-related tauopathy (PART) stands out with AD-like neurofibrillary tangles devoid of amyloid beta plaques. It is crucial to enhance our understanding of PART's unique molecular and genetic foundations. Recent studies using computer vision show feasibility in generating features from whole slide scanned images. Our study seeks to identify common risk variants linked to PART, gaining insights into the genetic and pathological mechanisms driving neurofibrillary degeneration.

METHODS: Initially, we conducted a thorough investigation using classical and advanced histopathological techniques on digitized whole slide images (WSIs) from our standardized PART cohort. We assessed the effectiveness of phenotypical quantification methods (Braak stage, positive pixel burden, and AI-derived traits) in capturing genetic variability related to tauopathy. The study further explores candidate genes from AD and PSP GWAS to identify risk alleles for PART, delving into the role of novel risk loci and candidate genes in neurofibrillary degeneration through genetic, biochemical, and histological analyses.

RESULTS: Preliminary data suggest that computationally derived features outperform conventional methods in predicting genetic variability. Furthermore, RBFOX1 emerges as a potential neuroprotective factor in tauopathy. The study identifies the top two genes—RBFOX1 and ATF6—and investigates changes in their expression at the RNA level. Exploring eQTLs, IHC on the protein level, and RNA-proximal DNA analysis enhances our understanding of the molecular drivers underlying PART.

CONCLUSIONS: This study clarifies PART's genetic landscape, underscoring the importance of a multi-modal approach. Identifying risk alleles, comparing quantification methods, and investigating candidate genes aim to unravel the complex mechanisms driving neurofibrillary degeneration in PART. Findings have therapeutic implications and enhance our understanding of tauopathies.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Brian Sweis
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Sensitivity to distinct types of regret recruits separate striatal networks

Romain Durand-de Cuttoli, Antonio Aubry, Long Li, Julian Sackey, Farzana Yasmin, Salma Elhassa, Sanjana Ahmed, Eric Nestler, Scott Russo, Brian Sweis

Regret describes recognizing that an alternative action could have led to a better outcome. Recently, we discovered there may exist fundamentally distinct types of regret processed in separable circuits. These types are defined by specific actions that lead to unique economic violations. Here, we leveraged brain-wide activation data to discover pathways encoding complex decision variables and harnessed the power of unbiased imaging data to reveal circuits implicated in counterfactual thinking. We characterized 40 outbred Swiss Webster male mice on the neuroeconomic task, “Restaurant Row.” Mice had 45-min to forage for their daily source of food investing in rewards of varying costs (delays, 1-30 s signaled by tone pitch) and value (unique flavors). On the final day of testing, mice engaged the task before being prepped for whole brain iDISCO+ tissue clearing and staining in 275 distinct brain regions for c-Fos expression, an activity-dependent immediate early gene. We found a wide range of individual differences in regret sensitivity. iDISCO+ revealed that the most robust bidirectional change in c-Fos+ cell counts was found in the amygdala. This was strongly correlated with accumbens activation. In contrast, orbitofrontal and hippocampus activation was strongly correlated with accumbens activation in mice uniquely sensitive to a distinct measure of regret. Preliminary in vivo recordings of single neurons using head-mounted Miniscopes implanted over the amygdala or hippocampus reveal distinct decision-making algorithms employed by each structure. These data implicate the involvement of multiple regions in dissociable roles of action-specific forms of counterfactual thinking. Our findings suggest that the ways in which regret-processing could become dysfunctional is multifactorial and stem from the integration of distinct circuits in the brain.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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The cognitive flexibility of middle-aged Alzheimer's model mice

BumJin Ko, Austin M. Baggetta, Keziah Diego, Angie Galas, Tristan Shuman, Denise J. Cai

BACKGROUND: Alzheimer's disease is a progressive disease for which aging remains the most significant risk factor. Although cognitive flexibility (e.g., ability to learn new information) declines both with AD and normal aging, it is still unclear how age-related factors interact with AD pathology and eventually impact cognition.

METHODS: We previously developed spatial memory task ("Circle track") to measure memory flexibility (i.e., learn new rewards location while suppressing no-longer rewarded location) in mice. In this task, the subject mouse has to remember the location of the ports and running direction (i.e., clock-wise) to receive rewards. During the reversal learning, the mouse had to update the location of rewarded port and adapt their behavior without indication. We tested how AD model mice (APP-knock-in mouse, APPNL-G-F) perform the "circle track" in their middle age.

RESULTS: Our former work showed that middle-aged mice are able to learn spatial task as fast as young adult mice, but showed reduced performance during reversal learning. Interestingly, APPNL-G-F mice learned the task faster than the control mice with higher motivation (i.e., increased laps).

CONCLUSIONS: This result suggest AD pathology might impact multiple aspects of cognition in addition to the aging component.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Department	Neurology

Characterizing the subcallosal cingulate gray matter in depression: implications for DBS optimization

Carlos Alcocer, Ki Sueng Choi, Jungho Cha, Ha Neul Song, Martijn Figee, Brian H. Kopell, Helen S. Mayberg

INTRODUCTION: Variation of neuroanatomy in the subcallosal cingulate cortex (SCC) may moderate differences in response to SCC deep brain stimulation (DBS) in treatment-resistant depression (TRD). We aim to characterize structural abnormality of SCC in TRD subjects and to explore the effects of structural asymmetry and SCC gray matter (GM) on DBS response.

METHODS: Participants included 47 TRD subjects who underwent bilateral SCC DBS and 16 healthy controls (HC). Segmentation of SCC was performed with FreeSurfer. Volume, volume of overlap between volume of tissue activated (VTA) and SCC GM, and the distance between VTA and SCC GM were extracted. These were compared between groups including between DBS responders and non-responders using ANCOVA. Linear regression was performed with measures including HDRS-17 changes at 2 years and time to stable response (TSR).

RESULTS: There was no significant SCC volume reduction between groups. Left SCC volume was significantly greater than right across all subjects ($p = 0.003$). There was no difference between responders and non-responders in VTA overlap volumes. However, increased overlap of the right ($p = 0.026$), mean lower ($p = 0.031$), and lower right bank of SCC ($p = 0.014$) predicted an increase in TSR. Non-responders demonstrated a greater distance ($p = 0.004$) between the right VTA and SCC.

CONCLUSIONS: Left-sided SCC volume laterality likely represents normal anatomical asymmetry. Placing the DBS lead too medial and inferior may slow the DBS response while positioning the lead too lateral can prevent response, likely due to missing critical white matter tracts. Therefore, optimal DBS response requires consideration of targeting WM tracts and the location of SCC GM in relation to the DBS leads.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Carmen Romero Molina
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Lactamase B as a novel mitochondrial AD risk gene in myeloid cells.

Carmen Romero-Molina, Wen Yi See, Tulsi Patel, Edoardo Marcora, Alison Goate.

Background: Our analysis integrating Alzheimer's Disease (AD) genetics and myeloid cell genomics reported that lower LACTB expression is protective for AD, and proteomic studies have confirmed it (Wingo et al., 2021). LACTB is a mitochondrial serin protein that may influence mitochondrial morphology and bioenergetics. LACTB levels are associated with succinyl-carnitine levels, a metabolite that has been linked to AD risk. LACTB has also been nominated as a tumor-related and an obesity gene, but its function is not well defined.

Methods: THP1 cells were treated for 6 days with siRNA to reduce LACTB expression. iPS cells were CRISPR-edited to obtain LACTB knock-out (KO) lines and differentiated into microglial cells (iMGLs). Functional experiments were performed. Collected samples were outsourced for RNAseq, metabolomics and lipidomics.

Results: We observed that LACTB expression is increased upon differentiation (in iMGLs compared to iPSC, and in THP1 macrophages compared to monocytes) and LPS stimulation. LACTB KD/KO led to an increase in succinyl-carnitine (predicted to be protective for AD), and in histone succinylation, which may modify the cell epigenetics. Transcriptomics revealed an increase in the oxidative phosphorylation, which was validated by Seahorse experiments, and in the immune response to interferon and virus. In addition, LACTB knock-down polarized THP1 macrophages towards a DAM-like state. Lipidomics reported a significant increase in ceramides, which may suggest lysosomal alterations, and a reduction in acyl glycerides, pointing towards changes in lipid droplet accumulation.

Conclusion: LACTB may play a role in cell differentiation and response to stimulus in myeloid cells. Unlike other AD risk genes, LACTB encodes an enzyme, reduced expression is protective, and succinyl-carnitine can be used as a biomarker, which highlights it as a promising therapeutic target.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Inhibitory neuron theta phase locking impacts seizure susceptibility

Cassidy Kohler, Zoe Christenson Wick, Paul A Philipsberg, Sophia I Lamsifer, Elizabeth Katanov, Tristan Shuman

Neurons tend to coordinate their firing with the theta oscillation, a phenomenon known as phase locking. We recently found that the phase locking of inhibitory neurons in the dentate gyrus is altered in a mouse model of temporal lobe epilepsy. This disrupted inhibitory firing may play a role in seizure susceptibility, as inhibitory theta phase locking is thought to be critical for maintaining excitatory-inhibitory balance. However, it is unclear which inhibitory neuron populations exhibit these deficits, and whether inhibitory phase locking causally impacts seizures. Thus, we aimed to test the hypotheses that inhibitory theta phase locking deficits are cell-type specific, and that phase locking affects seizure susceptibility.

We first used a Cre-dependent viral/transgenic approach to opto-tag and identify the preferred firing phase of hippocampal parvalbumin (PV)+ or somatostatin (SOM)+ cells in control and pilocarpine-treated epileptic mice. We then used a closed-loop optogenetic tool to stimulate these interneurons at their preferred or non-preferred theta phase while measuring seizure latency after a kainic acid injection.

We found that in control animals, both PV+ and SOM+ cells are phase locked to the trough of theta and rarely fire at the peak. In epileptic animals, SOM+ cells maintain this firing preference, but PV+ cells have distributed preferred firing phases. We have also found that shifting PV+ cell firing to the peak of theta increases seizure susceptibility in control mice, and preliminary evidence suggests that re-aligning PV+ cell firing to the trough of theta reduces seizure susceptibility in epileptic mice.

Our findings suggest that dentate PV+ neurons, which have altered theta phase locking in epileptic mice, play a causal role in determining seizure susceptibility.

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Full Name	Catherine Elorette
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The role of macaque frontal face patches in the integration of social and value information

Elorette, Catherine; Fujimoto, Atsushi; Fujimoto, Satoka H; Fleysher, Lazar; Russ, Brian E#; Rudebeck, Peter H#

Brain regions sensitive to faces in the temporal and occipital cortex are known to contribute to the visual processing stream, but these ‘face patches’ have also been observed in frontal cortex, where their function is unknown. One frontal face patch, area PO, is located within orbitofrontal cortex (OFC), a region implicated in valuation. OFC lesions result in inappropriate social behavior, suggesting that this area may be critical to combining perceptual representations of faces with internal representations of value to guide social decision making. We hypothesize that area PO, within OFC, specifically acts to update and maintain the value of a face. We tested two female rhesus macaques (Macaca mulatta) previously trained to perform behavioral tasks during awake functional neuroimaging on a behavioral task designed to isolate learned value associations for objects from learned value associations for faces. Animals learned to associate a high-value or low-value juice reward flavor with macaque face or object stimuli. To test the role of area PO in specifically updating value for faces, we periodically reversed the stimulus-reward associations. Awake whole brain functional images were acquired on a 3T MRI scanner (1.6mm isotropic voxels) while animals performed the reversal task. We examined neural signal changes via GLM contrast (reversed faces > reversed objects); this revealed a unilateral activation in area PO ($p<0.05$) when reward associations were updated for faces, but not for objects. Our results show that Area PO plays a role in updating stimulus-reward associations for faces, as compared to object stimuli. This suggests that this face patch is a critical mediator of face and value information, two streams of information vital for social valuation.

2024 Neuroscience Retreat

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Full Name	Charles Mobbs
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A novel approach to drug discovery using machine learning: Novel therapies and mechanisms for Alzheimer's and other neurological and psychiatric conditions. Kun-Hyung Roh and Charles Mobbs.

In contrast to the standard target-based approach to drug discovery, which has not been notably successful to develop therapies for Alzheimer's or other age-related diseases, we developed a novel approach using phenotypic screens combined with novel machine-learning (ML) resources to discover drugs and elucidate mechanisms of disease. We developed a high-throughput screen using an Abeta transgenic model of C. elegans to carry out high-throughput screening to discover small molecules which reduced proteotoxicity (not Abeta production) (Litke et al.). The most promising class of compounds from this screen were phenothiazines, which of were of interest due to their efficacy to treat psychosis and depression, psychiatric conditions associated with Alzheimer's. We then carried out structure-activity studies which led to the synthesis of novel compounds, of which GM310 was the most promising based on its protective effect against proteotoxicity and inhibition of inflammation. The likely protective effect of GM310 in Alzheimer's Disease was corroborated novel ML resources we developed using the CMAP, scREAD and PANTHERDB databases. These analyses also led to the discovery of the most robust molecular effects of phenothiazines which we had already demonstrated were involved in the protective mechanisms of dietary restriction, and which were also produced by GM310. We used these algorithms to predict other small molecules likely to produce similar molecular responses and thus protect in Alzheimer's Disease. These studies also suggested that the Sigma-1 receptor mediates protective effects of GM310, and we calculated that GM310 has the highest affinity of any known ligand for the Sigma-1 receptor. These studies indicate the utility of these novel ML resources to develop drugs and elucidate novel mechanisms for neurological and psychiatric conditions.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Christabel Mclain
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Transcriptional mechanisms of female stress susceptibility.
Christabel Mclain, Orna Issler, Eric Nestler.
BACKGROUND: Chronic stress produces sex-specific neurobiological and behavioral outcomes which are associated with greater stress susceptibility and prevalence of depression in females. Our understanding of the molecular mechanisms driving sex-differentiated stress responses is limited. In this project, we aim to map the distinct contributions of female sex hormones and sex chromosomes to stress-induced transcriptional regulation in the nucleus accumbens (NAc) and medial amygdala (MeA), brain regions implicated in stress and sex differences.
METHODS: We conducted ovariectomies in WT female mice and utilized a chronic variable stress (CVS) paradigm followed by a battery of anxiety- and depression-like behaviors and RNA-sequencing in our brain regions of interest (ROIs). In current experiments, we are conducting CVS in the four-core genotype (FCG) mouse model, in which sex chromosomes are dissociated from gonadal sex. Using the FCG model, we will characterize the contribution of sex chromosomes to stress-induced behavioral changes, and transcriptional outcomes in our ROIs. Additionally, we are currently isolating nuclei expressing receptors for the female hormone estrogen in our ROIs. We plan to use CUT&RUN to examine how estrogen receptor DNA binding patterns change after chronic stress.
RESULTS: We found that ovariectomy (OVX) increases anxiety- and depression-like phenotypes following chronic stress, and that stress produces divergent effects on NAc and MeA gene expression in OVX vs. sham surgerized animals. Further, we identified hub genes which drive networks involved in hormonal regulation of stress using gene co-expression analyses (MEGENA).
CONCLUSIONS: Ultimately, we will leverage our large-scale datasets to identify key genes and test their causal role in driving molecular changes and female stress susceptibility, using pan-neuronal and cell-type-specific viral-mediated gene transfer. Altogether, this project will enhance our understanding of sex-specific mechanisms of stress susceptibility and pave the way for future translational work.

2024 Neuroscience Retreat

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Chronic cocaine exposure alters the balance of approach/avoidance decision-making.

Clementine Blaschke,1* Tiffany Lin,1* Kinneret Rosen,1 Angélica Minier-Toribio,1 Tamara Markovic,1 Freddyson J. Martínez-Rivera,1 Antonio Aubry,1 Eric J. Nestler1

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Approach/avoidance (A/A) conflicts require balancing the pursuit of rewards with the potential for undesirable outcomes, a delicate balance disrupted in neuropsychiatric disorders like drug addiction. Despite the prevalence of these disruptive A/A dynamics in drug addiction, the mechanism underlying the interaction between drug exposure and natural reward-seeking during A/A conflict is poorly understood.

This study used a platform-mediated avoidance (PMA) paradigm—where we condition mice to avoid tones paired with foot shocks by stepping onto a platform at the cost of losing access to saccharine-water rewards. We then exposed them to chronic cocaine or saline injections (20 mg/kg intraperitoneal) for five days. Following a 5-day drug-free period, we tested their decision-making biases under extinction conditions (tones associated with foot shock are present, but no foot shock occurs).

Our results reveal that chronic cocaine exposure selectively modulates A/A dynamics, increasing reward-seeking while decreasing avoidance during tone rather than inter-tone periods. To explore the neurobiology underpinning this heightened natural reward-seeking behavior and facilitation of avoidance extinction, we employed a combination of brain immunolabeling and 3D-volume imaging techniques, including iDISCO+, RNAScope, and viral-mediated gene transfer. Our preliminary iDISCO+ results revealed that chronic cocaine induces widespread ΔFosB expression, a transcription factor implicated in addiction-related outcomes, notably in the nucleus accumbens (NAc) and the prefrontal cortex (PFC).

Ongoing experiments aim to elucidate whether induction or repression of ΔFosB in the NAc and PFC contributes to the observed increase in reward-seeking approach over avoidance. Additionally, we will more specifically dissect the circuitry by selectively manipulating levels of endogenous ΔFosB in NAc neurons expressing either dopamine D1 or D2 receptors, which are known to differentially signal A/A decision-making.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Daniel Garcia
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Department	Neuroscience

Decision Making as a Predictor of Cannabis Use Disorder-like Behavior

Daniel Garcia, Yasmin L. Hurd, Jacqueline-Marie N. Ferland

BACKGROUND: Cannabis legalization has been an important step for reducing arrests and incarceration for its use, especially in marginalized communities. However, it has been met with repercussions like a rise in the belief that cannabis is not addictive, despite 10-30% of regular cannabis users meet the criteria for cannabis use disorder (CUD). There is also a notable lack of animal models of CUD that has left gaps in our understanding as to how certain risk factors, including deficits in decision making and impulsivity, contribute to CUD development.

METHODS: We used a translational animal model to determine the association between decision-making, impulsivity, and edible THC consumption in male and female rats. Decision making and impulsivity were measured using a preclinical analogue of the Iowa Gambling Task, the Rat Gambling Task (rGT). After task acquisition, rats then were given daily access to control or edible THC gelatin. The THC concentration started at 0.133 mg/g of gelatin for 5 days and was doubled to 0.27 mg/g for another 8 sessions.

RESULTS: Echoing results from human cannabis users, rats with poor decision-making and elevated impulsivity consumed significantly more THC at both concentrations. This contrasted with rats with optimal task performance, as these animals consumed low amounts of drug or titrated intake. Prominent sex differences were also observed, with males consuming significantly more THC. Using biochemical assays, there were marked changed in mRNA expression of endocannabinoid-related genes and cFos particularly in the nucleus accumbens core in rats between high and low consumers of THC, indicating endocannabinoid signaling may contribute to both cognitive deficits and THC intake.

CONCLUSIONS: This model provides a foundation to further interrogate epigenetic, behavioral and neural circuit alterations underlying cannabis use disorder-like behavior.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Danielle Russo
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Verbal Learning and Memory Deficits in Schizotypal Personality Disorder and Schizophrenia: Frontal Lobe Volume Correlates

Danielle L. Russo, Sean Hollander, Sabrina Ng, Sana Aladin, and Erin A. Hazlett

Background: Cognitive deficits, known as negative symptoms, have been observed across schizophrenia-spectrum disorders (SSD) with verbal learning and memory (VLM) being among the most severe. Individuals with schizotypal personality disorder (SPD) and more severely ill patients with schizophrenia share cognitive and attentional deficits hypothesized to result from deficits in the prefrontal and temporal lobes. This is the first study to examine VLM, symptom severity, and MRI correlates on a within-subject basis and across the spectrum.

Methods: VLM performance was examined with the Hopkins-Verbal-Learning-Test Revised (HVLT-R) in three age- and gender-matched groups of participants: 48 healthy controls (HCs), 32 individuals with SPD, and 44 individuals with schizophrenia. High-resolution magnetic resonance imaging (MRI-3T Siemens Magnetom) scans were conducted, and volume of key frontal lobe (FL) regions were examined using Freesurfer. Outcome variables included correctly-recalled words, learning-to-learn score, serial ordering, and semantic clustering. All study participants received a structured diagnostic interview, and the Positive and Negative Syndrome Scale was administered to determine symptom severity across the spectrum.

Results: Compared with HCs, schizophrenia patients recalled significantly less correct words, utilized the semantic-clustering strategy less, and showed poorer learning over three consecutive trials. SPD patients were intermediate between the other two groups and, compared with HCs, utilized a less efficient serial ordering strategy more. Across patient groups, fewer correctly-recalled words and less semantic clustering were associated with greater negative symptom severity. Additionally, in patients, poorer memory performance was associated with smaller volume of key FL regions.

Conclusions: These findings suggest SPD-related deficits in VLM are intermediate between HCs and schizophrenia. Taken together, the findings suggest that FL areas are important targets for improving cognitive deficits in SSD.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Differential contributions of functional and structural connectivity to chronic stress symptoms
David O'Connor, Charbel Gharios, Mandy van Leent, Helena L Chang, Shady Abohashem, Michael Osborne, Cheuk Y Tang, Audrey E Kaufman, Philip Robson, Sarayu Ramachandran, Claudia Calcagno, Venkatesh Mani, Maria Giovanna Trivieri, Antonia Seligowski, Sharon Dekel, Willem Mulder, James Murrough, Lisa Shin, Ahmed Tawakol, Zahi Fayad.

Introduction
Chronic stress is a long-standing health concern. Its effects are particularly evident in post-traumatic stress disorder (PTSD). In this study we investigate the effects of chronic stress on the brain using functional and structural MRI connectivity estimates.
Methods
Data was collected from 70 participants (19 PTSD, 35 trauma controls, and 16 healthy controls). Task (hariri) and rs-fMRI, diffusion MRI and T1 images were collected. Questionnaire data included the Perceived Stress Scale (PSS), Conor Davidson Resilience Scale (CDRISC), State-Trait Inventory for Cognitive and Somatic Anxiety (STICSA), and PTSD checklist for DSM-5 (PCL-5). MR data were preprocessed using fMRIPrep and QSIPrep. Connectivity matrices were generated using the Shen 368 atlas. The network-based-statistic (NBS) was used to identify discriminating functional and structural connections. The resulting discriminating networks were then related to questionnaire summary, with adjustment for age and sex.
Results
A task-based functional network which discriminated PTSD subjects from controls was found ($p=0.063$). A structural network was also found ($p=0.078$). Each network associated with CDRISC, PSS, PCL, and STICSA ($p<0.001$). The brain regions most represented in the task network were the left fusiform gyrus, secondary visual areas, primary motor area, and cerebellum. The brain regions most represented in the structural network were the left and right amygdala, pars orbitalis, and insula.
Conclusions
We find functional and structural connectivity networks which are sensitive to resilience, stress, trauma, and anxiety. These results highlight the benefit of multimodal approaches to investigating brain-behavior relationships.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Davide Folloni
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Department	Neuroscience

TITLE: Neural mechanisms of affective states in the primate brain

AUTHORS: Davide Folloni, Fred Stoll, Peter H. Rudebeck

BACKGROUND: Determining how fluctuations in context contingencies regulate our affective states is key to understand the role of the environment on the etiology and prevention of mood disorders like Major Depressive Disorder (MDD). The neural mechanisms of MDD are, however, still poorly understood. Depressed patients quickly recover after deep brain stimulation in the subgenual anterior cingulate cortex (sACC) but it is still unclear why this therapeutic effect happens and, crucially, what is the role of sACC circuits. Here we investigated how sACC and a set of interconnected areas represent choices and outcomes in a reward-guided learning with context manipulation.

METHODS: Macaque monkeys performed a three-armed bandit task with transitions across multiple value contexts for fluid reward while neural activity was recorded from sACC, amygdala, striatum, insula and ventrolateral prefrontal cortex (vlPFC). Simultaneous autonomic activity was also recorded. Monkeys learned choice-outcome contingencies in one context and then used them to guide their behavior as they transitioned among other value contexts.

RESULTS: Context transition and their specific order affected animals'. Neurons in sACC showed separate encoding signals associated with the timing of choice and with reward onset. Similar signals were encoded also in areas within the proximal sACC: amygdala, striatum, insula and vlPFC. Concomitant heart rate similarly changed across the different value contexts and was modulated by their transition orders.

CONCLUSIONS: Context contingencies have a crucial impact on our mood and sACC represent a key hub for treatment of mood-related disorders. Here we show that different value contexts affect monkeys' behavior and their autonomic states differently. We also show that activity in sACC and within interconnected areas in limbic and prefrontal cortex encode both choices and the outcome resulting from these decisions.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Lab	Neuropsychoimaging of Addictions and Related Conditions (NARC) Research Program
Department	Psychiatry

Sex differences in outcome among individuals with opioid use disorders in their first episode of outpatient medication-assisted therapy: A nationally representative “real world” study

Eduardo Butelman(1), Yuefeng Huang(1), Alicia McFarlane(2), Carolann Slattery(2), Rita Z. Goldstein(1), Nora D. Volkow(3), Nelly Alia-Klein(1)

(1)NARC, Department of Psychiatry and Neuroscience, ISMMS, (2)Samaritan Daytop Village, (3)National Institute on Drug Abuse

Background: The opioid epidemic takes a major toll on public health in the United States. The standard for treating opioid use disorder is medication-assisted therapy (MAT; e.g., methadone or buprenorphine). It is unclear if there are “real world” sex differences in treatment outcomes nationally.

Methods: De-identified epidemiological data from the SAMHSA TEDS-D platform (2019), examining discharges from outpatient MAT for individuals where an opioid (e.g., heroin or fentanyl) is the primary substance used. The binary outcome was non-medical opioid use in the month preceding discharge, indicating either continued use or relapse. A multiple logistic regression (n=11,545) adjusting for major socio-demographic and clinical features, and univariate analyses, were carried out.

