The Friedman Brain Institute *and the*
Neuroscience Graduate Program *presents*

The 14th Annual Neuroscience Retreat

MAY 13th, 2022

Icahn School of Medicine at **Mount Sinai**

The Friedman Brain Institute

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14th Annual Neuroscience Retreat Committee

Retreat Organizers:
Xiaosi Gu, PhD (Psychiatry and Neuroscience)
Roland Friedel, PhD (Neuroscience and Neurosurgery)

Retreat Administrators:
Vena Persaud, Jenny Rivera, Danny Roldan and Veronica Szarejko

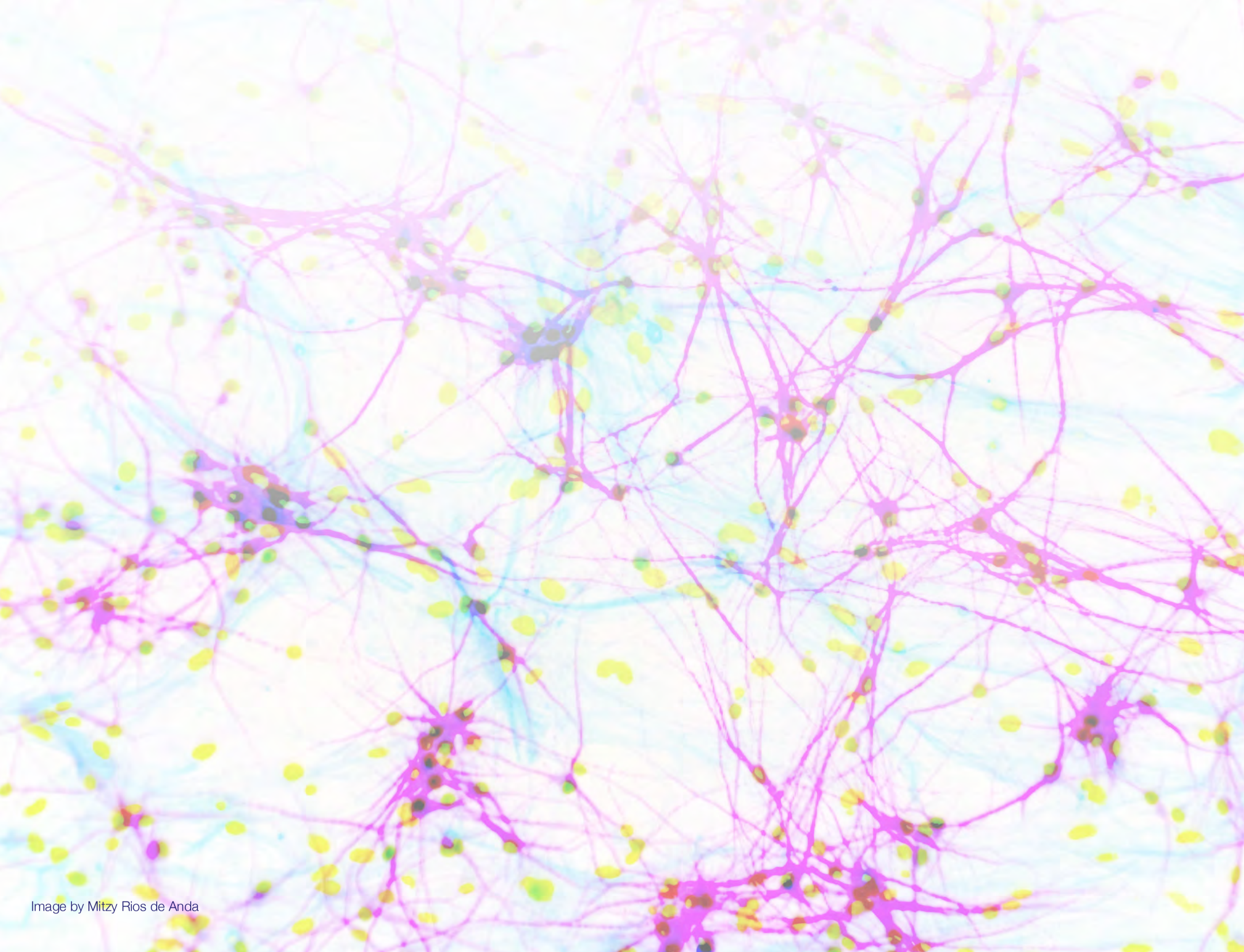

Image by Mitzy Rios de Anda

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AGENDA

8:30am
Check-in at South Hall Lobby, Coffee in Assembly Hall

8:55 am
Brief intro: **Xiaosi Gu & Roland Friedel**

9:00 am
Eric Nestler on Friedman Brain Institute

9:15 am
Paul Kenny on Nash Family Department of Neuroscience

9:30 am
George Huntley on Graduate Student Program

9:40 am
Vanna Zachariou on new T32 Addiction Program

9:50 am
Keynote Speaker 1: Hirofumi (Hiro) Morishita "Maturation of Frontal Circuits for Cognitive and Social Behavior"

10:20 am
Coffee Break in Assembly Hall

10:40 am
Duo 1: Silvia Rubeis & Zhuhao Wu: "Global mapping of altered neural circuits in a mouse model of DDX3X mutations"

11:00 am
Duo 2: Hongyan (Jenny) Zou & Dolores Hambardzumyan:
"Mapping niche-specific immune contexture in GBM"

11:20 am
Kevin Braunscheidel: "Nicotine CCK-ing: evidence for brain-body interactions underlying drug addiction"

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AGENDA

11:30 am
Insup Choi: "Roles of Microglial Autophagy in Alzheimer's Disease"

11:40 am
Data Blitz 1

Audrey Warren: "Structural studies of psychedelic activity at the serotonin receptors 5-HT1A"

Sarah Montgomery: "Dopamine and naturalist behavior"

Leanne Holt: "Elucidation of the Astrocyte-Specific Transcriptome Following Exposure to Cocaine"

Saraswathi Subramaniyan: "Selective vulnerability of excitatory molecular signaling networks in Alzheimer's disease"

Susana Isabel Ramos: "Mapping pre- and postnatal gliogenesis in the human neocortex using snATAC-seq"

Sango Kang: "A two-phase response of microglia to glioblastoma invasion governed by host age, immune status and Plexin-B2"

12:10 pm
Boxed Lunch Start (in South Hall + Lobby)

12:30 pm
Poster Session 1 (in South Hall + Lobby)

1:30 pm
(Assembly Hall)

Zachary Pennington – Postdoc Association

Kelsey Lucerne – MINDS

1:40 pm
Keynote Speaker 2: Erin Rich: "Neurons, populations, and tuning curves: Neural coding for flexible cognition in prefrontal cortex"

2:10 pm
Duo 3: Laura Berner & Vincenzo Fiore: "Too sticky to stop: Impaired belief updating and devaluation in bulimia nervosa"

2:30 pm
Duo 4: Ignacio Saez & Fedor (Ted) Panov: "Human intracranial research in epilepsy patients"

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2:50 pm
Coffee Break

3:10 pm
Megan Fredericks: "Neural circuit in learning"

3:20 pm
JoColl Burgess: "Longitudinal caicum imaging in fear conditioning"

3:30 pm
Data Blitz 2

Sanan Venkatesh: "Transcriptome Wide Association Study of Individually Imputed Genetically Regulated Gene Expression in the Million Veteran Program"

Kaustubh Kulkarni: "Computational mechanisms of craving and addictive decision-making"

Azzurra Invernizzi: "Shifts in local neuroplasticity in World Trade Center responders with post-traumatic stress disorder"

Yosif Zaki: "How does a fearful experience alter past memories?"

Zoé Christenson Wick: "Closed-loop control /seizure and cognition"

Ana Catarina Ferreira: "TIMP2 remodeling of the extracellular matrix regulates hippocampus-dependent cognitive function and plasticity"

4:00 pm
Poster Session 2 / Reception (in South Hall + Lobby)

5:20 pm
Award Ceremony

5:40 pm
End

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Presentations

Kevin M Braunscheidel
Department of Neuroscience

Nicotine CCK-ing: evidence for brain-body interactions underlying drug addiction

Background: In addition to the direct effects of nicotine on hedonic neurocircuitry, recent evidence implicates the periphery in nicotine habit formation. Circulating cholecystokinin (CCK), an upper-gut satiety-signaling hormone, levels are disrupted in smokers. Yet, a causal relationship between the CCK system and smoking has not been explored. Here, we investigate the effect of CCK receptor manipulation on nicotine intake and hypothesize that CCK receptors in gut-innervating vagal sensory neurons potentiates nicotine signal transmittance similar to CCK's regulation of appetite.

Methods: We used an enzyme immunoassay to detect plasma CCK levels in nicotine (1.5 mg*kg-1,IP)-treated mice. We then stimulated CCK receptors using the periphery-restricted agonist, CCK-8 (10 µ*kg-1,IP) and measured the effect on nicotine self-administration and conditioned place aversion. In a separate study, CCKR+ nodose ganglia were selectively ablated using CCK-saporin prior to testing nicotine-related behaviors. Finally, snRNAseq was performed on the nodose ganglia following a single nicotine injection.

Results: Nicotine increased postprandial, but not fasting plasma CCK concentrations. Enhancing peripheral CCKR signaling decreased, whereas systemic CCK receptor blockade or selective nodose CCK receptor-expressing neuronal knockout increased, nicotine related behaviors. Finally, a single nicotine injection drastically altered the transcriptional profile of the nodose ganglia.

Conclusions: Peripheral CCK receptors regulate nicotine intake due in part to actions on vagal sensory afferents. The existence of this novel "bottom-up" regulation of nicotine intake by circulating hormones and the nodose ganglia may prove useful for the development of novel addiction therapies for two reasons: first, direct vagal stimulation has been validated as a treatment for other neurological disorders; and second, CCK levels & vagal activity can be altered by non-invasive means.

Insup Choi
Department of Neurology

Autophagy restricts senescence and enables microglia to engage amyloid plaques in neuroprotection

Background: Microglia are essential for maintaining brain homeostasis, but when dysregulated, exert pathogenic functions in Alzheimer's disease (AD). Recent evidence has implicated senescent/dystrophic microglia in the pathogenesis of AD. It is unclear, however, whether microglial senescence is a cause or consequence of AD pathogenesis. Autophagy is a cellular degradation pathway that clears up protein aggregates and damaged cellular organelles. Autophagy is known to exhibit anti-aging/senescence effects. Here we report that autophagy restricts cellular senescence of microglia and confer neuroprotection in mouse models of AD.

Method: To examine the roles of autophagy in microglial senescence, we have established a microglia-specific autophagy-deficient mouse line using tamoxifen-inducible Cx3cr1CreER mice and Atg7Flox/Flox mice. To determine the impact of senescent microglia on AD, we crossed microglia-specific Atg7-deficient mice with 5xFAD mice which recapitulate amyloid plaque pathology in human AD.

Results: Cellular senescence-associated phenotypes, such as reduced proliferation, increased level of p21Cip1/Cdkn1a, a well-known cyclin-dependent kinase inhibitor that causes cell-cycle arrest and cellular senescence, accumulation of lipofuscin, and reduced the complexity of branch morphology, were observed in autophagy-deficient microglia at 6- and 12-months after silencing Atg7. Further, through single-cell RNA sequencing, we identified senescence-associated microglia (SAM) in Atg7-deficient microglia. Lastly, AD-associated phenotypes, including levels of oligomeric amyloid-beta, phosphor-Tau, and dystrophic neurites, were increased in 5xFAD mice harboring Atg7-deficient microglia compared to normal microglia.

Conclusion: Our study demonstrates that autophagy prevents microglia senescence, protecting the brain against AD.

Megan Fredericks
Department of Neuroscience

The impact of pathway specific chemogenetic inhibition of amygdala to ventrolateral PFC projections on probabilistic learning

Background: In non-human primates both the amygdala and ventrolateral prefrontal-cortex are required for probabilistic reward learning. There are extensive connections between these two regions that are reciprocal, such that information is sent from amygdala to ventrolateral prefrontal cortex, and from ventrolateral prefrontal cortex back to amygdala. We hypothesize that amygdala is responsible for maintaining the current stimulus value and that during learning inputs from amygdala are essential for providing feedback information (reward/no-reward) to ventrolateral prefrontal cortex (VLPFC). By contrast, VLPFC maintains a representation of the choice that was made, and updates stored representations of stimulus value based on feedback.

Methods: We developed a touch screen based dynamic two-choice probabilistic learning paradigm where the time between making a choice and receiving a reward was manipulated. After macaques completed training and testing for non-specific effects of the activating ligand, DCZ, animals underwent surgery. Here we introduced inhibitory chemogenetic receptors into amygdala to ventrolateral projections by bilaterally injecting a retrograde CAV- 2 Cre into ventrolateral prefrontal cortex, and a cre-dependent hM4Di virus into bilateral amygdala.

Results: Following surgery, when DCZ is administered to macaques, extending the time between choice and reward impacts the animal's ability to learn stimulus reward associations. This remains true on different versions of the tasks with different parameters. Discussion: Our data indicate that projections from amygdala to VLPFC are essential for associating feedback information with prior choices during probabilistic learning, especially when there is a delay between a choice and feedback. The impairments seen are attributed to an impairment in learning as the animal's motivation and task completion time are not altered following DCZ administration.

JoColl A. Burgess
Department of Psychiatry

Longitudinal recordings of in vivo calcium dynamics of basolateral amygdala neurons during unpredictable and predictable fear conditioning

Background: Pavlovian fear conditioning is used to explore the mechanisms that underlie aversive learning and memory, but it typically uses predictable sensory cues to induce learning. In the real world, cues that predict danger rarely have temporal predictability, and environmental unpredictability enhances aversive memory. Despite this, it is unknown how unpredictability leads to stronger aversive memories. The basolateral amygdala (BLA) is one brain region that contributes to aversive memory formation. Here, we compare local network dynamics in the BLA during predictable versus unpredictable fear conditioning.

Methods: We injected AAV in the BLA of CB57BL/6 male mice to express GCAMP6s. A microendoscopic fi¬ber and lens were placed over the BLA to visualize calcium activity during fear conditioning (Day 1) and a long-term auditory memory test (Day 4). Mice received either predictable (n=5; 6 tones presented with footshock always 20-s after tone onset) or unpredictable (n=5; 6 tones with footshock either 6, 12, 18, 24, 30, or 36-s after CS onset) fear conditioning. The memory consisted of 10 tones (40-s) presentations.

Results: We found a sub-population of BLA neurons that exhibited elevated CS-US calcium responses in fear conditioning and recall ("Winners"), also spatially clustered. Another BLA neuronal population exhibited tone-shock convergence during training but failed to display tone responses during recall ("Losers"). However, the overall level of tone-shock convergence within single neurons was low across both Winners and Losers. Predictable and unpredictable training resulted in similar proportions of Winners and Losers, but Winners from mice that received unpredictable training exhibited more correlated activity during the tone, as well as greater 'emergent' convergence across Winner neighbor pairs.

Conclusions: The overall number of neurons recruited to an aversive memory is stable across different memory strengths, but the local network dynamics supporting those memories differ in essential ways. Our data suggest that spatially clustered units form weak versus strong memories differently when developing weak versus strong memories.

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Data Blitz

Sanan Venkatesh
Genetics and Genomic Sciences

Transcriptome Wide Association Studies of Individually Imputed Genetically Regulated Gene Expression in the Million Veteran Program

Most neuropsychiatric disorders are moderately heritable but characterized by many genetic risk variants with weak effects. As such, it is difficult to point to direct causes or elucidate mechanisms of action. Despite the ease in gathering genetic data from humans, genetic data does not easily explain mechanistic effects. Gene expression on the other hand, which can more easily explain mechanistic effects, is harder to gather, especially in brain regions that are critical to the understanding of neuropsychiatric disease. To address this, we developed methods to impute genetically regulated gene expression (GReX) from genotypes and imputed GReX in over 440,000 European individuals in the Million Veteran Program (MVP) for a wide variety of tissues and cell types.

We use EpiXcan (based on PrediXcan) to develop machine learning models from training genotype, expression, and epigenetic data. We use custom scripts to impute individual GReX and perform a variety of downstream association analyses, including GReX Phenome Wide Association Studies (PheWAS) and Transcriptome Wide Association Studies (TWAS). Results show an overlap in Schizophrenia genes identified by individual level TWAS and those identified by summary level TWAS informed by GWAS. Inverse-variance metaanalyzed single gene imputation efforts across ancestries confirm clinical results obtained from COVID-19 positive individuals in both IL10RB and IFNAR2. GREx PheWAS for these particular genes using a novel negative binomial distribution for phecodes confirm COVID-19 related phenotypes. Finally, we describe various enriched pathways found in a COVID-19 TWAS, including immunological pathways.

GReX presents a unique solution to integrate effects across the genome and increase sample size in gene expression analyses. We are pursuing the creation of additional EpiXcan models, improved statistical methods for downstream association analyses, and replication efforts across biobanks. We plan to perform these analyses in all ancestries, available EpiXcan and PrediXcan models, and phenotypes.

Kaustubh Kulkarni
Department of Neuroscience

Computational Mechanisms Underlying Drug-Based Decision Making and Momentary Craving in Chronic Cannabis Users

Background: Craving is a core feature and a key target of investigation in understanding addiction. However, to date, the computational mechanisms underlying craving remain largely unknown. In this study, we developed a novel computational approach to test the hypothesis that momentary drug craving arises from discrepancies between expected and received drug rewards, i.e., drug-related prediction error (PE). Methods: We recruited cannabis users (n=37) through a web-based research platform (Prolific). Participants completed a modified two-armed bandit task with either drug/money rewards and intermittent self-reports of craving, as well as surveys assessing baseline craving, use, and demographic information. Four candidate temporal difference reinforcement learning (TDL) models were utilized to track values, and prediction error signals were then used to generate predictive models of momentary craving.

Results: The TDL model with separate learning rates for +/- prediction errors (PE) was overall the best fit for participant choices for both conditions ((BIC) _best≈ 96.9; (BIC) _alt≈98-108). There were significant differences in parameter estimates for learning rates for the +/- PEs. Importantly, we found that the best performing craving model ((BIC) _best≈65; (BIC) _alt ≈70- 175) included choice values, PEs, and temporal delay of rewards, and outperformed a model with only cue effects.

Conclusions: Our results provide the first computational evidence supporting a hypothesis that momentary craving evoked during a drug-based decision-making task is best accounted for by a mental model that computes the deviations of outcomes from one's expectations about drug rewards. The computational model proposed here thus provides a concrete, mechanistic link between subjective craving state and addictive decision-making.

Azzurra Invernizzi
Department of Neuroscience

The impact of pathway specific chemogenetic inhibition of amygdala to ventrolateral PFC projections on probabilistic learning

Background: In non-human primates both the amygdala and ventrolateral prefrontal-cortex are required for probabilistic reward learning. There are extensive connections between these two regions that are reciprocal, such that information is sent from amygdala to ventrolateral prefrontal cortex, and from ventrolateral prefrontal cortex back to amygdala. We hypothesize that amygdala is responsible for maintaining the current stimulus value and that during learning inputs from amygdala are essential for providing feedback information (reward/no-reward) to ventrolateral prefrontal cortex (VLPFC). By contrast, VLPFC maintains a representation of the choice that was made, and updates stored representations of stimulus value based on feedback.

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Joe Zaki
Environmental Medicine & Public Health

Shifts in local neuroplasticity in World Trade Center responders with post-traumatic stress disorder

Introduction: World Trade Center (WTC) responders have high prevalence (23%) of persistent, clinically significant WTC-related post-traumatic stress disorder (PTSD). Recent structural magnetic resonance imaging (MRI) studies demonstrate anatomical differences between WTC responders with and without PTSD. We used resting state functional (rs-fMRI) to investigate neural mechanisms underlying WTC-PTSD and identify changes in local brain areas associated with WTC exposure.

Methods: Using graph theory analysis of rs-fMRI data, we calculated eigenvector centrality (EC) to measure connectivity in 111 brain areas in WTC responders with PTSD (WTC-PTSD, n = 45) and matched responders without PTSD (non-PTSD, n = 51). Permutation statistics quantified EC differences; partial least squares discriminant analysis (PLS-DA) modeled the divergence in EC values between groups. Associations between WTC-exposure duration (months on site) and EC in identified brain areas were examined using general linear model (GLM) regression, adjusting for medication usage and comorbid depression. Generalized weighted quantile sum (WQS) regression was used to examine associations between an index of PTSD symptoms and EC values.

Results: PLS-DA analysis of EC values enabled effective discrimination (auc: 0.749 (0.651- 0.847)) of WTC-PTSD from non-PTSD; EC in nine brain regions (right/left anterior inferior temporal gyrus, right superior parietal lobule, right anterior parahippocampal gyrus (PHG), right anterior/posterior temporal fusiform cortex, right caudate nucleus, left amygdala (AMG) and brainstem) differed significantly and contributed the most to differentiate functional neuro-profiles between groups. The association between exposure duration and EC differed significantly between WTC-PTSD and non-PTSD in PHG and AMG (p= 0.010, 0.005, respectively). Within WTC-PTSD, the index of PTSD symptoms was positively associated with EC values in PHG and brainstem.

Conclusions: Our results confirm hypotheses about key brain areas associated with PTSD and extend our understanding of neural mechanisms linking WTC exposure with PTSD. Better understanding of neural mechanisms leading to WTC-PTSD would help guide intervention and treatment.

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Data Blitz

Zoé Christenson Wick
Department of Neuroscience

Closed-loop control of inhibitory theta phase locking: Investigating a modulator of seizure activity and cognition

Background: The precise timing of single-unit spiking relative to network-wide oscillations (i.e., phase locking) has long been thought to maintain excitatory-inhibitory homeostasis and coordinate cognitive processes. We recently found that epileptic mice with spontaneous seizures and cognitive deficits show altered inhibitory theta phase locking in the dentate gyrus, but the causal influence of this phenomenon has never been determined. Thus, we aimed to causally test the hypothesis that inhibitory theta phase locking can bidirectionally control seizures and cognitive performance in control and epileptic mice.

Methods: To test these hypotheses, we developed a low-latency closed-loop optogenetic system to bidirectionally control inhibitory phase locking to theta in head-fixed control and epileptic mice navigating a virtual track. Using opto-tagging strategies, we first identified the preferred firing phase of parvalbumin+ and somatostatin+ dentate interneurons in control and epileptic mice. We then applied our closed-loop system to lock the spiking of these dentate interneurons to their preferred or non-preferred phase of theta while measuring seizure activity and accuracy of navigation.