Results: In the multiple logistic regression, males had significantly greater odds of non-medical opioid use in the month prior to discharge, compared to females. Univariate analyses (Bonferroni-corrected) show that these sex differences occurred especially at younger ages (range 18-39), and for persons who stayed longer in treatment (e.g., 1 year or more).

Conclusions: This nationally representative “real world” study revealed significant sex differences in treatment outcomes for MAT. Also, the study identified major conditions (including younger age and longer duration of treatment) under which males have more frequent negative outcomes, compared to females. These findings can provide insights for the development of sex- or gender- optimized interventions, paving the way for more personalized treatment.

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2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Enhanced Neural Interoceptive Processing is associated with Treatment Response Trajectory in Deep Brain Stimulation for Treatment-Resistant Depression

Elisa Xu, Jacob Dahill-Fuchel, Samantha Pitts, Jacqueline Overton, Tanya Nauvel, Patricio Riva Posse, Andrea Crowell, Martijn Figee, Sankar Alagapan, Christopher Rozell, Kisueng Choi, Helen Mayberg, Allison Waters

Background: Change in interoceptive processing may be important to the mechanisms by which deep brain stimulation (DBS) to the subcallosal cingulate (SCC) affects treatment-resistant depression (TRD). A measure of interoceptive processing is the heartbeat evoked potential (HEP), which is time-locked to the cardiac cycle. HEP is thought to reflect cortical processing of cardiac sensation and may be suppressed in depression. This study investigated whether SCC DBS enhances interoceptive processing, as well as the relationship between HEPs and depression severity at monthly time points over 6 months of SCC DBS for TRD.

Methods: Eight patients with treatment resistant depression were studied as part of an ongoing experimental trial of SCC DBS for depression. HEPs were extracted from resting EEG recordings acquired with DBS off at monthly time points throughout a 6-month program of therapeutic SCC DBS.

Results: A comparison between conditions Baseline and 6 months revealed significant differences in the heartbeat evoked potential amplitude in all 8 patients (1 significant positive cluster, $p = 0.02$). Change in heartbeat evoked potential amplitude over 24 weeks of treatment was inversely correlated with latency of treatment response (rho = -0.75, 95% CI, -0.95 to -0.11, P=.03). We also observed an overall negative association between patients' increase in HEP magnitude and decrease in HAMD-17 scores at monthly time points (rho = -.169, p=.21).

Conclusions: These findings examining the effects of SCC DBS on neural interoceptive processing in relation to therapeutic outcome, could represent initial indications for the development of a biomarker to predict treatment responses and lead to improved clinical progress.

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Full Name	Elley Ishikawa
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Magel2 Deficiency and Feeding Behavior in Mice: Implications for Prader-Willi Syndrome
Authors: Elley Ishikawa, Paul J.Kenny, Richard M. O'Connor

Background: Prader-Willi syndrome (PWS) is the most common cause for life-threatening childhood obesity. Infants and young children with PWS show a failure to thrive. This is followed by insatiable hyperphagia that emerges around 3-8 years of age. PWS is caused by dysregulated silencing on chromosome 15. Obesity related symptoms including hyperphagia, weight gain, increased fat mass, and reduction of voluntary activity have been specifically linked to the silencing of the Magel2 gene. Magel2 is normally densely expressed within the lateral hypothalamus (LH) a brain region key to the regulation of motivated behaviors and energy expenditure. However, the impact of the absence of Magel2 on PWS associated changes to food-related motivation is still not fully understood. As such we hypothesized that mice lacking functional expression of Magel2 would show disruptions to motivated behaviors.
Methods: To assess homeostatic feeding, we food-restricted the mice before allowing them to consume standard laboratory chow. To measure food-related hedonic drive we allowed the same mice to consume calorically dense palatable food items while fully sated. Finally we gave separate cohorts of mice unlimited access to both chow and palatable food and recorded weight gain and food intake.
Results: Homoeostatic feeding was unchanged in Magel2-null mice. Surprisingly, hedonic feeding was impaired in these same mice. When granted free access to both standard chow and palatable food Magel2 null mice gained more weight than their wild-type counterparts despite consuming the same amount of total calories. However, magel2 null mice obtained a large portion of their calories from the palatable food source compared to wild-type mice.
Conclusion: An absence of Magel2 expression leads to complex changes to food-related motivation that is dependent on the palatability of the food source.

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Full Name	Emily Teichman
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Department	Pharmacological Sciences

TITLE: Design and validation of brain-penetrant HCN channel inhibitors to ameliorate social stress-induced susceptibility phenotype in mice

AUTHORS: Emily M. Teichman#, Jianping Hu#, Anthony Blando, Xiaoping Hu, Husnu Umit Kaniskan, Sarah E. Montgomery, Min Cai, Ming-Hu Han†, Jian Jin† and Carole Morel†

BACKGROUND: Depression is a devastating disease, and many who suffer from it require novel therapeutics. One novel target is the upregulated HCN channel currents found on hyperactive VTA dopamine (DA) neurons following CSDS. Previous research demonstrated that inhibiting HCN channels with Cilobradine decreases firing rate and ameliorates CSDS-induced depressive-like behaviors. In this study, we aimed to identify novel Cilobradine analogs to improve neural tropism and inhibitory efficacy, and to ameliorate CSDS-induced depressive-like behaviors.

METHODS: We designed and synthesized 8 novel Cilobradine analogs, which we tested utilizing slice and in vivo electrophysiology for inhibitory efficacy, followed by BBB permeability analysis. Finally, we examined our top compound's effects on CSDS-susceptible mouse behaviors, measuring social interaction (SI test) and cognitive flexibility via the probabilistic reversal learning task (PRLT).

RESULTS: We saw a variety of effects on VTA DA neurons ex vivo from loss of all efficacy (compound 8) to improved efficacy (MS7710 and MS7712) as compared to Cilobradine. MS7710 and MS7712 improved BBB permeability, and inhibited firing rate and bursting activity of VTA DA neurons in vivo in CSDS-susceptible male and female (MS7710) mice. Finally, we saw that a single IP injection of 5 mg/kg MS7710 resulted in a long lasting amelioration of social deficits and cognitive inflexibility in CSDS-susceptible mice.

CONCLUSIONS: Our data demonstrates that a small, targeted analog series can yield a compound that not only improved neural tropism but also improved efficacy at lower doses as compared to its parent compound. MS7710 ameliorated complex depressive-like behaviors, and represents a new therapeutic candidate for future antidepressant drug discovery.

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Degree of Disconnection as a Mechanism of Language Impairment in Multiple Sclerosis

Emma Dereskewicz, Jonadab Dos Santos Silva, Francesco La Rosa, Julia Galasso, Robin Graney, Nadia Garcia, Sarah Levy, Erin S Beck, James Sumowski

The degree of disruption of white matter tracts yields a potential mechanism for disability in multiple sclerosis (MS). Using the human Disconnectome, we seek to conduct an analysis of how the localization of WMLs contributes to the disruption of connectivity between brain regions and how this degree of interference correlates with clinical measures of disability in the RADIEMS cohort.

We included the RADIEMS cohort of early relapsing-remitting MS (diagnosed <5.0 years, n=105, 69 [65.7%] female, age 34.2 ± 8.0 years). Participants underwent 3T MRI, clinical and cognitive assessment. WMLs were segmented semiautomatically. The BCB toolkit was used to generate a disconnectome map for each subject and to calculate the proportion of each tract affected by the WML burden. A forward linear regression model adjusted for age and sex was used to select the tracts whose degree of disruption secondary to WML could predict worse cognitive performance among people with MS.

Worse rapid automatized naming (RAN) performance was associated with higher lesion load (r=0.26, P<0.001), lower brain volume (r=-0.25, P=0.001), lower white matter volume (r=-0.32, P<0.001), but not gray matter volume, all adjusted for age and sex. Given that lower WML was associated with worse RAN performance, we assessed tract integrity. Out of all white matter tracts, worse object naming ability was predicted by greater disruption of the posterior segment of the left arcuate fasciculus (β=0.43, P<0.001).

Object naming performance is impaired in MS and associated with higher WML burden. Tract-specific analysis revealed that MS-related damage to the posterior segment of the left arcuate fasciculus, crucial for language, is the main predictor of poorer object naming performance.

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Full Name	Emma Hays
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Microglial dopamine receptor expression and its influence on neuronal activity

Emma Hays, Hayley Strasburger, Vinaya Sahasrabuddhe, Anne Schaefer

Background: Research regarding the dopaminergic system has long focused on neurons. Microglia, the brain-resident macrophages, may present a new axis of dopaminergic regulation. A growing body of literature suggests that microglia possess the ability to express receptor transcripts for and respond to an array of neurotransmitters and neuropeptides, and that expression of these may vary with region, activity, or disease state. Our lab has uncovered a unique subpopulation of microglia that express the dopamine receptor DRD1 (D1) in the striatum. Microglia can also modulate neuronal activity, and preliminary data from our lab have demonstrated that D1+ microglia influence the neuronal and behavioral response to dopamine.

Methods: We have performed behavioral assays of dopamine driven behaviors on transgenic knockout mouse lines of both the microglial D1 receptor and the D1+ microglia subpopulation. Gene expression analysis, including qPCR, RNA sequencing, and in situ hybridization have been performed on these mice, as well as on primary microglia cultures treated with a number of factors, including, dopamine, ATP, and poly I/C.

Results: The behavioral response to cocaine and D1 agonist are altered in these mice, interestingly in opposite directions. Gene expression changes accompany these effects, most significantly in signaling, immediate early gene, and inflammatory response pathways. Preliminary data show that aged, but not young, D1+ microglia knockout mice, may show impaired motor behavior, suggesting that these microglia may play a role in the dopaminergic dysfunction seen in diseases of aging.

Conclusions: Our findings suggest that D1+ microglia may serve to modulate the neuronal response to dopamine. Exploring the role of microglia in dopaminergic signaling may be provide new insight into the dopaminergic dysfunction that characterizes numerous neuropsychiatric and neurological disorders and could provide novel therapeutic targets.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Faith Adams
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Lab	Muhammad Parvaz
Department	Psychiatry

Revealing Cumulative Environmental Impact on Youth Alcohol Initiation: PolyeXposure Alcohol Risk Scores (PXARS) from ABCD Study

Faith Adams, Yixuan He, Wes K. Thompson, Chirag J. Patel, Muhammad A. Parvaz

Background: Early alcohol initiation, before age 15, escalates the risk of alcohol dependence, with both genetics and the environment playing significant roles. Despite advancements in genetics, exploration of non-genetic factors (i.e., the exposome) remains limited. This study aims to utilize Exposure-Wide Association Study (ExWAS), akin to genome-wide association study (GWAS), to create PolyeXposure Alcohol Risk Scores (PXARS) similar to polygenic risk scores, to probe the environmental impact on youth alcohol initiation.

Methods: This study analyzed 3,926 youth aged 9-14 from the Adolescent Brain Cognitive Development (ABCD) cohort. We identified 201 quality-controlled measures encompassing various aspects of youth's environment. First, we conducted ExWAS for univariate associations while accounting for standard demographics and assessment site and family ID. We then used multivariate modeling to identify the strongest associations and computed PXARS, a weighted sum of the final significant variables.

Results: Among 201 exposures, 11 significantly distinguished between alcohol initiators and non-initiators (pFDR <0.05). Notably, screen media activity (HR = 2.2, pFDR < 0.001), sexual orientation discrimination (HR = 2.8, pFDR < 0.01), neighborhood crime (HR = 0.73, pFDR < 0.01), and family conflict (HR = 1.32, pFDR < 0.01) were prominent predictors from ExWAS. In the multivariate model, neighborhood crime, screen media activity, and the proportion of American Indian and Alaska Native individuals remained significant, contributing to PXARS calculation. PXARS was significantly higher in alcohol initiators compared to non-initiators (p = 0.005). The goodness of fit evaluation showed an 8% improvement from baseline covariates only [0.505; 95% CI 0.462, 0.621] to PXARS model [0.558; 95% CI 0.513, 0.674).

Conclusions: This approach assesses the combined impact of diverse environmental exposures, ensuring simplicity and interpretability.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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AI predicts neurologic changes from video data in critically ill neonates

Alec Gleason, Florian Richter, Nathalia Beller, Naveem Arivazhagan, Rui Feng, Benjamin Glicksberg, Maite LaVega, Madeline Fields, Katherine Guttmann, Girish Nadkarni, Felix Richter

Background: In neonates, neurologic changes are assessed by physical exam, which is conducted at limited time points, can be delayed, is highly subjective, and may not discern subclinical changes. We hypothesized that pose recognition, an AI method to track movements, can predict neurologic phenotypes in the Neonatal ICU.

Methods: We collected video-EEG data from infants with corrected age ≤1 year (4,705 video hours, 115 babies). We annotated videos with medications and EEG abnormalities from epileptologist reports. We utilized DeepLabCut, an AI approach that performs well on animal tracking, to train an infant pose recognition algorithm on video feeds. We labeled 14 anatomic landmarks in 25 frames/baby and evaluated with L2 pixel error. We then trained classifiers to predict sedation and cerebral dysfunction.

Results: Infant pose was highly predictive on training data, held out frames, and held out babies (L2≤4.6 pixels). We observed high performance based on ROC-AUCs (>0.82) and percentage correct points within reference threshold (>95%). The proportion of video with ≥7 body parts visible was 47%. Movement increased with age and was lower with sedatives and cerebral dysfunction (all permutation P<0.005). We next developed neonatal sedation and cerebral dysfunction classifiers. Our best sedation classifier performed well on held-out frames and babies as did cerebral dysfunction prediction (all ROC-AUCs>0.76). As an example, in a baby undergoing therapeutic cooling, predicted sedation deepened first with increasing epileptiform activity and again after phenobarbital administration.

Conclusion: We used AI to quantify neonatal movement from video and predict cerebral dysfunction and sedation. Applications include neuro-telemetry, trial outcomes, molecular associations, and technology that could help the growth and development of all infants.

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7T MRI-derived Brain Age Exceeds Chronological Age in Both Early and Longstanding Multiple Sclerosis

Francesco La Rosa, Jonadab Dos Santos Silva, Gaurav Verma, Julia Galasso, Priti Balchandani, Daniel S. Reich, Hayit Greenspan, Erin S. Beck

Background

Brain age (BA) is estimated with machine learning (ML) methods from brain magnetic resonance imaging (MRI). The gap between chronological age (CA) and BA, known as BA difference (BAD), is a marker of disability in neurological diseases.

Methods

A DenseNet model was trained on ~5500 publicly available T1-w MRI scans of HV acquired at 1.5 or 3T at 72 sites to predict BA. We fine-tuned the model on 351 HV 7T T1w MP2RAGE images (median age 32 years, range 19— 75 years; 52% female participants). DenseNet was evaluated on 7T MP2RAGE images from 28 HV imaged at Mount Sinai. DenseNet was then applied to 7T MP2RAGE images from 50 people with longstanding MS scanned at the NIH and 26 subjects diagnosed with MS within the previous year.

Results

The median BAD in the HV testing set (median age 31 years, range 26 — 53 years; 16 [57%] female participants) was 2.6 years (range -6 – 7). In the early MS cohort (median age 36 years, range 24 — 55 years; 14 [54%] female participants), the median BAD was 9.9 years (range -9 – 32, interquartile range [IQR] 17), greater than 0 (P = 0.008), and correlated with 9HPT (r=0.44, P=0.02). In the longstanding MS cohort (median age 47, range 30 — 77 years; 32 [64%] females), the median BAD was 10.3 years (range -17 – 28, IQR 13), greater than 0 (P = 0.002), and correlated with SDMT (r=-0.41, P=0.02),

Conclusions

Our 7T-enhanced ML model accurately predicts BA in HV and reveals increased BA in MS, even at the time of diagnosis.

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Full Name	Gabriela Chiarotto
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Introducing Intraurothelial Nerve Fiber Density (IUNFD) Assessment as a Biomarker for Autonomic Innervation in Non-Human Primates

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BACKGROUND: Urinary bladder dysfunction presents a major challenge in the clinical management of patients suffering from multiple neuropathological conditions. Presently, diagnostic tools for mechanistic evaluations of detrusor dysfunction are limited, and emerging new treatments to reverse bladder conditions are sparse. We aim to evaluate the feasibility of the use of bladder biopsies to assess intraepithelial nerve fiber density (IUNFD) in primates.
METHODS: We performed a punch biopsy from the neck, lateral wall, and dome bladder regions in a control series of neurologically intact rhesus macaques (n=5). Cryosections were prepared for immunofluorescence using anti-PGP9.5 antibody as a small fiber (C fiber) marker. Images were acquired by confocal microscopy and the crossing (vertical), and non-crossing (non-vertical) nerve fibers were counted in a minimum 1000μm urothelium length using ImageJ and Photoshop software. Quantification of IUNFD followed established methods for intraepithelial nerve fiber innervation in skin biopsies (Khoshnoodi et al., 2016; Freeman et al., 2020).
RESULTS: The results showed high-density fiber in the bladder neck. In addition, the number of non-vertical fibers by length was higher in the neck region. No differences were observed between vertical and non-vertical fibers in the lateral wall.
CONCLUSION: Our results demonstrated that bladder biopsies may provide a novel opportunity for studies of neuropathic conditions affecting autonomic functions in non-human primates. The bladder biopsies can also be performed as part of cystoscopy, thereby providing new opportunities for translational research studies in vivo and IUNFD may be determined in longitudinal studies.

Keywords: urothelium, sensory fibers, immunofluorescence.
Financial support: Adelson Medical Research Foundation (AMRF)

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DEMOGRAPHIC AND BIOLOGICAL FACTORS CONTRIBUTING TO VARIATIONS IN BRAIN MORPHOLOGY AND BEHAVIOR

Butler, Grace; Lizzano Alexia; Whitaker, Yolanda; Morris, Laurel; Murrough, James

Parsing out differences in clinical characteristics and brain morphology of those diagnosed with depression and anxiety-related disorders poses an unresolved debate in identifying potential neurobiological substrates of these diseases. Prior MRI research in clinically depressed populations and healthy controls reflect regional differences in the prefrontal cortex, hippocampus, and amygdala. In utilizing high resolution 7-Tesla neuroimaging, we can more accurately measure subcortical volumes and investigate brain structure through a finer lens, with a supplementary emphasis on biological factors influencing the brain and behavior.

Data was collected at The Icahn School of Medicine at Mount Sinai through the Depression and Anxiety Center for Discovery and Treatment. All participants (N= 142) completed a DSM-5 diagnostic interview to determine population group, with necessary exclusions. Healthy and patient (i.e. MDD, Anxiety) populations underwent a blood draw and Siemens 7-Tesla MRI scan where T1 structural volumetrics were collected to measure whole brain volume and regions of interest.

We will run a multivariate regression analysis controlling for comorbid diagnoses, medication use, age of onset, and symptom severity. Results aim to reflect regional brain differences across demographic variables and patient groups. Additional correlation with sex hormones (i.e. estradiol, testosterone, progesterone) will serve as an evaluation of more refined biological factors influencing behavior.

Assessing demographics contributing to brain volume across sex, race/ethnicity, age, and hormones, may pose insight into pinpointing behavioral and structural variation across patient and population groups. Current research studies of the human brain still lack inclusivity in identifying the various biological and demographic measures that may contribute to underlying influences on behavior. Comprehensive approaches to understanding the various factors contributing to psychopathologies are essential to progressing treatment across a more diverse spectrum.

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An hiPSC-derived midbrain organoid model of sporadic tauopathy

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Background:The accumulation of abnormal tau protein in neurons and glia in the human brain is the defining feature of tauopathies. Progressive supranuclear palsy (PSP) is a tauopathy typified by selective vulnerability of dopaminergic neurons and glia in the midbrain leading to movement disorders. Human induced pluripotent stem cell (hiPSC)-derived organoid models have emerged as a tool to more accurately recapitulate disease mechanisms in the brain.

Methods:Skin biopsies were collected from living patients or during autopsy. Fibroblasts were cultured and reprogrammed into hiPSCs using Sendai virus. HiPSCs were maintained with StemCultures FGF2-Discs to improve pluripotency and FACS confirmed pluripotency. To generate organoids, hiPSCs were seeded into spinner flasks, patterned using pharmacological-directed differentiation, and grown long-term. Reliable patterning was confirmed with qRT-PCR, immunohistochemistry and immunoblot using cell-type specific markers. Astrocytes were extracted from mature organoids, cultured, and screened.

Results:Seven fibroblast lines from PSP patients were reprogrammed into hiPSCs. Sanger sequencing confirmed the absence of MAPT mutations. HiPSCs grown with FGF2-discs were positive for pluripotency markers and negative for off-target genes. Patterning organoids displayed cytoarchitecture consistent with developing midbrain. Neural progenitor and dopaminergic markers were positive in a time-dependent manner, with mature dopaminergic neurons detected by day 30. GFAP-positive astrocytes appeared around day 100. Extracted astrocytes were positive for astrocyte-specific markers.

Conclusions:Sporadic PSP patient hiPSCs reliably differentiate into midbrain organoids, resulting in a model containing key cell-types affected in PSP. This cell collection could be a resource to investigate disease mechanisms and provide insight into cell-type specific drivers.

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UTILIZING INDUCED CARDIOMYOCYTES AND BRAIN ORGANOIDS TO INVESTIGATE MITOCHONDRIAL DISEASE AND CONGENITAL DISORDERS OF GLYCOSYLATION

Graeme Preston, Silvia Radenkovic, Rameen Shah, Irena Muffels, Eva Morava, Tamas Kozicz

BACKGROUND: Mitochondrial disease and congenital disorders of glycosylation (CDGs) are two classes of inborn errors of metabolism which effect thousands of individuals worldwide. Mitochondrial disease affects highly energetic tissues such as the brain and heart, and mitochondrial disease patients experience neurologic and cardiac pathology. CDGs are a group of over 130 disorders characterized by dysfunction in the synthesis, modification, or application of complex sugar glycans to protein molecules, resulting in a heterogenous and multisystem symptomatology, including neuropathy, dystonia, and metabolic dysfunction.

METHODS: Patient fibroblasts, as well as cardiomyocytes (iCMs) and brain organoids differentiated from pluripotent stem cells (iPSCs) induced from fibroblasts collected from individuals with mitochondrial disease and CDG are used to investigate oxygen consumption, ATP synthesis, electron transport chain complex enzymology, contractility/signal transduction, metabolomics, proteomics, , and transcriptomics.

RESULTS: Metabolic profiles of mitochondrial disease fibroblasts and iCMs have been characterized and drug repurposing efforts have identified a number of FDA-approved compounds which are capable of normalizing the metabolic and respiratory profiles in these cells. Robust metabolic and respiratory profiles have been elucidated in multiple CDG fibroblast, iCM, and brain organoid cell lines.

CONCLUSIONS: iCMs provide a robust and clinically relevant model for high energy cell types generally and cardiac tissues specifically in both mitochondrial disease and CDGs. iPSC derived brain organoids are an especially valuable in vitro model as they allow for the investigation into the complex neurologic pathology of rare disorders like MELAS and CDG in an organ which is extraordinarily difficult to assay. iPSC-derived tissues in MELAS also allow for the modeling of gene dose effects by selecting iPSC clones with varying heteroplasmy levels for the mutant allele of interest.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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White Matter Integrity Predicts Recovery Response Time of Deep Brain Stimulation for Depression
Ha Neul Song, Helen S. Mayberg, Ki Sueng Choi

Deep brain stimulation (DBS) targeting the subcallosal cingulate cortex (SCC) has proven effective for treatment-resistant depression (TRD). SCC is structurally connected with other brain regions via white matter (WM) bundles, and stimulation of all connections is crucial for DBS clinical outcomes. Despite consistent SCC targeting, variability persists in the recovery response time across patients, potentially linked to baseline variations in brain abnormalities. This study explores the status of WM integrity and their longitudinal changes in the critical WM pathways.

We assessed the time to reach a stable response in 33 TRD patients receiving SCC-DBS. The study examined the relationship between TSR and baseline fractional anisotropy (FA) of targeted WM bundles. Pearson correlation between TSR and FA along each WM bundle's trajectory was conducted, selecting the area with the maximum r value. Selected FA values in WM bundles served as features for linear regression predicting TSR. In the same areas, longitudinal FA changes were analyzed to compare fast and slow responders.

Our findings reveal a significant correlation between TSR and FA in bilateral midcingulate cortex, bilateral forceps minor, and left uncinate fasciculus adjacent to left hippocampus and left insula. A linear model of FA successfully predicted TSR. Moreover, post-hoc analysis found that the magnitude of FA increases in these regions over 6 months was associated with a faster response.

These findings suggest that WM abnormalities in critical WM bundles undergo repair with chronic SCC-DBS suggesting that DBS may facilitate neuroplasticity changes in selective activated WM pathways. This study sheds light on both sources of individual variability in SCC-DBS response time, as well as a potential mechanism mediating DBS antidepressant response.

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Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Parsing Depression and Social anxiety in Autism through Brain Structure and Social behaviors

Hannah Hao, Sarah M. Banker, Matthew Schafer, Sarah Barkley, Jadyn Trayvick, Arabella W. Peters, Abigaël Thinakaran, Xiaosi Gu, Daniela Schiller, Jennifer H. Foss-Feig

Background: Autism spectrum disorder (ASD) often co-occurs with depression and social anxiety, with amygdala and anterior cingulate cortex (ACC) abnormalities implicated in these conditions. This study examines the relationship between brain volume differences in these areas and their correlation with social power behavior and mental health in ASD.

Methods: A sex-balanced group of 59 high-functioning ASD young adults and 74 typically developed (TD) individuals underwent neuroimaging and social tasks assessing power dynamics, alongside self-reporting depression and social anxiety. Regression analyses accounted for sex, age, IQ, socioeconomic status, and intracranial volume.

Results: ACC volume was significantly reduced in ASD participants compared to TD ($p = 0.043$), with larger ACC associated with depression ($p = 0.006$) and larger amygdala with social anxiety ($p = 0.004$) within the ASD group. Self-reported ASD symptom severity correlated with both depression ($p = 0.002$) and larger ACC volume ($p = 0.034$), whereas clinician-endorsed symptoms did not correlate with these. ASD individuals with depression or social anxiety were observed to exhibit giving less social power in social interactions ($ps < 0.05$). Additionally, smaller amygdala volume was associated with giving lesser power ($p = 0.009$).

Conclusions: The study links ACC and amygdala volumes to depression and social anxiety in ASD, underscoring the role of brain structure in these co-occurring conditions. While correlational, the findings suggest that structural brain differences may represent unique variance in mood and anxiety issues in ASD than social behaviors and ASD symptoms. Future research should investigate the developmental course of the ACC and amygdala in ASD to enhance the understanding of mental health outcomes and social behaviors.

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Understanding the role of EED as an AD risk gene in human microglia

Hyo Lee, Sarah M. Neuner, Gloriia Novikova, Marcelina Ryszawiec, Edoardo M. Marcora, Alison M. Goate

Background: While Genome-wide association studies (GWAS) have identified more than 70 loci associated with Alzheimer's disease (AD), the genes and pathways through which these loci act to modify disease risk remain largely unknown. We previously discovered that AD risk variants are enriched in active enhancers of myeloid cells, implicating gene expression regulation in these cells as critical to disease etiology. Functional genomics analyses identified a novel candidate gene embryonic ectoderm development (EED) as a candidate causal AD gene in the traditionally-annotated PICALM locus, highlighting the importance of considering additional candidates beyond those closest to the GWAS-prioritized SNP.

Methods: We utilized siRNA and CRISPR-based approaches in human immortalized macrophages and induced pluripotent stem cell (iPSC)-derived microglia to understand the functional consequences of loss of EED in myeloid cells.

Results: Here, we showed that EED is involved in phagocytosis of myeloid cells. In response to LPS stimulation, EED RNA levels were increased, and EED relocated from nucleus to cytosol, indicating the importance of the cellular microenvironment to subcellular localization of EED. As EED and related polycomb proteins play important roles in regulation of gene transcription via maintenance of the repressive H3K27me3 mark as well as actin polymerization and intracellular signaling, future work will aim to identify the mechanism(s) by which EED regulates myeloid cell physiology and downstream AD susceptibility.

Conclusion: Overall, our work will provide important insight into the biological mechanisms by which prioritized genes and variants may impact individual susceptibility to AD.

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Timing of clinical symptoms and identification of novel treatment targets for DHDDS variants.

Muffels, I.J.J. Sadek, M., Shah, R., Kantautas, K., Perlstein, E., Kozicz, T., Morava-Kozicz, E.

Background: DHDDS variants are associated with seizures, intellectual disability and movement disorders, with limited treatment options available. Symptom onset is highly variable and underlying pathophysiological mechanisms remain unclear. Intriguingly, while DHDDS produces essential lipid carriers for glycosylation, hypoglycosylation has not been observed in patients.
Methods: First, we studied all literature cases and included 4 novel patients (IRB: 23-00591) to determine timing and onset of clinical symptoms. Next, we employed two model systems to unravel pathophysiology and identify treatment targets, including drug screening with 8.400 FDA-approved compounds in yeast expressing the DHDDS p.R205Q variant. Additionally, patient-derived fibroblasts were developed into iPSC-derived cortical brain organoids where we will perform glycoproteomics, lipidomics and multielectrode assays (MEA).
Results: Literature search yielded 54 patients. The median age of onset was 10 months. Global developmental delay had the earliest onset, while tremor, ataxia, myoclonus, seizures and dyskinesia usually observed around the age of 2 or 3 years. 56% of patients showed a progressive disease course. DHDDS variants were not associated with early- or late symptom onset.
Drug screening in yeast expressing the DHDDS R205Q variant revealed several classes of drugs increasing yeast survival, although not to the level of controls. Most classes interfered with the mevalonate pathway or reduced cholesterol production.
Conclusions: We show that symptom onset is usually observed early in life. Developmental delay is observed first, followed by epilepsy, while ataxia, tremor and dyskinesia develop later. These results can be used to determine a viable treatment window and can help anticipate treatment effects. In yeast, several drug targets were identified, which will be validated in cortical brain organoids, together with studies unraveling the underlying mechanism of disease.

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Post-mortem tissues from the ALS/FTD disease spectrum identify new biomarkers and mechanisms for patient stratification

Jack Humphrey, Towfique Raj

BACKGROUND: Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) are two fatal neurodegenerative diseases with overlapping genetics and pathologies. Nuclear loss and cytoplasmic aggregation of TDP-43 is found in 97% of ALS patients and half of FTD patients. Variability in survival, ranging from months to decades, confounds the organisation of clinical trials.

METHODS: The New York Genome Center ALS Consortium comprises RNA-seq and whole genome sequencing of 2,725 post-mortem human tissue samples from 721 unique donors across 15 brain and spinal cord regions, including patients with ALS, FTD and ALS/FTD. By integrating clinical variables with gene expression, mRNA splicing, and genetic variation, we are mining this resource for translational insight.

RESULTS: We have identified mis-splicing of STMN2 and UNC13A as markers of TDP-43 pathology (Prudencio, Humphrey et al, JCI, 2020; Brown et al, Nature, 2022). UNC13A is a genetic risk locus for both ALS and FTD and is associated with decreased survival, which we demonstrate is mediated by a genetic interaction with TDP-43 pathology. Secondly, we performed transcriptome analysis of FTD cortex/cerebellum (Hasan, Humphrey et al, Acta Neuropathologica, 2022) and ALS spinal cord (Humphrey et al, Nat Neuro, 2023), identifying increases in inflammatory glial cells. In ALS, disease duration was negatively associated with inflammatory microglia. Integrating genetic variants identified several GWAS loci that may act through glial cells.

CONCLUSIONS: Integrating multiple data types in post-mortem tissues has translational value, identifying multiple genes for patient stratification by protein pathology or disease course. We are now working on analysing all post-mortem tissues simultaneously, as well as confirming markers in living patient biofluids, and generating new single-cell-level data. We will discuss this ongoing work.

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Validating mood and anxiety symptom capture in the real-world and exploring the influence of physical activity

J.M. Beltrán, T. Hossain, M.M. Mehta, A.A. Adams, A. Delgado, J.W. Murrough, L.S. Morris

BACKGROUND: Mood and anxiety disorders are highly prevalent, yet poorly understood. Understanding the lived experience and temporal dynamics of symptoms as they relate to 'gold-standard' in-lab measures is critical.

METHODS: To monitor psychiatric symptoms in the real-world, we deployed a smartphone application to N=106 individuals with mood/anxiety disorders (MA) and healthy controls (HC). The app captured novel single-item measures of depression, anxiety and distress along with daily steps data for N=70 after preprocessing (N=34 MA, N=36 HC). Subjects also completed the Mood and Anxiety Symptom Questionnaire (MASQ) in-lab. Mixed-effects models adjusted for time and individual tested the association between daily self-reported symptoms and gold-standard in-lab measures, while Zero-inflated Poisson (ZIP) mixture models adjusted for time, group, and individual tested the association between self-reported symptoms and steps.

RESULTS: After preprocessing, N=101 participant data were available for analysis (N=52 MA, N=49 HC). There was overall moderate adherence over 30-days (MA=69.9%, HC=71.3% completion), with no group difference in adherence ($t(96.8) = 0.36$, $p = 0.72$). Daily real-world single-item measures of anxiety/distress/depression were associated with corresponding in-lab measures within our MA group (MASQ anxious-arousal/distress/depression: $t(46.9)=2.33$, $p=0.024$/$t(46.4)=4.65$, $p<0.001$/$t(46.9)=2.73$, $p=0.009$). ZIP models revealed that step counts were negatively associated with real-world distress and depression (IRR = 0.95, CI = (0.91 -1.00), $p = 0.037$/IRR = 0.93, CI = (0.89 – 0.97), $p =0.002$).

CONCLUSIONS: Preliminary findings suggest the utility of digital phenotyping for accurately monitoring psychiatric symptoms and environmental contingencies that impact mood in a patient population. All updated results will be presented.

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Full Name	Jacqueline Overton
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TITLE: Intracranial Mechanisms of Interoceptive Processing during Slow Breathing

AUTHORS: Overton, Xu, Murthy, Nuñez, Pitts, Marcuse, Mayberg, Figee, Jimenez-Shahed, Saez, Panov, Waters

BACKGROUND:
The profound impact of meditation and slow breathing practices on mental and physical well-being is widely recognized. Despite their therapeutic potential, the neurophysiological mechanisms underlying slow breathing remain poorly understood. Investigating these mechanisms could unveil novel therapeutic avenues for a range of conditions.

METHODS:
In this study, we employed intracranial neurophysiological recordings in human neurosurgical patients with medication resistant epilepsy. Patients engaged in a paced slow breathing exercises while neural activity was recorded with high spatiotemporal resolution. A neural index of interoceptive processing was extracted by time-locking recordings to the r-peak of the cardiac cycle. We compared interoception-evoked potentials, power, and phase coherence during slow breathing to baseline, and for different breathing rates. Anxiety and depression status were examined as potential mediators.

RESULTS:
Slow breathing reduced amygdala interoceptive evoked-potentials by 76% and significantly enhanced theta phase-locking in the insula compared to baseline. Transitioning from 8 to 6 breaths per minute induced significant alpha power enhancement, a decrease in theta phase-locking along with increased phase-locking in alpha and beta bands across the whole brain. Alpha power enhancement was evident in the insula, whereas the amygdala exhibited an enhancement in high gamma.

CONCLUSIONS:
Our findings highlight the intricate neural dynamics underlying slow breathing-induced interoceptive processing. The observed alterations in brain activity, particularly in regions implicated in emotion regulation such as the amygdala and insula, underscore the therapeutic potential of slow breathing interventions for managing stress and enhancing well-being. Understanding these mechanisms may pave the way for personalized therapeutic approaches as well as technology-assisted neurofeedback to increase accessibility of meditation and breathing exercises in neuropsychiatric populations.

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A medial amygdalar- ventromedial hypothalamic circuit drives acute stress-induced hyperglycemia

Jamie R.E. Carty, Kavya Devarakonda, Richard O'Connor, Paul J. Kenny, Sarah A. Stanley

BACKGROUND
The response to environmental stressors is evolutionarily critical and necessary for survival. An essential part of the response to acute stress is the rapid mobilization of glucose for use in escape. Threat-related sensory signaling converges on the medial amygdala (MeA), which sends stress-relevant input to the ventromedial hypothalamus (VMH), responsible for the regulation of metabolic processes. Taken together, we hypothesize that threat exposure activates the MeA to initiate stress-induced hyperglycemia via circuits involving the VMH.

METHODS
We performed in vivo calcium imaging and in vivo optogenetic studies to dissect the MeA-VMH circuit response to different stressors and its role in the induction of hyperglycemia. Using fiber photometry to record calcium signaling in the MeA and in the MeA projections to the VMH, we exposed mice to different sensory stressors and measured the changes in population activity. Using optogenetics, we activated neurons in the MeA and MeA neurons that project to the VMH to examine the effect on glucose, as measured by changes in circulating blood glucose and glucose tolerance.

RESULTS
MeA neurons are activated by different sensory modality stressors, including restraint, shock, territorialized cage, and visual attack stress but not auditory stressors. MeA - VMH projection activity is also increased in response to these stressors. These neurons, when transiently activated, increase circulating blood glucose and alter glucose tolerance.

CONCLUSION
The MeA-VMH circuit activity spikes in response to tactile, olfactory, and visual sensory stressors. These neurons, when optogenetically stimulated to mimic stress-induced activity, signal a stress response and drive stress-induced hyperglycemia. These data suggest that MeA neurons projecting to the VMH induce a rapid elevation of glucose that is needed for an acute response to sensory stressors.

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Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Title:
Unraveling the relationships between childhood adversity, psychopathology, and the rostral anterior cingulate cortex: A transdiagnostic study across diverse non-psychotic psychiatric disorders.

Authors:
van Oort, J., Tendolkar, I., Vrijsen, J.N., Collard, R., Duyser, F.A., Fernández, G., Bachi, K., van Eijndhoven, P.F.P

Abstract:
BACKGROUND: Childhood adversity (CA) is the leading preventable risk factor for mental illness. While CA can lead to affective symptoms and emotion regulation problems across psychiatric disorders, the impact of CA on the brain has been studied almost exclusively in stress-related disorders, such as depression and anxiety disorders. We set out to disentangle the relationships between CA, psychopathology and brain structure across a broader range of psychiatric disorders.
METHODS: We studied 227 patients with stress-related and/or neurodevelopmental disorders and 95 healthy controls. We applied a region of interest approach, focusing on the rostral anterior cingulate cortex (rACC), as this region is highly impacted by CA and has a pivotal role in affective functions across psychiatric disorders.
RESULTS: The presence of CA was associated with decreased left rACC thickness across the whole sample, independent of psychopathology. Moreover, the severity of CA was negatively correlated with the thickness of the left rACC. Additionally, we found an association between the contralateral right rACC and psychopathology, with psychiatric patients having a thinner rACC compared to controls, which was most pronounced in the stress-related group. Importantly, there were no interaction effects between CA and psychopathology.
CONCLUSIONS: These findings support a key role for the rACC in relation to both CA and psychopathology. The impact of CA on the left rACC may contribute to emotion regulation problems that are common across diverse psychiatric disorders. Additionally, we discuss how CA-related changes in brain structure may contribute to specific symptom profiles in different psychiatric disorders.

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Full Name	Jeremy Sherman
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Multimodal RNA-sequencing of the dorsal striatum identifies a link between H3K27 dysregulation and neurodegenerative phenotypes in heroin use.

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Background: The dorsal striatum is a critical structure for the development of habitual and compulsive behaviors, but its molecular pathophysiology relevant to opioid use disorder remains understudied. Methods: We conducted bulk RNA-sequencing of two dorsal striatal subregions and single-nucleus RNA-sequencing to discern subregion and cell-type specific transcriptional changes. Hypothesis: Our previous work identified striatal changes in H3K27 acetylation of genes related to synaptic plasticity, so we hypothesized that these alterations would be specific to medium spiny neurons (MSN), the major striatal cell-type. Results: Bioinformatic analyses revealed a network of genes regulated by the polycomb repressive complex 2 (PRC2) and involved in axon guidance upregulated in the posterior dorsomedial striatum. PRC2 is known to regulate H3K27 and MSN identity. Single-nucleus RNA-sequencing demonstrated a loss of MSN-specific marker expression. Notably, differentially expressed genes in neurons involved in neurodegenerative disorders following heroin self-administration recapitulated bulk RNA-sequencing striatal results from post-mortem human heroin users. The downregulation of MSN-specific markers was reproduced in a separate human single-nucleus RNA-seq dataset. Furthermore, administration of JQ1, a bromodomain inhibitor that blocks the functional readout of genes downstream of the loss of PRC2, reversed effects on genes in neurodegenerative pathways. Conclusions: These results suggest volitional heroin use induces a neurodegenerative-like phenotype in the dorsal striatum through epigenetic mechanisms regulating the post-translational modification of histone H3K27. Implications include potential adverse neurocognitive consequences of chronic opioid use, highlighting the importance of non-opioid treatments for opioid use disorder while the molecular pathways and perturbations identified might serve as novel drug targets.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Department	Psychiatry

Experience-driven visual cortical circuits perturbations in a mouse model of autism

J.Lukin, M.Garcia-Forn, L.Dierdorff, R.Muñoz-Castañeda, W.Wang, Y.Park, P.Ola, Z.Wu, S.De Rubeis

BACKGROUND: Circuits alterations are described in individuals with autism spectrum disorders (ASD) and ASD-relevant genetic mouse models. Mutations in DDX3X cause a neurodevelopmental condition (DDX3X syndrome) often presenting with ASD. Our lab generated the first mouse model for DDX3X mutations and showed that Ddx3x+/- female mice have abnormal neocortical development and present anxiety-like behavior in open field exploration (OF). Understanding how mutations in DDX3X regulates brain circuits might offer a new key to decipher the complexity of circuit alterations in ASD.

METHODS: Using a Ddx3x+/- female mouse line, we 3D-mapped brain neuronal activity after 10min Open Field (OF) exploration combining iDISCO technique, c-Fos immunostaining and light-sheet microscopy to identify affected regions influencing abnormal behaviors. To investigate one of them, the anterolateral visual cortex (VisAl), I performed chemogenetics experiments manipulating VisAl circuits with excitatory/inhibitory DREADDs before OF in Ddx3x+/- and control females. I studied how circuits manipulation affected OF behavior and cFos activation. Additionally, I am investigating VisAl connectivity by injecting anterograde virus carrying GFP in the VisAL and evaluating GFP+ staining in different brain regions.

RESULTS: Ddx3x+/- mice exhibit a distinct pattern of neuronal activation upon OF experience compared to a Ddx3x+/+ control, displaying exacerbated activation in the sensory cortex (e.g. in the VisAl) and lower activity in different brainstem regions. I also confirmed by cFos immunostaining that OF triggers a robust activation of the VisAl. Chemogenetics approach showed VisAl circuits implication in Ddx3x+/- females maladaptive anxiety-like behavior. Viral tracing experiments are ongoing.

CONCLUSIONS: Our findings in the visual cortex provide basis to understand the circuitry behind anxiety-like abnormal behaviors in Ddx3x+/- mice and offer a possible target for a malleable and amenable intervention.

2024 Neuroscience Retreat

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Full Name	Jing Li
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Department	Neuroscience

Dynamic self-efficacy updating as a computational mechanism of mania emergence

Jing Li, Angela Radulescu

BACKGROUND: Bipolar disorder (BD) is a mental health condition characterized by large fluctuations in goal-directed energy and mood. BD is defined by the presence of at least one lifetime episode of mania, a prolonged period of excessive goal-directed behavior, hyperactivity and elevated mood.

METHODS: We use reinforcement learning (RL), a principled model of goal-directed behavior and learning, to show how a model-free Q-learning agent with dynamic self-efficacy beliefs that learns in sequential grid-world environments can give rise to a range of symptoms characteristic of the mania phase of BD.

RESULTS: Our simulations demonstrate that a model-free RL agent that dynamically updates its self-efficacy beliefs learns optimistic overgeneralized value representations. We further show that agents with more sensitive self-efficacy beliefs display increased willingness to exert effort in order to achieve higher goals even in the face of costs, a characteristic that is observed in individuals at risk for BD. Finally, unrealistically high self-efficacy beliefs that emerged with learning were accompanied by behaviors such as distractibility and compulsive action selection that have clinical parallels to symptoms of mania.

CONCLUSIONS: This study aimed to formalize the hypothesis that a higher sensitivity of self-efficacy beliefs to goal-directed feedback could provide a mechanism for the emergence of mania in bipolar disorders. We proposed a computational model based on reinforcement learning that augments model-free RL agents with dynamic self-efficacy beliefs. We showed that, in sequential learning settings, this simple mechanism is enough to give rise to several cognitive and behavioral features observed in mania, including: optimistic overgeneralization of reward expectations; consequent increased drive and motivation for pursuing goals; impatience in pursuing goals; and an increased tendency to exert effort in pursuit of higher and more difficult to attain goals.

2024 Neuroscience Retreat

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Full Name	Johana Alvarez
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Stress promotes peripheral immune interactions at the brain endothelium.
Alvarez J, Cathomas F, Chan KL, Parise LF, Ramakrishnan A, Estill M, Russo SJ

BACKGROUND: Chronic psychosocial stress is a significant risk factor for the development of stress-associated psychiatric disorders, including major depressive disorder, which causes profound debilitation and has increasing worldwide prevalence. Pre-clinical and clinical studies have linked peripheral immune system alterations to stress-related disorders, such as elevated levels of proinflammatory immune cells and cytokines in circulation. Endothelial cells are critical components of the blood-brain barrier (BBB), as they interface directly with immune cells and their released factors, which can enter the brain parenchyma to regulate local neural activity. Current research suggests region-specific differences in brain endothelial permeability, which may be related to differences in the local production of chemoattractants and adhesion molecules for immune cells after chronic psychosocial stress. A causal mechanistic understanding of how these changes occur in stress-responsive brain regions, including the nucleus accumbens (NAc), is not fully demonstrated.

METHODS: Endothelial cell mRNA was collected from the NAc of male mice following chronic social defeat stress (CSDS) using translating ribosome affinity purification. Differential gene expression analysis between stress-susceptible, resilient, and control animals was completed in R using DESeq2. Gene set enrichment analysis was investigated using Enrichr and Ingenuity Pathway Analysis.

RESULTS: Following RNA sequencing and analysis, we observe that CSDS strongly affects NAc endothelial cells, such that stress-susceptible mice display an increased expression of genes associated with endothelial cell junction organization and adhesion compared to stress-resilient and control mice.

CONCLUSIONS: Current work aims to virally manipulate the expression of endothelial-specific genes related to immune cell recruitment to the endothelium and BBB permeability. This work will uncover unique mechanisms through which endothelial cells respond to chronic stress and provide insight for developing novel therapeutics for stress-associated psychiatric disorders.

2024 Neuroscience Retreat

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Full Name	Jonadab Dos Santos Silva
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In Newly Diagnosed Multiple Sclerosis, Cortical Lesions are Prevalent and Associated with Worse Cognitive Performance

Jonadab dos Santos Silva, Francesco La Rosa, Julia Galasso, Emma Dereskewicz, Faye Bourie, William A Mullins, Govind Nair, James Sumowski, Erin S Beck

Cortical lesions (CL) are common, widespread, and connected to worse physical and cognitive outcomes in multiple sclerosis (MS). 7T MRI has greatly improved CL detection and shown that CL burden predicts clinical deterioration. In newly diagnosed MS people, we wanted to investigate CL prevalence and its link to physical and cognitive performance.

Participants underwent physical and neuropsychological evaluations and 7T brain MRI (MP2RAGE and T2*w-GRE). Using 0.7mm3 T1w-MP2RAGE images, we performed brain tissue and white-matter lesion (WML) segmentation. Two blinded raters manually segmented CL using the 0.5mm3 T1w-MP2RAGE and T2*w-GRE.

Twenty-two MS/CIS participants within a year of diagnosis (age 33±5years, 81% female) and 12 healthy volunteers (age 30±8years, 62.5% female) were included. CL were found in 86% of MS participants (median 19 lesions [range 0–63]). Most CL were subpial (median 67% [range 0–100%]), and 77% of MS participants had at least one CL while HV had none. CL and WML volumes were similar and correlated ($r=0.60$, $P<0.001$). Despite this resemblance, higher CL (but not WML) burden was linked with lower brain volume ($r=-0.64$, $P=0.02$) and worse cognitive performance ($r=-0.70$, $P=0.006$), adjusted for age and sex. WML volume was linked with total cortical ($\rho=0.62$, $P=0.033$) and subpial lesion volumes ($\rho=0.61$, $P=0.033$). Higher leukocortical lesion volume was associated with worse verbal memory ($r=-0.61$, $P=0.02$), adjusted for age and sex.

Most newly diagnosed MS patients have cortical lesions, which are related to poorer cognitive performance and lower brain volume. In early MS, CL and WML are similar, suggesting that most CL form early. Early CL detection may inform clinical decisions and mitigate MS cognitive decline.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Kelsey Aguirre
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Department	Psychiatry

Title: The Effects of Deep Brain Stimulation on Choice-Behavior Modeling in Reversal-Learning for Severe OCD

Authors: Kelsey Aguirre, Amber McLaughlin, Andrew Smith, Vincenzo Fiore

Abstract: Obsessive-compulsive disorder (OCD) is a common, chronic, and long-lasting disorder in which a person has uncontrollable, reoccurring thoughts (“obsessions”) and/or behaviors (“compulsions”) that the person feels the urge to repeat over and over. In severe cases, OCD can cause an impaired ability to adapt to changing conditions and reversal-learning tasks have been used to compare and further understand the deficits of cognitive flexibility in patients with severe OCD.

In this study, we tasked N=10 patients diagnosed with severe OCD symptoms (YBOCS >24) with a 3-option reversal learning task (4 blocks of 20 trials each, 1.25 reversals on average per block). We compared three different models of choice selections, in which behavior was modeled as controlled by: 1) simple heuristic (the probability to either switch or repeat a choice would increase or decrease by a fixed amount); 2) Reinforcement learning (the values estimated for each available choice were updated following a classic reward prediction error); 3) static Bayesian inference (a single parameter was used to control the pace of belief updating, which was considered fixed per subject, BIC = 62.2); 4) Dynamic belief updating, in which the pace of belief updating varied, trial-by-trial, as a function of the confidence in prior beliefs. Model comparison with BIC score revealed the fourth construct was associated with the highest precision in predicting choice behavior.

This result suggest the update of beliefs in OCD participants varies as a function of their own confidence, with possible implications for our understanding of the neurocomputational mechanisms underlying the disorder.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Kenny Chan
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Stress-activated brain-gut circuits disrupt intestinal barrier integrity and social behavior

Kenny Chan, Long Li, Lyonna Parise, Flurin Cathomas, Katherine LeClair, Yusuke Shimo, Hsiao-Yun Lin, Romain Durand-de Cuttoli, Antonio Aubry, Johana Alvarez, Tory Drescher, Aya Osman, Chongzhen Yuan, Rachel Fisher-Foye, Manuella Kaster, Glaucia Furtado, Sergio Lira, Jun Wang, Wenfei Han, Ivan de Araujo, Scott Russo

BACKGROUND: Major depressive disorder (MDD) represents the leading cause of disability worldwide. Emerging literature recognize a correlation between MDD and chronic low-grade inflammation; however it is not fully known how this inflammation is initiated. Recently, several inflammatory conditions have been associated with increased intestinal permeability. We hypothesize that chronic psychosocial stress disrupts gut barrier integrity, allowing translocation of gut microbial byproducts into circulation, triggering systemic inflammation associated with depression-like behavior.