Results: Our data suggests that, in epileptic mice, re-aligning inhibitory spiking to the preferred phase of theta diminishes seizure activity compared to stimulating at a nonpreferred phase of theta. Further, preliminary data suggests that enforcing preferred dentate inhibitory neuron spiking improves performance on a navigation task while locking their firing to a non-preferred phase impairs performance.

Conclusions: Theta phase locking of inhibitory spiking seems to play an important and causal role in the two most concerning elements of epilepsy: seizures and cognitive deficits. Gaining deeper insights into the impacts of inhibitory theta phase locking may reveal its potential as an epilepsy therapeutic uniquely capable of treating both seizures and cognitive deficits.

Ana Catarina Ferreira
Department of Neuroscience

TIMP2 remodeling of the extracellular matrix regulates hippocampus-dependent cognitive function and plasticity

Aging is the major risk factor for neurological disorders such as Alzheimer's disease (AD), and exposure to youthful-blood factors counteracts age-related decline. The blood-borne youth-associated factor, tissue inhibitor of metalloproteinases-2 (TIMP2), was shown to revitalize aged mouse hippocampus, while its depletion impairs long-term potentiation, yet its mechanism of action and how its function relates to age-related disorders remains unclear. To define how TIMP2 regulates hippocampal function, we characterized its source of expression and putative cellular targets. We find that TIMP2 is expressed by adult hippocampal neurons and its deletion alters hippocampal expression in genes related to synapse organization, memory, and neurogenesis. Mice in which TIMP2 is deleted exhibit impaired dendritic spine plasticity and reduced adult hippocampal neurogenesis, with concomitant deficits in hippocampus-dependent cognition. TIMP2-deficient hippocampi exhibit altered levels of TIMP2's target MMP2 with a corresponding accumulation of extracellular matrix (ECM) proteins in contact with synapses, arguing for dysregulated ECM turnover adjacent to synapses. We report that migration of immature neuroblasts is also impaired in the absence of TIMP2, likely as a result of stiffness imparted by dysregulated ECM. Finally, peripheral and hippocampal TIMP2 levels are decreased in mouse models of AD pathology, phenocopying deficits observed in aging and suggesting interactions with pathology. Loss of TIMP2 exacerbates amyloid pathology, and TIMP2 gain-of-function mitigates AD-associated deficits in cognition. Together with new tools we developed, these results help define mechanisms through which TIMP2 regulates hippocampus-dependent function to potentially inform novel therapies for aging and AD-associated therapies.

NIA/NIH, BrightFocusFoundation, Katz-Martin FBI Scholar Award

Audrey Warren
Department of Pharmacological Sciences

The impact of pathway specific chemogenetic inhibition of amygdala to ventrolateral PFC projections on probabilistic learning

Background: The rise of interest in psychedelic medicine calls for further exploration into the mechanisms underlying the therapeutic nature of these drugs. Psychedelic effects are thought to be mediated by the receptor 5-HT2A, but there is compelling evidence that 5-HT1A may also play a role. Studies into 5-MeO-DMT, a psychedelic secreted by the Colorado River toad, show selectivity for 5-HT1A over 5-HT2A. However, the molecular mechanisms of 5-MeO-DMT and other psychedelics at 5-HT1A are enigmatic, requiring further studies into their pharmacological properties.

Methods: Novel derivatives of the psychedelic 5-MeO-DMT were synthesized. The actions of these drugs and existing psychedelics were explored via in vitro functional assays probing Gprotein and beta-arrestin activity and cryo-EM.

Results: A series of 5-MeO-DMT derivatives were screened at 5-HT1A and 5-HT2A in Gprotein and beta-arrestin assays. Structure-activity relationship studies indicate a hydroxyl at the fourth position instead of the fifth, such as seen in psilocin, the psychoactive component of magic mushrooms, results in decreased 5-HT1A potency. Addition of a fluorine at the fourth position results in increased 5-HT1A potency and decreased 5-HT2A potency. A structure of the highest potency 5-MeO-DMT derivative bound to a 5-HT1A G-protein complex was solved to a resolution of 2.85Å, revealing residues critical for compound affinity.

Conclusions: These studies have begun to reveal the structural and chemical determinants of psychedelic activity at 5-HT1A. Additionally, this work has identified a novel psychedelic derivative with selectivity towards 5-HT1A, which can be used in future studies to delineate the precise role of 5-HT1A in psychedelic physiology. 2

Sarah Montgomery
Department of Neuroscience

Innate neural dopamine profiles shape naturalistic behavior and predict individual alcohol drinking

Innate variability in response to reward is a striking but understudied phenomenon. Individual differences can be prominently seen in the emergence of mental health and addictive disorders within the human population. Examination of recreational alcohol use most accurately captures this individual variation; some drink casually while others drink in an uncontrolled or compulsive manner. The mesolimbic dopamine system is critical in encoding the reinforcing properties of rewarding and drug stimuli, yet how innate differences in neural dopamine activity drive the individuation that shapes and defines this phenotypic divergence remains unknown.

Following measurement of individual behavioral responses to natural reward, we electrophysiologically characterize, in vivo, dopamine neurons' activity and their response to ethanol. We then utilize in vivo fiber photometry in freely behaving mice to record projectionspecific dopamine dynamics elicited by natural rewards and investigate how voluntary alcohol drinking is predicted by these dopamine dynamics. Using chemogenetics we manipulate these activity patterns and subsequently control alcohol consumption. Finally, we investigate molecular mechanisms via RNA-sequencing of individual alcohol profiles.

We identify that heterogeneous yet distinct dopamine firing profiles are mirrored by innate behavioral responses to reward. We then establish that individual alcohol profiles are associated with pre-existing dopamine dynamics and find that individuals with a hyperdopaminergic activity profile have a lower neuronal response to alcohol and develop a lower preference for alcohol in the future. Through two distinct chemogenetic manipulations, we prevent, as well as induce, voluntary alcohol drinking.

By assessing the mechanisms underlying innate variability in response to rewardsnaturalistic and drug-this project provides novel insights into the individual dopamine neural dynamics driving the phenotypic divergence we see amongst individuals, specifically those that consume alcohol.

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Data Blitz

Leanne Holt
Department of Neuroscience

Elucidation of the Astrocyte-Specific Transcriptome Following Exposure to Cocaine.

BACKGROUND: Drug addiction represents an enormous healthcare burden. To better understand its biological underpinnings, investigations of the transcriptional response to drugs of abuse have demonstrated lasting changes in gene expression throughout the brain's reward circuitry. Historically focused on neurons, emerging evidence increasingly implicates astrocytes in disorders of the nervous system, including addiction. Indeed, candidate genes in astrocytes have been identified and, furthermore, manipulation of astrocyte function has been demonstrated to influence rodent behavioral responses to cocaine administration. However, the astrocyte-specific transcriptome following exposure to drugs of abuse has not yet been investigated.

METHODS: We utilized whole cell sorting of astrocytes and RNA-sequencing to investigate the astrocyte-specific transcriptome in several key brain regions involved in rewardprocessing, including the nucleus accumbens (NAc) and prefrontal cortex (PFC), following cocaine self-administration, withdrawal, and "relapse". Additionally, viral manipulation of transcription factor CREB activity in NAc astrocytes was performed in combination with cocaine conditioned place preference (CPP).

RESULTS: We determined that astrocytes exhibit a robust transcriptional response, including regionally and contextually-specific transcriptional signatures. Subsequent gene ontology analysis revealed a variety of pathways, including synaptic regulation, calcium signaling, and GPCR signaling in both brain regions as being prominently regulated by cocaine exposure. Subsequent analysis revealed CREB as a predicted upstream regulator of this abnormal transcription. Furthermore, overexpression of CREB in NAc astrocytes resulted in increased CPP for cocaine.

CONCLUSIONS: The astrocyte transcriptome robustly responds to cocaine administration, with both regional and contextual specific signatures, and viral manipulation of astrocytic CREB alters behavioral responses to cocaine. Current studies are directed at the role of astrocytic CREB's contribution to the pathophysiology of addiction.

Saraswathi Subramaniyan
Department of Neurology

Selective vulnerability of excitatory molecular signaling networks in Alzheimer's disease

Background: In Alzheimer's disease (AD), the pathology of hippocampal and neocortical brain areas affected reflect predominant glutamatergic neuronal degeneration in associative cortical areas and the hippocampal formation while inhibitory interneurons are resistant to tau accumulation and degeneration. However, the molecular mechanisms that cause damage and loss of susceptible excitatory neurons are not understood. This project has focused on the molecular mechanisms of vulnerable excitatory neurons and related pathways that regulate tau-mediated neurodegeneration in comparison to inhibitory neurons. Selective molecular excitatory neuronal vulnerability to tau pathology and neuronal loss is crucial for understanding the pathogenesis and progression of AD and identifying potential therapeutic targets.

Methods: We performed cell-specific viral translating ribosome affinity purification (vTRAP) and RNA sequencing, Slice electrophysiology and Immunohistochemistry techniques from frontal cortex to reveal molecular and physiological differences between inhibitory and excitatory neurons, and regional vulnerability using WT animals and tauopathy model, PS19 animals. For molecular profiling using vTRAP, we used AAV9-EF1a-FLEX-EGFPL10a-WPREhGH to target genetically defined neuronal populations in vivo.

Results: vTRAP analysis revealed that the unique molecular changes appeared in excitatory neurons compared to inhibitory neurons. Differential analysis identified genes related to neuroinflammatory and synaptic activity enriched in excitatory neurons of tauopathy animal model. The predominant changes appeared in the frontal cortex compared to other brain regions. The amplitude of mEPSC in the prefrontal (WT vs PS19) is reduced, but not in the hippocampus and visual cortex.

Conclusion: Our data reveal that excitatory neurons in the frontal cortex have predominant molecular and physiological changes.

Susana Isabel Ramos
Department of Pharmacological Sciences

Mapping pre- and postnatal gliogenesis in the human neocortex using snATAC-seq

Background: Prenatal neocortical gliogenesis occurs in the later stages of human gestation, continuing postnatally to expand the macroglial pool. The cellular diversity in these stages remains relatively unresolved compared to earlier stages in which neurogenesis is more prevalent. A recent single-cell transcriptomics study uncovered a multipotent intermediate progenitor cell (m-IPC) population that arises at mid-gestation. It is hypothesized to differentiate into interneuron, oligodendrocyte, and astroglia progenitors; thereby, heralding the start of the gliogenic phase. However, this study was restricted to early- and midgestation and the later fate of m-IPCs is unknown.

Methods: To determine the role of m-IPCs from mid-gestation onwards, we generated a single-nucleus ATAC sequencing (snATAC-seq) atlas of over 37,254 nuclei isolated from the neocortical germinal matrix of non-pathological, postmortem samples ranging from 17 to 28 gestational weeks and 3 to 6 postnatal weeks.

Results: Using trajectory analysis, we observed an m-IPC to interneuron lineage in the prenatal germinal matrix. Postnatally, however, m-IPCs showed commitment towards a glial intermediate progenitor cell (g-IPC) fate with astrogenic and oligodendrogenic potential. Transcription factor (TF) enrichment analysis showed that the TCF12 motif is enriched in the prenatal m-IPC to interneuron and oligodendrocyte lineages. In the postnatal germinal matrix, TCF12 enrichment becomes restricted to the g-IPC to oligodendrocyte progenitor lineage.

Conclusions: Here, we showed that m-IPCs are neurogenic in the prenatal germinal matrix but commit to gliogenesis postnatally. We, moreover, identified TCF12 as a potential driver of oligodendrogenesis in m-IPCs and their postnatal counterpart, g-IPCs. Most importantly, we generated an atlas of normal gliogenesis that will serve as a reference for future disease studies, including our own study into the neurodevelopmental programs hijacked by glioblastoma stem cells.

Sangjo Kang
Department of Neuroscience

Innate neural dopamine profiles shape naturalistic behavior and predict individual alcohol drinking

Innate variability in response to reward is a striking but understudied phenomenon. Individual differences can be prominently seen in the emergence of mental health and addictive disorders within the human population. Examination of recreational alcohol use most accurately captures this individual variation; some drink casually while others drink in an uncontrolled or compulsive manner. The mesolimbic dopamine system is critical in encoding the reinforcing properties of rewarding and drug stimuli, yet how innate differences in neural dopamine activity drive the individuation that shapes and defines this phenotypic divergence remains unknown.

Following measurement of individual behavioral responses to natural reward, we electrophysiologically characterize, in vivo, dopamine neurons' activity and their response to ethanol. We then utilize in vivo fiber photometry in freely behaving mice to record projectionspecific dopamine dynamics elicited by natural rewards and investigate how voluntary alcohol drinking is predicted by these dopamine dynamics. Using chemogenetics we manipulate these activity patterns and subsequently control alcohol consumption. Finally, we investigate molecular mechanisms via RNA-sequencing of individual alcohol profiles.

We identify that heterogeneous yet distinct dopamine firing profiles are mirrored by innate behavioral responses to reward. We then establish that individual alcohol profiles are associated with pre-existing dopamine dynamics and find that individuals with a hyperdopaminergic activity profile have a lower neuronal response to alcohol and develop a lower preference for alcohol in the future. Through two distinct chemogenetic manipulations, we prevent, as well as induce, voluntary alcohol drinking.

By assessing the mechanisms underlying innate variability in response to rewardsnaturalistic and drug- this project provides novel insights into the individual dopamine neural dynamics driving the phenotypic divergence we see amongst individuals, specifically those that consume alcohol.

2022 Neuroscience Retreat

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Multidimensional phenotyping of youth with early alcohol use initiation

Faith Adams, Md Ashad Alam, PhD, Iliyan Ivanov, MD, Muhammad A Parvaz, PhD

Background: Early alcohol use initiation (i.e., sipping) predicts problematic drinking in adolescents. Studies have identified individual environmental (e.g., less restrictive parenting), clinical (e.g., psychopathology) and brain/behavioral (e.g., brain activation and task behavior) factors associated with early alcohol use initiation. However, current knowledge regarding the interplay of, or interactions between, these multifaceted biopsychosocial factors is limited and requires assessments with large and generalizable samples of adolescents using cutting-edge data science approaches.

Methods: In a subsample of 500 participants from the Adolescent Brain Cognitive Development (ABCD) study, we applied Generalized Kernel Machine (GKM), a multivariate data integration approach, to examine triplets from environmental (19 variables), clinical (15 variables) and brain/behavior (49 variables) that best distinguish between alcohol initiators (n=111) and non-initiators (n=389). Subsequently, we explored interactions between variables in each triplet using logistic regressions to examine specific associations.

Results: Of the 13,956 possible triplets, 307 differentiated the groups at p<.05. Some notable triplets that significantly differentiated between groups included those with: (i) more friends who drink, higher stress symptoms, and lower reward-related right rostral anterior cingulate cortex (ACC) activation; and (ii) lower household income, higher total psychiatric symptoms, and lower reward-related medial orbitofrontal cortex (OFC) activation. Across the significant triplets, variables that appeared most frequently were: environmental [school involvement (24 triplets), peers getting drunk (23 triplets), neighborhood safety (23 triplets)], clinical [anxiety disorder (27 triplets), oppositional defiant disorder (27 triplets)], and brain/behavioral [inhibitory control related activations of the anterior insula (22 triplets), and reward-related activations of the nucleus accumbens (19 triplets)].

Conclusions: Application of GKM to multi-dimensional data in a pilot sample considerably reduced the variable space and isolated multidimensional features that significantly differentiated unsupervised initiators from non-initiators.

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Determining correlation between neural activation in parasympathetic signaling brain regions and pancreatic nerve innervation in diabetes

Lucia Alexeyev, Rollie Hampton, Alexandra Alvarsson, Maria Jimenez, Rosemary Li, Kavya Devarakonda, Sarah Stanley

BACKGROUND: Autonomic nerves innervate pancreatic islets and regulate hormone secretion. Studies suggest that a high fat diet (HFD) changes neural input to the pancreas. However, these studies rely on secondary measurements of neural activity and do not explain the direct impact of HFD on pancreatic nerve structure and function. The aim of this study is to determine pancreatic structural and functional changes in a HFD as well as neural changes.
METHODS: C57Bl6 WT mice were fed a 60%-HFD and control diet for four weeks and dissected for immunohistochemistry. Pancreata were immunolabeled, imaged with light sheet microscopy, and analyzed on Imaris. Central nervous system (CNS) samples were labeled with cFos in the dorsal motor nucleus of the vagus (DMV) to assess neural activity before being imaged by fluorescent microscopy and analyzed with Fiji.
RESULTS: In HFD mice, α and β cell volumes, overall islet count, and sympathetic exocrine and β cell innervation modestly increased. Sympathetic α cell innervation significantly increased. Parasympathetic innervation showed a decreasing trend. cFos positive cells showed no significant differences between control vs. HFD groups.
CONCLUSION: β cell volume increased less than expected to compensate for increased blood sugar. Increased sympathetic innervation in α cells corresponds with α cell glucagon secretion, a feature of type 2 diabetes. Lack of parasympathetic changes may suggest a HFD doesn't affect parasympathetic signaling and innervation, or there may be functional changes without structural ones. Future studies will determine pancreatic endocrine and neural changes with long-term HFD and changes in pancreatic nerve function.

2022 Neuroscience Retreat

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Chronic Variable Stress Drives Similar Behavioral and Neuronal Activity Patterns in Parkinson's Disease-Linked LRRK2-G2019S Knockin and Control Mice

Kumayl Alloo, Kyomi Blake, Nikhat Meman, Christopher A. Guevara, Deanna L. Benson, and George W. Huntley

BACKGROUND:

Parkinson's Disease (PD) induces various motor and non-motor symptoms. The latter includes psychiatric symptoms (depression and anxiety) which can precede motor symptoms. But while most research has focused on motor control, the circuit-basis for non-motor symptoms remains obscure.

The G2019S mutation in leucine-rich repeat kinase 2 (LRRK2-G2019S) is one of the most prevalent risk factors for hereditary PD. Additionally, stress is a common risk factor for psychiatric symptoms. However, it is unclear how both risk factors collaborate to produce PD-associated, depression-and anxiety-like behaviors. Here we use a LRRK2-G2019S mouse model and activity-based cFos labeling as a proxy to map and compare circuit activity following chronic stress.

METHODS:

To induce stress, we applied a 28d-chronic variable stress (28d-CVS) paradigm to young adult wildtype and LRRK2-G2019S mixed-sex mice. Following the last day of CVS, we perfused mice and immunofluorescently labeled brains for cFos. Through image analysis, we compared the number of cFos-labeled somata in five brain regions implicated previously in psychiatric-like symptoms: mPFC, dorsal and ventral striatum, amygdala, and ventral hippocampus.

RESULTS:

All five brain regions were labeled and patterns were reproducible within genotypes and

across sexes. However, we found no significant differences between genotypes in cFos labeling in any of the five brain regions. These data are consistent with the absence of genotype-dependent effects on a variety of post-stress behaviors analyzed.

CONCLUSIONS:

These data suggest that following CVS, G2019S and WT mice have similar patterns of neuronal activation. Other brains regions may be contributing to behavioral adaptations, or differences could exist in other metrics like cFos intensity, which was not analyzed. These results were unexpected as there are strong, genotype-dependent differences following chronic social defeat stress. Our data contribute to identifying areas and stimuli that can drive the onset of nonmotor symptoms—areas which may ultimately serve as therapeutic targets for PD.

2022 Neuroscience Retreat

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Title: Multilevel Characterization of Approach-Avoidance Biases Linked to Social Stress

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Background: Under approach-avoidance scenarios, healthy individuals balance their decisions towards the most favorable outcomes. However, individuals with major depressive disorder (MDD) display blunted approach towards rewards and excessive avoidance.

Methods: We combined a platform-mediated avoidance (PMA) task and chronic social defeat stress (CSDS) to assess the impact of social stress on decision-making under approach-avoidance conflict in mice. Following CSDS, mice were classified as resilient (RES) or susceptible (SUS) based on a rapid social interaction test. Next, along with a control group (not receiving CSDS), RES and SUS mice were trained in the PMA task whereby they learn to avoid a tone signaling a footshock by losing access to pressing a lever for saccharine-water. Lever presses and time on platform were recorded as approach and avoidance learning, respectively. After ten days of acquisition, mice received four days of extinction (footshocks were not delivered).

Results: While we did not observe significant differences in the acquisition of avoidance or approach among groups, SUS mice displayed elevated levels of freezing to the tone. Conversely, during extinction, RES mice showed reduced avoidance and increased lever pressing, suggesting facilitation of extinction learning. In contrast, SUS mice exhibited elevated avoidance and blunted lever pressing. Ongoing experiments combining whole brain-wide mapping of neural activity and cell-type-specific chemogenetics aim to reveal brain regions and cell types that signal these biases in SUS or RES.

Conclusions: These findings indicate that RES mice bias their behavior towards approach when contingencies change, whereas SUS mice bias their behavior towards avoidance. Our ongoing work provides a neurobehavioral profile of maladaptive decision-making after social stress and highlights novel neurobiological targets to treat MDD and other stress-related syndromes.

2022 Neuroscience Retreat

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Ensemble-Specific Deficit in Neuronal Intrinsic Excitability in Aged Mice.

Austin M. Baggetta*, Taylor Francisco*, Lingxuan Chen, Steve Ramirez, Roger L. Clem, Tristan Shuman, Denise J. Cai

***These authors contributed equally.**

BACKGROUND: With the prevalence of age-related cognitive deficits on the rise, it is essential to identify cellular and circuit alterations that contribute to age-related memory impairment. Increased neuronal intrinsic excitability after learning is important for memory consolidation, and changes to this process could underlie memory impairment in old age. Some studies find age-related deficits in hippocampal neuronal excitability that correlate with memory impairment, but others do not, possibly due to selective changes only in activated neural ensembles. It is important to measure ensemble-specific intrinsic excitability changes to better understand how aging affects memory processes.

METHODS: We used an activity-dependent virus cocktail of AAV9-cFos-tTA and AAV9-TRE-eYFP that labels neurons expressing the immediate early gene c-Fos in a doxycycline-dependent manner to label CA1 neurons activated during learning. We then recorded their intrinsic excitability 5 hours or 7 days post-training using whole-cell patch-clamp in acute brain slices. A novel object location task was used to assess age-related deficits in hippocampal memory.

RESULTS: We found that normal aging particularly affects neuronal intrinsic excitability in ensemble cells shortly after learning. As predicted, younger mice exhibited temporarily increased excitability of ensemble cells hours after learning, which returned to baseline days later. Aged mice with impaired hippocampal memory performance exhibited deficit in post-learning excitability of ensemble cells. Neuronal excitability of non-ensemble cells remained constant across ages, suggesting that age-related excitability deficit after learning was specific to ensemble cells.