METHODS: To capture behavioral and biological changes relevant to human psychiatric disorders in mice, we used the chronic social defeat stress (CSDS) paradigm. We measured gut inflammation by flow cytometry, and intestinal permeability by orally gavaging mice with FITC-Dextran. To identify neurocircuitry regulating stress-induced intestinal pathophysiology, we used retrograde tracing and chemogenetic strategies to manipulate brain-gut circuits.

RESULTS: Mice exposed to CSDS showed increased pro-inflammatory Th1 cells and decreased anti-inflammatory Th2 cells in the colon compared to unstressed control mice. Moreover, stressed mice exhibited greater intestinal permeability, along with elevated circulating lipopolysaccharide (LPS) levels. Using retrograde tracing from the enteric neurons in the colon, we found that corticotropin-releasing hormone (CRH)-expressing neurons in the paraventricular nucleus of the hypothalamus (PVH) innervate the gut. Using chemogenetic manipulation of PVH CRH+ neurons, we found that these neurons can regulate intestinal inflammation, barrier permeability, and social avoidance induced by CSDS.

CONCLUSIONS: Collectively, our results illustrate a brain-gut circuit where stress activates specific neurons in the brain to trigger intestinal inflammation and disrupt intestinal barrier function, potentially promoting depression-like behavior.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Sexually divergent traits in approach/avoidance biases transmute the psychedelic experience.

Kinneret Rosen1, Clementine Blaschke1, Tamara Markovic1, Angelica Minier-Toribio1, Arthur Godino1, Giselle Rojas1, Eric Nestler1. 1Mount Sinai.

Effective decision-making strategies are crucial for adaptive behavior and rely on emotional regulation. Sex-specific maladaptive decisional biases, featured in anxious and depressive traits, shape differential approach and avoidance (A/A) strategies. These manifestations result in unique neurobiological and behavioral profiles that are decisive in neuropsychiatric diagnosis. Females emerge as most vulnerable, exhibiting heightened stress susceptibility and a greater prevalence of depression. Converging evidence implicates serotonin (5HT) neurotransmission in medial prefrontal cortex (mPFC) in processing such reward vs threat scenarios, and sex differences in mPFC 5HT2A receptor binding affinity may coordinate A/A strategies. Fittingly, psychedelics are under study for managing treatment-resistant depression via 5HT2AR agonism, representing a promising and timely tool to understand depressive-like behaviors exhibiting sex-related divergence. Here, we highlight baseline sex-differences in A/A conflict and demonstrate that administration of the psychedelic compound, LSD, induces dynamic, anxiety- and depression-like phenotypes, with dramatic sex-specificity. By use of in vivo photometry, we identified sex differences in baseline mPFC 5HT release driving reward-approach strategies during A/A conflict, a phenomenon exacerbated following LSD treatment. Further, reduced avoidance behavior triggered by repeated LSD administration reflects changes in mPFC reward-related 5HT neurotransmission in females, but not males. Given that dysregulation of mPFC 5HT neurotransmission is a hallmark of several psychiatric disorders, and that psychedelics show promise in treating some of these illnesses, our findings provide fundamental insight into a region- and sex-specific alteration that may impact therapeutic outcomes in clinical applications.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Kion Winston
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Perturbation of Genes Specific to Oxidative Phosphorylation in Relation to Opioid Exposure

Kion Winston, Jeremy Sherman, Randy Ellis, Tanni Rahman, Joseph Landry, James Callens, Jacqueline Ferland, Alex Chisholm, Teesta Naskar, Yasmin L. Hurd

The opioid epidemic has continued to be a major public health issue within the United States. Many of the current treatments available have aimed at mitigating the cravings associated with opioid use disorder leveraging other opioids. Long term exposure remains a consequence of these current strategies. Retrospective studies into electronic health records demonstrated an increased likelihood of neurocognitive disease within individuals with opioid exposure. Potential mechanisms facilitating this vulnerability though remain unclear. Utilizing bulk RNA-sequencing, we measured fluctuations in gene expression in the human dorsal striatum, a region implicated in both goal directed and habitual behaviors. In addition to replicating previous findings relevant to behaviors related to the effects of opioids, we also identified genes responsible for oxidative phosphorylation and the electron transport chain to be altered. These genes, which were predominantly downregulated, were also found to be enriched in KEGG ontology pathways related to several neurodegenerative diseases such as Alzheimer's and Parkinson's. In a preclinical model, we employed a self-administration approach in rats to elucidate whether changes observed in these oxidative phosphorylation specific genes were a product of acute heroin exposure or long-term changes specific to behavior. Quantitative polymerase chain reaction demonstrated a trending change in some of the genes of interest specific to oxidative phosphorylation within the dorsal lateral striatum. Finally, a correlation matrix revealed a relationship between our genes of interest and the amount of heroin consumed, with the relationship being stronger 24 hours following exposure versus 1 hour. These findings suggest mitochondrial perturbations as a consequence of repeated opioid exposure that might relate to neurodegenerative phenotypes that will be tested in future studies.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Kohei Yoshitake
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Department	Psychiatry

Retrosplenial cortical ensemble regulates social distance in mice

Kohei Yoshitake*, Camille Casino*, Justin Riceberg, Tadaaki Nishioka, Nanami Kawamura, Hirofumi Morishita (*equal contribution)

BACKGROUND
Animals regulate the distance between themselves and others during social interaction. Social interactions with others require perception and control of social distance. Of note, dysregulation of social distance is implicated in psychiatric disorders including schizophrenia and autism spectrum disorder. However, little is known about the specific neural circuit mechanisms causally regulating the social distance with conspecifics. Here, we aimed to identify specific cortical ensemble in control of social distance using a mouse model.

METHOD
Mesoscopic whole-cortex calcium imaging was employed to ident Fiber photometry imaging was conducted from the identified cortical area during social interaction. Social distance and associated behaviors were quantified using the deep learning-based tool SLEAP. Chemogenetic approach was utilized to examine the causal contribution of the cortical area to social distance regulation. The Fast Light and Calcium-Regulated Expression (FLiCRE) system was used to examine if the cortical ensemble activated by social distance shrinkage can directly regulate social distance.

RESULT
Mesoscopic calcium imaging revealed that the medial retrosplenial cortical area (mRSA) is particularly responsive to an approaching visual stimulus. We further found that RSA activity is sensitive to social distance changes during free-moving social interactions, and that chemogenetic modulations of RSA neuronal activity bi-directionally change the social distance. FLiCRE system revealed that a specific mRSA ensemble, which includes sub-cortical projections, is activated by a close proximity of another mouse to increase social distance.

CONCLUSION
These results suggest that mRSA acts as a hub for sensory-motor transformation to regulate social distance with conspecifics, laying the groundwork for future studies that expand the analysis to inputs and outputs of the RSA at the brain-wide network.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Lailun Nahar
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Department	Neuroscience

In Vivo Characterization of A New Fluorescent Oxytocin Peptide Sensor for Social Behavior

Lailun Nahar, Ian Glaaser, Paul Slesinger

BACKGROUND: Oxytocin is a neuropeptide and hormone that plays a crucial yet complex role in various biological, cognitive-behavioral, and social functions. Dysfunctions in oxytocin signaling are implicated in psychiatric conditions such as autism, mood disorders, and substance abuse, of which treatments are limited. Oxytocin's vast therapeutic potential warrants investigation of how it modulates neuronal activity and behavior. To facilitate this investigation, genetically-encoded fluorescent sensors have been developed to detect oxytocin in real-time but their spatial and temporal resolution are limited. A new GFP-based GPCR sensor, MTRIA-OT, has been reported to detect oxytocin in vivo. However, its ability to detect oxytocin in key brain regions that are known to have oxytocin signaling and overlap in many psychiatric conditions, such as the VTA, need to be confirmed to further advancements.

METHODS: We obtained the MTRIA-OT cDNA created by the Hibino lab, generated AAV2/8, and stereotaxically injected into the VTA of C57BL6 mice. Fiber photometry and social behavioral paradigms were used to examine real-time changes of endogenous release of oxytocin. Optofluidic fiber photometry was used to apply exogenous oxytocin locally in the brain and test the sensor's ability to detect oxytocin.

RESULTS: The sensor responded to exogenous local oxytocin in a dose-dependent manner. Detection of endogenous oxytocin while simultaneously employing behavioral paradigms were variable.

CONCLUSIONS: It is imperative to characterize the properties of the MTRIA-OT sensor to validate its universal efficacy and thus understand and accurately depict the causal role of oxytocin in neuronal and behavioral functions across brain regions and brain states. Local administration of exogenous oxytocin that complement biologically relevant levels in specific brain regions or during behaviors may help provide more information on its mechanism of modulation.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Motor deficits in a mouse model of DDX3X syndrome: molecular to circuit level approaches

L.Dierdorff, J.Lukin, M.Garcia-Forn, Y.Park, P.Ola, S.De Rubeis

BACKGROUND: DDX3X syndrome is a monogenic form of ASD that affects primarily females and presents with motor impairment. DDX3X syndrome is caused by mutations in the X-linked RNA helicase DDX3X, known to regulate mRNA metabolism. Circuits underlying the motor phenotype in DDX3X syndrome, however, are unexplored. We generated a Ddx3x+/- haploinsufficient mouse with construct and face validity for loss-of-function mutations. Ddx3x+/− females have motor deficits and misplacement of subcerebral projection neurons (scPNs) in primary motor cortex (M1), which are important for motor function. Corticopontine projection neurons are one type of scPN may be particularly vulnerable to Ddx3x mutations as they initiate the cortico-ponto-cerebellar pathway.

METHODS: To measure the impact of Ddx3x haploinsufficiency on the translatome of corticopontine projection neurons I employ a TRAP technique, which enables the isolation of translating mRNA transcripts that can be quantitatively measured by RNAseq. To investigate corticopontine circuits, I inject a retrograde virus carrying GFP into pontine nuclei,perform the rotarod test, and stain for the immediate early gene c-Fos to as a proxy for corticopontine neuron activation in control and Ddx3x+/− females. Finally, I employ chemogenetics to investigate whether DREADDs can ameliorate cellular activation and subsequently motor performance.

RESULTS: I have established a corticopontine-specific Ddx3xflox;Colgalt2-TRAP DU9 mouse and have validated that EGFPL10a is expressed in corticopontine neurons innervating pontine nuclei. I am performing IPs and RT-PCR to detect corticopontine-specific mRNAs and EGFP mRNA. Following rotarod behavior, Ddx3x+/- mice exhibited fewer cFos+ positive neurons in layer V of M1 and decreased latency to fall. I am assessing the effects of activating DREADDS in corticopontine neurons on rotarod outcomes.

CONCLUSIONS: Motor circuits in Ddx3x+/- mice are altered functionally following behavior, and these findings motivate further investigation.

2024 Neuroscience Retreat

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microRNA Regulation of Transcriptomics in Molecular Subtypes of Alzheimer's Disease

Linh Chu, Marjan Ilkov, Ryan Neff, Erming Wang and Bin Zhang

Background: MicroRNAs (miRNAs) are short non-coding RNA molecules that play a critical role in gene transcription. Differentially expressed miRNAs (DEmiRNAs) in the brain between AD and healthy control are involved in amyloid pathology, tau phosphorylation, inflammation, oxidative stress, and mitochondrial dysfunction. Our previous work based on large-scale transcriptomic data in multiple brain regions systematically identified five molecular subtypes of AD. This present study aims to understand the microRNA alterations and regulations of transcriptomics in AD.

Method: We employ a framework that include matched miRNA and mRNA sequencing in the prefrontal cortex from 183 control and 313 AD subjects from the Religious Orders Study - Memory and Aging Project (ROSMAP) cohort. Two approaches further dissect the underlying regulatory mechanism of miRNA: 1) study the targets of DEmiRNAs and 2) examine the targets of "influential" miRNAs that have widespread impacts on multiple subtypes. We also validate the predicted targets of miRNAs by comparing the targets of certain candidate miRNAs to previously published AD perturbation signatures in mouse models.

Results: Pathway analysis highlights common and subtype-specific signatures. The positively correlated genes of hsa-miR-132 in the turquoise and yellow subtype are enriched for 20% of the downregulated genes in the AAV-mediated VGF overexpression signature, and these enriched targets are involved in synaptic signaling. Additionally, the positively correlated genes of hsa-miR-223 in the blue and yellow subtype are enriched for approximately 50% of the downregulated genes in the absence of TYROBP signature and these enriched targets are associated with immune responses.

Conclusion: The miRNA-mRNA co-expression networks in AD subtypes offer a new avenue to understand the molecular mechanisms of AD and pave a way for developing novel and personalized therapeutics for AD.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Lyonna Parise
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Alterations to the Blood-Brain Barrier Promote Changes in Alcohol preference.

Lyonna F. Parise, Kenny Chan, Flurin Cathomas, RomainDurand-de Cuttoli, Antonio V. Aubry, Johana Alvarez, Tory Drescher, Rachel Fisher-Foye, Long Li, Hsiao-Yun Lin, Arman Tavallaei, Scott J. Russo

Background: Major depression is a serious public health concern and is commonly comorbid with alcohol use disorder. Interestingly, these highly prevalent syndromes share many similarities when it comes to pro-inflammatory peripheral immune activation suggesting that at least in part, subsequent maladaptive behaviors are driven by a breakdown of the blood brain barrier (BBB), which can facilitate the infiltration of peripheral inflammatory factors. We assessed drinking behavior, stress reactivity, BBB permeability, and peripheral cytokine/chemokine profile after chronic moderate binge drinking, in male and female mice.

Methods: After 4 weeks, alcohol was discontinued and mice were left undisturbed for 2 weeks. At this time, all mice were exposed to a microdefeat and behavioral reactivity was assessed. Peripherally injected Evans's Blue (EB) dye was used to assess BBB permeability. In a separate group of mice, the tight junction protein, Claudin 5, was virally knocked-down to assess whether directly altering tight junction expression would influence alcohol preference.

Results: Surprisingly, male but not female mice showed increased stress susceptibility when exposed to a subthreshold stressor. Accordingly, only male mice showed increased infiltration of EB after 4 weeks of alcohol exposure or after a stress challenge. Interestingly, only male mice had decreased expression of the tight junction protein Claudin 5 whereas neither male nor female mice showed decreased expression within the prefrontal cortex. Additionally, Male mice are more sensitive to changes in alcohol preference as a consequence of tight junction protein manipulations.

Conclusions: These data suggest that alcohol-induced stress-susceptibility occurs in both a sex- and region-specific manner and can be mediated by reduced integrity of the BBB.

2024 Neuroscience Retreat

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Investigating Effects of Oxidative Stress on an Inducible Tau Aggregation Model

Lyucheng Zou, Marcos Schaan Profes, Kurt Farrell, John F. Crary

BACKGROUND: Tauopathies are neurodegenerative disorders characterized by pathological modifications of tau protein deposited at various brain regions, with tau hyperphosphorylation and aggregation being the most prominent feature. However, the molecular pathways linking tau aggregation and neuronal loss remains elusive. Multiple studies have suggested a possible crosstalk between oxidative stress and tau aggregation, and mixed opinions were given regarding the upstream or downstream effect of oxidative stress on tau aggregation. In our study, we aim to investigate how oxidative stress manipulation can affect tau aggregation in our cellular optogenetic inducible tau aggregation (Opto-tau) system.

METHODS: Our group created an Opto-tau system in which tau are fused with Cry2, that will oligomerize upon blue light activation. Expression of this construct in immortalized cell lines allows for tau aggregation induction with high spatiotemporal resolution. Stable inclusion is observed in live-imaging and the presence of oligomers are confirmed in western blot on transfected HEK293 cells with blue light stimulation. We will use this model to test effects of oxidative stress driver, such as H2O2, or reactive oxygen species (ROS) scavengers, including ascorbic acid, on tau aggregation in our opto-tau system by comparing the oligomerization level of tau in live-imaging, immunocytochemistry, and western blot. Key players involved in ROS clearance and proteolytic pathways will also be assayed.

RESULTS: We hypothesize that ROS inducers will worsen the level of aggregation, but ROS scavengers can relieve or slow down protein aggregation.

CONCLUSIONS: This study permits us to know how oxidative stress can affect tau oligomerization in a pro-aggregating condition. Studying pathways involved in ROS clearance can provide mechanistic insights for relieving aggregation in tauopathies.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Madeline Bacon
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Chemotagging: a method to identify cell types in vivo with Miniscope calcium imaging

Authors: Madeline Bacon, BumJin Ko, Yosif Zaki, Denise J. Cai

Background: Single-photon miniscope technologies are commonly used to record calcium dynamics from thousands of cells in vivo in freely behaving mice. Current tools are limited to recording from one broad cell population, sacrificing the ability to target subtypes of cells. Recording from one subset of cells is possible, but at the loss of observing activity from other cell types. Here, we present a novel technique to record calcium dynamics from one broad population of neurons before post-hoc identifying a cell subtype of interest using chemogenetics.

Methods: We recorded calcium dynamics from neurons while identifying the inhibitory neurons among the recorded population. Using Gad2-Cre mice, we co-infused a viral cocktail of Cre-dependent hM3Dq-mCherry and synapsin-driven GCaMP into the dorsal CA1 of the hippocampus and implanted a lens, allowing us to record calcium dynamics from all neurons and to excite specifically inhibitory neurons. We demonstrate that exciting the inhibitory neurons (using an hM3Dq agonist) robustly drives calcium oscillations in a subset of recorded neurons, serving as an identifying feature to tag these neurons in vivo.

Results: To confirm that only GAD+ neurons exhibited calcium oscillations we imaged hippocampal slices from Gad2-Cre mice expressing Cre-dependent hM3Dq-mCherry and synapsin-driven GCaMP. After bathing on hM3Dq agonist, we confirmed the calcium oscillations were confined to mCherry+ cells. To validate that the hM3Dq virus had only expressed in GAD+ neurons, we post-hoc immuno-stained the tissue for GAD expression and confirmed significant overlap between immuno-stained GAD and mCherry.

Conclusions: This novel approach offers a way to identify and record activity from multiple cell types in vivo using single-photon Miniscopes and can be expanded to be used with any genetically defined ensembles of neurons.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Frontiers in Brain Metabolism: Updates and Innovations from the Neurometabolomics & Neurobioinformatics Core

Manuel Gonzalez-Rodriguez, Jake Vaynshteyn, Isaac Marin-Valencia

BACKGROUND: The field of neurometabolism has seen a surge in scholarly interest, paralleling important domains like cancer biology or immunology. The complex interplay of metabolic variables and the demanding nature of interpreting metabolic data from the brain frequently pose challenges to research teams, hindering their ability to forge significant breakthroughs. Our mission is to continue expanding our educational platform, analytical methods, and data analysis tools to offer increasing support to the research community at Mount Sinai and abroad.
METHODS: Over the past year, we have developed new mass spectrometry methods, bioinformatics pipelines, statistical modeling, and interactive apps to better analyze the metabolic architecture of nervous system and provide a better and more efficient service.
RESULTS: In the calendar year of 2023, we provided support for twenty-one projects, with the majority (76%) originating from Mount Sinai, with contributions from Yale University (5%) and Columbia University (9%). We have conducted twenty-two consultative sessions through our dedicated clinic and have been instrumental in the development and submission of various grants, including three R01 grants, one K08, and two foundation grants. In addition, we have established three innovative mass spectrometry protocols tailored for the analysis of fatty acids across different chain lengths, from short to very long chains. Furthermore, we have launched five web-based applications aimed at streamlining data analysis, facilitating the drafting of recommendation letters, and simplifying the budgeting process for grant applications.
CONCLUSIONS: Our core facility transcends the traditional role of a service entity. We are committed to streamlining users' investigative processes to accelerate discoveries. Our goal is to demystify the field of neurometabolism, making it more accessible and practical in the quest to address neurological disabilities of people with brain metabolic diseases.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Marco Rizzo
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Effects of maternal depression at delivery on children neurodevelopment: an EEG pilot study
Rizzo M, Tubassum R, Kaplan C, Castro J, Rommel AS
BACKGROUND: Antenatal maternal depression represents a global health concern, impacting pregnant women and their children. Evidence suggests that maternal depression during pregnancy adversely affects child development, influencing cognitive and psychosocial domains. The prenatal period is a critical phase for child neurodevelopment, where maternal depression emerges as a risk factor for neurodevelopmental disorders, including autism spectrum disorder (ASD). This pilot study aims to explore the consequences of antenatal maternal depression on children neurodevelopment.
METHODS: Participants were recruited from the Generation C cohort. To assess depressive symptoms during pregnancy, ten mothers retrospectively completed the Edinburgh Postnatal Depression Scale (EPDS). The EPDS scores range from 0 to 30, with a score ≥ 13 indicating an elevated risk of developing depressive syndrome. Electroencephalographic (EEG) data were recorded from children (mean age 3.34±0.19) while performing an inhibitory control task (Go/No-Go) and a face-processing task. The Go/No-Go task elicits the N2, an event-related potential (ERP) associated with response inhibition. The face-processing task elicits the face-specific N170 component. Parent-reported Social Responsiveness Scale (SRS) was administered to measure autism-like traits in children. Linear regression will test the hypothesis that higher EPDS scores are associated with lower ERPs amplitude, lower accuracy during the tasks, and higher scores in the SRS (typically observed in children with ASD). The analysis will be adjusted for fetal sex and gestational age at birth covariates.
RESULTS: Regression coefficient (CI 95%) and p-value will be reported for ERPs amplitudes, response accuracy, and SRS scores. We aim to present the results at the 16th Annual Neuroscience Retreat.
CONCLUSIONS: This pilot study aims to elucidate the dynamics of prenatal maternal depression effects on children neurodevelopment, introducing electrophysiological (EEG) metrics as a dimension of investigation.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Marcos Schaan Profes
Job Title	Postdoctoral Fellow
Lab	Crary Lab
Department	Pathology

Modeling tau aggregation using cryptochrome 2-based optogenetic system

Marcos Schaan Profes, Lyucheng Zou, Kurt Farrell, John F. Crary

BACKGROUND: The molecular etiology of neurofibrillary degeneration remain poorly understood, reflecting in the low success of clinical trials. Our group performed GWAS using tau as a quantitative trait and have identified JADE1 as potentially neuroprotective. Thus, there is a critical need to better understand the molecular basis of tauopathies.

OBJECTIVE: to develop a reliable tau aggregation system that will help in investigating the differences in tau aggregation kinetics, the burden of tau isoforms, and mutations and that will be suitable for high-throughput analysis of tauopathy-associated factors, through optogenetics.

METHODS: We developed a cellular model using the light-activated CRY2 protein to enable spatiotemporal control over tau aggregation. We will use CRY2-tau constructs to assess aggregation kinetics and cellular burden due to imbalances in tau isoforms and mutations. Tauopathy-associated factors will be assayed with biochemistry, and challenge optogenetic tau aggregation with their overexpression and knockdown.

RESULTS: overexpression of our construct, showed mCherry stable tau inclusions after light stimulation, which are not present when the backbone alone is transfected and are less frequent without light stimulus. These inclusions where phosphorylated as assessed by immunocytochemistry and western blotting confirmed the presence of aggregated tau. Live-imaging highlighted differences in light-induced tau levels kinetics when comparing different tau proteoforms. JADE1S overexpression elicits a 4R Tau-specific reduction in light-induced tau levels. These data strongly support the feasibility of generating tau aggregates in our cellular system and suggests an implication of JADE1 in tau proteostasis.

CONCLUSIONS: This system has the potential to enhance the screening process of tau aggregation drivers allowing to analyze in real-time tau aggregation and being compatible to be performed in parallel with biochemical assays. This model could also pose a new suitable model for drug screening.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Marianna Liang
Job Title	PhD student
Lab	Zhenyu Yue/ Nan Yang
Department	Neuroscience

Characterization of a novel vulnerable neuron type in Parkinson's disease

Marianna Liang, Xiaoting Zhou, Insup Choi, Qian Wang, Minghui Wang, Wei Wang, Lily Sarrafha, Lap Ho, Kurt Farrell, Kristin G. Beaumont, Robert Sebra, John F Crary, Tim Ahfeldt, Joel Blanchard, Drew Neavin, Joseph Powell, David A. Davis, Xiaoyan Sun, Zhuhao Wu, Bin Zhang, Nan Yang, and Zhenyu Yue

BACKGROUND: Parkinson's disease (PD) is the second leading neurodegenerative disorder characterized by degeneration of neuromelanin-containing dopaminergic (DA) neurons in the substantia nigra (SN). Whether non-DA neurons are vulnerable in PD is poorly understood. We previously generated snRNAseq data from aged human SN in healthy controls and idiopathic PD. Immunostaining and validation against independent datasets resulted in the identification of molecularly distinct subtypes of DA-related neurons, including a RIT2-enriched population. RIT2 was previously identified as a PD risk gene with RIT2 variants being linked to PD. Validation in mouse and human SN identifies a RIT2 population that partially overlaps with TH, with the RIT2+/TH- subpopulation found to be vulnerable in PD.

RESULTS/METHOD: To investigate the RIT2-enriched population we generated a RIT2-Cre mouse to label RIT2+ populations by crossing with Ai9 reporter mouse or by injection with AAV fluorescent reporter into the SN. Vast distribution of RIT2+ cells is observed in regions of the midbrain, neocortex, and dentate gyrus. A RIT2+/TH- subpopulation in mouse SN was found mainly localized in the lateral portion. With these models we characterize this RIT2-enriched population in the whole brain as well as the SN.

CONCLUSION: We previously identified distinct DA neuronal subtypes in the SN. Of particular interest is a RIT2-enriched neuronal population that partially overlaps with TH in the SN with vulnerability in PD. It is not known whether non-DA neurons are also vulnerable in PD. This study characterizes the novel vulnerable RIT2-enriched population in the SN.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Marjorie Xie
Job Title	Postdoctoral Researcher
Lab	Angela Radulescu and Xiaosi Gu Labs
Department	Psychiatry

Title: Effects of attention and learning on mood dynamics

Authors: Marjorie Xie, Xiaosi Gu, Angela Radulescu

BACKGROUND: Mood instability pervades psychiatric disorders, necessitating a causal understanding of mood in terms of its function for the organism and its dependencies. Informational accounts depict mood as a signal used for decision-making, reflecting positive/negative alignment between the environment and the organism's goals. Reinforcement Learning (RL) models have described mood as tracking the mismatch between expected and actual reward, or reward prediction errors (RPEs) (Eldar et al., 2016). While RL holds potential for causal explanations, existing models focus on tasks with simple reward structures, neglecting mechanisms of real-world decision-making. In naturalistic environments, attention influences predictions by selecting subsets of features for decision-making, biasing value and RPE signals in the brain (Leong et al., Radulescu et al., 2019). Here, we investigate how attention and learning shape mood dynamics.

METHODS: We simulate an RL agent learning a contextual bandit task similar to that in Leong et al., and following Eldar et al., we define mood as a recency-weighted average of RPEs. To test how the breadth of attention changes mood dynamics, we define two attentional strategies: agents with narrow attention only learn about one feature of the state, while agents with broad attention learn about all features.

RESULTS: We find that broadening attention increases variability in RPEs, and thus variability in mood dynamics. The relationship between attention and mood depends on both the agent's attentional strategy and the statistics of reward in the environment: in deterministic environments, narrow attention leads to mood stabilization and broad attention leads to mood instability; in probabilistic environments, broad attention also leads to transient mood dynamics, albeit in service of better task performance.

CONCLUSION: Our work offers a novel perspective on mood dynamics in terms of attention, reward statistics, and uncertainty.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Mason Dallegge
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Lab	Waters Lab
Department	Neuroscience

EEG-Guided Neuromodulation to Enhance Deep Sleep in Parkinson's Disease

Mason Dallegge, Sanjana Murthy, Emmanuel During, Joohi Jimenez-Shahed, Allison C. Waters

Background: In Parkinson's disease (PD), sleep disruption is common and often associated with symptoms of insomnia and daytime sleepiness, which contribute to reduced quality of life and are associated with a worse prognosis. However, safe and effective therapies are currently limited.

Transcranial Electrical Stimulation (TES) has shown promise in enhancing both objective and subjective sleep quality. Previous studies have demonstrated its ability to increase total sleep time (TST), enhance deep (N3) sleep, and reduce daytime sleepiness. However, its appropriateness has not been fully examined within PD, despite its direct relevance to the underlying deficits that contribute to sleep disruptions present in the patient population.

Methods: Patients diagnosed with PD are recruited for participation in a one-week experimental design. They are provided with an at-home sleep TES apparatus (Sleep WISP) consisting of a bedside nanocomputer and EEG/TES capable headband. The technology detects precursors to deep sleep and then administers alternating current to entrain slow wave oscillations. The study design includes two nights of acclimatization, two nights randomized between sham-TES and experimental intervention, and two final nights of applied TES.

Results: While the primary outcome of this study is to assess feasibility of device usage in this patient population, we also report on changes in objective and subjective indices of sleep quality. These include changes in sleep architecture, duration of N3 sleep, daytime activity (actigraphy), subjective daytime sleepiness and neurocognitive functioning.

Conclusion: Despite its extensive role in the presentation and progression of PD, a significant unmet treatment need exists for sleep dysfunction experienced by these patients. As such, our trial seeks to further investigate the feasibility and tolerability of TES as a neuromodulatory treatment option within PD.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Mate Kiss
Job Title	Postdoctoral Fellow
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Department	CVRI

Insufficient sleep compromises adequate central nervous system drainage and instigates lymphadenopathy with autoantibody production in brain-draining cervical lymph nodes

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BACKGROUND: Sleep is integral to health and humans should spend one third of their life asleep. However, at least 35% of Americans sleep get insufficient sleep. There is substantial clinical evidence linking insufficient or poor-quality sleep with increased risk of developing immunological disorders including autoimmune diseases, such as systemic lupus erythematosus (SLE). Whether sleep impacts the neuro-immunological interface connecting the central nervous system (CNS) with the periphery to affect autoimmune pathologies is unclear.

METHODS & RESULTS: Here, using a mechanical model of sleep fragmentation in mice we find that persistent sleep fragmentation in mice activates Nlrp3 in microglia and induces heightened oxidative stress in the meninges, while altering its immune composition. Increased drainage of meningeal immune cells as well as Nlrp3 inflammasome-derived interleukin-1-beta (IL-1β) via the cerebrospinal fluid induces lymphadenopathy in CNS-draining cervical lymph nodes in an Nlrp3-dependent manner. The phenomenon is characterized by dendritic cell activation and germinal center hyperactivity, culminating in heightened production of antibody-secreting cells with subsequent hyperimmunoglobulinemia. Large-scale autoantigen array revealed that sleep fragmentation propagates the expansion of autoantibodies targeting self-molecules, such as complement proteins and antigens associated with systemic lupus erythematosus (SLE). In a mouse model of lupus, sleep fragmentation exacerbates SLE-like syndrome characterized by meningeal inflammation, accelerated cervical lymphoproliferative disease, augmented autoantibody titers towards double stranded DNA and clinical signs of anemia. In healthy humans, six weeks of sleep restriction increases the number of circulating follicular helper T cells and antibody-secreting plasmablasts in the peripheral blood with elevated IgG titers against oxidation-specific neoepitopes.

CONCLUSION:Our findings suggest that sleep maintains adequate immunosurveillance at the meningeal-cervical neuroimmune interface to preserve self-tolerance in CNS-draining peripheral lymph nodes, thereby protecting from autoantibody-mediated autoimmune complications.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Maxine Marchidan
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Department	Psychiatry

Appetite and Motivation in Depression

Maxine Marchidan, Laurel Morris

BACKGROUND: Depression is one of the most common psychiatric disorders, with roughly 18% of the US population receiving a depression diagnosis over their lifetime. Changes in appetite and feeding behaviors in patients with MDD are common. Hypophagia, a reduced food intake, occurs in nearly half of patients with a typical MDD presentation. Hyperphagia, or an increase in food intake, can affect between 23-35% of patients with MDD and is often a discerning symptom in diagnosing atypical subtypes of depression. Despite its prevalence, the variance of appetite-related symptoms remains less explored. In this study, we investigate how motivation, which is strongly implicated in MDD pathology, and eating behaviors may be affected in participants who experience depression.

METHODS: In a large online study (N=249), data on appetite, dietary sugar and fat intake, and mood symptoms were collected. Additionally, participants completed the internal motivation task (IMT), a computerized task assessing extrinsic and intrinsic motivation. In an in-person replication sample of MDD participants (N=40), participants completed similar self-report measures and the IMT in and out of a 7T MRI scan.

RESULTS: Preliminary results from the online study showed that high intake of sugar, a dimension of hyperphagia, was associated with lower anticipatory anhedonia and higher extrinsic motivation. These findings were reproduced in the in-person study, where hyperphagia was also associated with lower anticipatory anhedonia and higher extrinsic motivation.

CONCLUSION: These preliminary results uphold current understandings of the significant relationship motivation plays in the presence and perseverance of appetite-related dimensions of depression. Further correlation analysis will be run to further define the relationship between appetite and motivation. Regression analysis will be run to assess if the relationship between appetite symptoms and motivation are dependent on other symptoms typically present in MDD patients.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Michelle Kim
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The impact of juvenile social isolation on social behavior and VTA-DA neuron activity

Michelle Kim, Hala Harony-Nicolas

Background: In humans, isolation during development is known to increase vulnerability to conditions connected to maladaptive social behaviors, such as depression, anxiety, and substance use. Studies in rodents have also shown that isolation precipitates changes in social behavior. However, there is a gap in understanding how isolation during development creates long-term changes in social behavior and specific neuronal populations recruited during social interaction. Through the use of in vivo fiber photometry, I investigate how juvenile social isolation (jSI) impacts activity of dopaminergic (DA) neurons in the ventral tegmental area (VTA) and compare VTA-DA activity between group-housed (GH) and jSI rats during social behavior.

Methods: At P21, rats are assigned to either jSI or GH conditions for 3 weeks. Following isolation, rats are injected with TH-Cre and Cre-dependent GCaMP to express GCaMP in DA neurons in the VTA then re-housed with a novel age and sex-matched rat until adulthood (approximately P60). Upon reaching adulthood, rats are run in behavioral tasks to assess anxiety, social preference, and social reward-seeking. VTA-DA GCaMP6 signal is recorded during social interaction.

Results: jSI has no impact on anxiety-like behavior, social investigation, or social preference. However, while VTA-DA neurons in male GH rats display increased activity during social interaction, no increase in activity is observed in VTA-DA neurons of jSI rats. These differences in activity in VTA-DA neurons during social interaction are not observed in female rats.

Conclusions: While jSI does not impact social behavior in adulthood, it may impact VTA-DA activity during social interaction and possibly affect the processing of social reward. Currently, we are observing behavior following chronic social isolation to determine whether re-socialization may play a role in ameliorating deficits in anxiety-like or social behavior following isolation.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Michelle Lee
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Lab	Benson-Huntley Labs
Department	Neuroscience

Observing tyrosine hydroxylase innervation in LRRK2-G2019S and wild-type mice melanomas

Michelle Y. Lee1, Pamela Del Valle2, Jose Javier Bravo-Cordero3, Deanna L. Benson2

Melanoma patients are also more likely to develop Parkinson's, and vice versa. The mechanism underlying this association is not known. We are looking at the intersection of melanoma and the LRRK2-G2019S(GS) mutation, one of the most common genetic risk factors for Parkinson's, and how nerves are integrated into that association. What is the role of the GS mutation in the melanoma microenvironment? More specifically, I am looking at how tyrosine hydroxylase(TH, sympathetic nerve marker) expression changes over time in the wild-type(WT) and GS tumors.

I looked for the percent colocalization of anti-TH antibody and endogenous tdTomato (TH-Cre) expression in WT and GS knockin tumors. This was done through area percent calculations of confocal images on ImageJ, from isolated GFP-Yumm1.7 melanomas that were immunolabeled with anti-TH antibody and DAPI.

From the data collected so far, the colocalization percentage data points have only been derived from images from one tumor. With the group of images from that tumor specifically, there were only 3 images where TH was detected in the tumor, not the skin. Even then, there were difficulties with actual TH detection, resulting in many protocol adjustments. Throughout the images, TH has colocalized with tdTomato in some areas, but not throughout entire nerve bundles. I cannot compare WT and GS samples yet, due to insufficient data.

After cycling through different antibodies and modifying the immunolabeling protocol, we have decided to alter our approach. This means that I will be looking for different markers moving forward. When I do finish acquiring my data, I would hope for these results to be helpful towards my mentor's overarching project on LRRK2's role in melanoma and Parkinson's.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Michelle Lu
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Lab	Bond Lab
Department	Neuroscience

The Role of APOE on Hippocampal Neural Stem Cell Development and Function

Michelle Lu, Allison Bond

Background: Increased frequency of the E4 variant of the Apolipoprotein E (APOE) gene results in higher risk of late onset Alzheimer's Disease (AD) in adults. The hippocampus is the first region of the brain that degenerates in AD, resulting in memory impairment. APOE is expressed in neural stem cells in the dentate gyrus region of the hippocampus during development with an increase during the early postnatal period, a critical period when peak neurogenesis and astrogenesis occurs and neural stem cells transition to quiescence. Through understanding the effects of APOE4 expression on hippocampal development, we can better understand its role in AD risk and disease progression.

Methods: We will use human APOE3 and APOE4 knock-in mice to investigate the impact of the APOE4 allele on the timing of neural stem cell quiescence, and cell genesis and maturation for neurons, astrocytes and oligodendrocytes. First, quantification of proliferative and quiescent neural stem cells in the dentate gyrus of APOE3/4 KI mice across early postnatal timepoints will reveal the impact of APOE4 on neural stem cell pool maintenance. Then, we will use EdU birthdating at multiple timepoints throughout development to determine the birthdate of neurons, astrocytes, and oligodendrocytes in specific hippocampal subregions. Finally, we will use immunostaining with developmental stage-specific markers for neurons, astrocytes, and oligodendrocytes to describe the impact of APOE4 on the timeline of cell maturation in the hippocampus.

A better understanding of the role of APOE4 in neural stem cell development in the hippocampus could lead to novel therapeutic targets to prevent or delay the effects of AD in APOE4 carriers.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Mohammad Jodeiri Farshbaf
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Lab	Ables
Department	Psychiatry

Diabetes affects mitochondria in cholinergic neurons in reward circuitry and leads to behavioral abnormalities.

Mohammad Jodeiri Farshbaf, Yacoub Alokam, Molly Estill, Romain Durand-de Cuttoli, Tamara Markovic, Jessica L. Ables

BACKGROUND: Diabetes is a complex metabolic disorder that correlates with genetic and environmental factors. As a result, diabetes leads to multiple neurocognitive and neuropsychiatric sequelae such as dementia and depression. The brain's reward circuitry has a fundamental role in controlling mood and shows altered function in mood disorders. However, a large gap remains in our understanding of how diabetes affects reward circuitry function. The cholinergic medial habenula (MHb) is a part of reward circuitry implicated in anhedonia, a core feature of depression. Diabetes is a metabolic stress to neurons and impacts the metabolic pathways in them. We have profiled gene expression in cholinergic neurons in MHb in mouse models of diabetes. We observed significant changes in the expression of mitochondrial pathways since disease onset. Our behavioral assessment showed impulsivity in diabetic male mice. These findings open new perspectives on how mitochondrial pathways and cholinergic neurons contribute to reward-seeking behavior in diabetes mouse model. METHODS: Male ChAT-NuTRAP mice (8-10 weeks old) were injected intraperitoneally with streptozotocin (STZ; 50 mg/kg) in HBSS for 5 consecutive days. After 6 and 12 weeks of hyperglycemia, we dissected MHb to trap RNA (for RNA-seq) from cholinergic neurons. RESULTS: Our results showed mitochondrial ETC complexes, detoxification, and fatty acid oxidation genes significantly changed in cholinergic neurons. Moreover, we found impulsive behavior is increased in male mice during hyperglycemia and diabetes progress.

CONCLUSIONS: Our finding suggests that mitochondrial pathways are susceptible to diabetes in cholinergic neurons. Change in mitochondrial pathways represents in behavioral level. These findings will open new therapeutic avenues to discover the impact of diabetes on reward circuitry.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Moussa Konde
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Department	Department of Psychiatry; Environmental Medicine and Public Health

The association between prenatal exposure to SARS-CoV-2 and infant neurodevelopment

Moussa Konde, Anna Rommel PhD.

Background: A knowledge gap exists concerning the potential long-term neurodevelopmental effects for children exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in utero. This study aimed to determine whether there is an association between prenatal exposure to SARS-CoV-2 infection and infant neurodevelopment.

Methods: To address this, we leveraged the Generation C Cohort, a prospective pregnancy cohort of 2,734 participants established at The Mount Sinai Health System (MSHS) in April 2020. Maternal SARS-CoV-2 infection status was assessed through a combination of serological and molecular testing, complemented by electronic medical records (EMR) and self-reporting. Neurodevelopmental assessment was conducted using the Ages & Stages Questionnaire, 3rd Edition (ASQ-3) of infants age 6 months.

Results: Of the 358 infants included in the analysis, 80 had been exposed to SARS-CoV-2 prenatally, while 278 showed no indication of prenatal exposure. Analysis revealed that infants exposed prenatally to SARS-CoV-2 exhibited marginally lower mean scores across all ASQ-3 subdomains; however, no statistically significant differences were observed between the exposed and unexposed groups.

Conclusions: The study suggests that prenatal SARS-CoV-2 exposure is not associated with neurodevelopmental outcomes at age 6 months, providing reassurance on the short-term effects of such exposure. Nevertheless, ongoing research comparing children born before and during the pandemic, as well as longitudinal monitoring of pandemic-born children, remains imperative to comprehensively elucidate any possible sequelae.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Mu Li
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Exploring the VTA Circuitry of Anhedonia in Major Depressive Disorder using Ultra-HighField 7T MRI
Authors: Mu Li1, Laurel S. Morris1.
Animal models of depression suggest that ventral tegmental area (VTA) hyperactivity underlies depressive symptoms and anhedonia. However, due to the limited resolution of 3-Tesla (3T) MRI, the VTA circuitry related to motivation in human patients with MDD has not been adequately studied. Fortunately, ultra-high field 7-Tesla (7T) MRI is more sensitive, therefore, we used 7T resting-state MRI to explore the correlation between different levels of anhedonia and VTA with whole-brain functional connectivity across MDD patients and healthy controls, in order to investigate the relevant VTA circuitry.
We scanned MDD (n=31) and healthy subjects (n=26) using ultra-high field 7T resting-state MRI and assessed the level of anhedonia using two dimensions of the Temporal Experience of Pleasure Scale (TEPS): TEPS Anticipatory Subscale (TEPSA) and TEPS Consummatory Subscale (TEPSC). We analyzed VTA-whole brain functional connectivity across both groups, with TEPSA and TEPSC scores as covariates. We performed a voxel-wise analysis with a threshold of $p < 0.005$, and cluster-level family-wise error correction was applied.
Across MDD and healthy controls, higher anticipatory anhedonia was associated with higher VTA connectivity with the left thalamus, right inferior frontal gyrus and medial prefrontal cortex. Higher consummatory anhedonia was associated with higher VTA connectivity with the left inferior frontal gyrus, right medial frontal gyrus, and right thalamus.
Higher anhedonia was associated with higher functional connectivity between VTA and various clusters in the brain. This aligns with animal studies showing hyper-connectivity in the VTA circuit in depressive phenotypes. Additionally, the findings suggest that higher levels of anticipatory anhedonia are associated with stronger functional connectivity between VTA and mPFC, replicating our previous findings. Our study is ongoing and will involve more subjects.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Natalia Biscola
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Department	Neurology

Sexual Dimorphism and Asymmetry in the Cervical Segment of the Human Vagus Nerve
Biscola NP, Bartmeyer PM, Stern E, Mihaylov PV, Ward MP, Powley TL, Havton LA

BACKGROUND: Neuromodulation by vagus nerve stimulation (VNS) may be used as adjunctive treatment of medication-refractory epilepsy and clinical depression. However, the mechanisms of action are not well understood, and implementation of VNS treatment protocols are limited by off-target effects. An improved understanding of the human vagus nerve fascicular and sub-fascicular organization is needed for the development of refined stimulation protocols and VNS strategies.
METHODS: We performed light and transmission electron microscopic mapping of the human cervical vagus nerve procured from deceased transplant organ-donors (n=27).
RESULTS: Studies of laterality showed a higher number of fascicles, a larger fiber and endoneurium area on the right side compared to the corresponding left-sided cervical vagus segment. Studies of sexual dimorphism showed a significantly higher total number of fascicles in the cervical vagus nerve for women compared to men. Ultrastructural studies showed extensive variability between fascicles with regards to fiber type compositions based on size and myelination criteria. Assisted by an action potential interpreter tool, nerve fiber morphology was used to predict conduction properties and expected compound nerve action potentials with findings supportive of the notion that nerve fiber populations within individual fascicles of the human cervical vagus nerve show extensive functional heterogeneity.
CONCLUSIONS: Significant differences in laterality and sexual dimorphism were detected. The right side exhibits greater fascicle numbers and cross-sectional fiber areas, while women have a higher fascicle count compared to men. Ultrastructural analyses highlight extensive variability in fiber type compositions within fascicles, indicating functional heterogeneity. These findings increase our understanding of the cervical vagus nerve structure, opening avenues for future research in physiological processes and potential therapeutic interventions.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Natalie Hackman
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Department	Depression and Anxiety Center for Discovery and Treatment

Characterizing the Constructs of Motivation

Natalie Hackman, Mu Li, Phillip Neukam, James Murrough, and Laurel S. Morris

Background: Motivated behavior is commonly differentiated into extrinsic and intrinsic motivation. Extrinsic motivation describes behavior prompted in response to external reinforcers while intrinsic motivation is the manifestation of internally generated incentive. Although there is computational similarity between extrinsic and intrinsic motivation, delineation of internal value functions has proven more difficult. Motivational deficits are a signature attribute of major depressive disorder (MDD). The manifestation of motivational deficit is classified in the DSM-5 as anhedonia. However, established measures of motivation do not address internally generated motivation. Hence, the understanding of the neurocognitive mechanisms which underlie intrinsically motivated behavior, and its deficits are restricted.

Methods: We have developed a multi-modal ultra-high field 7T MRI protocol which provides a significant improvement in the signal to noise ratio. We have also created the Internal Motivation Task (IMT) which serves as a novel measure of internally generated motivation. The IMT involves a choice cue followed by a decision in which participants utilize either extrinsic or intrinsic motivation to attain a reward.

Results: MDD individuals exhibit a statistically significant reduction in extrinsic motivation, but do not exhibit a statistically significant reduction in internally generated motivation compared to healthy individuals. In N=15 healthy controls who completed the task so far, we found differential activation in the occipital cortex ($Z=4.9$) and bilateral anterior insula ($Z=4.3$) during extrinsic control relative to intrinsic control (voxelwise $p<0.005$, $K>350$, $alpha<0.05$). All updated neuroimaging results in both groups will be presented.

Conclusions: There does not appear to be a dimensional association between lower intrinsic motivation and anhedonia. Perhaps there is a higher sense of agency with intrinsic motivation than extrinsic motivation which accounts for there being less of a difference between healthy and MDD individuals.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Natalie McClain
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Department	Psychiatry

Beyond self-report in characterizing drug addiction: Using behavior to inform treatment adherence.

McClain, N*, Ceceli, AO*, Kronberg, G, Alia-Klein, N, Goldstein, RZ. (*equal contribution)

Background: Drug addiction accompanies enhanced salience attribution towards drug over nondrug cues—a bias underutilized in understanding clinical endpoints. Clinical trials largely employ subjective reports of drug use, or categorical urine status, to inform treatment outcomes with limited success. In inpatient, urine-negative, individuals with heroin use disorder (iHUD) we tested whether objective behavioral markers of drug bias better inform treatment adherence.

Methods: At baseline, 59 iHUD and 29 age-/sex-matched healthy controls (HC) underwent a battery of drug use questionnaires (i.e., subjective measures) and behavioral tasks (i.e., objective measures). The former comprised Heroin Craving Questionnaire, Severity of Dependence Scale, and lifetime heroin use (years). The latter comprised a fluency task whereby participants generated drug and nondrug words, and a choice task whereby they selected to view drug or nondrug (i.e., positive, negative, neutral) images, reflecting simulated drug-seeking. A factor analysis reduced dimensionality and preselected representative measures to inform treatment adherence [i.e., post-treatment attendance (y/n)].

Results: The iHUD had higher drug-biased fluency than HC (drug>nondrug words; $p=0.0083$), also showing higher simulated drug seeking (drug>nondrug image selections $p=0.036$). Among the preselected variables, the representative subjective measure (lifetime heroin use) was not associated with treatment adherence. In contrast, higher drug>pleasant choice (representative objective measure) was significantly correlated with lower post-treatment attendance ($p=0.0499$), explaining more of the variance in this outcome measure than its subjective counterpart ($R2=0.123$, $p=0.038$).

Conclusion: Extending drug-biased fluency and choice results from cocaine to heroin addiction, for the first time we illustrate that objective measures of drug bias outperform the commonly employed subjective drug use measures in informing prospective treatment adherence. These results implicate drug-biased behavior as a powerful marker of addiction severity and treatment success.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Natalie Suhy
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Lab	Blanchard
Department	Neuroscience

Using human stem cell-derived neurodegeneration models to investigate interactions between APOE4 and ketogenic diet in Alzheimer's disease

Natalie Suhy, Emily Sartori, Braxton Schuldt, Andrea Perez-Arevalo, Louise Mesentier-Louro, Jessica Schwarz, Ana Forton-Juarez, Camille Goldman, Anna Bright, and Joel Blanchard

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease and the sixth leading cause of death in the United States. Ketogenic diets have been used as treatment for AD, however therapeutic benefits are limited to patients who do not possess an APOE4 polymorphism, with limited understanding of why this occurs. APOE4 is the strongest genetic risk factor for AD, present in 40-60% of individuals with AD.

To investigate interactions between APOE and diet, we developed comprehensive models of human stem cell-derived brain tissue grown in cell culture media where glucose is replaced with ketones, with emphasis studying glial cells. In vitro findings are being complemented with in vivo studies involving ketogenic diet-fed SCID mice subcutaneously injected with gel-matrix 3D human stem cell-derived models of the blood-brain barrier (iBBBs) expressing APOE3 or APOE4, with human vasculature inside iBBBs able to integrate with mouse vasculature, and later able be extracted for analysis of ketogenic-diet induced inflammatory and AD-relevant changes specific to APOE genotype.

We found that ketogenic conditions exacerbate cholesterol accumulation in APOE4 oligodendrocytes and astrocytes, yet alleviate cholesterol accumulation in APOE3 cells. We found that APOE3 oligodendrocytes improve myelination in ketogenic conditions, but APOE4 oligodendrocytes do not. Additionally, we found that APOE4-expressing iBBBs in keto conditions accumulate amyloid deposits in a model of cerebral amyloid angiopathy.

Our data show that cholesterol dysregulation unique to APOE4 carriers adversely interacts with ketogenic conditions, triggering cell-specific neuroinflammatory processes relevant to AD pathogenesis. This provides critical insight into clinical observations that APOE4 AD patients fail to show cognitive improvements in response to treatment with a ketogenic diet.

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Microglia contribution to sexual dimorphism and remodeling of the developing brain.
Paloma Bravo and Florence L. Marlow

Establishment of sex-specific differences in the brain, and how sexual dimorphism contributes to the morphology, molecular signals, and behaviors associated with sex-biased neurological disorders is still not well understood. Microglia are the immune cells of the nervous system and are thought to refine neural connections during development and promote remodeling of neural circuitry. Microglia are also associated with neurodegeneration and neurodevelopmental diseases with behavioral deficits, but their contributions to remodeling of the developing brain and establishing novel social behaviors are unclear. In zebrafish, sex is determined at around 30 days post-fertilization and females retain the plasticity to switch their phenotypic sex to male in response to environmental or genetic factors that impair fertility.