CONCLUSION: These results indicate that CA1 may be susceptible to post-learning changes in excitability with normal aging, and age-related ensemble-specific excitability deficit after learning may underlie memory deficits. This underscores the need to selectively measure ensemble-specific changes in the brain.

2022 Neuroscience Retreat

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Title: The regulation of microglial responses to Alzheimer's Disease by the polycomb repressive complex 2

Authors: Matthew Challman, Pinar Ayata, PhD, Jessica Crowley, Anne Schaefer, MD, PhD

Microglia, the brain-resident macrophages, perform a variety of functions depending on the local environment, which requires crosstalk between external signal transduction and regulation of transcriptional state. This crosstalk plays a key role in the microglial response to Alzheimer's Disease, where microglia respond to extracellular amyloid plaques and adopt a unique transcriptional state, which requires signaling through the Triggering Receptor Expressed on Myeloid cells (TREM2) pathway.

Our lab has shown that region-specific microglial transcriptional and functional states are regulated epigenetically by the polycomb repressive complex 2 (PRC2), which catalyzes the repressive histone modification H3K27me3. Interestingly, loss of microglial PRC2 downregulates many genes in the TREM2 signaling pathway, implicating PRC2 in the transcriptional regulation of amyloid responses. Beyond its epigenetic role, PRC2 has been shown to play a role in the cytoplasm for signaling processes and actin polymerization. These data raise the possibility that PRC2 plays a dual role in regulating amyloid responses in microglia – transcriptional control over TREM2 signaling genes and modulation of cell signaling through this pathway. I hypothesize that PRC2 is required for the microglial response to amyloid pathology. Furthermore, I propose that it regulates this response through nuclear transcriptional control and cytoplasmic signal transduction.

Using an Alzheimer's Disease mouse model with PRC2-deficient microglia, I have shown that microglial PRC2-deficiency disrupts the microglial amyloid response and leads to acceleration of disease pathology. Moreover, treating microglia in culture with PRC2 inhibitors causes rapid functional changes at timepoints indicative of a signaling, rather than transcriptional disruption. These data support a multifunctional and potentially coordinated role for PRC2 in the microglial response to amyloid pathology. If correct, this model would place PRC2 in a unique regulatory position, where its distinct functions of epigenetic regulation and signal transduction converge to control a single functional response.

2022 Neuroscience Retreat

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Microglial Responses to Peripheral Influenza Infection

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As resident macrophages of the central nervous system (CNS), microglia are key regulators of tissue homeostasis through their ability to sense and respond to changes in their local microenvironments. For instance, microglia can detect excessive neuronal activity and help dampen it through the production of adenosine. While many microglial functions are induced in response to local signals, microglia are also capable of sensing changes in the periphery such as infection or tissue damage. However, the functional nature of their response to distant challenges is unknown. We hypothesized that microglia act as sentinel cells of the brain following peripheral infection. We therefore adopted a sublethal peripheral influenza infection paradigm to study microglia and other CNS responses. We used translating ribosome affinity purification (TRAP) to profile the responses of microglia at different timepoints after infection. Microglia activation preceded the peak of peripheral response to the virus as well as the onset of sickness behaviors. Following these early transcriptional changes in microglia, we observed a subsequent reduction in myelin-related genes highly expressed by oligodendrocytes. This was correlated with changes in oligodendrocyte numbers and myelination, suggesting that peripheral influenza infection of the lungs could lead to far-reaching impacts on neuronal health and function. Importantly, our work identifies microglia as an early responding population in the CNS following peripheral infection and motivates additional experiments to investigate their specific contributions to oligodendrocyte and myelin alterations.

2022 Neuroscience Retreat

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RECOVER: A Multi-site Observational Study of Post-Acute Sequelae of SARS-CoV-2 (PASC) Infection in Adults

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Background: Little is still known about the aftermath of COVID-19 infections such as the underlaying pathophysiology. Most common reported symptoms have been related to neurophysiology such as depression, trauma, and brain fog. Therefore, RECOVER aims to better understand individuals infected with Post-Acute Sequelae of SARS-CoV-2 (PASC), characterize PASC's biomechanisms, and be an essential resource for neuroscience researchers.

Method: 17,680 individuals with and without COVID-19 infection will be enrolled across 17 sites in the United States. Participants will complete surveys about their demographics and health, have biospecimen collected for biobanking, and have clinical tests done. If abnormal findings are found, participants will be asked to do tier 2 and 3 surveys and tests for further testing on their PASC infection.

Results: This poster will present the overview of the RECOVER study design and how the study can used as a resource once data collection is complete. Mount Sinai began recruitment in December 2021. Since then, we have enrolled 247 participants, becoming the top recruiter in study. In total, we have 1530 biospecimens in blood, saliva, urine, and nasopharyngeal swabs. 98 participants have triggered tier 2 testings.

Conclusion and Future Direction: Collecting different data types and building a biobank is essential for characterizing PASC. RECOVER will be an invaluable resource for neuroscience researchers to better understand how the brain is affect after PASC infection.

2022 Neuroscience Retreat

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Title: Neural population geometry reveals strong abstraction of context supporting reward encoding in anterior cingulate cortex

Background: Previous work has proposed the importance of random nonlinear mixes of behavioral variables in single units across neural populations, a phenomenon termed "mixed selectivity." However, subsequent studies have also argued for nonrandom mixes of behavioral variables, resulting in apparent disagreement. Here, we analyze the properties of macaque frontal neural populations and discover only semi-random structure, modified to allow flexible interpretation of feedback in a context-dependent manner.

Methods: We analyzed well-isolated single-unit spiketrains in two male rhesus macaque subjects, aged 6 and 10 years; brain regions recorded include the dorsal and ventral banks of the anterior cingulate cortex (ACC), as well as the medial orbitofrontal cortex (OFC), central OFC and insular cortex (IC). Single-unit data were aggregated into pseudopopulations and submitted to several analyses, including recently proposed algorithms designed to identify signatures of abstraction in neural population codes and to test the randomness of mixed selectivity, as well as classic analyses such as representational similarity analysis, support-vector-machine decoding, and single-neuron regression analysis.

Results: Population encoding of context dominates over other behavioral variables in all regions analyzed but is particularly strong in the dorsal bank of ACC and in the IC. The dominance of context encoding is also form of abstraction. Though this emphasis on context reduces the randomness of the population and evinces a "tendency toward" pure selectivity for context, it ensures that information about the present context, necessary for the interpretation of task feedback, is present in all task conditions. Remarkably, this dominant encoding of context is consistent with predictions from separate studies of artificial neural networks.

Conclusion:

Neural population geometry reveals a tradeoff: the flexibility of full randomness is sacrificed to allow organization necessary for flexible stimulus-response pairings.

2022 Neuroscience Retreat

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Exposing the “gap of discovery” between rare and common genetics

Lucia Corte, Paul F. O’Reilly, Judit García-González

BACKGROUND: Complex diseases are influenced by both rare and common DNA variants located across the genome (Musunuru et al, 2019). Different diseases can differ in their genetic architecture, involving the number of DNA variants conferring risk to disease, how common or rare the risk alleles are in a population, and the magnitude of their effect (odds ratio). Assessing the relationship between risk allele frequency and odds ratio across different complex diseases would be useful to (1) better understand their genetic architecture and (2) highlight gaps in the discovery of genetic variants predisposing to disease. However, a systematic assessment of this relationship has not been performed to date. This project aimed to discover different patterns in the risk allele frequencies and effect sizes of genetic variants associated with seven diseases and traits.
METHODS: Thirty studies were reviewed and information about allele frequency and odds ratio was extracted when possible. For four diseases for which data was available, plots comparing allele frequency and odds ratio were generated in RStudio.
RESULTS: Common alleles tend to have lower odds ratios while rare alleles have high odds ratios, as anticipated based on previous genetics research. However, the odds ratio and allele frequency patterns varied based on the population trait prevalence: Rare variants associated with common diseases (such as type 2 diabetes) tended to have lower odds ratios and higher allele frequencies than those found in less prevalent diseases. A ‘gap in discovery’ was observed for depression symptoms.
CONCLUSIONS: Our results highlighted differences in the distribution of rare and common risk alleles and their odds ratio across diseases and suggest such differences may be related to disease prevalence.

2022 Neuroscience Retreat

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Effects of Phenothiazines on TNF-a Secretion in Alzheimer's Disease

S. Cox, D. Gonzalez, and C. Mobbs

Background: Alzheimer's disease is a serious neurodegenerative disease causing major cognitive decline in individuals. Several genetic factors associated with Alzheimer's disease include; the APOE4 gene, amyloid beta plaque build up, and cytokine-mediated microglial inflammation. The cytokine tumor necrosis factor alpha (TNF-α) is key in regulation of immune cells and has been a recent subject of Alzheimer's research. Elevated levels of TNF-a have been implicated in the pathology leading to Alzheimer's disease. Utilizing the CMAP database, we have found several phenothiazine candidates that appear to reduce TNF-α expression.

Methods: To prepare for these experiments we have cultured mice BV2 microglial cells in cell culture media and plated them on 96 well assay plates. Two microliters of each drug and 2 microliters of lipopolysaccharide (LPS) were added to the wells. An MTT assay was performed to assess metabolic activity of cells and an ELISA was performed to quantify TNF-α secretion.

Results: These results include 10 drugs found in the CMAP database. Each drug trial compares the effects of LPS or absence of LPS on TNF-α secretion in cells and the cell viability. A considerable amount of the drugs show protective effects of decreasing TNF-α secretion in BV2 cells, while still keeping the cells viable, compared to the DMSO control.

Conclusion: From these results, we corroborated that drugs, including, mianserin, sulfadiazine, and ciclopirox have the most protective effects and show a promising future for repositioning to treat Alzheimer's Disease. A future direction we will take is performing a cytokine array on the BV2 cells.

2022 Neuroscience Retreat

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Modulation of neuroprotective and neurotoxic microglia subtypes via PU.1 dosage

Jessica Crowley, Pinar Ayata, Matthew Challman, and Anne Schaefer

Microglia are the resident macrophages of the brain and perform critical functions including pruning of synapses and releasing inflammatory cytokines in response to insult. These cells have been shown to be heterogeneous by displaying unique transcriptional and functional patterns in a brain region dependent fashion. Moreover, in the contexts of aging and neurodegenerative disease unique microglia subpopulations arise such as inflammatory and interferon responsive populations. The mechanism by which these diverse subtypes arise remains a critical question.

One possible regulator, and the focus of my work, is the transcription factor PU.1, which controls lineage identity and cell activation state. Specifically, the expression level of PU.1 determines the commitment between myeloid and lymphoid lineages and controls inflammatory transcriptional programs in macrophages. PU.1 is enriched in microglia and recent work has implicated PU.1 expression levels in mediating the risk of developing the neurodegenerative disease Alzheimer's Disease, where the protective variant confers lower expression of PU.1. We have found that the expression of PU.1 in the healthy adult mouse brain is heterogeneous. Moreover, our novel genetic models of microglia specific PU.1 knockdown and overexpression suggest clear differences between PU.1-low and PU.1-high expressing microglia at the transcriptional and functional levels. Collectively, this suggests that PU.1 level may regulate microglia activation states in response to different stimuli, such as inflammatory triggers, neuronal activity and/or amyloid plaques. Based on our preliminary data, we hypothesize that microglia with low PU.1 expression represent a preexisting population in the brain that has neuroprotective activities and an attenuated capacity to engage in pro-inflammatory activation. By understanding the role of PU.1 in regulating microglia functional states in the healthy brain, we can elucidate ways to promote neuroprotective activity in the context of aging and neurodegenerative conditions.

2022 Neuroscience Retreat

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Investigating Region and Cell-Specific Vulnerability in Parkinson's Disease between Midbrain and Hypothalamic Organoids using Democratized Deep Learning Models

Authors: Jillian Darcy, Ricardo Reyes, Lily Sarrafha, Tim Ahfeldt, Joel Blanchard

Parkinson's Disease (PD) is the second-most common neurodegenerative disease. PD is characterized by increased vulnerability of dopaminergic neurons to cell death in the midbrain compared to other brain regions and non-dopaminergic cells. Parkin, a causal gene associated with familial PD, encodes a ligase necessary for regulating mitochondrial health. It remains unclear if a loss of function mutation in Parkin reflects region and cell-type specific vulnerability in early PD development. A major challenge for understanding mitochondrial dysfunction in PD is the objective quantification of subtle mitochondrial phenotypes through fluorescence and electron microscopy. To address this, we trained deep learning models to perform semantic segmentation of mitochondria. Parkin was knocked out in human pluripotent stem cells (hPSCs) using CRISPR technology. The Parkin knock-out hPSCs and isogenic controls were differentiated into midbrain and hypothalamic organoids. Astrocytes were transduced with a genetically encoded fluorescent reporter to visualize the mitochondria, and the electron microscopy images were acquired from axons. First, we successfully fine-tuned MitoSegNet, a pre-trained, ready-to-use deep learning model, to segment fluorescent mitochondria in astrocytes. In a separate experiment, we trained a pre-built model from Segmentation Models, an open-source python-based library, and segmented neuronal mitochondria with 87% accuracy. We found that the Parkin knockout genotype generated different morphological patterns of mitochondria between the midbrain and hypothalamic regions. The Parkin knockout genotype also caused neuronal mitochondria to change morphology in both regions whereas changes in astrocyte mitochondria were specific to the midbrain. Overall, we observed that the midbrain mitochondria experienced a harsher effect whereas the hypothalamus showed more compensatory dynamics. Democratized deep learning tools make it possible for non-machine learning experts to segment and quantify complex organelle morphology. Our results with organoid models suggest that mitochondria may be important for defining brain region and cell-type specific vulnerability in PD.

2022 Neuroscience Retreat

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Dynamic Quantitative Trait Loci Associations Reveal eQTL Variability with Substance Use

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BACKGROUND: Integrating environmental exposures with gene expression analysis is key to understanding the mechanisms underlying genetic risk for complex disorders. To further study the neurobiology underlying substance use, we conducted a search for context-specific eQTLs related to drinking and smoking habits.

METHODS: We used gene expression and whole-genome sequencing datasets from the Genotype-Tissue Expression project. eQTLs were generated for 19,394 samples in 54 tissues from 980 individuals. Environmental variables included drinking and smoking variables. Surrogate variable analysis was run on each expression dataset, preserving each variable of interest. eQTLs were generated with the variable of interest as an interaction term. Here, GxE-genes are genes with at least one gene-level Bonferroni significant eQTL.

RESULTS: Across all tissues, the number of GxE-genes were 15,114 for percent-years drinking, 14,812 for drinking status, 15,571 for drinking daily units, 16,867 for percent-years smoking, 16,393 for smoking status, and 16,785 for smoking daily units. Within tissues, GxE-genes overlapped more with GxE-genes from the same substance category. Tissues with the most GxE-genes were adipose and esophagus for drinking, and esophagus and transverse colon for smoking. Pathways enriched for drinking GxE-genes were eGFR signaling and ciliary landscape in esophagus, and mRNA processing in adipose and esophagus. For smoking, pathways were androgen receptor in transverse colon, ciliary landscape in esophagus, and mRNA processing and adenocarcinoma in both tissues.

CONCLUSIONS: Our results suggest variability in genetic regulation of gene expression across tissues and environmental exposures. This technique can be used for multiple future analyses that wish to integrate gene expression, genetic, and environmental data.

2022 Neuroscience Retreat

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NEURAL MECHANISMS UNDERLYING COMORBID PARKINSON'S AND MELANOMA

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BACKGROUND: Epidemiological studies have shown that patients with Parkinson's disease (PD) have a significantly higher risk of developing melanoma. Alternatively, patients diagnosed with melanoma have a higher risk of having PD in their family tree history. Despite a copious amount of evidence of this 2-way relationship, research on this comorbidity is sparse.

One possible point of convergence lies in the sympathetic nervous system. Sympathetic nerves are present and active in the tumor microenvironment of various cancers. Studies have shown that activating sympathetic axons residing in breast adenocarcinomas increases cancer growth, and that patients with malignant melanoma who take sympathetic activity inhibitors have increased survival rates in comparison to those who do not. Therefore, we hypothesize that LRRK2-G2019S, the mutation that is the most common genetic contributor to PD, increases the risk of developing melanoma by regulating the activity and innervation of sympathetic axons.

METHODS AND RESULTS: To investigate this, we are characterizing melanoma progression and its neural microenvironment in WT and LRRK2-G2019S-knock in (GSKI) mice. Our data show that GSKI mice implanted with melanoma cells have altered patterns of sympathetic innervation, macrophage infiltration, interleukin 17 signaling, and CD103+ T cell activation. These and additional data will be used to establish conditions and timing for testing whether (1) these are LRRK2-G2019S-mediated alterations and (2) whether these alterations, especially those involving the immune system, lie downstream of local sympathetic axonal activity.

CONCLUSIONS: Studying the downstream effects of sympathetic axonal activity and innervation in the melanoma microenvironment will create a fuller understanding of the neural mechanisms connecting PD and melanoma.

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Cortical Circuits Driving Motor Deficits in a Mouse Model of DDX3X Syndrome

Authors: Lauren Dierdorff, Wei Wang, Marta Garcia-Forn, Zhuhao Wu, Silvia De Rubeis

Background: Motor deficits are frequent in intellectual disability (ID). Mutations in the X-linked gene DDX3X cause DDX3X syndrome, a form of ID in females that presents with motor manifestations and brain malformations. The DDX3X gene encodes an RNA helicase regulating mRNA metabolism. Its functions during brain development are emerging. Our lab generated a Ddx3x haploinsufficient mouse (Ddx3x+/− females) with construct validity for loss-of-function mutations. Ddx3x+/− females have motor delays and deficits, and a misplacement of subcerebral projection neurons (scPNs) in primary motor cortex, which are neurons important for motor function. My project seeks to identify the cortical circuits driving motor deficits in Ddx3x+/− mice.

Methods: We first investigated corticopontine circuits. We injected a retrograde virus carrying GFP into the pontine reticular nucleus, a region important for motor behavior and innervated by scPNs. We then performed motor tests and stained for the gene c-Fos to investigate whether the corticopontine neurons are activated by the tasks. We used the same tracing strategy and performed tissue-clearing via iDISCO. Lastly, we performed neurodevelopmental and adult motor tests on a forebrain-specific line (Emx1-Ddx3x).

Results: Corticopontine neurons formed ectopic axon collaterals in the cortex of Ddx3x+/− mice. Execution of certain motor tasks elicited neural activity in the cortex of control mice, however, the c-Fos+ cells did not overlap with corticopontine neurons. Emx1-Ddx3x mutant mice show developmental delays and gait anomalies.

Conclusions: These deficits in cortical development in Ddx3x+/− mice provide basis to dissect the neural substrates of motor deficits observed in DDX3X syndrome.

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2022 Neuroscience Retreat

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TITLE: The paradox of a stable memory representation in the presence of representational drift

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BACKGROUND: Spatial memory is thought to be stored in a stable neural ensemble in the hippocampus. However, recent findings suggest that the firing pattern of the hippocampal ensemble changes across time, despite no change in the environment (i.e., "representational drift"). Most studies characterizing representational drift have animals running on a linear track, without any memory demands. Hence, we ask how imposing memory demands affects representational drift. Does a stable spatial map require a stable hippocampal neural ensemble?

METHODS: We used Miniscopes to record hippocampal activity while mice ran on two circle tracks, each with their own set of environmental cues and water-reward locations. We then used Bayesian decoding analysis to predict animals' locations both within an environment across days and across environments. We also used a dimensionality reduction technique to reduce the neural activity space into low dimensional space.

RESULTS: We found that animals can differentiate the two tracks and show a stable memory of the reward ports for each track. While we observe that hippocampal ensemble patterns change across time for the spatial locations that are not rewarded, our preliminary results suggest that the hippocampal ensemble pattern for the reward locations remains stable across time. In addition, the low-dimensional representation of the neural population dynamics remains stable across days suggesting that there is consistent structure of the firing patterns across neurons despite representational drift.

CONCLUSION: Representational drift is present even when there is demand in remembering spatial maps and the associated reward locations for each environment. However, some aspects of the representation may remain stable despite drift.

FUNDING: NIH

2022 Neuroscience Retreat

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ARID1A Mutation Associated with Shorter Progression-free Survival in Atypical Meningiomas

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Background: The oncologic outcomes for atypical meningiomas range from favorable to grim. Generally, patients that have had a prior recurrence have a substantially elevated risk of a future recurrence. Additionally, certain tumor genomic profiles have been shown as markers of poor prognosis. We sought to characterize the genomic differences between primary and recurrent tumors as well as assess if those differences had implications on recurrence.

Methods: From our institutional cohort, we identified primary and recurrent gross totally resected WHO grade II meningiomas with > 30 days of follow-up. Using data obtained from next-generation targeted sequencing, we compared the mutational prevalence across recurrence status. For a gene of interest, we assessed the time to radiographic recurrence using adjusted cox-regression.

Results: We identified 88 meningiomas (77 primary, 16 recurrent) with a median follow-up of 5.33 years. Mutations in ARID1A found in association with recurrent tumors (7/16 recurrent tumors vs 5/72 primary tumors, p<0.001). In the whole cohort, mutations in ARID1A were not associated with alterations in time to recurrence after adjusting for recurrence status (p=0.713). When restricted to primary tumors, ARID1A is associated with a 625% increase in the hazard of recurrence (HR = 7.26 [1.42-37.0]; p=0.017).

Conclusion: We demonstrate mutations in ARID1A, a chromatin remodeling gene, in a higher prevalence in recurrent tumors. We further demonstrate that when mutations in ARID1A are present in primary atypical meningiomas, these tumors tend to have worse prognosis. Further prospective study may validate ARID1A as a prognostic marker. Additionally, this finding may have implications for the treatment of select meningiomas with HDAC inhibitors that specifically target the alterations in chromatin structure.

2022 Neuroscience Retreat

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Shisa7 expression in the orbitofrontal cortex — a translational target of heroin addiction relevant to drug-seeking and reversal learning identified using machine learning

Randall J. Ellis, Jacqueline-Marie N. Ferland, Joseph Landry, James Callens, Gaurav Pandey, Yasmin L. Hurd

BACKGROUND: Opioid use disorder (OUD) contributes to the death of more than 47,000 Americans per year. Developing novel treatments requires a deeper understanding of the molecular pathophysiology of OUD, a complex disorder that involves dysregulation of reward and neurocognitive processes. A brain region of particular interest for substance use disorders is the orbitofrontal cortex (OFC) which plays a critical role in cognitive flexibility and motivated behavior.