Using genetic models that lack microglia at stages when primary sex is determined, individually or together with models that undergo female-to-male sex reversal, we aim to determine if the development and remodeling of sexually dimorphic features is microglia dependent. We are using immunohistochemistry and light-sheet microscopy to map microglia distribution and morphology to investigate potential microglia contributions to the cellular changes that occur after sex is established and after sex reversal.

Our analysis of individual areas in the wild-type brain revealed that female and male adult brains, but not juvenile, show structural differences in areas associated with sex-specific social behaviors, and in microglia numbers and morphology. In contrast, brains of fish lacking microglia show no distinction between females and males, suggesting a role for microglia in establishing developmental differences between sexes.

This work will determine if microglia contribute to sexual dimorphism in the developing brain or the remodeling and establishment of new social behaviors and will reveal the cell types and mechanisms regulating sex-specific differences in brain structure and behavior.

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Identifying the Basis of Melanoma and Parkinson's Association

Pamela Del Valle, Michelle Lee, J. Javier Bravo-Cordero, Deanna L. Benson

In order to identify cellular events that drive a shared risk for melanoma and Parkinson’s, we are developing a microscopy-based analysis pipeline based on tissue clearing. We investigate GFP-tagged YUMM1.7 melanoma allografts in wildtype mice and in mice carrying a knockin mutation for one of the most common genetic risk factors for Parkinson’s: Lrrk2-G2019S.

In each melanoma allograft, we (1) capture intravital cellular dynamics using 2-photon microscopy, (2) clear and 3D reconstruct the same cellular elements using light sheet microscopy, and (3) immunolabel cell types of interest after reverse-clearing the tumor. Host melanocytes and sympathetic axons are visualized by Cre-dependent tdTomato expression driven by a tyrosine hydroxylase promoter.

Our preliminary data has confirmed the overall strategy works. In melanoma in both wildtype and Lrrk2-G2019S mice, tumor cell motility is modest and host melanocytes are widely recruited. At the same time, innervation patterns are notably distinct and are likely to reflect additional differences in tumor composition, observations that are being pursued.

We believe this strategy will define key events in melanoma progression and reveal how changes in cellular composition or dynamics may drive shared risk between melanoma and Parkinson’s.

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Full Name	Qixiu Fu
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Department	Neuroscience

Selective impacts of depressive, but not anhedonic symptoms on social decision-making

Qixiu Fu, Blair Shevlin, Arianna Neal Davis, Xiaosi Gu, Helen S. Mayberg

BACKGROUND: Depression and anhedonia are commonly seen across many psychiatric and neurological disorders. Depressive symptoms commonly include sadness, pessimism, crying, guilt, etc, whereas anhedonia refers to a diminished ability to experience pleasure. Due to their high comorbidity with each other, it is typically difficult to tease apart the effects of depression and anhedonia in standard laboratory studies due to limited sampling and it remains elusive how these symptoms might differentially impact cognition and behavior.

METHODS: We leveraged a large sample of online participants with a wide range of depressive and anhedonic symptoms and selected four subgroups that differed on these two symptom dimensions measured by the Beck Depression Inventory (BDI-II; cutoff = 13) and Positive Valence System Scale (PVSS; cutoff = 142): healthy (n = 57), depression only (n = 17), anhedonia only (n = 26), both (n = 36). All participants performed a social decision-making task (Ultimatum Game) during which they accepted or rejected an unfair offer from a partner.

RESULTS: We found that depression, but not anhedonia, affected psychomotor slowness indexed by overall reaction time (depression vs. healthy, $t(31) = -2.19$, $p = 0.05$; depression vs. anhedonia, $t(35) = -2.19$, $p = 0.02$). Furthermore, depressed, but not anhedonic, participants showed a higher rejection rate in low offers (depression vs. healthy, $t(36) = -2.76$, $p = 0.01$; depression vs. anhedonia, $t(40) = -2.78$, $p = 0.01$).

CONCLUSIONS: Together, these preliminary results demonstrate the selective effects of depressive symptoms on social decision-making. Despite their common co-occurrence, these symptoms may have distinct underlying neurocomputational mechanisms and may constitute subtypes of patients who require personalized treatments and interventions.

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BACKGROUND: One prominent symptom of many stress-induced psychiatric disorders, including major depressive disorder (MDD) and schizophrenia (SCZ), is anhedonia: the loss of interest for hedonic stimuli. In recent years, clinical studies have shifted from exploring physical anhedonia, like the loss of pleasure in food, to exploring social anhedonia, like the loss of pleasure in social interaction. Social anhedonia may lead to the manifestations of social avoidance and isolation present in most stress-induced psychiatric disorders. However, there is a lack in the development of preclinical models to measure social anhedonia.

METHODS: Here, we develop an operant-based approach to measuring social learning and motivation. The social self-administration (SSA) task involves fixed ratio active lever pressing to gain access to a novel juvenile mouse behind a mesh barrier. We explore alterations in learning this lever-pressing behavior in mice after chronic exposure to social defeat stress (CSDS). We then investigate social reward deficits by using a progressive ratio design, where there is a gradual increase in the number of correct responses needed to receive a social reinforcement. Following SSA, we use iDISCO+ tissue clearing and light-sheet imaging to assess whole-brain differences of c-Fos activity in stressed and non-stressed mice.

RESULTS: We found that mice exposed to CSDS showed a significantly slower acquisition of the SSA task compared to their non-stressed controls. However, we did not find a significant difference in motivation between stressed and non-stressed mice during the progressive ratio portion of the task. We further explore the regional differences in c-Fos activity between the control and stressed mice tied to the SSA task.

CONCLUSION: Our results indicate that chronic stress causes deficits in acquiring a social reward task. This study will provide a critical understanding of the complex role social anhedonia plays in stress-induced psychiatric disorders.

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MULTIPLEXED IMMUNOFLUORESCENCE PROFILING OF MICROGLIA AND THEIR CELL-STATE MARKERS IN ALZHEIMER'S DISEASE BRAINS

Rachel A. Tejiram, Dan Meyer, Elizabeth McDonough, Lisa Lowery, Patrick R. Hof, Merina Varghese

BACKGROUND: Alzheimer's disease (AD), the most prevalent neurodegenerative disease, is linked to cognitive deficits, accumulation of amyloid-beta proteins, tau hyperphosphorylation, and neuronal loss. Pyramidal neurons expressing nonphosphorylated neurofilament protein within prefrontal cortex (PFC) layers 3 and 5 are more susceptible to AD neuropathology than the primary visual cortex (V1), which appears more resilient. We aim to assess the distribution of microglia and their cell-state markers within the PFC and V1 of AD and control brains to understand changes in the microenvironments of vulnerable neurons.

METHODS: Postmortem brains from 12 humans were stained using multiplexed immunofluorescence. QuPath was utilized for image analysis, including cell segmentation and classification of cells positive for ionized calcium-binding adaptor molecule 1 (IBA1), cluster of differentiation 68 (CD68), or translocator protein (TSPO). For data analysis, RStudio was used.

RESULTS: Clinical dementia rating (CDR), Thal stage, and Braak stage were indicators of AD progression. An upward trend was observed for the number of IBA1+ cells within PFC layer 3 with each indicator. An upward trend was also observed for the number of IBA1+, IBA1:CD68, and IBA1:TSPO cells with increased Braak stage in PFC layer 3. Overall, statistical significance was found for IBA1+ cells in PFC layers 1 and 3 with Braak stage and V1 layer 6 with CDR. Notably, IBA1:CD68 in CDR 0.5 and Thal pre-AD and IBA1:TSPO cells in Thal pre-AD displayed higher variance compared to control or AD in PFC layer 3.

CONCLUSIONS: The expression of CD68 and TSPO in microglia emphasizes the importance of assessing cell-state markers to better understand cell function in the microenvironment of AD-vulnerable neurons. Further research will assess other glial, vascular, and neuronal markers.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Glycosylation defects and altered gene expression in ALG13-CDG brain organoids provide insight into neuronal pathology.

Rameen Shah, Silvia Radenkovic, Rohit Budhraja, Graeme Preston, Alexia Tyler King, Charlotte Bleukx, Ibrahim Shammas, Steven Sloan, Akhilesh Pandey, Eva Morava*, Tamas Kozicz*

Background: Asparagine-linked glycosylation 13 (ALG13) is an enzyme important for the placement of GlcNAc sugar on glycan chains. ALG13-congenital disorder of glycosylation (CDG) is an X-linked disorder caused by missense variants in ALG13 that impair ALG13's ability to synthesize glycans for protein N-glycosylation. Unlike most other N-linked CDGs, ALG13-CDG patients' blood and fibroblast do not show glycosylation defects. Nevertheless, ALG13-CDG patients present with neurological symptoms, including seizures, intellectual disability, and developmental delays. These observations led us to hypothesize that ALG13-CDG primarily affects the brain.

Methods: We developed cortical brain organoid models (cBOs) of ALG13-CDG by differentiating induced pluripotent stem cells from patient fibroblasts into cBOs. At 77-92 days of differentiation, we conducted multiomics profiling on these cBOs, including single-cell RNA-seq, proteomics, glycoproteomics, and metabolomics.

Results: Our investigation unveiled significant changes in glycosylation and gene expression of molecules essential for brain development and function. For the first time, we showed that ALG13-CDG causes reduction in glycosylation of proteins crucial to axon growth, neuronal migration, lipid metabolism, and neuronal excitability. Interestingly, proteins involved in these same pathways were dysregulated in our proteomics data. Furthermore, our scRNAseq showed an irregular developmental trajectory in ALG13 deficient cBOs. Differential gene expression analysis in the radial glia, glutamatergic, and GABAergic clusters revealed alteration in transcripts related to lipid metabolism, neuronal migration, axon growth and neuronal excitability. Our metabolomics investigations highlighted an elevation in GlcNAc (a substrate for ALG13)
levels.

Conclusions: Overall, our multi-omics studies on ALG13-deficient BOs provide valuable insights into brain-specific disturbances underlying the key neurological phenotypes of ALG13-CDG and offer promising avenues for therapeutic interventions.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Title: Neurophysiological Arousal to Unpleasant Cues as a Potential Biomarker for Impaired Social Role Functioning in Schizophrenia

Author: Shaik R, Siddiqui A, Bel-Bahar TS, Ferster KS, Khan AA, Velthorst E, Parvaz MA
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Background: Deficits in social functioning are a hallmark of Schizophrenia (SCZ). Effective social functioning relies on emotional awareness and management; however, this connection is yet to be established in SCZ. This study aims to investigate the relationship between emotional arousal and social functioning in schizophrenia, using the EEG-derived Late Positive Potential (LPP) as an objective measure of emotional processing.
Methods: Individuals with SCZ (n=9, female=3) and healthy controls (HC; n=17, female =8) viewed a series of pleasant, unpleasant, and neutral pictures, while the EEG data was collected. Participants also completed the Role Functioning Scale which assesses. EEG analyses focused on the Late Positive Potential (LPP), an index of affect arousal, during 400 –1000 ms post-picture onset. Group differences in LPP amplitudes were assessed using the Mann-Whitney test and the association between LPP and RFS score was assessed using Spearman correlations.
Results: These results show that SCZ has diminished arousal to unpleasant cues compared to HC ($Z = -2.18$, $p = .029$). Across all participants arousal to unpleasant cues positively correlated with the RFS score ($r = 0.541$, $p = 0.005$), however, this association was driven specifically by SCZ ($r = 0.749$, $p = 0.033$), and not by HC ($r = 0.303$, $p = 0.292$).
Conclusions: These results are preliminary, given the limited sample size. However, they suggest that blunted reactivity during unpleasant contexts may be one of the neurophysiological mechanisms underlying limited social role functioning in Schizophrenia.

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Prediction of future dementia among patients with mild cognitive impairment (MCI) by integrating multimodal clinical data

Andrew Cirincione, Kirsten Lynch, Jamie Bennett, Jeiran Choupan, Bino Varghese, Nasim Sheikh-Bahaei, Gaurav Pandey

BACKGROUND: Accurate prediction of future dementia for patients with mild cognitive impairment (MCI) is a major clinical goal. Currently, the clinical standard for diagnosing dementia utilizes multimodal data like cognitive tests, MRI and PET scans, and other biomarkers. However, efficiently and objectively analyzing these complex, diverse data can be difficult in the clinical setting, contributing to high rates of under- or mis-diagnosis of dementia. Machine learning (ML) offers a potentially more efficient and objective methodology to integrate these multimodal data for the prediction of future dementia among MCI patients.

METHOD: Here, we introduce Ensemble Integration (EI), a multi-modal ensemble-based ML framework, and conducted an assessment of EI's ability to predict the future development of dementia using multimodal data from The Alzheimer's Disease Prediction of Longitudinal Evolution (TADPOLE) Challenge. Specifically, we developed a predictive model of dementia from data of 672 MCI patients collected at their first visit (baseline), and evaluated this model and several benchmark methods on baseline data from a test set of 169 MCI patients.

RESULT: For predicting the future development of dementia among MCI patients in the test set, the EI-based model performed better (AUROC=0.81, F-measure=0.68) than the more commonly used XGBoost (AUROC=0.68, F-measure=0.57) and deep learning (AUROC -=0.79, F-measure=0.61) approaches. This model also suggested that MRI-derived volumes of the left middle temporal gyrus, right posterior cingulate and left inferior lateral ventricle were predictive of this progression, a conclusion supported by the literature.

CONCLUSION: EI is an effective framework for predicting if an MCI patient will develop dementia in the future, as well as identifying neuroanatomical features that may be associated with this progression.

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Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Identifying diabetes-induced transcriptional and functional alterations in cholinergic interneurons of the nucleus accumbens

AUTHORS:
Samantha O. Brown, Romain Durand-de Cuttoli, Zainab M. Oketokoun, Mohammad Jodeiri Farshbaf, Molly Estill, Jessica L. Ables

BACKGROUND: Patients with diabetes are twice as likely to develop depression compared to the general population. Yet few studies have investigated how diabetes might induce transcriptional and functional changes in brain regions involved in reward processing. Within the brain's reward circuitry, cholinergic interneurons (CIN's) respond to dynamic fluctuations in insulin and regulate depressive-like behaviors, thus underscoring the importance of studying this neuronal cell type in the context of diabetes.

METHODS: Using a rodent model of streptozocin (STZ)-induced diabetes, we performed cell-type-specific TRAP mRNA sequencing of CIN's in the nucleus accumbens (NAc), a brain region involved in the aberrant reward processing observed in major depressive disorder. In addition, we also conducted pilot in vivo fiber photometry recordings of NAc CIN's in diabetic and control mice during the approach toward rewarding stimuli (palatable food and social target) in the home cage.

RESULTS: Our preliminary RNA sequencing results demonstrate that NAc CIN's demonstrate significant alterations in genes regulating synaptic neurotransmission, mitochondrial function, and glucose metabolism as a result of chronic diabetes. In addition, our fiber photometry recordings suggest that NAc CIN's in diabetic mice show increased activity in response to the consumption of high-fat/high-sugar palatable food. We did not observe significant differences between diabetic and control mice in the firing activity of NAc CIN's during social interaction with a novel juvenile mouse.

CONCLUSIONS: Our ongoing studies suggest that diabetes alters the transcriptional landscape of NAc CIN's and influences how these neurons response to palatable food rewards. Future experiments will further probe how the altered activity of NAc CIN's in diabetic mice might contribute to affective behavioral states.

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Altered history-dependent frontal-visual projection activity underlies visual attention deficits in a mouse model of Fragile X Syndrome.

Samuel Allen, Tadaaki Nishioka, Yury Garkun, April Serratelli, Hirofumi Morishita

BACKGROUND: Attention deficits in Fragile X syndrome and in the relative mouse model (Fmr1KO) have long been demonstrated, but the underlying cognitive circuit disruptions remain unclear. Previously, frontal-visual projection activity before stimulus presentation was found to be essential for attention function, specifically following error trials. Moreover, we recently demonstrated in mice that frontal-visual projection neurons undergo a developmental shift in local input connectivity during adolescence that is disrupted in Fmr1KO mice, leading to a persistent hyperlocal state in adulthood.

METHODS: To understand how this increased local connectivity promotes attention deficits in Fmr1KO mice, we utilized fiber photometry recording of calcium and glutamate signaling in frontal-visual projections in adult Fmr1KO mice during 5 Choice Serial Reaction Time Task (5CSRTT) to monitor circuit activity.

RESULTS: While frontal-visual projection calcium activity during the anticipatory period, before the stimulus is presented, in WT (Wildtype) mice was highest in correct trials following errors (E-C) during the late anticipatory period, in Fmr1KO mice, calcium signaling during the anticipatory period was significantly driven by post-correct performance history (C+1) relative to post-error history. Similarly, glutamate input onto frontal-visual projection neurons during the anticipatory period were highest following correct trials.

CONCLUSIONS: These findings demonstrate that frontal-visual projection activity is altered during attentional behavior in adult Fmr1KO. Moreover, the output calcium activity of projections in Fmr1KO is shifted closer to the glutamatergic input dynamic which may be a consequence of retained hyperlocal connectivity. Future experiments will seek to identify the reduced error signaling by evaluating acetylcholine signaling using a ACh sensor in Fmr1KO and Wildtype mice.

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Cortical Interoceptive Processing and the Rapid Antidepressant Effect of Ketamine

Sanjana Murthy, Jacob Dahill-Fuchel, Elisa Xu, Jacqueline Overton, James Murrough, Rachel Fremont, Allison C. Waters

Background: Depression is a debilitating psychiatric condition and one of the leading causes of disability worldwide. An aspect of depressive pathology is thought to arise from disruptions to interoceptive processing, or bodily sensation. The NMDA-receptor antagonist, ketamine, has demonstrated rapid and robust antidepressant effects, however, the role of interoceptive processing in ketamine's antidepressant effect remains unclear. The current study investigates whether interoceptive processing is enhanced after a single dose ketamine infusion, and whether this change predicts the antidepressant response.

Methods: An emerging measure of neural interoceptive processing is the heartbeat evoked potential (HEP), a brain electrophysiological signal time-locked to the sensation of the heartbeat in the chest cavity. HEP is thought to reflect cortical processing of interoceptive sensation. Study participants completed a battery of tasks designed to manipulate interoceptive attention and arousal with simultaneous EEG recording. Analysis of a healthy control group (n=39) instructs the approach to work with depressed patients undergoing a single-session of treatment for depression with ketamine. Rapid antidepressant effects of ketamine will be measured the Montgomery-Asberg Depression Rating Scale at follow-up visits within 7 days of EEG recording.

Results: We demonstrate that that the HEP signal is modulated by attention to bodily sensation and bodily arousal, $F(1,38)=7.9$, $p=.008$, but not predictive of depression or anxiety ($p>.05$) in a community sample of adults. However, a preliminary examination of patient data quality and signal reliability (n=2) provides evidence of study feasibility in the context of treatment with ketamine.

Conclusions: Elucidating the role of interoceptive processing in ketamine's antidepressant effects informs models of treatment efficacy and holds potential for application as a treatment response biomarker.

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Deletion of PAC1 receptors in the respiratory rhythm generator disrupts fear expression and metabolic function

S. Shetty, S. J. Duesman, S. Patel, P. Rajbhandari, A. Rajbhandari

Background: There is an intricate relationship between breathing, metabolism, and fear especially under stressors. The brain region preBötzinger complex (preBötC) in the brainstem responsible for respiratory rhythms highly expresses the neuropeptide PACAP receptor, PAC1. PACAP-PAC1 system is important for regulating stress-related behavioral and autonomic functions. Yet the mechanisms by which preBötC-PAC1 regulates central and peripheral stress responses, and metabolic function are unclear. We hypothesized that preBötC-PAC1 receptors are necessary for integrating stress-related behavioral and metabolic functions.

Methods: In PAC1-floxed mice, we injected AAV2-GFP-Cre/AAV2-GFP virus in the preBötC for Cre-mediated deletion of PAC1 receptors. After three weeks, mice underwent the stress-enhanced fear learning (SEFL) protocol, which recapitulates aspects of PTSD-like fear. Cardiorespiratory measures were concurrently recorded during SEFL. Anxiety-like phenotypes were evaluated with open-field light gradient and elevated plus maze tasks. Lastly, changes in metabolism were assessed using indirect calorimetry.

Results: Following the SEFL protocol, we observed a notable increase in cFos+ cells in the preBötC. PreBötC-PAC1 ablation alone increased freezing behavior, indicating heightened fear. In preBötC-PAC1 ablated SEFl mice we observed increased HRV. Furthermore, indirect calorimetry revealed reduced O2 consumption and CO2 production, and energy expenditure but increased food consumption. We noted no differences in anxiety measures.

Conclusion: PreBötC-PAC1 deletion increased freezing in non-SEFL mice, while decreasing HRV in SEFL group. We hypothesize that trauma-like stress and preBötC -PAC1 deletion results in shorter breaths evidenced by lower O2 consumption and CO2 production. Additionally, PAC1 deletion in SEFL group correlates with metabolic dysregulation—lower energy expenditure and increased food consumption. These findings indicate that alterations in preBötC PAC1 receptors affect fear and metabolic functions, offering avenues for further research in integrating stress and autonomic functions.

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Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Sarah Boukezzi
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Neurite orientation dispersion and density imaging (NODDI) reveals microstructural alterations in the threat circuitry of individuals with mood and anxiety-related disorders

Authors: Sarah Boukezzi, Laurel Morris, Philipp T Neukam, Yael Jacob, Yolanda Whitaker, Priti Balchandani, James Murrough

Background: Preclinical and clinical investigations showed that individuals experiencing mood and anxiety-related disorders exhibit structural alterations in regions implicated in the threat and reward circuitries. Neurite Orientation Dispersion and Density Imaging (NODDI) represents a diffusion MRI model grounded in disparities in the diffusion of water molecules within and outside neurons. Our hypothesis posits that individuals with anxiety and depression demonstrate alterations in both GM and WM microstructures implicated in emotional regulation.

Methods: The study encompassed 47 healthy controls (HC), 17 individuals diagnosed with Major Depressive Disorder (MDD), and 44 individuals with anxiety disorders (ANX). Participants underwent an MRI scanning session during which three NODDI parameters: Orientation Dispersion Index (ODI), Intra-Cellular Volume Fraction (ICVF), and Extra-Cellular Volume Fraction (ISOVF)—were computed.

Results: Preliminary data analyses showed positive correlations between general distress and ODI values in two distinct regions: the left hippocampus (k=188; MNI=-30, -26, -13) and the left hippocampus and amygdala (k=71; MNI=-31, -10, -23). Anhedonia was correlated with a cluster including the entorhinal cortex and right hippocampus (k=60; MNI=19, -12, -32). All patients showed elevated ODI scores in multiple regions including the right insula (k=256; MNI=39, -12, 11); the right parahippocampal gyrus and right amygdala (k=144; MNI=18, 2, -21); the left amygdala (k=44; MNI=-20, 0, -23); and the right hippocampus (k=60; MNI=32, -16, -23).

Conclusion: Our findings illuminate elevated ODI values in patients relative to HC across various regions integral to the threat circuitry, such as the insula, amygdala, hippocampus. These heightened ODI values suggest an increased dispersion of axons and dendrites within GM of these structures.

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Full Name	Sarah King
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Verbal recall of a drug-related movie stimulus in individuals with heroin use disorder

Sarah King, Greg Kronberg, Nancy Zhang, Natalie McClain, Ahmet Ceceli, Nelly Alia-Klein, Rita Goldstein

Drug addiction is marked by enhanced salience attribution to an individual's substance of choice, including to substance-related cues in the natural environment, potentiating further drug use. Unstructured, spontaneously generated speech may provide unique insights into a person's current psychological state following exposure to salient drug stimuli, with clinically meaningful implications including for outcome prediction.

Forty inpatients with heroin use disorder (HUD) and 32 control participants (CTL) viewed 17 minutes of the addiction-related movie Trainspotting during fMRI, then verbally recalled the events and their subjective experience of the movie. Participants repeated the task following 15 weeks of treatment. Transcriptions were embedded into 512 linguistic features using a pretrained large language model (BERT) for contextual analysis. Semantic similarity was assessed using cosine similarity. First and third person pronoun frequencies were also quantified to assess self-referential and descriptive features of participants' recall.

A 2(Group) x 2(Session) ANOVA revealed a significant interaction on semantic similarity ($F=9.90$, $p=.002$). Post hoc testing showed this was driven by a significant group difference at pre-treatment (CTL>HUD) and a session difference in HUD (post>pre). A 2(Group) x 2(Session) x 2(Pronoun) ANOVA revealed a significant 3-way interaction effect ($F=5.17$, $p=.024$), driven by significant group differences at pre-treatment for first (HUD>CTL) and third (CTL>HUD) person and a session effect in HUD (first: pre>post, third: post>pre).

Our results demonstrate quantifiable linguistic markers of the dynamic subjective experience of drug-related stimuli in treatment-seeking HUD individuals, including increased group coherence and reduced self-reference with treatment. Ongoing work includes representational similarity analysis of speech embeddings and inter-subject correlation in fMRI during movie viewing to assess the representation of hypothesized default mode network regions in linguistic expression during recall.

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Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Sarah Philippi
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APOE4-associated changes to the systemic environment influence hippocampal phenotypes

Sarah Philippi, Catarina Ferreira, Brittany Hemmer, Kailash BP, Manav Kapoor, Towfique Raj, Joseph Castellano

The APOE4-ε4 allele is the greatest genetic risk factor for Alzheimer's disease (AD), increasing risk by 3-12-fold relative to the ε3 allele. Work investigating changes in blood-CNS communication across aging found youth-associated blood-borne proteins were sufficient to revitalize aged brains. It is currently unknown whether additional systemic states can be manipulated for CNS therapies. We hypothesized that the plasma proteome differs between APOE4 and APOE3 individuals, and these systemic changes account for differences in brain function according to genotype. Aptamer-based profiling of human APOE4/4 and APOE3/3 plasma identified differentially abundant proteins and canonical pathways linked to CNS functions/processes. Next, we examined the plasma proteome in APOE3 or APOE4 mice and evaluated conserved pathways. To identify molecular processes within the brain regulated by systemic APOE, we characterized hippocampal transcriptomic changes following parabiotic blood-sharing between APOE4 and APOE3 mice relative to isogenic controls. To probe CNS cell types mediating these effects, we isolated hippocampal nuclei from parabionts for snRNAseq. We find that expression of APOE4 is associated with perturbed plasma proteins related to the ECM and inflammation pathways relative to APOE3. Pathways associated with hippocampal APOE3 expression that were disrupted in APOE4 mice were restored following exposure to APOE3 blood via parabiosis. Deleterious phenotypes were identified in the hippocampi of APOE3 mice exposed to APOE4 blood, suggesting that APOE4-associated brain phenotypes are, in part, mediated by how APOE4 alters the systemic compartment. We find that APOE alleles differentially alter the systemic environment to confer changes in brain phenotypes. Ongoing experiments will investigate the protective impact of the APOE3 systemic environment on molecular processes within the APOE4 hippocampus, which may inform our understanding of increased AD risk in APOE4 subjects.

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Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Cell-type specific and activity-dependent characterization of non-coding autism de novo variants in human stem cell-derived neurons

Sarah E. Williams, Justin Koesterich, Linda L. Boshans, Kayla Townsley, Anat Kreimer, Kristen Brennand, Nan Yang

Background: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder with a complex genetic architecture. Thousands of non-coding de novo variants (DNVs) have been identified (An et al. 2018), but the functional contribution of these DNVs to ASD etiology remains uncertain. Regulatory activity is highly context-dependent, so to determine whether non-coding DNVs may impact gene regulation in a cell type relevant to ASD, our lab annotated the enhancers present in human stem cell-derived excitatory and inhibitory neurons, at baseline and depolarized states, and intersected these results with the 255k ASD DNVs.

Methods: Using a massively parallel reporter assay (MPRA), we will determine whether these non-coding DNVs found in neuronal enhancers alter cis-regulatory activity in glutamatergic or GABAergic human neurons in baseline or activated states. Further, we performed the activity-by-contact model to identify the genes regulated by DNV-containing enhancers. To validate cis-regulatory activity and to compare trans-effects on downstream gene networks, a CRISPR inhibition screen will be performed targeting a subset of ASD DNV-containing enhancers and their predicted gene targets.

Results: We identified 2,495 ASD DNVs within neuronal enhancers, hundreds being cell-type specific or activity-dependent. Gene-enhancer mapping revealed that a subset of DNV-containing enhancers is predicted to regulate high-confidence ASD genes.

Conclusions: I hypothesize that ASD DNVs will have context-specific effects on enhancer activity and subsequent gene expression in human neurons, with a modulatory impact on genes and gene networks associated with ASD. These results would indicate a functional role for non-coding de novo variation in autism etiology.

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Unbiased Identification of a Novel Hypothalamic Nucleus That Regulates Persistent Stress Sensitization Following Trauma

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BACKGROUND: Severe stress can lead to long-term enhancements in stress responses, contributing to the development of mental health conditions. To deepen our understanding of these changes, we examined whole-brain activity using iDISCO, revealing the anterior hypothalamic nucleus (AHN) as a potential regulator of heightened stress responses in trauma-exposed mice. To further understand how the AHN contributes to persistent fear and anxiety-like states following severe stress, we examined the functions of GABAergic and glutamatergic AHN neurons.

METHODS: GAD2-Cre and vGlut2-Cre mice experienced a trauma of 10 strong footshocks. Memory recall was assessed in the trauma environment, anxiety behavior in the light-dark test, and stress sensitization with exposure to novel aversive stimuli. We manipulated GABAergic and glutamatergic AHN neurons using uPSEM/HM3Dq receptors.

RESULTS: Inhibiting GABAergic AHN neurons reduced fear responses and stress sensitization, while activation intensified fear responses. However, manipulating these neurons' activity was without effect on anxiety-related behavior. In contrast, inhibiting glutamatergic AHN neurons reduced anxiety-like behaviors but had no effect on sensitized stress responses.

CONCLUSIONS: Overall, our findings emphasize a pivotal role of the AHN in regulating stress-induced changes in defensive behavior, and indicate that GABAergic and glutamatergic neurons play a role in unique defensive microcircuits within the AHN.

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Investigating the Differential Neurobiological Markers in Prenatal Cannabis Exposed Children during Reward Processing: An ABCD Study

Siddhartha Peri, Karan Lingineni, Ananth Ramakrishnan, Muhammad Parvaz

Background: With greater legalization, prenatal cannabis exposure (PCE) has increased, furthering the risk of intellectual deficits and externalizing behaviors. The impact of PCE on reward processing is unclear with conflicting animal studies and sparse human research.

Methods: We investigated the reward-processing-based neurobiological markers in PCE children using the Adolescent Brain Cognition Development (ABCD) study. We subsampled 25 participants for each group (PCE: μage = 9.95±0.65 years, 44% female; n-PCE: μage = 9.75±0.56 years, 48% female) and used their baseline 2018 Monetary Incentive Delay (MID) fMRI data. Pertinent conditions involved successfully obtaining a monetary reward (R+), unsuccessfully obtaining a reward (R-), successfully avoiding a loss (L+), and unsuccessfully avoiding a loss (L-). We did a group difference analysis between PCE and n-PCE beta contrasts.

Results: In R+ trials, we found PCE hypoactivation in the left middle frontal gyrus (MFG) ($t = 2.10$, $p = 0.022$) and left precuneus ($t = 2.02$, $p = 0.026$). The left MFG was also hyperactivated in the PCE group during R- trials ($t = 2.76$, $p = 0.005$). We observed hyperactivation in the PCE group during L+ trials in the left occipital lobe ($t = 2.69$, $p = 0.006$) and right angular gyrus ($t = 2.51$, $p = 0.009$). L- trials demonstrated PCE hyperactivation in the right hippocampus ($t = 2.87$, $p = 0.004$).

Conclusion: While similar meta-analyses also implicate the MFG, precuneus, and hippocampus, we observed novel differentially activated regions like the occipital lobe and angular gyrus, regions involved in visual and attention processing. We aim to conduct these same analyses with 225 more children and employ dynamic causal modeling analysis involving the left MFG to uncover mechanistic and connectivity differences.

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Full Name	Sita Sadia
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The Role of Plexin Receptors in Glioma Stem Cells

Sita Sadia, Chrystian Junquiera-Alves, PhD Hongyan Zou, MD, PhD and Roland Friedel, PhD

Background: Glioblastoma (GBM) is a rare but aggressive brain tumor that is highly invasive, and its mechanism of invasion is not well understood. Plexin receptors are axon guidance molecules present on the cell membrane. They work with its ligand, Semaphorins to become activated and are involved in many processes such as neurodevelopment, bone homeostasis and wound healing. There are many families of Plexins and Semaphorins. Our interest is in Plexin B2 and Plexin D1 (PB2/D1) because previous studies have shown that they're found to be upregulated in GBM.

Methods: By use of a lentiviral vector and CRISPR, patient-derived glioma stem cell (GSC) lines (SD2, SD3 and SD4A) were engineered to incorporate the PB2/D1 double knockout (dKO). Next, EdU assays were used to look at proliferation rates. Imaging and immunostaining aided in analyzing the cytoskeletal arrangement, differentiation states, expression of PB2/D1 and cell morphology. Lastly, western blot analysis was used to verify the PB2/D1 dKO.

Results: The PB2/D1 dKO shows long projections known as microtube formations (visualized by staining F-actin) and a strong network forming amongst the dKO cells. The nuclei were also smaller which is indicative of differentiation occurring. TUJ-1, DCX stain show neuronal and neural differentiation in SD2 and SD3 GSCs respectively. Immunostaining revealed less expression of PB2/D1. A slight reduction in proliferation rates was seen in the dKO in comparison to Wild-Type (WT) GSCs. The Western Blot showed less protein expression in the dKO further verifying the results.

Conclusions: These findings suggest that PB2/D1 influences the cytoskeletal arrangement, stemness and invasiveness of GSCs.

2024 Neuroscience Retreat

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Socioeconomic Heterogeneity in Adolescents with Family History of Substance Use and their Neurobehavioral Characterization.

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Icahn School of Medicine at Mount Sinai, New York

Summary:

Background & Methods :Family history of substance use (FH-SU) and adverse environmental exposures are known risk factors for the initiation and progression of alcohol use in adolescents. Here, we aim to examine the heterogeneity within adolescents with FH-SU based on sociodemographic,environmental variables using unsupervised learning methods and compare them on neurocognitive and clinical measures.

Results: From the ABCD cohort, we selected 2,718 adolescents aged 9-10 years who endorsed FH-SU and using k-means clustering, based on a set of sociodemographic and environmental variables, and identified 5 subgroups. Subgroup 1 (n=300) and 2 (n=747) comprised of adolescents with strong of school involvement, moderate social engagement and acceptance of parenting; subgroup 3 (n=201) comprised of adolescents with moderate school involvement and limited social engagement, and low acceptance of parenting; subgroup 4 (n= 267) comprised on adolescents with mixed school involvement and low social engagement, and low acceptance of parenting with parents reporting as they were ‘Never Married’; and subgroup 5 (n=443) comprised of adolescents with low school involvement, low social engagement, and low acceptance of parenting.

Comparisons with youth without FH-SU, Subgroups 3 and 4 showed greater impulsivity and higher internalizing and externalizing symptoms, whereas subgroup 4 showed lower cognitive perception of risk. Analyses with other cognitive (e.g., reward prediction error) and neurobiological measures (e.g., neuronal density) are currently underway.

Conclusion: These findings reveal an objective stratification of at-risk populations based on their sociodemographic and environmental features, which may hold implications for targeted interventions and prevention strategies for reducing the risk of alcohol use initiation and progression.

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Full Name	Swati Gupta
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Impairment in adaptive synaptic down-scaling in striatal projection neurons expressing Parkinson's linked LRRK2-G2019S mutation

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Nash Family Department of Neuroscience at Mount Sinai

Cognitive impairment and altered stress responses are observed in young adult male mice expressing the pathogenic Parkinson's (PD)-associated mutation Lrrk2-G2019S, akin to prevalent non-motor symptoms in PD patients. These behaviors depend on corticostriatal circuits which fail to exhibit LTP, potentially attributed to saturation of GluA1-containing AMPARs. This saturation is evident in the abnormal cell-surface accumulation of GluA1-containing calcium-permeable AMPARs, particularly within Lrrk2-G2019S-expressing D1R striatal projection neurons (SPNs), in part driven by impaired trafficking of GluA1-containing AMPARs. Normally, saturation is prevented by homeostatic mechanisms such as synaptic scaling that regulate synaptic strengths by adjusting the levels of surface AMPARs in response to alterations in network activity. Thus, we are testing whether synaptic scaling is impaired in Lrrk2-G2019S expressing SPNs. In mature wildtype cortico-striatal co-cultures, modulation of network activity using either TTX or bicuculline elicited increase or decrease in surface GluA1 levels, respectively as measured by surface biotinylation assay and confirmed in Darpp32-identified SPNs through surface immunolabeling for GluA1. However, in Lrrk2-G2019S SPNs, downscaling of GluA1-containing AMPARs was impaired, while upscaling remained intact. To specifically manipulate D1R-SPN activity in vivo, we used CRE-dependent DREADDs in Drd1a-Cre and Lrrk2-G2019S x Drd1a Cre mice and measured adaptive changes in synaptic strength using whole-cell patch clamp electrophysiology. Consistent with the in vitro results, Lrrk2-G2019S expressing D1R-SPNs exhibited impaired downscaling, while neighboring non-DREADD expressing D2R SPNs remained unaffected by the change in D1R-SPN activity. On-going experiments are probing molecular mechanisms that drive homeostatic downscaling in the striatum, identify how Lrrk2-G2019S disrupts this process, and will test pharmacological approaches that can restore the normal dynamic range for synapse plasticity.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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Title: Cholinergic modulation of frontal sensory cortical projections is associated with post-error attention adjustment

Authors: Tadaaki Nishioka, Leah Waltrip, Yury Garkun, April Serratelli, Samuel Allen, Kevin Norman, Priscilla Maccario, Ting-Jiun Chen, Yulong Li, Takaomi Saido, Joseph Castellano, Schahram Akbarian, Hirofumi Morishita

Background: The anterior cingulate cortex (ACA) plays a crucial role in cognitive control after errors, but the mechanisms modulating ACA neurons for improved performance remain unclear. Our recent study focuses on ACA's top-down frontal sensory cortical projections to the visual cortex (VIS) (ACAvis), revealing their causal role in post-error attention (Norman et al Neuron 2021). However, little is known about inputs activating ACAvis and their contribution to attentional adjustment. Here, we investigated to what extent it serves as the key input onto ACAvis for post-error attentional enhancement.

Methods: Using intersectional viral methods, we screened possible contributions of glutamate, dopamine, acetylcholine (ACh), and norepinephrine by expressing relevant biosensors selectively in ACAvis neurons, conducting fiber photometry during the 5-choice serial reaction time task (5-CSRTT). The causal role of ACh release onto ACA on post-error performance was further assessed by optogenetic suppression of basal forebrain (BF) cholinergic terminals in ACA during 5-CSRTT. RNA sequencing and CRISPR-based receptor knockout in ACAvis were employed to examine the contribution of specific ACh receptors in attentional adjustment.

Results: Fiber photometry revealed elevated ACh release before correct choices following error trials, aligning with ACAvis activation. Optogenetic suppression during this period reduced performance accuracy after errors. Knocking out ACh receptors, specifically subunit alpha7, in ACAvis confirmed its role in attentional adjustment.

Conclusions: Our study emphasizes the pivotal role of BF cholinergic inputs onto ACA neurons, via particularly nicotinic ACh receptors subunit alpha7, in enhancing attentional performance after errors. ACh receptors in frontal sensory projection neurons may serve as potential therapeutic targets for cognitive control deficits in neuropsychiatric disorders.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

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AXONAL PLASTICITY IN LEARNING

Taelor Matos, Adriana Mendez, Jillian Haller, Jake Tetenman, Yacoub Alokam, Ki Goosens, Jessica Ables

BACKGROUND: Fear-learning depends on synaptic changes that lead to lasting modifications at the dendrite and axon. Long-term memory formation depends on local protein translation (LPT) at the synapse, yet, little is known about the role of LPT in presynaptic terminals in learning. Presynaptic plasticity in the medial-habenula (MHb) cholinergic axons within the interpeduncular nucleus (IPN) affects the freezing response during fear conditioning. Furthermore, studies that ablated cholinergic projections from the mHb to the IPN led to impairments in fear-learning. We seek to understand how LPT is regulated in-vivo to determine its role in fear-learning, hypothesizing that synaptic plasticity in the mHb-IPN circuit and the associated behavioral expression of fear relies upon stimulus-induced LPT.

METHODS: We used Translating Ribosomal Affinity Purification (TRAP) to capture RNA transcripts from actively translating ribosomes from cholinergic terminals in the IPN. We microdissected the mHB and IPN from ChAT-NuTRAP mice exposed to cued fear-conditioning or controls and then performed TRAP-sequencing 1h later (n=10 mice/group/sex/sample, biological triplicates). Differentially expressed genes among the fear and control groups are validated using RNAscope in a separate cohort (n=5 mice/group/sex).

RESULTS: TRAP-sequencing data indicates that there are several differentially expressed genes (DEGs) among the fear conditioned and control groups. FosB, a marker of neuronal activation, is upregulated in fear conditioned mice, indicating robust mHB activation with fear conditioning, as expected. Interestingly, the effect is seemingly driven by male mice, although further analysis is needed.

CONCLUSIONS: Our results indicate that fear learning induces LPT in cholinergic terminals within the IPN of ChAT-NuTRAP mice. Our research suggests that LPT may be a potential therapeutic target for neuropsychiatric disease states like PTSD.

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Cannabis Exposure in Humans and Translational Rodent Model Impacts the Placenta Tryptophan Degradation Pathway

Teesta Naskar, Anissa Bara, Randy J Ellis, Yasmin L Hurd

Background:
Cannabis is widely used drug during pregnancy, with an estimated prevalence of 3 to 16% among pregnant women in the United States. Though the long-lasting effect of prenatal cannabis exposure on fetal brain development is evident from clinical and preclinical studies, the underlying molecular mechanism remains unclear. In this study, we explored the effects of prenatal cannabis exposure on placenta across human and rodent models.

Methods: Placental biopsies were obtained from cannabis exposed/non-exposed pregnant women during delivery. Placental specimens were collected between gestational-day 16 and 21 from pregnant rats exposed to vapor containing THC (50 mg/mL) + CBD (5 mg/ml) or vehicle. Proteomics was performed using LC MS/MS on human and rat placental tissue.

Results: 2642 (FDR<0.05) differentially expressed proteins (DEPs) were evident in the cannabis-exposed human placental specimens and 671 DEPs in the rat model (FDR < 0.05). Several common pathways including antigen processing and presentation, Fc gamma R mediated phagocytosis, cholesterol metabolism, SNARE interactions, long term depression and Tryptophan metabolism were impacted both in humans and rats. SNARE protein complex play crucial role in releasing neurotransmitters and dysfunction of this complex could lead to psychiatric disease vulnerability. Close examination of the DEPs involved in tryptophan degradation pathway identified potential candidate proteins such as IDO1, KMO, 3HAAO, and QPRT relevant to kynurenine and serotonin synthesis.

Conclusion: Kynurenine and serotonin are also well known to promote immune suppression, and serotonin-kynurenine balance could play a pivotal role in psychiatric disease particularly in depression. These results provide critical clues to mechanistically explore our previous transcriptomics results that prenatal cannabis exposure impacts the placental immune system, and the placental co-expression gene network are associated with depression in children.

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Full Name	Tessa Spangler
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Department	Neuroscience

Basic behavior tests in ADNP mouse model

Tessa Spangler, Herbert Zheng Wu

BACKGROUND: Autism spectrum disorder is a developmental disorder known to cause intellectual and social disabilities. Mutations in the activity-dependent neuroprotective protein (ADNP) have been associated with autism in children with developmental delay and social difficulties. The ADNP gene plays a critical role in neuroprotection, gene expression regulation, protein translation machinery, and microtubule-assisted proteins. Adult Adnp haploinsufficient mice exhibit social and cognitive deficits including abnormal social recognition and memory. Most of the clinically identified ADNP mutations are truncating mutations that may be translated and are characterized by two distinct and partially opposing classes of genomic DNA methylation signatures. In this proposal, we will evaluate the social and motor behavior of a new mouse model carrying p.Asn832Lysfs*, a frequent mutation with a Class I signature accounting for ~18% of ADNP syndrome.

METHODS: We tested adult homozygous and heterozygous animals carrying the p.Asn832Lysfs* mutation as well as wildtype littermate controls. These tests include open field, elevated plus maze, social memory, rotarod, and Pavlovian fear conditioning.

RESULTS: Our open field results suggest less exploration behavior in homozygous and heterozygous mice when compared to controls. Our elevated plus maze results suggest that the homozygotes and heterozygotes spend more time in the closed arms of the maze than controls. Our fear conditioning results suggest longer freezing times for the homozygotes and heterozygotes versus controls during the learning phase. There are no clear phenotypes demonstrated in social memory or rotarod.

CONCLUSIONS: Our results suggest that the homozygous and heterozygous ADNP mice demonstrate higher levels of anxiety. In the future we plan to study the neural and transcriptomic mechanisms underlying the changes in anxiety level. We will study their higher-level cognitive social behavior in a novel cooperative paradigm we have developed.

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Full Name	Ting-Jiun Chen
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Locomotion-induced enhancement of visual response is mediated by nicotinic activation of deep layer Somatostatin interneurons in mouse visual cortex

Ting-Jiun Chen, Justin Riceberg, Kohei Yoshitake, Tadaaki Nishioka, Yury Garkun, Tatsiana Mankouskaya, Masato Sadahiro, Hirofumi Morishita

BACKGROUND: Locomotion enhances visual-evoked responses of excitatory pyramidal neurons in the primary visual cortex (V1) in awake mice. Previous studies revealed a contribution of locomotion-induced ACh release to V1 to this effect, but the molecular and circuit mechanisms remain poorly understood. Here, we examined the contribution of deep layer of SST interneurons expressing α2 subunit containing nicotinic acetylcholine receptors (nAChRα2) in V1 to the locomotion-induced modulation of visual response.

MEDTHODS: We conducted fiber photometry imaging of ACh-sensor or calcium-sensor expressed in V1 nAChRα2+SST interneurons of awake mice, allowing them to run on a head-fixed running disc. We also examined the impact of enhancing (hypersensitive nAChR α2 knock-in mice) or dampening nACh signaling (by CRISPR-based knock down of nAChRs) in deep layer SST interneuron on GCaMP expressing pyramidal neurons in response to drifting grating visual stimulation when mice are either immobile or mobile on the running disc.

RESULTS: We found that locomotion increases ACh release onto V1 deep layer SST interneurons, and enhances visual response of this cell-type. Notably, enhancing nicotinic signaling in deep layer SST interneurons was sufficient to enhance visual response of V1 pyramidal neurons, while dampening nAChR signaling in the SST interneurons dampened locomotion-induced enhancement of visual responses in V1 pyramidal neurons.

CONCLUSIONS: These results suggest nAChR signaling in deep layer SST interneurons as a key mediator of locomotion-induced visual response enhancement. Given that deep layer SST interneurons provide monosynaptic inhibition onto Parvalbumin expressing interneurons, our study also highlights SST->PV disinhibitory pathway as a possible circuit level mechanism of locomotion-induced visual response modulation.

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Effect of fluoxetine on stress-induced gut pathophysiology

Tory Drescher, Kenny Chan, Lyonna F. Parise, Scott J. Russo

BACKGROUND

Major depressive disorder (MDD) is a debilitating psychiatric condition that is a leading cause of suicidality and disability worldwide and shares high rates of comorbidity with irritable bowel syndrome (IBS), a painful gastrointestinal disorder; recurrent stress serves as a risk factor for both disorders. Chronic, low-grade inflammation is a physiological feature of MDD, and recent work has pointed to stress-induced intestinal permeability and subsequent circulating endotoxins as contributing to this inflammatory state. Despite these novel findings, the biological intricacies of this gut-brain interaction are still relatively unknown, especially in the context of pharmacological intervention. Antidepressants are frequently employed in the treatment of both MDD and IBS indicating their mechanism of action could have implications on the gut-brain axis that have not yet been explored.

METHODS

Here, mice displaying a depression-like phenotype following chronic social defeat stress (CSDS) underwent a two-week course of fluoxetine treatment. Animals were later subjected to additional social stress via a microdefeat. A FITC dextran assay was performed to assess intestinal permeability after stress.

RESULTS

Prior to assessing antidepressant effects, we found that CSDS prompts an immediate increase in intestinal permeability with this phenotype diminishing after two unstressed weeks. Incorporating a microdefeat after these two weeks was effective in reinstating leaky gut and can therefore be utilized in assessing antidepressant effects on gut-brain interplay. Fluoxetine treatment protected animals from microdefeat-induced depression-like behavior.

We plan to further investigate the role of fluoxetine treatment on intestinal permeability using the aforementioned assay.

CONCLUSION

The antidepressant effect of fluoxetine may be partially achieved via its protective role in maintaining intact gut epithelium after chronic stress. This process could prevent the circulation of endotoxins and systemic inflammation that has been historically linked to MDD.

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Prenatal Cannabis Exposure Leads to Immune and Cytoskeletal Disturbances in Human and Rat Models of Addiction

Tracy Okine, Gregory Rompola, Anissa Bara, Jacqueline M. Ferland, Yasmin L. Hurd

Background:
Cannabis legalization has increased due to changing sociopolitical attitudes. This shift has reduced the perceived risks of cannabis, making it the primary substance amongst youths with substance use disorders in the US. Vulnerable populations, particularly pregnant women, are also affected by this trend. Despite extensive research on cannabis and its main psychoactive component THC, the impact on the developing brain remains poorly understood.

Methods:

Human fetal brains were collected from terminated pregnancies of cannabis users, as well as from controls. Using unbiased RNA-sequencing approaches, we explored the transcriptional and epigenetic profiles in the dorsal and ventral striatum, brain areas central to decision making, goal-directed behavior, as well as emotional regulation.

Rat fetal brains: Female Long-Evans rats were exposed to a vapor (containing either THC [50 mg/mL] + CBD [5 mg/ml] or VEH). from gestational day 5 to gestational day 21 for 30 minute sessions, 2x1sec puffs every 5 mins daily.

Results:
Prenatal cannabis exposure induced differential expression of genes related molecular and cellular networks in the dorsal striatum in an upregulated and downregulated mechanisms related to calcium ion transport and the sarcoplasmic reticulum. In the ventral striatum, genes related to dendritic growth and potassium ion were upregulated, and ones related to the cell cycle were downregulated.

Conclusions: These pilot studies suggest specific effects of prenatal cannabis exposure in the dorsal and ventral striatum via regulation of a complex set of networks involved in cell cycle signaling and ion transport. We continue to conduct a similar analysis in rat tissue to determine the causal relationship of THC to the biological alterations evident in with prenatal cannabis exposure in humans.

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Resilient Specific Sex-Conserved Transcriptomic Changes in the Nucleus Accumbens Following Chronic Social Defeat Stress in Mice

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Major depressive disorder (MDD) is a leading cause of disability and a leading contributor to suicide according to the World Health Organization. Chronic stress is a primary risk factor for MDD and is modeled in rodents using the chronic social defeat stress (CSDS) paradigm. This paradigm allows for identifying animals across a continuum of responses from those that develop depression-like behavioral abnormalities, termed susceptible, to those that maintain mostly normal behavioral function, termed resilient. Given that depression is more prevalent in women, it is crucial to investigate potential sex-specific molecular mechanisms underlying susceptibility vs. resilience. We conducted RNA-sequencing on female mice subjected to an adapted model of CSDS and identified transcriptional changes associated with the susceptibility-resilience spectrum across multiple brain regions.