METHODS: We used a machine learning approach with RNA-seq data obtained from human post-mortem OFC tissue to classify subjects as either heroin users or controls based on gene expression patterns and to identify predictive transcripts. We validated the top transcript with a translational self-administration rodent model of heroin use disorder, and overexpressed this transcript to determine causal effects on drug-seeking and reversal learning behavior, along with its effects on the transcriptome.

RESULTS: Machine learning analyses highlighted Shisa7, an auxiliary subunit of GABAA receptors, as predictive of heroin use. Shisa7 was reduced in the human OFC and in the OFC of rats that self-administered heroin. Viral overexpression of Shisa7 in OFC augmented heroin-seeking, along with sucrose reversal learning, demonstrating the direct relevance of this transcript to heroin-related and cognitive behaviors. Moreover, Shisa7 overexpression rescued transcriptomic perturbations induced by heroin self-administration.

CONCLUSIONS: Shisa7 represents a novel, translational neurobiological target related to addiction and cognition, identified using a machine learning pipeline

FUNDING: NIDA, F31 DA051183; T32 GM062754-19

2022 Neuroscience Retreat

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Hippocampal-Entorhinal Desynchronization in Chronically Epileptic Mice

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BACKGROUND: Temporal lobe epilepsy is one of the most common types of epilepsy in adults and causes pervasive memory impairments which significantly impact patients' quality of life. In pilocarpine-treated epileptic mice, we have recently found desynchronized interneuron firing between the CA1 and dentate gyrus regions of the hippocampus (HPC). The medial entorhinal cortex (MEC) is the upstream region sending and receiving direct spatial inputs into and from HPC. However, it remains unclear whether synchronization deficits in HPC reflect impaired inputs from MEC and when these deficits emerge following epileptogenesis. Cognitive processes require precise communication between circuits, suggesting that altered timing between HPC and MEC may contribute to epilepsy-associated cognitive deficits.

METHODS: We have performed simultaneously in-vivo electrophysiology with 512-channel silicon probes in HPC and MEC of epileptic and control mice running in virtual reality. We recorded at two time points (3-wk and 8-wks post pilocarpine) to capture progressive changes during the development of epilepsy.

RESULTS: We found that in HPC, epileptic mice show theta and gamma power deficits early in disease progression, with progressive deficits in theta coherence within HPC. Between MEC and HPC, coherence deficits in epileptic animals emerged later than local HPC deficits and were only detected at the later time point.

CONCLUSIONS: Together, this data reveals a progressive impairment in the timing of MEC inputs into HPC through the development of epilepsy, which may contribute to the altered spike timing we have previously found in epileptic mice. Future analysis will focus on single unit analysis to determine whether sublayers or distinct cell types are specifically altered in epileptic mice.

FUNDING: R01NS116357, CURE Taking Flight Award, AES Junior Investigator Award

2022 Neuroscience Retreat

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Cell type specific functional impact of NRXN1α splicing

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BACKGROUND: Neurexins are critical pre-synaptic cell adhesion proteins involved in organizing the complex synaptic connections in the brain. We are investigating the molecular function of NRXN1 alternative splicing, a complex phenomenon that is fundamental to diverse neurocircuitry and is strongly implicated across neuropsychiatric disorders.

METHODS: Leveraging patient NRXN1+/- hiPSCs with unique loss- and gain-of-function deletions, we applied advance transcription factor lineage-induction protocols to generate human glutamatergic (iGLUT:ngn2) and GABAergic (iGABA: ascl1/dlx2) neurons. We evaluated neuronal function via MEAs and patch-clamp electrophysiology. Currently, we are applying a novel, RNA-targeting CRISPR (CasRx), to manipulate wildtype and patient-specific splicing repertoires.

RESULTS: We observed broad alterations in spontaneous activity of both iGLUT and iGABA NRXN1+/- neurons compared to healthy individuals. iGLUT neurons demonstrated a ~50% reduction in mean firing rate (MFR), while iGABA neurons demonstrated a 2-fold increase in early-induction activity and a ~50% reduction of MFR late-induction. Patch-clamp recordings revealed unchanged passive and excitable membrane properties across iGLUT and iGABA neurons, but dynamic changes in synaptic function. Neurotransmitter measurements revealed a significant decrease in glutamate release probability, and aberrant GABA release.

CONCLUSIONS: Our electrophysiological dissection into complex NRXN1+/- phenotypes revealed broadly altered glutamate and GABA neuronal activity, specifically impacting synaptic function. We are currently evaluating the mechanistic role NRXN1α splicing in regulating excitatory: inhibitory neurotransmission using CasRx to selectively perturb wildtype or patient-specific splice repertoires. Ultimately, we aim to investigate the

functional diversity of individual wildtype and mutant NRXN1α isoforms, and its role in modulating neurotransmission.

2022 Neuroscience Retreat

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Identification and analysis of a cortical subpopulation in a mouse model of DDX3X syndrome

Flores, M., Garcia-Forn, M., Ola, P., Mueffling Von, A., De Rubeis, S.

BACKGROUND: DDX3X syndrome is a rare neurodevelopmental disorder that primarily affects females. It is caused by mutations in the X-linked gene DDX3X. The neurobiological mechanisms underlying DDX3X syndrome remain elusive. Ddx3x (Ddx3x+/- females) mice exhibit developmental and behavioral deficits that closely resemble the clinical phenotype of DDX3X syndrome. Further, Ddx3x+/- pups (postnatal day 3; P3) show a surplus of glutamatergic neurons co-expressing molecular markers that lead to opposite cell fates: CTIP2 for subcortical neurons and BRN1 for intracortical neurons. Little is known about this CTIP2+BRN1+ subpopulation and how it is altered in Ddx3x+/- mice.

METHODS: We examine the co-expression timeline of CTIP2 and BRN1 by immunostaining cortices from Ddx3x+/- and control mice (Ddx3x+/+ females) at different postnatal timepoints. We define the temporal window of neurogenesis for CTIP2+BRN1+ neurons by marking progenitors with bromodeoxyuridine at different embryonic timepoints. To identify the targets innervated by CTIP2+BRN1+ neurons, we trace their projections by injecting a GFP-expressing retrograde AAV into cortical and subcerebral targets of Ddx3x+/- and Ddx3x+/+ mice.

RESULTS: We observed an excess of CTIP2+BRN1+ neurons in the primary motor cortex of adult Ddx3x+/- mice, in line with our previous observations at P3. CTIP2+BRN1+ neurons are decreased in the premotor and primary somatosensory cortices of Ddx3x+/- mice. This imbalance might be due to changes in neurogenesis. We expect this imbalance to also be reflected at earlier postnatal timepoints. Finally, we expect CTIP2+BRN1+ neurons in Ddx3x+/- mice to display altered projections.

CONCLUSIONS: Changes in the CTIP2+BRN1+ cortical subpopulation may underlie the developmental and behavioral impairments in Ddx3x+/- mice. Defining the nature of these neurons and their alterations in Ddx3x+/- mice will enhance our understanding of DDX3X syndrome.

2022 Neuroscience Retreat

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Role of the lateral septum in rodent rearing behavior

Sofia C. Gaydos, Long Li, Scott J. Russo

BACKGROUND: The lateral septum (LS) has been associated with motor activity, anxiety and stress response, while the role of the LS in rearing behavior is unknown. Moreover, the biological significance of rearing behavior is largely understudied, especially at the neurocircuit level.

METHODS: In this study, the neural subtypes and circuit inputs of the lateral septum and its function in rearing behavior were examined through fluorescence in situ hybridization (FISH), retrograde Adeno-associated virus tracer and GCaMP6-based fiber photometry. And the stress effect on rearing behavior was tested after chronic social defeat stress (CSDS). And the stress effect of CSDS was validated using the open field test (OFT).

RESULTS: From the FISH analysis, it was found that most neurons in the LS are GABAergic. The retrograde Adeno-associated virus circuit input tracing revealed 6 brain regions with robust input into the LS. The GCaMP6-based fiber photometry indicates that rearing behavior provokes response of LS neurons. After CSDS, the mouse stayed less time in the center zone of the open field, while there was no difference on rearing behavior before and after CSDS.

CONCLUSIONS: From the experiments conducted above, we found GABAergic neurons in the lateral septum respond to rearing behavior. There are several brain regions showing strong input into LS, which are possibly involved in rearing behavior. Chronic social defeat stress affects anxiety level but not rearing behavior.

2022 Neuroscience Retreat

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Title: Determining the effects of GBA-knockdown on α-synuclein pathology in stem cell derived models of synucleinopathies

Authors: Camille Goldman, Joel Blanchard

Background: A-synuclein aggregation is the primary cellular pathology of synucleinopathies such as dementia with Lewy bodies (DLB) and Parkinson's disease (PD). We still do not understand 1) whether α-syn aggregates are a primary driver or a secondary consequence of disease, 2) how aggregates contribute to neurodegeneration, and 3) why α-syn aggregates in some individuals but not others. In addition to direction mutations to the α-syn gene, numerous studies have identified GBA and APOE as risk factors for DLB and PD. However, no single risk factor is a great predictor of disease, suggesting genetic and environmental interactions likely influence the initiation, severity, and clinical outcomes of synucleinopathies.

Methods: I model synucleinopathies using induced pluripotent stem cell (iPSC)-derived dopaminergic neurons and astrocytes. Since α-syn accumulates in response to loss-of function GBA mutations, I use CRISPR/CasRx mediated knockdown of GBA as a model for synucleinopathy. A-syn aggregation is associated with other neurodegenerative relevant phenotypes, including oxidative stress, lysosomal and mitochondrial dysfunction, and DA neuron-specific death. I examine these phenotypes using genetically encoded fluorescent markers and biochemical assays in dopaminergic neuron and astrocyte monocultures, and in genetically mixed co-cultures to distinguish cell-type specific contributions.

Results: I validated GBA-knockdown CRISPR/CasRx in iPSCs, iPSC-derived astrocytes, and midbrain organoids. Through bulk RNA-seq analysis I identified genes perturbed in response to decrease GBA expression, including another risk factor for synucleinopathies, APOE. I have developed imaging tools to examine mitochondrial and lysosomal dynamics in live-cells and will use them to interrogate the neurodegenerative mechanisms underlying PD and DLB.

Conclusions: I will study GBA knockdown in the context of other PD and DLB associated risk factors: SNCA copy-number variants and APOE allelic variants. By coupling multiple genetic risk factors into a multi-cell type model, I will pioneer new technology and approaches to dissect epistatic mechanisms that influence α-syn pathology.

2022 Neuroscience Retreat

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Title: Common and divergent pathways in early stages of glutamate and tau-mediated toxicities in neurodegeneration

Authors: Kirill Gorbachev, Abhijeet Sharma, Joon Ho Seo, Arthi Ramakrishnan, Eric Schmidt, Li Shen, Ana C. Pereira

Background: The major glutamate transporter in the brain, the excitatory amino acid transporter 2 (EAAT2) that regulates glutamate levels synaptically and extrasynaptically has been shown to be deficient in AD brains. We have shown that astrocytic EAAT2 heterozygous deficiency in mice causes excitotoxicity which leads to accelerated cognitive decline, induces inflammatory dysregulation and transcriptional profile changes that overlaps with human aging and AD. Finding overlapping pathways dysregulated by glutamate dyshomeostasis and NFTs in the excitatory pyramidal neurons of the hippocampus could lead to identification of novel therapeutic targets.

Methods: To investigate the relationship between glutamate dyshomeostasis and tau toxicity we used mouse models of glutamate dyshomeostasis (EAAT2-/-) and mutant tau (P301S) in conjunction with BAC-TRAP technology. We isolated CA3 neuron specific mRNA from the hippocampus of male EAAT2-/- and P301S mice and performed RNA sequencing.

Results: TRAP data revealed pathways altered by EAAT2 deficiency, including NFκB signaling pathways and P301S mutation, including oxidative phosphorylation and mitochondrial disfunction. Among these pathways, the data showed overlaps between EAAT2-/- and P301S. The overlaps included caveolar-mediated endocytosis, the pentose pathways and CREB signaling among others.

Conclusion: These common pathways represent a potential target for ameliorating glutamate-mediated toxicity and tau-mediated toxicity during early stages of AD that need to be further validated in future studies.

2022 Neuroscience Retreat

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CRF neurons establish resilience via stress-history-dependent modulation

Sherod E Haynes, Anthony Lacagnina, Hyun Seo Seong, Muhammad Afzal, Carole Morel, Aurelie Menigoz, Kanaka Rajan, Roger L Clem, Helen S Mayberg, Donald G. Rannie, Larry J. Young, Ming-Hu Han

BACKGROUND: While many researchers explore individual differences in stress vulnerability, one long-standing question is of when does divergence occur? We uncover the unexpected finding that the stress neuropeptide CRF secreting neurons are not only necessary for deciding the fate of stressed mice. We localized the action to the oval nucleus of the Bed Nucleus of the Stria Terminalis (BNSTov).

METHODS: Mice subjected to 10 days of Repeated Social Defeat Stress were assessed via social interaction (SI) and sucrose-preference tests. To simultaneously manipulate and record the activity of BNSTovCRF neurons in vivo, Crf-Cre mice were injected with viral constructs (DREADDs and calcium-indicators) and ferrule cannulae implanted. To record electrical activity of BNSTovCRF neurons, Crf-cre::TdTomato reporter mice were used and cell-attached electrophysiology was used to record the spontaneous firing rate. RNAScope was used to detect Crhr1 RNA within CRH-containing cells.

RESULTS: We observed that BNSTovCRF neurons determined the point at which mice diverge into susceptible/resilient phenotypes in a stress-dose dependent manner ($F(2,201) = 76.63$; $P<0.0001$; $n = 206$). Cell-type-specific chemogenetics reveal the necessity and sufficiency of BNSTov CRF neurons for promoting the development of depressive- and anxiety-like behaviors. Firing rate changes correlated with the emergence of the resilient phenotype. Surprisingly we uncovered that resilient mice that featured Crfr1 had increased prominence on Crf neurons of resilient relative to susceptible mice.

CONCLUSIONS: Altogether these findings reveal that the crf-system plays a fundamental role in the formation of resiliency in stress adaptation, contrary to established work. The novel role of CRF has wide implications for how we think about its role in developing stress-related disorders. This discrete period of neuroadaptation may present a window of opportunity for targeting molecular mechanisms with the possibility of preventing the onset of depression in stress-susceptible populations.

2022 Neuroscience Retreat

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Microglial influence over adapting neuronal response to cocaine

Emma Hays, Hayley Strasburger, Philip Hwang, Anne Schaefer

With repeated administration of drugs of abuse such as cocaine or amphetamines, mice exhibit a successive amplification of locomotor response. Our lab has shown that this phenomenon, termed behavioral sensitization, is further potentiated by the ablation of microglia. In addition to their canonical functions of surveillance and phagocytosis, microglia have recently been identified as modulators of neuronal activity. In support of these findings, my preliminary data show that microglia may alter patterns of Fos expression (Fos is an immediate early gene used to indicate neuronal activity) in neurons in response to acute and chronic cocaine. I will use a lineage-tracing FosTRAP mouse model to discriminate those populations of neurons activated by acute and chronic cocaine administration and observe how these populations are affected by the presence or absence of microglia. Our lab has also demonstrated that microglia can modulate striatal neuron activity by sensing synaptically released ATP and converting it to adenosine, which exerts inhibitory feedback on neurons. To determine if this is the mechanism by which microglia may amplify behavioral sensitization, we will perform locomotor assays and neuronal excitability recordings in response to repeated cocaine in a mouse model where the rate-limiting enzyme for this neuromodulatory process, CD39, is knocked out. Elucidating the mechanisms by which microglia modulate the changing neuronal response to a repeated stimulus like cocaine is important for understanding how their interactions shape neuronal circuit responses and behavior.

2022 Neuroscience Retreat

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Blood-borne regulation of microglial function in aged hippocampus

Brittany Hemmer, Catarina Ferreira, Jeffrey Zhu, Annie Phan, Joseph Castellano

Nash Family Department of Neuroscience, Friedman Brain Institute, Loeb Center for AD

The brain exhibits diminishing function with age that manifests as cellular, molecular, and cognitive changes. Aging renders the brain susceptible to neurological disorders, such as Alzheimer's Disease (AD), for which aging is the strongest risk factor. Given the urgent and unmet need to lessen the impact of AD, novel approaches are needed to curtail the influence of risk factors for the disorder. Emerging evidence has revealed rejuvenation of the aged CNS by exposure to young blood factors, raising the possibility that CNS function can be improved by targeting pathways in the systemic environment. Studies have yet to evaluate how microglia may sense and respond to youth-associated plasma factors. Using heterochronic parabiosis, we find that aged mice sharing blood with young mice exhibit a reduction in microglial activation. Systemic treatments of aged mice with two youth-associated blood-borne factors, TIMP2 or CSF2, decrease microglial activation in hippocampus compared to vehicle-treated aged mice. Upon exposure to aging debris, a subset of microglia acquire a disease-associated microglia (DAM) phenotype thought to be protective. In addition to its role as a secreted protein acting on cells, we find that TIMP2 is expressed by microglia and is a marker of the DAM transcriptional profile, indicating that TIMP2 may play a cell-autonomous role regulating microglial state. Transcriptomic differences were observed between primary microglia isolated from TIMP2 KO and WT mice by RNA-seq. Our current results argue that microglia are responsive to youth-associated plasma proteins and may regulate aging-relevant phenotypes. Characterization of blood-CNS communication may facilitate development of therapies that target detrimental aging processes to limit onset of neurodegenerative diseases.

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2022 Neuroscience Retreat

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Thyroid-stimulating Hormone Receptor Regulates Anxiety

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Background: TSH, released from the anterior pituitary gland, binds to TSH receptors (TSHRs) in the thyroid gland to regulate metabolism. Previous studies revealed TSHR gene expression in non-thyroid tissues, including the brain. However, the functional role of TSHR outside the pituitary is unknown. The object of this study is to examine the contribution of brain TSHR to anxiety.

Methods: To assess anxiety, we administered unpredictable fear conditioning to heterozygous TSHR (HET) and WT female littermate mice. Training consisted of six 40-s tones followed by 1-s foot shocks at unpredictable intervals within each tone. We then conducted contextual and auditory fear recall. In another cohort, we administered a TSHR agonist (MS438) in CB57/6L mice. Mice received either 0, 6.25, 12.5, 25, or 50ug of MS438. One hour after injection, we assessed performance on the elevated plus maze and 1-hr later collected blood. We used RM-two-way ANOVA followed by Tukey's multiple comparison to assess statistical significance.

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Results: HET mice displayed elevated freezing during the contextual and auditory fear tests compared to WT mice. Additionally, a dose-dependent effect of MS438 was observed on the EPM: higher doses of MS438 led to less time spent in the open arms compared to the vehicle-treated mice. Lastly, T3 and T4 serum levels did not differ between treatment groups.

Conclusion: We investigated the role of TSHR in anxiety states using two behavioral tests of anxiety. Collectively, our results suggest that TSHR regulates anxiety.

2022 Neuroscience Retreat

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TITLE: Understanding and Exploring New Strategies to induce hPSCs Differentiation into Interneuron Subtypes

AUTHORS: Ruiqi Hu, Maggie Cai, Linda Lee, Carlos Sanchez-Priego, Yvette Somersel, Alexander Tsankov, Nan Yang

Background: Increasing evidence implicates dysfunction of GABAergic neurons in a host of neuropsychological conditions. Recent advances in identifying genetic risk factors and in human induced pluripotent stem (iPS) cell-based models have given us a unique opportunity to develop in vitro models for mechanistic investigations. To move from the commonplace idea that disturbed excitatory-inhibitory balance is associated with neuropsychological conditions toward a mechanistic understanding of the contribution of different subtypes to unique pathophysiology, it is essential to derive specific GABAergic cell types from human pluripotent stem cells (hPSCs). However, no approach has effectively generated homogeneous populations of distinct GABAergic subtypes.

Methods: Our previous work showed that transient expression of Ascl1 and Dlx2 in hPSCs can generate three largely non-overlapping GABAergic subtypes: CR-, CB-, and SST-expressing neurons. Here, we use single-cell transcriptomics to determine: 1) the origins of subtype diversity; 2) to what extent transcription factor-directed differentiation recapitulates a developmental trajectory.

Results: Ascl1 and Dlx2 rapidly induce marker genes of mesodermal and neuronal cells in hPSCs. As the cells mature, the non-neuronal lineage is largely depleted. Over 80% of the neurons express GAD1/2 and SLC32A1 by week 6 and resemble human hypothalamic interneurons. By contrast, the GABAergic neurons generated using patterning factors to recapitulate early development are similar to human telencephalic neurons. However, this method yields a mixed population consisting of immature neurons and proliferative progenitor cells. We also found that several TFs when expressed in MGE-progenitors, can promote the rapid maturation of neurons while retaining forebrain marker FOXG1 expression.

Conclusions: In this study, we characterized the regional and subtype identity of interneurons generated using the transcription factor-mediated lineage reprogramming method and patterning factors, laying the foundation for further induction of specific GABAergic neuron subtypes. Our study also provides a basis for constructing and selecting models in vitro.

2022 Neuroscience Retreat

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Characterization of Parkinson's disease mutant LRRK2-G2019S in dysregulating microglial secretion of lysosomal proteins

Bik Tzu Huang, Ravi Ghotra, Insup Choi and Zhenyu Yue

Background: G2019S LRRK2, one of the mutant forms of LRRK2 exhibiting increased kinase activity, has been found both in familial and sporadic Parkinson's disease (PD). Accumulating evidence has shown that a subset of Rab GTPases, regulators for intracellular vesicle trafficking, become phosphorylated by LRRK2. We recently found that Rab12 is a physiological substrate of LRRK2 in the mouse brain. In our scRNAseq analysis, we found LRRK2 is highly expressed in microglia of human PD brains. Therefore, we sought to investigate whether and how LRRK2 kinase activity affects Rab12 phosphorylation and subcellular localization in microglia.
Method: We employed primary microglia cultured from G2019S-LRRK2, LRRK2 knock-out (KO) microglia and zymosan, a well-known stimulator for immune cells. After zymosan treatment, we measured the levels of phosphorylation of Rab12 by Western blot. Further, we examined the subcellular localization of LRRK2 and Rab12, in primary microglia or LRRK2 or Rab12-transfected BV2, a microglial cell line, by immunostaining and biochemical subcellular fractionation. Lastly, we did media collection to observe secretion differences between genotypes.
Results: We observed that pRab12 is found primarily in membrane compartments in a subcellular fractionation assay. G2019S-LRRK2 and Rab12 are highly colocalized at Lamp1-positive late endosome/lysosome structures. Also, G2019S-LRRK2 showed higher secretion of lysosomal proteases, Cathepsin D and B in response to zymosan.
Conclusions: Rab12 is a LRRK2 substrate in cultured primary microglia and LRRK2 interacts with Rab12 in the lysosome. Our data suggests that PD mutant LRRK2-G2019S alters microglial secretion of lysosomal proteins.