Initial comparison of this new dataset with published findings on male mice replicated earlier findings of striking sexual dimorphism in adaptations associated with susceptibility or with resilience in female vs. male mice in the brain regions studied. Despite this dimorphism, we identified a cluster of genes uniquely upregulated in the NAc of resilient female mice that overlapped ~50% with a previously identified resilient-specific gene network in NAc of male mice. Within this gene network, two key driver genes, Gprin1 and Stx1a, were predicted to regulate other genes in the network. To elucidate the role of these key driver genes, we are investigating the consequences of viral manipulation within medium spiny neuron subtypes of the NAc in both male and female mice prior to CSDS.

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Fear Learning and Extinction in Mice with LRRK2-G2019S, a mutation linked to PD

Victoria Samojedny, Harper Snyder, Swati Gupta, George Huntley, Deanna Benson

Parkinson's (PD) features non-motor symptoms such as depression, anxiety, and cognitive impairments, which may manifest decades before diagnosis and precede degeneration of dopaminergic neurons, the primary cause of motor symptoms. These non-motor symptoms often impact patients' quality of life more than motor symptoms, yet precise neurobiological mechanisms underlying them remain elusive. Our investigation aimed to elucidate whether fear memory and extinction are disrupted in mice carrying the Lrrk2G2019S (GS) mutation, one of the most common genetic determinants associated with familial PD. Wild-type mice and GS mice underwent training on a cued fear conditioning paradigm and subsequent testing for consolidation after 24h, followed by extinction over five days. Our findings reveal that both wild-type and GS mice demonstrate comparable learning abilities at the 24-hour mark, supporting that task acquisition, memory formation and consolidation were unaffected in these mice. However, GS mice exhibited impaired fear extinction compared to wild-type mice, persisting in elevated freezing. Mice receiving no shock, which were included as controls, showed no genotype-dependent differences, ruling out heightened cue sensitivity or generalized freezing in GS mice. Subsequently, both wild-type and GS mice underwent recall testing, returning to the original context where cue-shock association occurred. While wild-type mice exhibited increased freezing, indicative of successful recall, GS mice failed to do so. To assess whether differences in extinction reflected differences in regional activation patterns, we isolated brain regions implicated in the fear circuit – the amygdala, hippocampus, and prefrontal cortex – from both wild-type and GS mice 60 minutes after reinstatement and used Western blot assays to analyze the expression levels of immediate early gene, cFos, and activation of ERK within these regions. These metrics revealed no genotype-dependent differences.

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Bulk and spatial chemical architecture of temporal lobe epilepsy

Watit Sontising, Manuel Gonzalez Rodriguez, Jake Vaynshteyn, Yoav Hadas and Byron Ramirez, Francine Yanchik-Slade, Mohamed Boutaghou, Patrick Hof, Merina Varghese*, Dalila Pinto*, Isaac Marin-Valencia* (*senior authors)

BACKGROUND:Epilepsy affects 1% of the population, with temporal lobe epilepsy (TLE) being its most common form. TLE is characterized by progressive temporal lobe atrophy, resulting in intractable seizures that require surgical intervention in a third of the patients. The pathogenesis of seizure refractoriness remains unknown. In recent years, the metabolic characterization of lesional seizures has become an indispensable tool to develop new diagnostic and therapeutic strategies for individuals with drug-resistant epilepsy in general, and with TLE in particular.

METHODS: Leveraging our expertise in bulk and spatial metabolomics, we have incorporated mass spectrometry methods for in vivo metabolic flux analysis and advanced spatial chemical mapping to dissect the metabolic landscape of the epileptic focus in TLE patients. Integration of spatial chemical maps with cell density maps from immunohistochemical detections of neurons and astrocytes enabled us to pinpoint cellular pathology associated with altered metabolism.

RESULTS: Bulk metabolomic analysis posited anaplerosis as an alternative route to circumvent the defective pyruvate dehydrogenase complex activity in the epileptic tissue. Spatial metabolomic data revealed a heterogeneous metabolic composition within the resected tissue, with non-uniform metabolite distributions particularly pronounced in areas of cellular pathology. Correlational assessments indicated a robust relationship between creatine and phosphocreatine levels with neuronal density, supporting the notion that energy metabolism is significantly impaired in the epileptic zone.

CONCLUSIONS: Our comprehensive approach to dissect the metabolic underpinnings of TLE posits a major role for energy metabolism pathways and constitutes a pivotal resource to identify new biomarkers and therapeutic targets in this condition.

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Parkinson's Disease-associated LRRK2 Forms a Complex with RAB12 to Regulate Primary Ciliogenesis and Centrosome Homeostasis in Astrocytes

Xingjian Li, Hanwen Zhu, Bik Tzu Huang, Xianting Li, Heesoo Kim, Haiyan Tan, Yuanxi Zhang, Insup Choi, Junmin Peng, Ji Sun, and Zhenyu Yue

Background: Leucine-rich repeat kinase 2 (LRRK2) phosphorylates a subset of RAB GTPases, and this phosphorylation is elevated by Parkinson's disease (PD)-linked mutations of LRRK2. However, the precise function of the specific RAB GTPase targeted by LRRK2 signaling in the brain remains to be elucidated.
Methods: Cryo-EM, molecular biology techniques, and in vivo and in vitro models were used.
Results: We solve the cryo-EM structure of RAB12-LRRK2 protein complex and reveal a physiological role of RAB12 in the brain. We find that RAB12 corporates with LRRK2 to inhibit primary ciliogenesis and regulate centrosome homeostasis in astrocytes through enhancing the phosphorylation of RAB10 and recruiting Rab interacting lysosomal protein like 1 (RILPL1), while the functions of RAB12 require direct interaction with LRRK2 and LRRK2 kinase activity. Furthermore, the ciliary deficits and centrosome alteration caused by the PD-linked LRRK2-G2019S mutation are prevented by the deletion of Rab12 in astrocytes.
Conclusions: Our study identifies a central role for the RAB12-LRRK2 complex in regulating ciliogenesis and centrosome homeostasis, and the RAB12-LRRK2 structure offers guidance in the therapeutic development of PD by targeting the RAB12-LRRK2 interaction.

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Full Name	Xueming Hu
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A Spinal Circuit for Identifying and Prioritizing Visceral Pain

Xueming Hu, Xingliang Yang, Hongzhen Hu

Background: Sensory perceptions are regulated by both external and internal cues that are critical to survival and psychological needs. Compared with somatic pain, visceral pain is inescaple and evolutionarily more salient than somatic pain and preferentially processed cognitively in the brain. Interestingly, animal studies showed that noxious stimuli applied in the colon inhibit the nociceptive tail flick reflex in response to noxious temperatures applied cutaneously, suggesting that counter-irritation in the colon can inhibit pain in the skin. However, the neural circuit involved in this phenomenon is not known. This study revealed a unique population of spinal dorsal horn neurons mediating visceral pain but inhibiting somatic pain.
Methods: Tacr3Cre, Lbx1Flpo, Vglut2Flpo, VgatFlpo, ReaChR, DTR mouse lines were used in this study. Somatic pain behaviors were evaluated by mechanical allodynia, thermal hyperalgesia, spontaneous pain, and using formalin test or capsaicin injection. Visceral pain behaviors were evaluated by colorectal distention (CRD)-induced visceromotor reflex (VMR) recording. Aversion behaviors were evaluated by Conditioned place and real-time place aversion. AAV-ChR2, hM3Dq, hM4Di virus were injected in the spinal dorsal horn for both gain or loss of function manipulations. The synaptic connection was detected by patch-clamp recordings with opto-stimulations.
Results: Spinal Tacr3+ neurons form monosynaptic contacts with visceral primary afferents and sense visceral pain stimuli. Intersectional genetic ablation or silencing of spinal Tacr3+ neurons inhibits CRD-induced VMR, but promotes somatic pain responses. Optogenetic or pharmacogenetic activation of Tacr3+ excitatory neurons or PBN terminals is sufficient to induce visceral pain but suppress somatic pain. Pharmacogenetic activation of Tacr3+ inhibitory neurons suppresses somatic pain responses.
Conclusion: Spinal Tacr3+ excitatory neurons mediate visceral pain signaling projecting to PBN. Spinal Tacr3+ inhibitory neurons mediate the inhibition of somatic pain signaling by visceral pain in the colon.

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Full Name	Yang Shen
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Assessing the Role of the Prelimbic Cortex to Understand the Neurobiological Underpinnings of Cannabidiol's Action in Attenuating Opioid Relapse

Yang Shen, Alexandra Chisholm, and Yasmin L. Hurd

Background: Drug addiction is a chronic, recurring condition characterized by compulsive drug use, periods of abstinence, and relapse. Research is exploring the use of Cannabidiol (CBD), a non-intoxicating cannabinoid, as a potential anti-relapse treatment. CBD can reduce cue-induced heroin-seeking behavior. CBD can decrease cravings and anxiety in individuals with heroin use disorder who are abstinent. However, the specific mechanisms responsible for CBD's ability to prevent relapse are not yet fully understood. The objective of the current study was to assess the effects of CBD treatment on heroin-seeking in conjunction with transcriptomic profiling of the prelimbic cortex (PrL).

Methods: Male Long Evans rats were trained to intravenously self-administer heroin over 15 days followed by 14 days of forced abstinence. Rats were acutely administered either vehicle or CBD (5 or 10 mg/kg, i.p) 24 hours prior to a drug-seeking session. Blood was collected 1 hr after the CBD administration, and brains extracted 1.5 hours following the drug-seeking session. Plasma was used to measure endocannabinoid and CBD levels. PrL tissue was dissected and bulk RNA sequencing performed.

Results: All rats exhibited clear heroin self-administration. Both doses of CBD attenuated heroin-seeking during the drug-seeking test when compared to vehicle control subjects. Acute CBD treatment at the 10 mg/kg dose enhanced 7-OH-CBD, anandamide and arachidonic acid levels. Ingenuity pathway analysis revealed that CBD reversed canonical pathway alterations induced by heroin in pathways relevant to G-protein coupled receptor, ERK/MAPK, GABAergic receptor, and synaptogenesis signaling. Additionally, CBD reversed upstream regulator alterations induced by heroin, particularly in transcriptional regulators.

Conclusions: These findings suggest that CBD reduces cue-induced drug-seeking behavior associated with normalizing PrL biological pathways and transcriptional regulators impacted by heroin.

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Full Name	Yolanda Whitaker
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Using sleep quality and 7T MRI to explore structural differences in the Locus Coeruleus in PTSD and Anxiety

Yolanda Whitaker, Philipp Neukam, Korey Kam, Priti Balchandani, James Murrough, Laurel Morris

Background:
Sleep disturbances are common among patients with PTSD and pathological anxiety. Brainstem structures, one being the Locus Coeruleus (LC), involved in sleep/wake regulation are hypothesized to contribute to the development of PTSD and Anxiety. The LC is a major regulator of norepinephrine in the brain controlling bodily arousal states, including sleep-wake cycles. The present study is the first evaluation of structural LC measures in vivo using high field 7T MRI, with self-reported sleep quality in individuals with anxiety and PTSD.

Methods:
The sample included patients with Anxiety-Related disorders (ANX) (N=40, 77.5% female, mean age=31.3) PTSD (N=22, 68.2% female, mean age=35.5), and Health Controls (N=34, 47.1% female, mean age=34.4). Participants underwent an ultra-high field 7T MRI scan to measure LC volume and LC signal intensity. Masks of the LC were automatically segmented using a gaussian mixture modeling and a supervised masking approach. Clinical symptoms related to sleep were measured by the Pittsburgh Sleep Quality Index (PSQI), a self-report measure assessing sleep quality and disturbances. Pearson's correlations were conducted to investigate relationships between LC functioning and sleep symptoms.

Results:
Within the patient group alone (ANX and PTSD combined), sleep quality negatively correlated with LC mask volume [R(44)=-0.299, p=0.048], which was not seen within the HC group. Although not statistically significant, the patient group demonstrated a larger LC volume (mean=0.21) compared to the HC group (mean=0.01).

Conclusion:
This finding suggests that an enlarged LC may play a role in diminished sleep quality within clinical populations. Future research on this topic must be conducted to determine the extent to which there are LC alterations in sleep, in those with pathological anxiety and PTSD.

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Full Name	Yosif Zaki
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Lab	Denise Cai
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Aversive experience drives offline ensemble reactivation to link memories across days

Memories are encoded in neural ensembles during learning and stabilized by post-learning reactivation. Linking recent experiences into existing memories ensures that memories contain the most recently available information, but how neural ensembles integrate memories across time remains unknown. Here we show that in mice, a strong aversive experience drives the offline ensemble reactivation of not only the recent aversive memory but also a neutral memory formed two days prior, spreading the fear from the recent aversive memory to the previous neutral memory.

Using in vivo calcium imaging with Miniscopes, EEG/EMG recordings, chemogenetics, and novel behavioral assays, we tested how memories are integrated across time.

We find that fear specifically spreads retrospectively, but not prospectively, to neutral memories across days. Consistent with prior studies, we find reactivation of the recent aversive memory ensemble during the offline period following learning. However, a strong aversive experience also increases co-reactivation of the aversive and neutral memory ensembles during the offline period, likely linking the memories across days. Surprisingly, we find that this ensemble co-reactivation occurs during bursts of neural activity during quiet wake, but not during sleep. To investigate the contribution of excitatory/inhibitory neurons to ensemble reactivation, we developed a novel technique (i.e., chemotagging), and used this to classify cell types in vivo during the offline period. Finally, inhibiting hippocampal reactivation during this offline period abolishes the spread of fear from the aversive experience to the neutral memory.

These results demonstrate that strong aversive experience can drive retrospective memory linking through offline co-reactivation of recent memory ensembles with memory ensembles formed days prior. This provides a circuit mechanism by which memories can be integrated across days, which lends insight into how the brain can draw inferences about causal associations across long timescales.

2024 Neuroscience Retreat

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Full Name	You-Kyung Lee
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Department	Neurology

Title
Integrated proteomics reveals autophagy landscape and a bipolar disorder risk factor AKAP11 as autophagy receptor controlling PKA homeostasis and activity in neuron.

Authors You-Kyung Lee, Xiaoting Zhou, Xianting Li, Henry Kim, Xian Han, Haiyan Tan, Suiping Zhou, Yingxue Fu, Junmin Peng, Nan Yang*, Zhenyu Yue*

Background Autophagy is a conserved, catabolic process essential for maintaining cellular homeostasis. Malfunctional autophagy contributes to neurodevelopmental and neurodegenerative diseases. However, the exact role and targets of autophagy in human neurons remain elusive.
Methods We performed systemic investigation of neuronal autophagy targets through integrated proteomics. Deep proteomic profiling of multiple autophagy-deficient lines of human induced neurons, mouse brains, and brain LC3-interactome reveals roles of neuronal autophagy in targeting proteins of multiple cellular organelles/pathways, including endoplasmic reticulum (ER), mitochondria, endosome, Golgi apparatus, synaptic vesicle (SV) for degradation.
Result By combining phosphoproteomics and functional analysis in human and mouse neurons, we uncovered a novel function of neuronal autophagy in controlling cAMP-PKA and c-FOS-mediated neuronal activity through AKAP11-mediated degradation of the PKA-RI complex. Lack of AKAP11 causes accumulation of the PKA-RI complex in the soma and neurites, demonstrating a constitutive clearance of PKA-RI complex through AKAP11-mediated degradation in neurons. AKAP11-deficiency causes aberrant PKA activity, disrupts phosphorylation of a set of synaptic proteins, and impairs neurotransmission.
Conclusions Our study thus reveals the landscape of autophagy degradation in human neurons and identifies a physiological function of autophagy in controlling homeostasis of PKA-RI complex and specific PKA activity in neurons. Our findings may provide insight into the molecular mechanism underlying subtypes of bipolar disorder.

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Full Name	Yuan Cheng
Job Title	Post-Doc
Lab	Herbert Wu lab
Department	neuroscience

Title: Neural Mechanisms of leader-follower Dynamics in Cooperative Behavior
Author/s: Yuan Cheng, Herbert Wu
BACKGROUND: How members of a group achieve coordination is a key question in the study of social behavior. A distinct leadership structure is a common strategy to enable effective coordination in flocks of birds, schools of fish, and groups of humans. However, a significant gap exists in the neurobiological understanding of the leader-follower dynamics. Deficits in forming and maintaining these relationships also profoundly impact individuals with neuropsychiatric disorders such as autism. I propose to investigate the neural mechanisms of leader-follower dynamics in mice using a novel cooperative foraging paradigm.
METHODS: In this cooperative foraging task, two mice must navigate to the same reward area from several possible locations collaboratively to collect rewards. Utilizing machine learning tools, we quantified mouse behavior and identified brain areas involved using iDisco whole-mount immunostaining to detect FOS expression. Additionally, we utilized chemogenetics tools to investigate the causal role of the medial prefrontal cortex (mPFC) in cooperative behavior.
RESULTS: Upon behavioral analysis, we observed a stable division of labor emerging over time, with one mouse assuming leadership and preferring rewards. Leadership emergence appears related to motivation differences rather than social hierarchy. Subsequent inactivation of mPFC neurons significantly reduced cooperation and altered the leader-following dynamics.
CONCLUSIONS: Both male and female mice can be trained with over 80% cooperation rates. Well-trained mice adopt a stable leader-follower structure for effective coordination, suggesting that mice employ evolutionarily conserved, stable strategies in cooperation. Chemogenetics reveals that the mPFC may play a key role in the leader-follower dynamics. Further, I will keep investigating the functional roles of the mPFC using calcium imaging and optogenetics. My project will have significant relevance in helping those who struggle with social norms and group behavior, such as individuals with autism.

2024 Neuroscience Retreat

Presented by the Friedman Brain Institute and the Neuroscience Graduate Program

Full Name	Yuefeng Huang
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Title: Sex differences and menstrual cycle effects in cortico-striatal cue-reactivity, reappraisal, and savoring in human addiction

Authors: Yuefeng Huang, Eduardo R Butelman, Ahmet O. Ceceli, Greg Kronberg, Sarah G. King, Natalie McClain, Yui Ying Wong, Maggie Boros, Rachel Drury, Nelly Alia-Klein, Rita Z. Goldstein

Background: Sex differences and hormonal effects may contribute to drug addiction, as women often develop symptoms more rapidly and severely. Additionally, women smokers show increased ventral striatum responses to smoking cues during the follicular phase (high estradiol) and greater success in smoking cessation during the luteal phase (high progesterone). However, men are more vulnerable to overdose deaths and women's underrepresentation in neuroimaging research creates an understudied complex pattern of risk and resilience, especially the related underlying neurobiology, spanning emotional regulation.

Methods: Fifty-one men with heroin use disorder (HUD) and 32 women with HUD or cocaine use disorder (CUD, N=16 each) performed an fMRI drug cue-reactivity, reappraisal, and savoring task. Seventeen women (3 HUD and 14 CUD) were scanned twice (follicular vs. luteal phase). Sex differences and menstrual cycle effects were cluster-corrected to $Z>3.1$, $p<0.05$ and $Z>2.3$, $p<0.05$, respectively.

Results: 1) Drug cue-reactivity: Women>men in the ventromedial prefrontal cortex (PFC), which positively correlated with craving and estradiol level. 2) Drug reappraisal: Men>women in the frontal eye field (FEF)/dorsolateral PFC. Within women: luteal>follicular phase in the dorsal anterior cingulate cortex and inferior frontal gyrus. 3) Food savoring: No sex differences. Within women: follicular>luteal phase in FEF/dorsolateral PFC.

Conclusions: We found heightened limbic drug cue-reactivity driven by estradiol and increased drug reappraisal (cognitive control) activity influenced by progesterone in women, consistent with estradiol's role in craving/drug-seeking behaviors and the protective effects of progesterone in addiction; non-drug reward savoring necessitated more cognitive control during the follicular phase. The results could inform the development of hormonally-informed treatments for women with addiction.

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Full Name	Zhen Wang
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Department	Dermatology

A Mast Cell Sensory Neuron Axis Drives Visceral Pain and Inter-organ Sensitization

Zhen Wang, Zili Xie, Hongzhen Hu, Brian S. Kim

BACKGROUND: Visceral sensory disorders, including Interstitial cystitis/bladder pain syndrome (IC/BPS) and irritable bowel syndrome (IBS) are debilitating conditions with a cardinal painful symptom and functional disorder but unknown etiology. Strikingly, although bladder and colon pathologies exist as isolated clinical entities, they commonly co-occur with each other and overlap in symptom profiles. Neuroimmune interaction has been postulated as an important mechanism underlying somatosensory pain and itch, while lacking in-depth mechanistic understanding on its role in visceral pain and inter-organ sensitization.
METHODS: We interrogated signaling pathway involved in the crosstalk between mast cells (MCs) and visceral nociceptors using genetically manipulated mice, humanized mice, toxin and viral tracing, pharmacological, chemo-genetics, and virally mediated genetic manipulations, as well as neural activity recordings, and in vivo behavioral testing.
RESULTS: Bladder MrgprB2+ MCs -TRPV1+ visceral nociceptor signaling initiated and maintained the sensory neuron hypersensitivity underlying bladder pain and overactivity in IC/BPS. Remarkably, activation of bladder MrgprB2+ MCs induced persistent colonic mechanical hypersensitivity and motility disorders without overt inflammatory episodes. Furthermore, both Cholera Toxin B subunit (CTB) and virally mediated retrograde tracing revealed convergence of bladder and colon sensory innervation at the primary afferent level. Functionally, virally-mediated selective inhibition of TRPV1+ visceral nociceptor in bladder dampened the colonic pain and constipation induced by irritants triggered bladder inflammation. Moreover, leukotriene synthesis was involved in bladder-colon sensitization, but other MCs mediators including histamine were not involved in bladder pain and bladder-colon cross-sensitization.
CONCLUSIONS: Our findings demonstrate that MrgprB2+ mast cell-TRPV1+ visceral nociceptor clusters drive urinary bladder hypersensitivity and inter-organ cross sensitization, highlighting a novel neuroimmunology paradigm for studying interoceptive systems and inter-organ communications.

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multi-modal characteristics of LC with clinical profiles of pathological anxiety

Zihan Zhang, Stuti Bansal, Philipp Neukam,
Priti Balchandani, James Murrough, Yael Jacob*, Laurel Morris*

Substantial evidence has shown that the locus coeruleus (LC) acts as a trans-diagnostic mediator of pathological anxiety and its broader symptomatology. Our multimodal in vivo MRI study of the LC in conjunction with clinical profiles of patients aims to further our understanding of how patient clinical profiles correspond to neuroimaging features.

We recruited n=80 subjects, 29 healthy controls (HC) and 51 patients with anxiety disorders, and collected microstructure, functional and anatomical connectivity (FC), and responsiveness to threat data from 7T scans. We extracted seven neuroimaging features and imputed missing values using KNNImputer from the scikit-learn library in Python. We linked them with 11 clinical features using canonical correlation analysis (CCA) using CCA package from the scikit-learn library.

We obtained seven pairs of canonical variates from both datasets and calculated the correlation coefficients between them: 0.649, 0.441, 0.409, 0.358, 0.294, 0.250, and 0.096. Observing the loadings of the features from both datasets that contribute the most to the first pair of canonical variates, neuroimaging features such as LC Neuromelanin, FC_LC_Amy, and FC_LC_AntInsula have strong positive influence on the first canonical variate while LC_corrected_volume has strong negative influence. Clinical features including ATQEC Activation Control Score and ATQEC Attentional Control Score have strong negative influence on the first canonical variate while PSS score, STICSA Cognitive Sub-Score, STICSA Somatic Sub-Score, MASQ General Distress Score, MASQ Anhedonic Depression Score, and MASQ Anxious Arousal Score have positive influence.

From the preliminary results from running the CCA model, we showed that three features, LC Neuromelanin, LC FC with dorsal Anterior Cingulate Cortex, and LC ODI, from three MRI modalities (MTC, fMRI, and diffusion) are most strongly associated with all the clinical features.

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Piezo1 regulates gut motility and inflammation through the enteric nervous system

Zili Xie, Jing Feng, Timothy J Hibberd, Yonghui Zhao, Kaikai Zang, Xueming Hu, Xingliang Yang, Fang Gao, Nick J Spencer, Hongzhen Hu

BACKGROUND: Mechano-transduction, or the conversion of physical forces into biochemical signals, is essential for a variety of physiological functions such as hearing, touch, and gastrointestinal (GI) motility. The ability to sense luminal pressure in the GI tract is essential for proper peristalsis, digestion, and waste elimination. The enteric nervous system (ENS), known as the "second brain" in the gut, regulates GI motility, immunity, and barrier integrity. However, the molecular and cellular basis of mechanosensitivity in the ENS is poorly understood.

METHODS: We conducted single-cell qRT-PCR to identify the expression of Piezo1 and Piezo2 channels in enteric neurons. Whole-cell current recordings were used to record mechanically activated current mediated by PIEZO channels. We generated intersectional Piezo1flpo::ChatCre::ReaChRmCitrine mice to assess the impact of optogenetic activation of Piezo1+ cholinergic enteric neurons on colon motility. Colonic migrating motor complex (CMMC) recording was performed to study ex vivo colon motility. GI transit test was used to investigate the function of Piezo1 in gut motility in vivo.

RESULTS: Cholinergic enteric neurons functionally express the Piezo1 channels. Optogenetic stimulation of Piezo1+ cholinergic enteric neurons is sufficient to accelerate colon motility both ex vivo and in vivo. In contrast, Piezo1 deficiency in cholinergic enteric neurons reduces in vivo GI transit and the elevated ex vivo CMMC induced by rising luminal pressures. AAV virus-mediated knockdown of Piezo1 function in cholinergic enteric neurons also reduces colon motility. Additionally, Piezo1 mediates exercise-induced increase of GI motility.

CONCLUSIONS: Our findings demonstrate that mechanosensitive Piezo1 channels expressed by enteric neurons are necessary and sufficient for normal GI motility, thereby identifying potential therapeutic targets for the treatment of motility-related GI disorders.