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Age associated changes to microglia-adenosine based neuromodulation

Philip Hwang, Hayley Strasburger, Ana Badimon, Anne Schaefer

Aging in mice and humans is associated with alterations to neuronal circuit excitability and function, increased seizure susceptibility, and neurodegeneration. Our recent studies have identified microglia as novel regulators of neuronal activity and function, maintaining homeostatic levels of neuronal activation, thereby serving as brake pads for hyperexcitation. Preliminary evidence suggests this neuroprotective function may be altered in aging, potentially as a consequence of inflammatory microglia activation associated with aging and neurodegenerative disease. I hypothesize that microglia play a critical role in aberrant neuronal responses and network dysfunction in the aging brain. In support of this idea, we found that microglia are able to regulate neuronal function in an activity dependent manner by responding to ATP released during neuronal activation and metabolizing it into adenosine, thereby suppressing neuronal activity. We further found that age-associated increase in pro-inflammatory gene expression in microglia is associated with changes in P2ry12 and Entpd1, two key genes of this homeostatic mechanism. Using microglia specific knockout of the rate-limiting enzyme for adenosine generation (Entpd1/CD39), I will investigate the microglial role on adenosine generation in multiple brain regions and its effects on neuronal network function using in vivo recordings. These results will inform further investigations into how age may be affecting this modulatory function of microglia and how it may be inducing changes to P2ry12 and Entpd1. Additionally, given our recent data revealing the presynaptic and postsynaptic role of adenosine on neuromodulation, I will be investigating the microglial contribution to neuronal network function and synchronicity. This information is critical to our understanding of the cellular mechanisms by which microglia regulate neuronal function, leading to the development of novel approaches for the treatment of age-associated disorders.

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2022 Neuroscience Retreat

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Title: Patient-specific vs atlas-based tractography for connectomic subcallosal cingulate DBS

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Background:

Lead implantation surgery for subcallosal cingulate DBS for depression has been optimized using a patient-specific tractography approach. Consistent inclusion of four bundles required to achieve clinical response across studies. [1-3] It is yet unknown if a normative connectomic approach can archive similar clinical results. We, therefore, compared WM activation pathways associated with clinical improvement using individual and normative connectome datasets.

Methods:

Thirty-three patients with personalized tractography and 6-month clinical outcomes data (21 responders and 12 nonresponders) were analyzed using Lead DBS software. Preoperative T1 and postoperative CT images were merged using ANTs. The volume of tissue activated (VTA) was estimated based on the 6 month active stimulation settings using FieldTrip-SimBio. Structural connectivity between bilateral VTA and all other brain voxels was calculated using each patient's diffusion MRI (dMRI) data and the Human Connectome Project (HCP) dMRI dataset, producing whole-brain fiber-density maps in MNI space by Lead Connectome Mapper. Responder (defined as HDRS-17 improvement >= 50% at six months) and nonresponder heat maps were generated using both dMRI datasets and compared.

Results:

WM activation pathways show similar pattens for three of four required WM bundles between individual and normative datasets (forceps minor, uncinate fasciculus, and cingulum bundle). However, the normative connectome method fails to identify the expected fronto-striatal fibers, essential for recovery [Biological psychiatry]. In addition, individual tractography shows a higher sensitivity to distinguish between responders and nonresponders.

Conclusions:

These findings suggest that a patient-specific connectomic approach may be needed to define the optimal target location for future SCC DBS surgery in depression.

2022 Neuroscience Retreat

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Title: The impact of social isolation on social reward behavior and mesoaccumbens circuitry

Authors: Michelle Kim, Marie Barbier, Keerthi Rajamani, Hala Harony-Nicolas

Background: Social interactions during development are crucial for establishing adult social behavior, and an important facet of social behavior is the rewarding properties of social interaction. However, there is a gap in understanding how juvenile social isolation (jSI) may impact social reward processing in adulthood as well as the neural circuitry mediating reward.

Methods: At weaning age, rats are assigned to either jSI or group-housing for 3 weeks. Following jSI or group-housing, all rats are re-housed and re-socialized with a novel age- and sex-matched rat. Once rats reach adulthood, we use a battery of behavioral paradigms to assess locomotor activity, anxiety-like behavior, social recognition memory, and processing of social reward, the latter of which is assessed by presenting a rat with a novel social stimulus along with a competing reward (food).

Results: We found that male rats raised in jSI showed a lower preference for social interaction compared to group-housed male rats only when a social stimulus was presented along with another competing stimulus.

Conclusions: Our results suggest jSI affects the ability of male rats to assess the value of social interaction when presented with a competing stimulus, resulting in reduced social interaction. Future experiments recording neural activity at the VTA and dopamine release in the NAc during the social reward task will shed light on the impact of jSI on neural activity in VTA dopamine neurons and dopamine release in the NAc during social reward seeking and how changes in neural activity may underlie impairments in processing social reward.

2022 Neuroscience Retreat

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White matter impairments underlying human prefrontal-habenular structural connections in cocaine and heroin addiction

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Background: The lateral habenula (Hb) has emerged as a core regulator of drug-seeking behaviors in preclinical models of cocaine addiction, serving as a conduit for prefrontal cortical (PFC) control over the subcortical limbic system. The present study aimed to model PFC-Hb structural connectivity and elucidate its role in cocaine, as well as heroin addiction in the human brain.

Methods: Diffusion MRI was acquired for 31 individuals with cocaine use disorder [CUD: 16 currently using (CUD+)/15 short-term abstinent (CUD-)]; 24 individuals with heroin use disorder (HUD) on medication-assisted treatment; and 45 demographically matched healthy controls (CTL: 28 CUD-matched/17 HUD-matched). Probabilistic tractography was performed by seeding in the Hb and extracting streamlines with terminals in the PFC. Streamlines were anatomically constrained to white matter tissue and required to pass through an anterior stria medullaris waypoint. Fractional anisotropy (FA, a measure of diffusion coherence) was averaged along the modeled structural connections and analyzed using ANOVAs with Group (CTL/CUD+/CUD-; CTL/HUD; CUD+/CUD-/HUD) and Side (left/right) as factors.

Results: Compared with CTL groups, the PFC-Hb tract exhibited reduced FA in both CUD+/CUD- (Group $p = .003$) and HUD groups (Group $p = .012$), with no effect of Side or Group × Side interaction. Additionally, there were no significant differences in FA between CUD and HUD groups (Group $p = .684$). Notably, there was a significant positive correlation of PFC-Hb mean tract FA with age of first use of individuals' drug-of-choice across both addiction groups ($r = 0.30$, $p = .025$).

Conclusions: Microstructural abnormalities were present in PFC-Hb white matter in stimulant-addicted individuals, including currently using and abstinent cocaine-addicted individuals. Here we show for the first time that this effect is generalized to opiate-addicted individuals. Furthermore, a correlation with age of first drug use implicates a possible predisposing role of this circuitry in the onset of addiction. These results warrant further investigation of the functional significance of the PFC-Hb circuit to human drug addiction.

2022 Neuroscience Retreat

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Epigenome-wide Predictors of Response to Internet-Based Cognitive-Behavioral Therapy for PTSD in World Trade Center Trauma Survivors

Emily M. Kozik-Hicks, Robert H. Pietrzak, Laura M. Huckins, Adriana Feder

BACKGROUND: Posttraumatic stress disorder (PTSD) is a psychiatric disorder that is prevalent in individuals exposed to traumatic events such as the 9/11/2001 terrorist attacks on the World Trade Center (WTC). Large population-based studies of PTSD have illuminated the complex polygenic architecture of risk for this disorder, as well as notable gene x environment interactions. Epigenetic modifications such as DNA methylation present a mechanism by which PTSD gene x environment interactions may arise. Further, epigenome-wide association studies (EWAS) of PTSD have identified several epigenetic correlates of PTSD. While cognitive-behavioral therapy (CBT) is among the most effective treatments for PTSD, high rates of treatment avoidance, logistical barriers have limited the provision of CBT to those suffering from WTC-related PTSD. One solution to overcome such barriers is internet-based therapy. The purpose of the current study was to evaluate epigenetic correlates of baseline PTSD severity and response to internet-based CBT.

METHODS: In a randomized control trial, WTC responders and survivors with full or subthreshold PTSD underwent a therapist-assisted internet-based CBT or an internet-modified present centered therapy as a control intervention. Saliva was collected before (N=68) and after treatment (N=52) and analyzed for genome-wide DNA methylation to identify epigenetic correlates with baseline PTSD severity and treatment response.

RESULTS: Hypomethylation at cg02086790 (nearest gene: PTPN14, implicated in cell growth and differentiation) at baseline predicted increased responsiveness to aggregate treatment at 3-month follow up (p=9.187e-08). Sub-threshold associations that predicted 3-month treatment response were identified near genes implicated in lipid metabolism and mRNA splicing. Associations of global methylation levels with PTSD severity or treatment outcomes were not identified.

CONCLUSIONS: These results suggest potential epigenetic markers of CBT treatment response and epigenetic mechanisms of therapeutic action. Future work will include analyses of PTSD polygenic risk score (PRS) and epigenetic GrimAge for associations with PTSD severity and CBT treatment outcome.

2022 Neuroscience Retreat

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The role of tanycytic thyroid-stimulating hormone receptor in fasting-induced hypothalamic blood-brain barrier remodeling

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Background:
The blood-brain barrier (BBB) is maintained by fenestrated microvessels and tanycytes, specialized cells that line the third ventricle of the hypothalamus (H). Tanycytes and microvessels undergo remodeling in response to metabolic changes such as hunger. This remodeling includes the reorganization of tight junctions within tanycytes and increased fenestrated microvessel loops, promoting BBB permeability. Tanycytes strongly express TSH receptors (TSHR), and TSH levels are elevated by fasting, but the role of TSH in BBB permeability is unknown. We hypothesized that fasting-induced increased TSHR activity could trigger BBB remodeling.

Methods:
We compared hunger-induced BBB remodeling in wild-type (WT) mice and heterozygous TSHR knockout (HET) mice. Mice were either 24 hr-food deprived (FD) or fed ad libitum (AL). Immunostaining was used to visualize MECA-32 and Claudin-1 in the median eminence (ME); these label fenestrated endothelial cells and tanycytes.

Results:
WT-FD and HET-FD demonstrated an increase in MECA-32 and Claudin-1, indicating increased BBB permeability during fasting. However, the increased permeability was exacerbated in the HET-FD group. Interestingly, the HET-AL mice also showed higher MECA-32 and Claudin-1 RFI levels relative to the WT-AL mice.

Conclusion:
Our findings suggest a negative feedback mechanism in which increased activity at TSHR limits fasting-induced vascular permeability.

2022 Neuroscience Retreat

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Gene expression profiling of monocytes in recent-onset schizophrenia.

Raphael Kübler, Paul R. Ormel, Iris E.C. Sommer, René S. Kahn, and Lot D. de Witte

BACKGROUND: The innate immune system is increasingly recognized as an important player in pathophysiology of schizophrenia. The goal of this study was to understand changes observed in monocytes of patients with early-onset schizophrenia.

METHODS: We used RNA-sequencing to profile monocyte gene expression of twenty patients with early-onset schizophrenia and twenty matched healthy controls.

RESULTS: We validated expression changes of several genes that were differentially expressed in previous studies including TNFAIP3, DUSP2, and IL6. At a transcriptome-wide level, we found 99 differentially expressed genes. Effect sizes of differentially expressed genes showed a moderate correlation with differential expression in brain tissue. Upregulated genes were enriched for genes in NF-κB and LPS response pathways. Downregulated genes were enriched for glucocorticoid response pathways. We further validated expression changes of the previously reported monocyte QTL gene FES in our independent schizophrenia cohort.

CONCLUSIONS: The NF-κB and LPS response, and glucocorticoid pathways have been implicated in schizophrenia before and play a role in regulating the activation of myeloid cells. Interestingly, they are also involved in several non-inflammatory processes in the central nervous system, such as neurogenesis and neurotransmission. Future studies are needed to better understand how dysregulation of the NF-κB and glucocorticoid pathways affects inflammatory and non-inflammatory processes in schizophrenia. The fact that dysregulation of these pathways is also seen in brain tissue, provides potential possibilities for biomarker development. Paiva-Lopes et al. (2022) found several schizophrenia risk alleles within the FES gene that increased its expression in monocytes. Further research on the function of FES in schizophrenia and monocytes, especially regarding when and how risk alleles within FES become active, is needed.

2022 Neuroscience Retreat

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Amygdalar protein synthesis supports persistent trauma-induced shifts in negative valence

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Background: Traumatic stress has the ability to leave individuals more vulnerable to future stressors, perhaps due to its capacity to augment subsequent aversive learning. However, little is known about how aversive learning is modified by prior trauma. Defining the mechanism through which this change occurs may shed light on new treatment avenues for conditions like PTSD.

Methods: Mice were exposed to a brief 'trauma' consisting of 10 foot-shocks, or not. A week later, we assessed anxiety-like behavior in the light-dark test and sensitization of aversive learning by exposure to an auditory stressor in a distinct context. Additionally, we assessed whether trauma altered expression or learning of aversive memories, accomplished by pairing a tone with a weak foot-shock either before or after trauma and subsequently measuring fear of the tone. Lastly, we utilized intra-amygdala infusions of anisomycin after trauma to examine the contribution of amygdalar protein synthesis to later sensitization of aversive learning and anxiety.

Results: We found that an acute trauma is able to persistently increase anxiety-like behavior and learned fear in response to a novel aversive experience. Additionally, trauma had no effect on expression of an aversive memory acquired before trauma, but greatly enhanced a fear memory formed after trauma, indicative of heightened perceived valence of aversive stimuli. Lastly, trauma's ability to induce learning changes was dependent upon amygdalar protein synthesis after trauma.

Conclusion: This work highlights the essential role of amygdalar protein synthesis in inducing lasting changes in aversive learning after trauma by augmenting the perceived intensity of future aversive events. By dissecting how trauma alters psychological processes and neural function, this work will hopefully render insights into the variation in vulnerability to trauma.

2022 Neuroscience Retreat

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A stress-responsive circular RNA regulates depression-like behavioral abnormalities in mice

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Background: Circular RNAs (circRNAs) are formed by back-splicing of pre-mRNA transcripts to generate a circularized product, many of which may have regulatory functions in the brain. Functional abnormalities in the nucleus accumbens (NAc) may contribute to behavioral abnormalities in depression and other stress-related disorders. Here, we investigated the role of NAc circRNAs in murine stress-induced behavioral deficits.

Materials and methods: Depression-related behavioral deficits were induced using social defeat (SDS) or restraint stress (RS). circRIMS2 was overexpressed using an AAVDJ-sEF1a-ZKSCAN1-circRIMS2- sYFP vector. Single-cell RNA sequencing (scRNAseq) was performed using 10X Chromium.

Result: We found that expression of circRIMS2, derived from exons 20-22 of the RIMS2 gene, was increased in postmortem NAc from male, but not female, patients who suffered from major depressive disorder. SDS increased, whereas RS decreased, circRIMS2 levels in the NAc of male mice. Additionally, circRIMS2 expression varied across subcellular compartments (particularly the nucleus and synaptosome), and these patterns of expression were responsive to RS and SDS. Viral- mediated circRIMS2 overexpression in the NAc protected mice from SDS- and RS-induced anxiety and anhedonia-like behaviors. scRNAseq suggested that circRIMS2 acts in the NAc to alter cell type-specific transcriptional signatures evoked by SDS, particularly in putative cholinergic cell populations. The effected genes are primarily associated with cell metabolism and GPCR signaling. Currently, we are exploring the effects of circRIMS2 knockdown on stress-induced alterations in behavior.

Conclusions: circRIMS2 levels in the NAc are highly responsive to stress in terms of both expression and subcellular localization, and circRIMS2 acts in this area to regulate depression-related behavioral abnormalities.

Funding: NIH

2022 Neuroscience Retreat

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CHARACTERIZING THE ROLE OF THE POSTERIOR INTRALAMINAR COMPLEX OF THE THALAMUS IN SOCIAL BEHAVIOR IN MICE

Amanda Leithead, Arthur Godino, Marie Barbier, Nicholas Cordero, Hala Harony-Nicolas

BACKGROUND: The neuropeptide oxytocin is produced in the hypothalamus and is implicated in social behaviors. Within the hypothalamus, glutamate drives synchronized oxytocin cell firing and burst release of oxytocin. However, the origin of glutamatergic inputs to the hypothalamus and their role in social behaviors has been understudied. Of particular interest is the posterior intralaminar complex of the thalamus (PIL), which may relay sensory information to the hypothalamus for the processing of social stimuli.

METHODS: To characterize glutamatergic inputs to the hypothalamus in mice we combined viral retrograde tracing with immunohistochemistry for CaMKIIα, which is largely expressed in excitatory neurons. To identify specific inputs to oxytocin neurons, we utilized a novel modified rabies virus system. To investigate PIL activation during social interaction, we exposed mice to either a novel same-sex juvenile or object then analyzed brains with immunohistochemistry for the immediate early gene c-fos. Additionally, we performed fiber photometry recordings in PIL glutamatergic neurons during interactions with a same-sex juvenile, opposite-sex adult, object, or opposite-sex urine sample.

RESULTS: We found that the PIL sends excitatory inputs to the hypothalamus and projects directly onto oxytocin neurons. We observed significantly more c-fos+ cells in the PIL of mice exposed to social stimuli compared to object stimuli. Further, neural activity of PIL glutamatergic neurons was increased in males and females during social interaction with a same-sex juvenile or opposite-sex adult, but not with an object. Activity was increased during investigation of an opposite-sex urine sample in females but not males.

CONCLUSIONS: We demonstrate that the PIL projects to hypothalamic oxytocin neurons and is specifically activated during social investigation, which may vary by sensory modality and/or sex.

2022 Neuroscience Retreat

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TITLE: Using virtual reality to study the linkage of contextual memories across time in humans

AUTHORS: Veronica Lennon, Angela Radulescu, Denise J. Cai, Daniela Schiller

BACKGROUND: The ability to associate places with aversive experiences is critical for survival, and in humans, abnormalities in fear learning have been implicated in anxiety and trauma-related disorders. While rodent models have played a key role in advancing our understanding of the neural mechanisms underlying these behaviors, there remain significant challenges to studying contextual fear learning in humans. By developing a behavioral task in virtual reality, we were able to overcome these challenges and design a human study based on experiments performed by Cai et al. (2016) to investigate the role of time in the linkage of episodic fear memories.

METHODS: In our study, participants will tour three distinct virtual apartment environments over the course of one week, such that there is one week of time between their visits to the first and third apartments and only three hours between their visits to the second and third. Following this, participants will revisit the third apartment and undergo a fear experience there. Using data from eye-tracking and physiological measures of fear recorded during context testing, we will calculate correlations in fear responding to each of the three environments.

RESULTS: Based on the previous findings in mice as well as some evidence suggesting a role for temporal linking in human traumatic memory recall, we expect there to be a greater similarity between responses to the contexts encoded three hours apart in time compared to responses to the contexts encoded a week apart in time.

CONCLUSIONS: Using a novel virtual reality task in humans, we can assess the translational relevance of previous findings in rodents which have demonstrated temporal effects on the linkage of contextual fear memories.

2022 Neuroscience Retreat

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Regrouping after juvenile social isolation precipitates social behavior deficits in mice

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Background: Juvenile social isolation (JSI) is known to disrupt social behavior in adulthood, but little is known about the neural mechanisms by which JSI disrupts social experience-dependent brain maturation and causes adult social deficits to emerge. Previous studies suggest that, in male mice, there is a critical period between postnatal day (p) 21 and p35 when isolation will induce prefrontal cortex (PFC) abnormalities in adulthood that causally influence adult sociability. Interestingly, these circuit abnormalities were not present at the end of the isolation period (p35), raising the question of when and how JSI-induced social deficits emerge over the course of development.

Methods: To investigate the developmental progression of JSI-induced social dysfunction, we performed the 3-chamber sociability test on a weekly basis between the end of isolation and adulthood. Additionally, we conducted tests of affiliative behavior and aggression among cage mates during the post-isolation developmental period.

Results: We found that JSI-induced social dysfunction in the 3-chamber test is delayed (not fully emerging until between p50 and p57) and that dysfunction in the 3-chamber test, where subjects interact with novel mice, is preceded by negative social interactions between JSI cagemates during the first week after the end of isolation.

Conclusions: These results suggest that JSI may disrupt adult social behavior not only by impairing social development during the isolation period, but also by disrupting subsequent development during the post-isolation developmental period, highlighting a critical consideration for studies of social experience-dependent maturation. We propose that the prevailing “social deprivation model”, where adult social deficits are attributed to disruption of developmental processes occurring during the isolation period, should be supplemented by the “developmental mismatch model”, where social deficits are attributed to disruption of developmental processes occurring after the isolation period.
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2022 Neuroscience Retreat

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Title: GM-CSF in behavioral and molecular responses to cocaine

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Background: Peripheral systems, including the gut microbiome and the immune system, markedly effect behavioral and neurobiological responses to cocaine. We investigate the role of the cytokine GM-CSF as a mechanism underlying gut-immune-brain communication in cocaine use.

Methods: Serum multiplex analysis measured circulating cytokines in mice with intact or depleted gut microbiomes after chronic cocaine or saline. Cocaine conditioned place preference (CPP) assay to measure preference for cocaine was performed as a measure of addiction-like behaviors. Mice receiving daily injections of GM-CSF (10μg/kg) or vehicle, a knockdown (KD) of the GM-CSF receptor (GMCSFr) in the nucleus accumbens (NAc), or GM-CSF-/- underwent CPP. Locomotor activity was measured during CPP and following acute cocaine. Quantitative polymerase chain reaction (qPCR) and RNAscope in-situ hybridization quantified GM-CSFr expression in the NAc following cocaine. NAc tissue was used for RNA-sequencing.

Results: Multiplex analysis identified circulating granulocyte-macrophage colony-stimulating factor (GM-CSF) to be significantly increased by chronic cocaine only in animals with an intact gut microbiome. GM-CSF treatment, NAc KD of GMCSFr, and GM-CSF-/- mice display altered cocaine preference as measured by CPP. Both NAc KD of GMCSFr and treatment with GM-CSF alter locomotor response to cocaine. qPCR and RNAscope showed cell-type specific cocaine-induced GM-CSFr expression in the NAc. Further, RNA-sequencing found GM-CSF+cocaine treatment altered genes related to synaptic function in the NAc.

Conclusion: These data indicate GM-CSF participates in cocaine-induced behavioral and molecular plasticity, poising it as a novel peripherally-driven neuroimmune signal in cocaine use.

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2022 Neuroscience Retreat

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Convergence of activity-dependent synaptic regulation and genetic risk variation in childhood-onset schizophrenia

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BACKGROUND: Childhood-onset schizophrenia (COS) is a rare form of schizophrenia characterized by impaired neuronal functioning. Although family studies indicate high heritability, the underlying biological mechanism remains to be explored.

METHODS: Human induced pluripotent stem cell (hiPSC) derived neurons were isolated from six COS cases and five healthy controls. To measure the transcriptional and epigenomic changes after neuronal activation, we harvested these cells one and six hours after stimulation with 50mM KCl and under non-stimulating conditions, followed by RNA-seq and ATAC-seq profiling.

RESULTS: We comprehensively characterized depolarization-responsive changes in gene expression and gene regulatory element activity (chromatin accessibility) in hiPSC-derived neurons. After one hour of KCl depolarization, neurons invoked substantial activity-dependent changes in genes regulating synaptic functions, some of which are known to be perturbed in neuropsychiatric diseases, including schizophrenia and autism spectrum disorder. Extending to activity-dependent gene regulatory elements captured by chromatin accessibility, we found significant heritability enrichment for schizophrenia in the activity-inducible enhancers. Additionally, we nominated novel schizophrenia-associated loci regulated by neuronal activity. To systematically understand the regulatory functions of genes affected by neuronal activity, we used gene co-expression network analysis to identify modules of genes with shared expression patterns. We found 28 activity-dependent modules significantly associated with common and rare genetic risk variation in schizophrenia. Neuron Navigator 3 (NAV3), a schizophrenia-associated gene implicated in axon guidance, was identified to be a key regulator of those co-expressed modules.

CONCLUSIONS: Our framework not only offers an alternative approach to study the mechanisms of COS but also adds to converging evidence that activity-induced expression changes mediated by activity of regulatory elements might contribute to schizophrenia risk.

2022 Neuroscience Retreat

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Investigating the neural correlates of task-state representation learning

Author(s): Christina Maher

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Background: Representation learning is the process of mapping task observations to states, allowing generalization of experience to novel contexts. Efficient state representations integrate selective attention to relevant sensory features with information from previous observations stored in memory, therefore relying on coordinated attention and memory. Previous studies using fMRI have implicated prefrontal regions in representation learning, with hippocampal regions supporting learning based on similarity to past exemplars (Niv et al., 2015; Leong & Radulescu et al., 2017). However, how these brain regions and cognitive processes are functionally integrated is mostly unknown. Here, online participants played a behavioral task in which they maximize reward by selectively learning about and attending to relevant dimensions (either stimuli color or shape) in a multidimensional environment. Additionally, we leveraged intracranial electroencephalography (iEEG) recordings to examine hippocampal and prefrontal activity during play with high temporal and spatial resolution previously unavailable through neuroimaging methods.

Methods: We validated our multidimensional decision-making task ('gem hunters') in an online sample (n=50). Additionally, a neurosurgical iEEG patient performed the task while we recorded local field potential (LFP) activity from electrodes surgically implanted in prefrontal (orbitofrontal, lateral prefrontal cortices) and deep temporal (hippocampus, amygdala) regions (n=1).

Results: All online participants (n=50) performed above chance (percent correct > 0.33). When participants received a hint about the relevant dimension (shape/color), both the proportion of correct trials ($t(49)= 4.13$, $p < 0.001$) and percent of blocks in which the relevant dimension was learned ($t(49)= 4.31$, $p < 0.0001$) were significantly higher. Thus, participants understood the task's objective and effectively learned the relevant dimension in each block. Preliminary iEEG analyses suggest that power modulation in low-frequency band was increased in rewarded trials in orbitofrontal contacts.

Conclusion: iEEG reflects behaviorally salient (reward) task aspects, and may be well poised to reveal the coordinated roles of different brain regions, like the PFC and hippocampus, in human task-state representation learning. This may have important implications for

understanding psychiatric disorders with maladaptive symptoms associated with aberrant representation learning.

2022 Neuroscience Retreat

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Examining the role of hypoxia induced genes CXCR4 and NXPH4 for invasion of hypoxic glioblastoma cells

Valerie J. Marallano, Anirudh Sattiraju, Hongyan Zou, and Roland Friedel

Hypoxia (low oxygen) has been associated with adverse effects in tumor biology by increasing the capabilities of invasion, proliferation, and survival of tumor cells within the tumor microenvironment. I have engineered glioblastoma (GBM) cells with a novel hypoxia reporter, HRE-UnaG, to study areas of brain tumor hypoxia and the effects that these hypoxic cells have on tumorigenesis. Single cell RNA-seq analysis from a mouse intracranially injected with HRE-UnaG GBM cells revealed a shift of GBM cells to a mesenchymal state upon hypoxia (detected by expression of UnaG). I identified two genes, CXCR4 and NXPH4, as being specifically induced in the hypoxic population. My studies focus on the hypothesis that these two hypoxia-induced genes, CXCR4 and NXPH4, are upregulated in hypoxic GBM cells, which may allow tumor cells to become more aggressive and resistant to conventional forms of therapy. I have transduced GBM cells with lentiviral vectors for Dox inducible shRNA knockdown of CXCR4 or NXPH4 to test the specific contribution of these genes to the phenotypes of the hypoxic population, with particular focus on the change in invasion and overall tumor burden upon gene silencing.

Methods: 3D invasion assays, RNA sequencing analysis, Western blots, orthotopic intracranial injection of GBM cells into SCID mice, Lenti-virus-CXCR4-Dox inducible KD, Lenti-virus-NXPH4-Dox inducible KD, histology, and quantification of invasion, growth

My hypothesis, based on preliminary data, suggests that glioblastoma cells rely on CXCR4 and NXPH4 to be able to upregulate their invasive/migratory ability that is triggered as a response to hypoxia stress.

Funding: National Institute of Neurological Disorders and Stroke

2022 Neuroscience Retreat

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Aberrant Estimation of Controllability and Its Neural Underpinnings in Nicotine-Dependent Human Smokers

Caroline McLaughlin, Soojung Na, Matthew Heflin, Vincenzo Fiore, Xiaosi Gu

BACKGROUND: Humans live in complex environments that may or may not be controllable. As such, the ability to accurately estimate the level of controllability of the environment is crucial for survival. Previously, we found that healthy volunteers engage the ventromedial prefrontal cortex (vmPFC) to calculate the downstream effects of current choices – a mechanisms termed forward thinking – to exploit the controllability of their environment. However, it is still not fully understood how the breakdown of this neurocomputational mechanism might lead to maladaptive behaviors such as observed in individuals with substance use disorder.

METHODS: Using nicotine addiction as a test case, the current study investigates how human smokers (n=17) and non-smokers (n=25) differed in their computation of the controllability of social interactions. All participants performed a two-party exchange task where their current choices either influenced (“controllable) or did not influence (“uncontrollable”) partners’ future offers during functional magnetic resonance imaging (fMRI) of blood-oxygen-level-dependent (BOLD) responses.

RESULTS: Computational modeling reveals that both smokers and non-smokers engaged forward thinking to make their choices, but smokers inaccurately estimated a low level of social controllability. Furthermore, while vmPFC activity positively scaled with the projected total values of current actions during forward planning in non-smokers, neural signals activity in the same region were inversely associated with choice values in smokers.

CONCLUSIONS: Taken together, these results demonstrate that individuals with nicotine dependence have deficits in tracking controllability and the value of their actions in social environments, which might explain certain suboptimal behaviors related to the disorder.

2022 Neuroscience Retreat

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Dietary fiber metabolites mediate transcriptional homeostasis and cocaine-seeking behaviors

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Background: Psychostimulant use disorder represents a public health crisis leading to tremendous morbidity. Emerging evidence suggests that gut bacteria produce numerous neuroactive metabolites, which signal to the brain and modulate brain function. The strongest evidence exists for a class of bacterially-derived fiber metabolites known as Short-Chain Fatty Acids (SCFA), which have been shown to mediate molecular and behavioral effects in neuropsychiatric disease models. Our group has demonstrated that antibiotic treatment enhances conditioned place preference for cocaine and that supplementation with SCFA reverses these effects in mice. We sought to examine the effects of the microbiome and SCFA metabolites in a relapse-relevant rat model of cocaine use disorder.

Methods: Gut bacteria and their metabolites were depleted in Sprague-Dawley rats via addition of antibiotics to their drinking water and compared to vehicle-treated controls. Rats were trained to self-administer cocaine and subjected to either within-session threshold testing to evaluate motivation for cocaine at a range of doses or 21 days of abstinence followed by a cue-induced cocaine-seeking task. Nucleus accumbens was isolated and tissue processed for RNA-sequencing analysis.

Results: Antibiotic treatment enhanced motivation for low dose cocaine in a behavioral economics task and increased cue-induced cocaine-seeking following prolonged abstinence. Antibiotic-treated rats exhibited significantly altered gene expression in networks known to affect synaptic signaling and plasticity. Supplementation with SCFA metabolites reversed these behavioral and molecular effects.

Conclusions: Subjects lacking a complex gut microbiome exhibit altered gene expression and significantly increased cocaine-seeking behaviors. In the absence of a normal microbiome, supplementation of SCFA metabolites restores baseline behavior and gene expression. These findings suggest that gut bacteria via their metabolites may serve as homeostatic regulators of gene expression and behavior, positioning the microbiome as a promising translational research target.

2022 Neuroscience Retreat

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Title: 3D Image Analysis Reveals Abnormalities in Homer 1b/c and mGluR 1/5 in LRRK2 G2019S Parkinson's Mouse Model

Authors: Nikhat Meman, Emily Dodd, Alex Tielemans, Swati Gupta, George Huntley, Deanna Benson

Background:
Homeostatic Plasticity describes the ability of a neuron to maintain its activity within a certain range. Its modifications have yet to be understood within the context of Parkinson's disease and the striatum. We have observed that within the striatum of mice expressing a Parkinson's disease gene mutation, LRRK2 G2019S, glutamatergic synapses fail to show activity-dependent downscaling (unpublished data).

Methodology:
Studies done in other brain regions predict that Homer 1a mediated activation of mGluR 1/5 may be a possible mechanism by which scaling down occurs. Before Homer 1a is activated, mGluR 1/5 is anchored to the cell surface by Homer 1b/c. We investigated Homer 1b/c and mGluR 1/5 properties at baseline in the striatum of LRRK2 G2019S mice using a novel image analysis pipeline to understand their relationship 3-dimensionally. Using Z-stack images, we reconstructed the proteins through Imaris Image Analysis and were able to analyze and understand their interactions on a deeper level.

Results:
We found that at baseline, Homer 1b/c and mGluR 1/5 volumes were significantly larger in the striatum of mutant mice. We also found a greater percent colocalization in the mutant mice compared to wild-type. We are working to confirm these results in cell culture as well.

Conclusion:
These results indicate that the LRRK2 G2019S Parkinson's mutation has somehow modified the interaction between proteins involved in homeostatic mechanisms at synapses. Further research is needed to understand what exactly has changed when scaling down occurs and how this may cause the deficits observed. We hope to continue using our new approach to analysis to further characterize these relationships 3-dimensionally.

2022 Neuroscience Retreat

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Single-nuclei transcriptomics relates neurodevelopment to glioblastoma heterogeneity and infiltration.

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Background: Current understanding of glioblastoma (GBM) heterogeneity is largely derived from studies focused on the surgically resectable tumor core. However, cells at the infiltrative edge, which evade resection and chemoradiation, eventually become essential drivers of tumor recurrence that remain poorly characterized.

Methods: We microdissected and performed single-nuclei RNA sequencing on approximately 59,000 cells taken from the pathologically defined core and infiltrative edge of six GBM tumors with diverse genomic drivers, including IDH1, EGFR, PDGFRA, FGFR3, and NF1, and performed several downstream bioinformatics analyses.

Results: Unbiased clustering and copy number variation analysis allowed us to identify distinct neoplastic and non-neoplastic populations. After projecting signatures taken from comprehensive neurodevelopmental and adult datasets onto our GBM data, we found that approximately 91% of neoplastic cells recapitulate a prenatal neurodevelopmental signature. Analyzing the four tumors with the most accurate microdissection, we found that GBM cells at the tumor core were enriched for a prenatal interneuron signature while cells at the infiltrative edge were enriched for a common glial progenitor signature. Cells at the edge were also enriched for a third trimester signature, while cells at the core were enriched for second trimester signature. Lineage analyses revealed consistent patterns across all tumors, with velocity vectors pointing from the tumor core towards the infiltrative edge. Differential gene expression analysis comparing tumor cells at the infiltrative edge to those at the core reveal a migration signature dominated by EGFR, ERBB4, CADM2, DPP10, PCDH9, and PCDH15. Potential markers of invasion were validated by immunofluorescence in patient derived xenograft models.

Conclusions: Ultimately, this high resolution analysis of GBM heterogeneity at the infiltrative edge allows us to uncover potentially targetable drivers of tumor infiltration and recurrence.

2022 Neuroscience Retreat

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Activation of GIRK channels by PIP2 and novel PIP2 -independent gating mechanism in mutagenesis study

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BACKGROUND:
G protein -gated inwardly rectifying potassium (GIRK) channels are responsible for inhibition of excitable neurons in the brain. GIRK channels are activated by pertussis toxin sensitive G proteins when neurotransmitters, such as dopamine, bind to GPCRs, leading to membrane hyperpolarization. In addition, GIRK channels appear to require PIP2, a lipid molecule in the membrane, for complete activation - but how PIP2 opens the channel remains poorly understood. Prior high-resolution structures of WT GIRK2 channels in the presence of PIP2 show a conformation where the cytosolic domain (CTD) is in close proximity to the transmembrane domain (TMD) (i.e. 'engaged'). However, these GIRK structures do no reveal the fully open channel.

METHODS:
Here we used mutagenesis to alter the interaction of PIP2 binding to understand better how the WT channels open. Functional studies in HEK293T cells showed that mutation to tyrosine (Y) greatly increased the basal activity of GIRK2 channels, even in the absence of G protein activation. We next used a K+ fluorescent flux assay to study purified GIRK2 channels reconstituted into liposomes.

RESULTS:
We discovered that mutations (F & Y) at R92, which interacts with 1'-phosphate of the inositol head group of PIP2, appear to create a novel open channel that does not require PIP2 for activation.

CONCLUSIONS: These hyperactive, PIP2-independent gating mutations are promising candidates for structural cryo-EM studies to characterize a novel gating mechanism of GIRK channels and the structure of the elusive open state.

2022 Neuroscience Retreat

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Neurocomputational Mechanisms of Belief Update during Uncertainty

Madeline O'Brien, Vincenzo G. Fiore, Matthew Heflin, Xiaosi Gu

BACKGROUND: Nicotine users have been shown to compulsively perform smoking behaviors even after the onset of negative health consequences. Compulsive repetition of such costly behaviors can perhaps be explained in part by the inherent uncertainty of naturalistic environments, but it is unknown whether nicotine itself influences decision-making processes under uncertainty.

METHODS: In the current study, we use computational modeling of behavior during two multi-option decision-making games to validate the use of Bayesian belief updating while controlling for outcome accessibility in nicotine users (n=17) and matched controls (n=17).

RESULTS: Paired t-tests demonstrate the use of Bayesian belief updating in both smokers and controls regardless of outcome accessibility. Smokers and healthy controls updated their beliefs at similar rates; however, within the nicotine use cohort, smokers that reported feeling scared more often tended to update their beliefs more slowly (p=0.0085, r=-0.6937 without feedback; p=0.0096, r=-0.8562 with feedback). When provided with immediate feedback, slower belief updating after presentation of conflicting evidence was associated with higher social (p=0.0037, r=-0.7296) and non-social (p=0.00002, r=-0.9019) anxiety levels, and stronger nicotine cravings (p=0.0078, r=-0.6995). However, when evidence confirmed smokers' expectations, belief updating speed was not associated with self-reported mood or craving scores.

CONCLUSIONS: Under conditions of environmental uncertainty, both smokers and nonsmokers make decisions using similar Bayesian belief updating mechanisms. Within the nicotine use group, self-reported psychiatric symptoms and consistency of presented evidence affected the belief updating speeds. Once completed, ongoing whole-brain model-based imaging analyses will elucidate the neural signatures of task-related belief updating processes with and without the interference of nicotine. Data collection is actively underway; as such, results presented at the retreat will reflect the updated cohort sizes and statistical results.

2022 Neuroscience Retreat

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Cerebellar development in a mouse model of DDX3X syndrome.

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Background
DDX3X syndrome is a rare genetic condition associated with intellectual disability, autism, and motor abnormalities, caused by mutations in the X-linked gene DDX3X. DDX3X is highly expressed in the cerebral cortex and cerebellum, and both cortical and cerebellar malformations have been identified in individuals with DDX3X mutations. An extensive connection exists between the cortex and the cerebellum and is integral to regulating motor and cognitive functions.
The objective of this project is to address if and how DDX3X mutations affect formation of the cerebellum and cortico-ponto-cerebellar circuits.
Methods
We use immunostaining with cerebellar specific markers and Nissl staining to identify developmental changes in the genesis or homeostasis of cell populations in a haploinsufficient Ddx3x mutant mouse line. We then generated a Purkinje-specific Ddx3x knockout line (Pcp2-Ddx3x) to dissect the role of the Purkinje cells in the postnatal motor, sensory, and physical delays and adult motor deficits observed in Ddx3x mutant mice, through a battery of behavioral and developmental assessments.
Results
Immunostainings from adult mouse cerebella showed high DDX3X expression in Purkinje cells. Furthermore, the population of granule neuronal progenitor cells seemed to be increased in Pcp2-Ddx3x mice. Results from Nissl staining do not reveal stark differences in gross morphological foliation of the cerebellar cortex in the Pcp2-Ddx3x adult mice. We plan to investigate foliation at earlier developmental stages. Analyses of developmental milestones and adult motor behaviors in Pcp2-Ddx3x knockout mice are in progress.
Conclusions
These analyses are expected to reveal whether Ddx3x regulates cerebellum formation. Our findings will also lay the groundwork for a more comprehensive understanding of the establishment of cortico-cerebellar circuits during neurodevelopment.

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2022 Neuroscience Retreat

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“Decision making in the context of multi-attribute options”

Aster Perkins and Erin Rich

BACKGROUND: Often decisions are made between options that have multiple features, or attributes, that are relevant to one’s choice. For example, when deciding between snacks to purchase, one might factor cost and taste into a selection. The orbitofrontal cortex (OFC) has an important role in decision-making and OFC neurons represent associations between stimuli and their overall values. However, it is still unknown whether OFC only evaluates options on the basis of their integrated value, as suboptimal decision-making effects such as the attraction effect indicate that within-attribute comparison may also contribute to decision-making.

METHODS: To investigate how multi-attribute options are represented in neural activity, we trained two rhesus macaques on a multi-attribute decision making task, in which two simultaneously-presented options were represented by stimuli reflecting the sweetness of that option’s sucrose reward, and the probability of receiving that reward. These composite stimuli represented information about the attributes of the options with separate bars that either increased or decreased with increasing attribute value, allowing us to investigate both free-viewing gaze behavior and changes in choice behavior due to perturbations in attribute presentation. We recorded neurons in OFC and frontal eye fields (FEF) using acute electrodes and multi-contact linear probes.

RESULTS: We found that when comparable attributes did not share a presentation mode (e.g., reward bar A increased in size with increasing sweetness, while reward bar B decreased), choice behavior became suboptimal, implying a role for within-attribute comparison. Preliminary neuronal analysis indicates a greater presence of independent information relating to attribute than integrated value of the chosen option in OFC and FEF firing rates.

CONCLUSIONS: Our interim results support the notion that value-based decisions take place, at least partially, in the space of individual attributes, and may depend on attribute value representations in OFC.

2022 Neuroscience Retreat

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Differences in plasma proteome conferred by expression of the Alzheimer's risk allele ApoE-ε4

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The strongest genetic risk factor for late-onset, sporadic Alzheimer's disease (AD) is the apolipoprotein E (APOE) ε4 allele. Compared to the common ε3 allele, the ε4 allele increases AD risk by 3-12-fold, depending on number of alleles. Recent work exploring age-related cognitive decline identified changes in blood-CNS communication across aging. Youth-associated blood-borne proteins were sufficient to revitalize the aged brain and restore hippocampal function, increase adult neurogenesis, and restore dendritic spine plasticity. Characterizing plasma proteomic changes in a variety of contexts may thus be critical for the development of novel therapeutic strategies to combat AD. We hypothesized that APOE4 may disrupt the plasma proteome relative to APOE3. Because distinct pools of ApoE exist within the periphery and the brain, our work aims to identify how APOE isoform-dependent expression in the periphery alters the systemic proteome and differentially regulates brain function. Using an aptamer-based profile of ~1300 proteins on plasma from APOE-ε4/ε4 and APOE-ε3/ε3 human subjects, we identified differentially expressed proteins and associated canonical pathways linked to CNS functions and processes. To further elucidate the impact on the brain, we next used knock-in mice expressing human APOE3 or APOE4 under control of the mouse APOE promoter. To examine how the brain is altered by exposure to peripheral APOE4 expression, we evaluated transcriptomic changes by bulk hippocampal RNA-seq following parabiosis of APOE3 and APOE4 mice. Ongoing experiments will focus on investigating the protective potential of the APOE-ε3 allele relative to the deleterious APOE-ε4 allele on blood-brain communication mechanisms broadly, and in the context of AD pathology, ultimately informing our understanding of increased AD risk in ε4-carriers.

Funding: BrightFocus Foundation, Donors Cure Foundation

2022 Neuroscience Retreat

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Title: Dentate gyrus is required for both visually cued and uncued spatial navigation

Authors: Paul Philipsberg, Zoe Christenson Wick, Tristan Shuman

Background: The dentate gyrus (DG) is required for spatial learning in standard behavioral tasks in freely moving animals. However, certain techniques necessitate head-fixation, thus the development of hippocampal-dependent head-fixed tasks is of great utility. A recently developed head-fixed spatial task uses beaconed (visually cued) and unbeaconed (absent of visual cues) trials to assess spatial memory in virtual reality. This task has been shown to require medial entorhinal cortex stellate cells, which directly project to the DG. Thus, we predicted this task may also depend on the downstream DG and set out to test this hypothesis.
Methods: We adapted an established spatial navigation virtual reality task based on beaconed (visual cues signal the location of the reward zone) or unbeaconed (no visual cues, requiring a path integration strategy) rewards. We investigated the DG dependence of this task through chemogenetic inactivation using an inhibitory PSAM/PSEM system.
Results: We found that chemogenetic inhibition of DG neurons during recall induces a reversible deficit in both the visually cued and uncued versions of this task. Following washout, performance recovered to the fully trained performance level.
Conclusions: The head-fixed, DG dependent task described here will be a useful tool in investigating the behavioral effects of more sophisticated manipulations of DG function, and thus aid in further elucidating the mechanisms by which spatial information is processed in the DG.

2022 Neuroscience Retreat

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Cell-type-specific 3D genomic and transcriptomic alterations in the HIV-infected human brain

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BACKGROUND: HIV infection of microglia can lead to HIV associated neurocognitive disorder (HAND) and contributes to the formation of a potentially large viral reservoir, but the mechanisms of these processes remain poorly understood in part due to a lack of cell-type-specific genomic studies of the HIV infected brain. Here we perform the first integrative genomic studies of the human brain during active HIV infection, using HIV encephalitis (HIVE) as a model for active infection.

METHODS: All studies used postmortem frontal cortex tissue from the Manhattan HIV Brain Bank. Bulk nuclei were submitted for 10X Chromium single nucleus RNA-sequencing (snRNA-seq). In situ Hi-C was performed on fixed microglial nuclei sorted using fluorescence activated nuclei sorting (FANS). HIV integration site analysis was performed on FANS isolated neuronal and non-neuronal nuclei.

RESULTS: HIVE microglia underwent 3D restructuring of compartment structure, topologically associated domain structure, and loop structure in HIVE. Regions with compartment switching and loop changes displayed differential expression of genes by snRNA-seq. HIVE microglia overall showed decreased expression of homeostatic and neuronal support genes with increased expression of cell migratory and immune genes. Viral integration sites were found in highly expressed microglia genes and >75% were in regions of open chromatin defined by Hi-C. Furthermore, integration sites were enriched in regions that underwent changes in chromatin compartment and cis-chromosomal 3D contacts.

CONCLUSIONS: These findings link HIVE to changes in microglial gene expression and spatial genome organization that influence viral integration, providing important insights as to how HIV infection impacts microglial function and contributes to disease development and viral persistence.

2022 Neuroscience Retreat

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Title: Icer Dysregulation in the Nucleus Accumbens Core Mediates Impulsivity and Heroin Self-Administration Vulnerability

Authors: Tanni Rahman, Yanhua Ren, Joseph Landry, Jacqueline M. Ferland, Yasmin L. Hurd

Background: Impulsive behavior, mediated in part by the nucleus accumbens core (NAcC) and shell (NAcS) is a risk factor for heroin use disorder. We previously linked the cAMP Response Element Modulator (Crem) transcription factor to impulsivity and heroin addiction. This study now investigates the function of Crem isoforms, CremT and Icer, to gain additional insight into the mechanisms underlying impulsivity, and other vulnerability traits such as depression to heroin addiction.

Methods: We utilized a rodent model of impulsivity, consisting of the spontaneously hypertensive rats (SHRs), and of depression, the Wistar Kyoto rats (WKYs). Impulsive choice and impulsive action behavior were measured by the intolerance to delay (ITD) task. CremT and Icer gene expression were assessed in each strain. After lentiviral over-expression, animals underwent ITD, heroin self-administration (SA), forced swim test (FST), and sucrose preference (anhedonia).

Results: CremT was reduced in the NAcC, NAcS, and dorsal striatum, but not correlated to impulsive choice behavior in SHRs. No differences in Icer expression were observed between strain. Dichotomizing impulsive action into high or low groups irrespective of strain, showed reduced Icer mRNA specifically in the NAcC of WKYs with high impulsive action. Moreover, Icer in the NAcC negatively correlated with impulsive action in WKYs, but not SHRs. Additionally, heroin SA tended to reduce Icer mRNA in the NAcC of WKYs. Over-expression of Icer in NAcC neurons of WKYs reduced impulsive action, heroin SA, anhedonia, but increased depression-like behavior in the FST. Icer also reduced basal corticosterone levels and reduced impulsive choice after acute social isolation stress.

Conclusions: The results indicate that Icer may play a role in mediating impulsivity, heroin SA, and stress responses through separate mechanisms. Future directions will investigate Icer-mediated gene networks (RNA-sequencing) relevant to these behaviors.

2022 Neuroscience Retreat

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Fine-mapping of Alzheimer's Disease susceptibility loci identifies putative causal variants that show enrichment in myeloid cell enhancers

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Background: Recent genome-wide association studies (GWAS) have identified many common variants associated with Alzheimer's Disease (AD). However, linkage disequilibrium (LD) often makes it difficult to discern true causal variants for a given locus. Additionally, associated variants are often located in noncoding regions, limiting our ability to understand their regulatory mechanisms in AD.

Methods: We perform statistical and functional fine-mapping of 75 risk loci, including 42 novel loci, from the largest AD GWAS to date, published by the European Alzheimer's Disease Biobank (EADB) consortium to prioritize putative causal variants (Bellenguez et al. 2021). We compute posterior inclusion probabilities (PIPs), indicating likelihood of causality, and 95% credible sets containing lists of candidate causal SNPs using SuSiE (Wang et al. 2020), and calculate per-SNP heritabilities from functional annotations as fine-mapping priors utilizing PolyFun (Weissbrod et al. 2020).

Results: Preliminary fine-mapping reveals 61 AD risk loci with at least one significant SNP (PIP >= 0.1) and indicates that 58% of the published GWAS lead variants have significant PIP values (>= 0.1). Our results validate previous studies done with AD GWAS and microglia eQTL (Schwartzentruber et al. 2021, de Paiva Lopes et al. 2022). Particularly, missense variants in the TREM2, SHARPIN, and ABI3 loci are identified with significant PIP values. In addition, many intronic variants are found in myeloid lineage-specific cell enhancers identified by the Activity-By-Contact (ABC) Model (Fulco et al. 2019), and microglial chromatin-immunoprecipitation sequencing (ChIP-seq) peaks for the PU.1 binding motif. A number of variants are also identified in colocalization analyses with microglia eQTL, particularly in the BIN1, ECHDC3, and PICALM loci.

Conclusions: This study provides a comprehensive list of regulatory mechanisms that may serve as targets in the developments of more effective therapeutics for AD. Future analyses will include functional validation of fine-mapped variants with a massively-parallel reporter assay (MPRA) in iPSC microglia.

This study is funded by NIH NIA U01-AG068880 and RF1-AG065926.

2022 Neuroscience Retreat

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It is vital to understand the biology of alcohol use disorder (AUD) and drinks per week (DPW) to improve upon traditional treatments and uncover polygenic risk factors and pathways. In this study, we use multiple analyses across genomic and post-mortem data to fine-map areas highlighted by previous Genome-Wide Association Studies (GWAS) and combine this with transcriptomic data from Expression Quantitative Trait Loci (eQTL) to find differential genetic expression at single SNP resolution, as well as relate it to genetic alterations in AUD. The limitations of GWAS are that they are not able to identify how genes affect disease, only that they do. Our analysis delineates multiple genes that are differentially expressed in AUD phenotypes. Moreover, the analyses performed reference a range of phenotypes, from patients diagnosed with AUD to patients who abstain from alcohol. Not only does this provide a method of observing genetic differences and similarities between AUD and DPW, it suggests dissimilar gene expression pathways that may inform future functional studies and patient stratification efforts. We performed an SMR analysis of GWAS data and MetaBrain eQTLs which highlighted differentially expressed genes associated with AUD and DPW, and compared it with differential gene expression data from postmortem brain samples to further refine our image of gene expression in AUD.

2022 Neuroscience Retreat

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Title: MicroRNA-128 prevents seizures and premature death in a mouse model of Dravet syndrome

Authors: Diogo Ribeiro, Mary K. Duff, Philip Hwang, et al… Anne Schaefer

Epilepsy encompasses a diverse spectrum of disorders divergent in their causes, associated seizure types and severity, and accompanying clinical features. A common characteristic of sever epilepsy, such as the childhood onset Dravet syndrome, is the high degree of treatment refractory (>30%). None of the currently available anti-epilepsy treatments, most of them targeting ion channels, are able to treat this severe and frequently lethal disease. We identified a small RNA, microRNA-128 (miR-128), which is highly expressed in adult neurons, and which act as a potent modulator of neuronal MAPK/ERK signaling network and neuronal excitability. While a reduction in miR-128 expression in postnatal neurons causes increased motor activity and fatal epilepsy, mir-128 overexpression attenuates neuronal excitability and attenuates seizure susceptibility in mice. Here we demonstrate that genetic and viral overexpression of miR-128 in a mouse model of Dravet Syndrome (DS) dramatically attenuates its seizure phenotypes and prevents the premature death of the animals. This novel miR-based treatment has profound implications not only across epilepsy disorders but for other hyperexcitability disease states of the brain associated with aberrant MAPK/ERK signaling.

Fund: RegenxBio

2022 Neuroscience Retreat

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Link: https://docs.google.com/document/d/161ENj-F-2UnhtKzzg1E8UUoP2Z2NRH-JMPq5zzQXCe0/edit?usp=drivesdk Novel Methodology of Microglia-Targeted Connectivity Mapping Reveals Computational Repurposing of Tanzisertib for Treating Alzheimer's Disease

Kun Roh, Charles V. Mobbs

Background: Traditional drug discovery in the context of Alzheimer's Disease (AD) currently consistently fails to progress and there is no cure available. The complexity of AD pathogenesis poses a significant challenge to drug development. Computer-aided drug discovery targeting neuroinflammation, however, may accelerate this process.
Methods: Here, we report the results after conducting a computational drug screening for finding repurposable drugs to treat AD. First, we analyzed a publicly accessible single-cell RNA-sequence database to obtain a transcriptomic signature pronounced in AD-affected microglial cells. Through querying the signature against the Connectivity Map database, interesting drugs that effectively reverse the effects of genetic changes in microglia were found. Further analysis was performed to quantify its effects on other gene signatures as well.
Results: We have located Tanzisertib, a c-Jun N-terminal Kinase (JNK) inhibitor, as a top drug among the results. Tanzisertib robustly reverses the top 500 overexpressed genes in disease-affected microglia, as well as key genes implicated in AD pathology. There is in fact substantial evidence that suggests JNK signaling pathway is a major contributor in pro-inflammatory responses and neuronal dysfunction.
Conclusion: We show that Tanzisertib has the potential to reverse microglial dysfunction and possibly cure AD. This study is the first study to propose Tanzisertib for the purposes of treating AD and this study supports the hypothesis on JNK's potential as an attractive therapeutic target for AD.

2022 Neuroscience Retreat

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Title: Modeling gene by environment interactions in post-traumatic stress disorder

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Background: Post-traumatic stress disorder (PTSD) is a debilitating disorder that is underdiagnosed and under-treated. Better identification of genetic and environmental elements of PTSD susceptibility and resilience is important to mitigate disorder burden. We propose that integrating genomic loci with traumatic exposures may further elucidate gene by environment interactions that influence PTSD susceptibility. To test this, we performed an expression quantitative trait loci (eQTLs) analysis to identify SNPs that alter nearby mRNA expression across two PTSD-relevant cell types treated with the synthetic glucocorticoid hydrocortisone (HCort). eQTLs associate SNPs with nearby expression changes in a context-dependent manner and thus capture genetically- and environmentally-regulated expression. Our approach aimed to reveal cell type-specific and stress-dynamic eQTLs that may offer insight into the combined genetically- and stress-regulated contributions to PTSD.

Methods: Fibroblasts from combat-exposed veterans with PTSD (n=20) and without (n=20), were used to generate human induced pluripotent stem cell (hiPSC)-derived neurons (glutamatergic and GABAergic) and treated with HCort. I conducted transcriptomic analysis of PTSD-specific HCort-response, then used matched genotype and expression data to identify interactive effects between variants and HCort exposure.

Results: We identified 675 and 374 unique genes in GABA-ergic and glutamatergic neurons, respectively, with a SNP by HCort interaction. These genes enrich in GWAS catalog genes including generalized epilepsy (p=9.65E-08), bipolar disorder (p=9.36E-06), and body mass index (p=1.48E-07), traits associated with stress and glucocorticoid response. Genes with particularly strong interactions include PNPLA2 (p=5.6E-04), LRP8 (p=6.59E-04), and MXD4 (p=4.16E-04), which have been associated with chronic defeat stress, learning/memory formation, and amygdala signatures in a PTSD-like mouse model, respectively.

Conclusions: Our preliminary data suggests that integration of genetics and stress signatures identifies genes associated with genetically regulated stress response. Further fine-mapping

of eQTLs to disorder-relevant GWAS and validation in human cohorts may elucidate disorder relevance of these signatures.

2022 Neuroscience Retreat

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Role of CSRP1 in mediating protective effects of phenothiazines in Alzheimer's Disease

Authors: Lila Shapiro, Rachel Litke, Gang Ma, Charles Mobbs

BACKGROUND: Alzheimer's disease (AD) is a devastating neurodegenerative disorder with a substantial societal burden. In a large-scale drug screen using model organism C. elegans, many phenothiazines (a class of antidepressant and antipsychotic drugs) were protective against the effects of Alzheimer's-related proteotoxicity. However, the mechanisms of these drugs mediating these protective qualities are unknown.

METHODS: This study used data from the CMap database to compare gene expression patterns found in several phenothiazines to genes differentially expressed in Alzheimer's, in search of genes that may contribute to this protective mechanism. Resulting genes were then screened for protective effects in the CL2006 transgenic human Abeta model of AD in C. elegans.

RESULTS: Analysis showed that the gene CSRP1 was downregulated by many phenothiazines and upregulated in AD patients. Several studies have corroborated a likely role of CSPR1 in Alzheimer's pathophysiology. Interestingly, the gene FOX03's inhibition of CSPR1 mediated protective effects of the gene to reverse senescence in human cardiomyocytes. RNAi was used in C. elegans to test if inhibition of CSRP1 was protective against CL2006's paralysis phenotype of AD. Phenothiazines downregulating CSRP1 were also screened in C. elegans to assess if prevention of paralysis correlated to inhibition of CSRP1.

CONCLUSION: The bioinformatic analysis suggests that inhibition of CSRP1 contributes to the protective effects of phenothiazines in the C. elegans model of AD, potentially providing a novel drug target. Phenothiazines inhibiting CSRP1 trended towards protection against paralysis, corroborating with earlier drug screen data. RNAi inhibition of CSRP1 did not produce the expected protection in this phenotype. However, RNAi rarely inhibits mRNA levels by over 50%, which may not be sufficient to produce protective effects.

2022 Neuroscience Retreat

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Expression of glutamatergic synaptic genes characterize subregions of the dorsal striatum in models of motivation and compulsive heroin self-administration

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Background: Opioid use disorder (OUD) is a public health crisis in the United States with roughly 70,000 overdoses taking place in 2021. The striatum is a key structure implicated in OUD and glutamatergic inputs mediate different aspects of addictive behaviors, depending on the striatal subregion. For example, the dorsal medial striatum (DMS) is thought to drive motivated behavior, whereas the dorsal lateral striatum (DLS) is associated with compulsive drug taking. However, limited information is known about subregional glutamatergic perturbations in relation to aspects of motivated and compulsive self-administration behaviors.

Methods: Adult rats underwent various schedules of heroin self-administration either contingent on a single lever press, 10 lever presses (FR10) to model motivated drug-seeking, or on a second order schedule of reinforcement to model compulsive (non-contingent) heroin seeking. All rats in the heroin groups received equal amounts of the drug over their lifespans to account for amount of drug exposure. 'Control' non-drug conditions were also assessed with sucrose self-administration. Expression of glutamatergic-related genes, as measured by qPCR, was compared in subregions of the DS and RNA-sequencing conducted for unbiased assessment.

Results: Expression levels of Gria1, Gria2, and Grm5 were changed in the DMS but not DLS in the compulsive group only, while Fyn kinase, a regulator of the glutamate synapse implicated in OUD, was up regulated in both subregions for the compulsive heroin animals. Gene expression data for rats that exhibited motivated heroin seeking will be included in the final poster as well as RNA-seq.

Conclusion: Disturbances in regulation of the DS glutamatergic system due to heroin may be subregion- and behavior-dependent. This may have implications for understanding mechanisms underlying the shift from goal-directed to compulsive heroin use.

2022 Neuroscience Retreat

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Effects of High-Fat Diet on Fear and Metabolism

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BACKGROUND: Post-traumatic stress disorder (PTSD) is known to cause metabolic dysfunction and has been linked to increased risk of obesity and diabetes. Clinically, the link between stress and metabolic dysfunction is sex dependent. However, little is known about how diet influences stress in conjunction with metabolic dysregulation in males and females. We hypothesize that high-fat diet (HFD) alters stress responses and energy homeostasis in a sexually dimorphic manner.

METHODS: To test our hypothesis we placed two groups of mice on HFD or Chow and tested the effects of acute or repeated stress on fear and metabolism using a robust rodent model that recapitulates many aspects of fear called stress-enhanced fear learning (SEFL). In our experimental groups, we measured freezing behavior, metabolic functions, and glucose tolerance.

RESULTS: Males showed increased body weight while females showed a trend of increased freezing response when fed HFD for ten weeks. Both of these effects were significantly higher in repeatedly stressed mice compared to acutely stressed mice on HFD. Mice on HFD showed a decrease in respiratory exchange ratio (RER), which was even lower in males on HFD that were acutely stressed. All mice on HFD showed glucose intolerance, but males showed a significantly higher glucose intolerance than females with acute stress. Female mice on HFD that were repeatedly stressed showed higher glucose intolerance than acutely stressed female mice.

CONCLUSIONS: Our findings show sexual dimorphism in fear response and metabolic functions when HFD mice are paired with acute or repeated stressor. A decreased RER suggests an increase in the use of fat as an energy source, and increased glucose intolerance is associated with metabolic dysregulation commonly seen in hyperglycemic conditions. Repeated stress worsened fear expression and metabolic measures. Our findings have translational relevance for determining brain and body mechanisms that govern the link between stress and energy dysregulation.

2022 Neuroscience Retreat

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Progression of entorhinal spatial coding deficits in a mouse model of temporal lobe epilepsy

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BACKGROUND: Temporal lobe epilepsy (TLE) is a debilitating disorder characterized by spontaneous and recurring seizures as well as pervasive memory impairments, affecting an estimated 50 million people worldwide. Using rodent models of TLE, our lab has previously shown progression of learning and memory impairments along with spatial coding deficits in hippocampus. Whether these impairments in hippocampal spatial coding is due to only local processing deficits or can be attributed to altered spatial coding in upstream regions remains poorly understood. Indeed, hippocampal inputs from the medial entorhinal cortex (MEC) have been shown to be spatially modulated and their activity sufficient to facilitate hippocampal spatial memory and encoding. Furthermore, seizures have been shown to cause extensive reorganization of MEC due to cell death.

METHODS: To characterize how the progression of chronic epilepsy will alter MEC spatial coding, we will perform in vivo calcium imaging with miniature microscopes to record MEC inputs to hippocampus in either layer II stellate cells or layer III neurons in mice as they perform a variety of spatial navigation and memory tasks.

RESULTS: These experiments will allow us to track the precision, stability, and information content of layer specific MEC cells over the development of TLE. We expect to observe a progressive breakdown in the precision and stability of MEC spatially tuned cells in epileptic mice compared to control counterparts.

CONCLUSIONS: Together, this body of work will allow us to understand where, when, and how spatial coding is altered in chronically epileptic mice and potentially shine light on new regions of interest for targeted cognitive deficit therapeutics.

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2022 Neuroscience Retreat

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Dopamine signaling as a cognate microglia-neuron interaction in the striatum

Hayley J. Strasburger, Pinar Ayata, et al… Anne Schaefer.

Microglia are the tissue resident macrophages in the brain that perform diverse functions to maintain brain homeostasis. Microglia phagocytose dying cells and debris, secrete growth factors, and prune afunctional synapses. In order for this homeostasis to be maintained, microglia need to sense cognate changes in neuronal activity. One exciting possible mechanism by which microglia sense changes in neural activity is by expressing receptors for the neurotransmitters present in their microenvironment. Accordingly, we found that a subset of microglia in the striatum express the dopamine 1 receptor (D1R). Dopaminergic innervation is crucial for psychomotor functioning, and dysregulation is associated with neurological and neuropsychiatric disorders. We hypothesize that the unique subpopulation of D1R-expressing microglia in the striatum may actively sense changes in dopamine levels and relay these changes to striatal neurons by modulating their activity. To test the functional significance of this receptor on microglia, we deleted Drd1a selectively in microglia using a Cx3cr1CreErt2;Drd1afl/fl mouse line. In parallel, we also deleted the entire D1R+ microglia subpopulation using a Csf1rfl/fl; Tg(Drd1-cre) mouse line. Deleting the entire subpopulation allowed us to identify any additional functions unique to the D1+ microglia. Here I will discuss the observe changes in gene expression and behavior that occur as a consequence of ablating the microglial response to dopamine in the striatum. These findings highlight the important role of cognate microglia-neuron communication in regulating neuronal activity during homeostasis and in disease.

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2022 Neuroscience Retreat

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Emotion Regulation Circuit Dysfunction and Dysconnectivity in Women with Bulimia Nervosa

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Background: Bulimia nervosa (BN) is characterized by uncontrolled episodes of binge eating and purging. These defining behaviors are associated with self-reported difficulties with regulating emotion. However, the neural mechanisms underlying emotion dysregulation have not yet been established in BN.

Methods: In the current study, 29 women with BN and 29 matched healthy controls (HC) were scanned using functional magnetic resonance imaging during an emotion regulation task and at rest. Groups were compared on activation during attempts to downregulate negative emotion using a distancing strategy, and we applied a network analysis approach known as Group Iterative Multiple Model Estimation (GIMME) to examine resting-state connectivity within an emotion regulation network.

Results: During the task, participants with BN showed reduced activation compared to HC in the left inferior parietal cortex, a region critically involved in reorienting attention to alternative perspectives during distancing. At rest, the BN group had fewer unique connections within the emotion regulation network as compared to HC, most notably to the left IPL.

Conclusions: The results suggest dysfunction and dysconnectivity in the emotion regulation network that may be useful targets for BN treatment.

2022 Neuroscience Retreat

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Background:
The best replicated structural abnormality in patients with depression is decreased volume of the hippocampus measured using MRI. Few studies have focused on the association between treatment and hippocampal volume changes. We investigated the volume alterations of hippocampal subfields with treatment outcome and chronicity in treatment naïve depression patients to understand effects of treatment on these structures.

Methods:
A total of 215 patients treated with either SSRI or CBT from the PReDICT study were included. Two longitudinal high-resolution T1-weighted structural scans, acquired at pretreatment baseline and after 12 weeks, were used to calculate the volume of hippocampal subfields using Freesurfer 6.0.

Multiple analysis techniques were used to assess various factors including baseline hippocampus subfield volumes, effects of time in among different groups (treatment type, outcomes, and chronicity).

Results:
L_CA3 (left) volume was significantly smaller at baseline when compared to health controls and it decreased over time. However, only nonchronic groups shows L_CA3 volume reduction regardless of treatment outcome.

Closer analysis showed that L_CA3 volume reduction in the nonchronic group with treatment, regardless of outcome. Only chronic remitters showed decreased L_CA3 sub-region. This L_CA3 volume reduction was only driven by the SSRI group and no significant interaction effect was observed in the CBT group.

Conclusion:
Both chronicity and successful pharmacological treatment influenced the hippocampal volume in previously treatment naïve depression. Chronicity is the most significant contributor to these hippocampal volume findings, notable prior to any treatment, suggesting that brains with longer depression episodes (chronic group) might exist in a state where significant brain volume reduction, if any, has already occurred. Contrarily, patients with shorter episodes (nonchronic group) still can change regardless of outcome. Since this change effect is seen in medication treatment only patients, this further suggests that

medication catalyzes the underlying process for brain volume changes for nonchronic groups.

2022 Neuroscience Retreat

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Circuit-wide gene network analysis reveals a role for phosphodiesterase enzymes in cocaine addiction

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Background: Cocaine use disorder is a serious public health issue without an effective pharmacological treatment. Novel treatments for CUD are hindered in part by an incomplete understanding of the molecular mechanisms in the brain that drive long-lasting maladaptive plasticity and addiction-like behaviors.

Methods: We conducted unbiased gene co-expression network analysis on a published RNA sequencing dataset comprising 6 interconnected regions of the brain's reward circuity from mice that underwent saline or cocaine self-administration, followed by a 24-hour or 30-day withdrawal period and a saline or cocaine challenge. We ranked gene networks by their fold enrichment in genes whose expression is significantly correlated with an "addiction index" (AI) - a composite score developed using factor analysis to capture maladaptive, addiction-like behaviors during cocaine self-administration.

Results: We identify phosphodiesterase 1b (Pde1b), a Ca2+/calmodulin-dependent enzyme that catalyzes the hydrolysis of cAMP and cGMP, as a key driver of a gene network in the nucleus accumbens (NAc) that exhibits a strong negative correlation with the AI. Cell-type-specific measurements of Pde1b expression reveal dynamic regulation of Pde1b within Drd1- and Drd2-expressing medium spiny neurons (D1 and D2 MSNs) over the course of cocaine administration. Viral-mediated overexpression of Pde1b in D1 or D2 MSNs oppositely regulates the locomotor response to cocaine in male and female rodents. Our ongoing studies are investigating role of NAc Pde1b expression in regulating cocaine self-administration, cocaine-induced transcriptomic changes, and neuronal physiology.

Conclusions: In this study, we identify a novel role for phosphodiesterase enzymes in regulating the cell-type-specific actions of cocaine within the brain's reward circuitry. Given

2022 Neuroscience Retreat

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Identification of the Inhibitory Effect of a Novel Compound Series Derived From the Cardiac “Bradine” Drugs on VTA Dopamine Neurons

Emily Teichman, Jianping Hu, Carole Morel, Jian Jin, Ming-Hu Han

Background: Depression is a devastating disease, associated with profound neurophysiological alterations. Upregulation of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in ventral tegmental area (VTA) dopamine neurons is associated with depressive-like symptomology in mice. Inhibition of these channels by the HCN inhibitor Cilobradine alleviates those symptoms. Cilobradine is part of the “bradine” family of HCN-inhibiting cardiac drugs which includes Ivabradine, an FDA-approved drug to treat heart disease and heart failure. Here, we aim to augment and refine the HCN-inhibiting, blood brain barrier (BBB)-penetrant features of Cilobradine so as to improve the “bradine” series and establish rapid-acting and long-lasting therapeutic effects.

Methods: To improve inhibition efficacy and BBB permeability, 11 analogs of HCN inhibitor Cilobradine and 1 analog of Zatebradine were designed and synthesized. We investigated 8 analogs for their effects on VTA dopamine neuron Ih current and firing rate utilizing slice electrophysiology and local compound application.

Results: We first show that these 8 different compounds have a variety of inhibitory effects on Ih, including inhibitory effects comparable to parent compound Cilobradine. Compounds 10 and 12 were chosen for further study based on their strong inhibition of Ih. Cilobradine reduced the firing rate of VTA dopamine neurons by 66%, while compounds 10 and 12 led to 91.5% and 92.4% reductions, respectively. These results suggest an increase in use-dependency of the analogs as compared to the parent compound.

Conclusions: We demonstrate that minimal changes to the Cilobradine scaffold can alter, and even improve, its inhibitory effect on VTA dopamine neurons. Our results provide a new avenue of research for the development of novel therapeutics to alleviate psychiatric disorders associated with dopamine dysfunctions.

successful drug discovery efforts focused on other phosphodiesterase isoforms, this work may guide novel therapeutic development for cocaine use disorder.

2022 Neuroscience Retreat

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Convergent impact of schizophrenia risk genes

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BACKGROUND: Schizophrenia is a highly heritable psychiatric disorder with a complex genetic risk architecture that reflects the additive impact of hundreds of risk variants. While many schizophrenia-associated risk variants are thought to regulate the expression of target genes in a cell-type-specific manner, the mechanisms by which the effect of these myriad variants combine to contribute to risk remain unclear. We previously integrated hiPSC-based models with CRISPR activation and interference (CRISPRa/i) technologies to study top-ranked putative SCZ-GWAS target genes observing genotype-dependent transcriptomic differences, and resolving specific pre/post-synaptic perturbations. A CRISPR screen of putative GWAS target genes, associated with substantially smaller predicted effect sizes than loss-of-function genes, has not yet been reported in the context of psychiatric disorders.

METHODS: Here we resolved the convergent impact of twelve eGenes with strong evidence of up-regulation by Psychiatric Genomics Consortium (PGC3)-SCZ GWAS loci: CALN1, CLCN3, FES, INO80E, NAGA, NEK4, PLCL1, SF3B1, TMEM219, UBE2Q2L, ZNF823, ZNF804A. Two independent pooled single-cell RNA-sequencing CRISPRa-based experiments were applied to resolve the genome-wide transcriptomic consequences of activating SCZ eGene expression at two developmental timepoints in hiPSC-derived glutamatergic neurons.

RESULTS: Querying the shared neuronal impacts across risk genes uncovers a convergent effect concentrated on pathways of brain development and synaptic signaling. Our analyses reveal shared and divergent downstream effects of these twelve genes, independent of their previously annotated biological roles. General convergence of gene expression increases with increasing polygenicity, while the specificity of convergence increases between functionally similar genes. Convergent networks show brain-region and developmental period-specific enrichments, as well as disorder-specific enrichments for rare and common variant target genes across multiple disorders. These gene targets are drug-able and represent potential points of therapeutic intervention. Convergence is also resolved in the post-mortem brain.

CONCLUSION: Overall, convergence suggests a model to explain how non-additive interactions arise between risk genes and may explain cross-disorder pleiotropy of genetic risk for psychiatric disorders.

2022 Neuroscience Retreat

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Entorhinal-Hippocampal Desynchronization in a Mouse Model of Alzheimer's Disease Pathology

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Background: Alzheimer's disease (AD) is a devastating neurodegenerative disease characterized by memory loss and progressive age-related cognitive decline. Impairments in hippocampal function and spatial navigation are well established in AD, but it is unclear whether this is driven by local changes or by abnormal inputs, such as those from medial entorhinal cortex (MEC).

Methods: To understand how AD pathology impacts the entorhinal-hippocampal circuit, we used 3xTg mice, which express mutations in APP, presenilin, and tau. We performed acute in vivo silicon probe recordings to simultaneously record from hippocampus and inputs from MEC. Head-fixed mice were trained to run on a virtual reality track and recorded during active navigation. By recording in two age groups, we were able to compare neural activity before and after the onset of spatial memory impairments and examine how and when synchrony breaks down.

Results: Our data suggest that synchrony between MEC and hippocampus is impaired in 3xTg mice compared to WT controls. Decreased hippocampal theta power began to emerge by 6 months of age, prior to the onset of spatial memory impairments. However, more severe changes throughout the hippocampus were present at 8 months, when memory impairments were observed. We also found reduced theta coherence between MEC and hippocampus in 3xTg mice at 8 months, but no reduction in theta coherence between DG and CA1.

Conclusions: The observed reduction in hippocampal theta power and decreased coherence between MEC and hippocampus suggest a breakdown of communication between MEC and hippocampus. Possible factors driving early entorhinal dysfunction include hyperexcitability of MECII stellate cells and loss of MEC parvalbumin interneurons. These findings align with recent studies showing early entorhinal dysfunction mouse models of AD pathology.

2022 Neuroscience Retreat

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Title: Molecular basis of dysregulated top-down attentional circuit in a mouse model of Fragile X syndrome

Authors: Leah Waltrip, Lucy Bicks, Elisa Nabel Falk, Yury Garkun, Schahram Akbarian and Hirofumi Morishita

Introduction: Attention is a cognitive process often disrupted in autism spectrum disorder (ASD). Our recent study demonstrated that a key attention circuit involving the top-down frontal-sensory neurons projecting from the anterior cingulate area (ACA) to the visual cortex (VIS: ACAvis neurons) normally undergoes key maturation processes during adolescence. However, this process is dysregulated in mouse models of Fragile X syndrome, a leading genetic risk of ASD (Neuron 2021, Science Advances 2021). Here we aimed to determine the molecular basis of dysregulated attentional circuit maturation at the transcriptome level.

Methods: Adult FMR1KO, adult wild type (WT), and adolescent WT male mice (7-8 mice/group) on a cre-dependent TRAP-GFP background were injected with a retrograde-cre virus in the VIS to label ACAvis neurons. We used Fluorescence Activated Nuclei Sorting to collect GFP labeled ACAvis nuclei. Libraries were then sequenced on a HiSeq 2000 platform, followed by differential gene expression and gene set enrichment analysis.

Results: ACAvis neurons in adult FMR1KO mice showed dysregulated nicotinic acetylcholine receptor signaling including a decrease of Lynx1, an endogenous brake for nicotinic signaling. Intersection of enriched gene sets in both adult FMR1KO and adolescent WT ACAvis neurons revealed an unexpected increase in expression of multiple axon guidance-related genes, suggesting that axon guidance pathways in ACAvis neurons are not dampened following adolescence in FMR1KO mice.

Conclusions: Our findings not only revealed the molecular basis of recently reported dysregulation of nicotinic signaling in FMR1KO mice (Science Advances 2021), but also a previously unrecognized association of axon guidance pathways in adolescent circuit maturation. Our study provides promising circuit-based therapeutic targets for future studies to ameliorate attention deficits in neurodevelopmental disorders.

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Neuropathology of Parkinson's Disease in the Dorsolateral Prefrontal Cortex

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Background: The role of lewy bodies, amyloid plaques, and neurofibrillary tangles in Parkinson's Disease (PD) remains poorly understood. Larger sample sizes in histological analyses of PD brain tissue as well as inclusion of both living and postmortem human specimens are needed. Here we manually analyze brain tissue from the Dorsolateral Prefrontal Cortex (DLPFC) in a large cohort of living and postmortem individuals.

Methods: Living and postmortem human brain tissue was fixed, embedded in paraffin, and visualized using six stains: Hematoxylin and Eosin (HE), Luxol Fast Blue (LHE), Bielschowsky Silver and antibodies against phosphorylated tau protein (AT8), beta-amyloid (4G8) and alpha-synuclein (LB509). Whole slide images (WSIs) were generated from slides and manually scored based on the presence of pathological features.

Results: Analyses are ongoing and the initial results will be reported at the time of the retreat. Each WSI was evaluated for lewy bodies, amyloid plaques, and neurofibrillary tangles. We compared these tissue features across different sample groups defined by demographics such as diagnosis and age.

Future Directions: We plan to generate more WSIs to further improve the power of the study. We will analyze the WSIs using a deep learning technique known as clustering-constrained attention multiple instance learning (CLAM) to identify and cluster tissue regions into diagnostically relevant categories. Eventually, we will compare the neuropathology of these samples to genetic, transcriptomic and proteomic data generated for this same cohort. This project contributes to our understanding of the neuropathology of PD and to the holistic view of the biology of PD that the Living Brain Project seeks to achieve.

2022 Neuroscience Retreat

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Genetic regulation of gene expression in the frontal cortex through adulthood and aging

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Background
Genome-wide association studies have been a wildly successful tool for identifying genomic variants associated with psychiatric disorders. However, in order to generate large sample sizes, GWAS often aggregate samples across heterogeneous environments, therefore failing to consider what context-specific associations can inform us about the underlying disorder biology. Age is often considered a confounder in genetic and transcriptomic studies but can be leveraged as a useful tool to better characterize the dynamic regulatory architecture of the brain across human aging.

Methods
We combined paired post-mortem frontal cortex gene expression and genotype information from 1,435 individuals across 6 publicly available datasets in order to identify eQTLs associated with age. These analyses were twofold, one tested for an interaction effect between a variant and age, and a stratified approach involved conducting six independent eQTL searches using subsets of the total combined cohort split by age into bins representing decades (40-49,50-59, etc.).

Results
We identify 7,734 eGenes for which a corresponding eSNP showed a significant interaction with age. Gene set enrichment shows that eGenes with an age-interaction effect are enriched for GWAS gene sets for Autism Spectrum Disorder, schizophrenia, neuroticism, and Parkinson's Disease.

Conclusions
These preliminary results demonstrate the relevance of considering age as an important environmental context for the discovery of dynamic genetic regulation. We will present the final results from ongoing analyses to determine the temporal and tissue specificity of the frontal cortex-derived eQTLs, in addition to analyses testing for associations between temporally dynamic eQTLs and neuropsychiatric traits such as colocalization and PheWAS using the Mount Sinai BioMe biobank.

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AN ACTIVE INFERENCE MODEL OF EMOTION EPISODES

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BACKGROUND: The scientific study of emotion is embedded in a representationalist framework, relying on abstract constructs that may be deflated to neurocomputational mechanisms. Two prominent accounts—the theory of constructed emotion (Barrett, 2017) and component process model (Scherer, 2001)—contradict each other on the semantic surface, but can be integrated in mechanistic terms under the neurocomputational process theory of active inference (Friston et al., 2017).

METHODS: We develop a deflationary account of emotion episodes from first principles by building central mechanisms from both accounts into a partially observable Markov decision process model under active inference. Here, emotion episodes are hidden states of an internal generative model in the Bayesian brain, inferred as best explanations in the staggered processing of increasingly complex multimodal sensory information. We develop the model across three stages: the first with simultaneous sensory information, the second allowing staggered processing of sensory information, and third with explore-exploit capability. At each stage, we validate the model using simulations on both single trials as well as learning sequences starting with no knowledge and across different degrees of reward.

RESULTS: We demonstrate that the model successfully learns emotions from synthetic childhood into adulthood. In addition, when highly motivated to be correct about its emotion, it favors exploitation earlier during trial instead of exploring all available sensory information. However, this leads to alexithymia, or low emotional granularity, when overly rewarded.

CONCLUSIONS: In validating this integrative model's capacity to formalize emotional phenomena of interest, we provide proof of principle that two accounts of emotion can be merged under active inference. This unifying endeavor offers promising directions for the computational and empirical study of emotion and highlights theoretical implications for cross-disciplinary pluralism.

2022 Neuroscience Retreat

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Single neurons in macaque basolateral amygdala exhibit distinct patterns of collateral projections

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BACKGROUND: A major assumption of systems neuroscience is that the long-range projections of single neurons only target one other brain area. It is, however, well-documented that neurons often collateralize and target multiple brain areas, potentially coordinating activity across distributed brain networks. Until recently, assessing collateral projections at scale was out of reach. Here, using MAPseq, an anatomical technique that can resolve the connections of single neurons, we interrogated the projection patterns of macaque amygdala neurons.

METHODS: Injections of barcoded sindbis virus were made into the basolateral nucleus of the amygdala bilaterally in two rhesus macaques. After perfusion, brains were sectioned and target areas dissected, focusing on the frontal cortex, which the basolateral amygdala is known to densely innervate. Finally, RNA barcodes were sequenced from each of the four hemispheres individually to determine the extent of collateral projections.

RESULTS: Using MAPseq, we were able to assess the projection patterns of over 3000 single amygdala neurons. Approximately, one-third of these neurons did not have a projection target in the frontal cortex, one-third projected to a single target, and the remaining third projected to two or more targets. Those neurons with multiple targets tended to send collaterals to frontal areas that are known to be part of functionally- and anatomically-defined networks.

DISCUSSION: We found that a significant proportion of macaque amygdala neurons had multiple projection targets. We identified novel connectional motifs, which we are presently validating with traditional tract-tracing approaches. By optimizing MAPseq for use in macaques, we demonstrate the power of this tool both to assess projections in healthy animals and potentially to understand anatomical changes in macaque models of development or neurodegeneration.

2022 Neuroscience Retreat

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Title: The Landscape of Autophagy Degradation and Regulation in Neurons

Authors: Xiaoting Zhou, Carlos Sanchez-Priego, Henry Kim, Xianting Li, Xian Han, Junmin Peng, Nan Yang, and Zhenyu Yue

Background: Autophagy is a lysosomal degradation pathway and plays an important role in neuroprotection. It is often disrupted in neurodegeneration diseases and impairment of autophagy has recently been linked to neurodevelopmental disorders. However, the precise process of autophagy in human neurons remains poorly defined. The mechanism for how autophagy is disrupted in human neurodevelopmental diseases remains unclear.

Methods: We performed a systemic investigation of autophagy cargos and adaptors to understand autophagy pathways in neurons. We generated autophagy-deficient human-induced glutamatergic neurons (iNs)from human pluripotent stem cells. To enrich autophagy cargos, we suspended autophagy in neurons using CRISPR-inhibition technology to knock down ATG7 or ATG14. We also established neuron-specific atg7 or atg14 conditional knockout (cKO) mice. To enrich autophagy cargo, we generated ATG7 cKO mice expressing GFP-LC3, followed by affinity purification of LC3-interacting proteins. Quantitative proteomic analysis was performed to identify proteins with increased levels in ATG7 or ATG14-deficient human or mouse neurons. Both autophagy-deficient human iNs and mouse brains were used for validating pathways of interest identified from quantitative proteomics.

Results: Accumulations of known autophagy-associated proteins were observed in autophagy-deficient neurons. We identified novel autophagy cargos and adaptors involved in pathways including ER-phagy, synaptic vesicle, and PKA pathways. Calumenin was identified as a putative novel ER-phagy adaptor and its function in mediating ER degradation was characterized. We also observed that autophagy might regulate neuronal activity through mediating PKA pathway activation.

Conclusions: Our work revealed the landscape of autophagy degradation and regulation in mouse and human neurons. We identified novel autophagy cargos and adaptors. Our study underscores the complexity of the autophagy functions in neurons and sheds light on the mechanisms for the neuroprotective function of autophagy.

2022 Neuroscience Retreat

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Ensemble reactivation during an offline period links recent experience with past memories

Yosif Zaki, Taylor Francisco, Denisse Morales-Rodriguez, Zachary Pennington, Alexa LaBanca, Zhe Dong, Kanaka Rajan, Denise Cai

Background: The compilation of memories, aggregated across a lifetime, defines our human experience. But memories are not static representations of our experiences; rather, we are constantly updating and linking memories across time, especially when a past event can help us predict future outcomes. How are memories dynamically updated to make causal inferences about the world?

Methods: Using in vivo calcium imaging (with open-source Miniscopes in freely behaving mice), chemogenetics, and novel behavioral designs, we tested how hippocampal networks link an aversive experience to a neutral memory formed days prior.

Results: We found that fear from an aversive experience can transfer to a neutral event experienced days prior. We termed this phenomenon retrospective memory-linking. Memory-linking was asymmetric, as fear from an aversive experience did not transfer prospectively to a neutral event experienced days later. We found retrospective memory-linking was modulated by the negative valence; the more negative the aversive experience, the more likely fear would transfer to a past memory. We imaged hippocampal ensembles while mice learned a neutral context, received a strong or weak shock in a separate aversive context two days later, and while mice rested in their homecage after aversive learning. We found that mice that received a weak shock—and did not display memory-linking—displayed reactivation of the aversive ensemble, but not of the neutral ensemble from days prior. In contrast, mice that received a strong shock displayed reactivation of both the aversive and neutral ensembles. Finally, inhibiting ensemble reactivation during the offline period abolished memory-linking.

Conclusions: These results suggest that fear from an aversive event can transfer to neutral events experienced days prior, and is driven by reactivation of hippocampal ensembles representing multiple experiences. In nature, the causal link between predictors and outcomes is often uncertain; thus, it may be useful to link memories across days to predict future outcomes. Our work points to a neural mechanism that supports causal inference and explains how episodic memories are linked across days.

2022 Neuroscience Retreat abstract submission

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Please check Talk

The battering ram. Traumatic brain injury in headbutting bovids

NL Ackermans, M Varghese, TM Williams, N Grimaldi, E Selmanovic, A Alipour, P Balchrandani, JS Reidenberg, PR Hof

ABSTRACT

Traumatic brain injury (TBI) is a leading cause of death and neurologic impairment that remains poorly understood. Common laboratory models have yet to produce clinical therapies, and the exploration of larger and more diverse models is relatively scarce. Because of their headbutting behavior, we investigated the potential for brain injury in two bovid species by assessing neuromorphology and neuropathology through immunohistochemistry and stereological quantification. Postmortem brains of wild muskoxen (Ovibos moschatus, n=3) and bighorn sheep (Ovis canadensis, n=4) were processed histologically for evidence of TBI, specifically abnormalities in neurons, microglia, and astrocytes. Phosphorylated tau protein, a TBI biomarker found in neurodegenerative lesions, was used to detect possible cellular consequences of chronic or acute TBI. Multiple markers indicated high amounts of tau-immunoreactive neuritic thread clusters, neurites, and neurons concentrated in the superficial layers of the neocortex, preferentially at the bottom of the sulci in the muskoxen of both sexes. Tau-immunoreactive lesions were rare in the bighorn sheep. Our preliminary findings indicate that muskoxen and possibly other headbutting bovids suffer from chronic or acute brain trauma and that the males' thicker skulls may protect them to a certain extent.

2022 Neuroscience Retreat abstract submission

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Oxytocin Modulation of the Paraventricular Nucleus and Supramammillary Nucleus Differentially Regulates Social Recognition Memory

Keerthi Thirtamara Rajamani, Marie Barbier, Kristi Niblo, Nick Cordero, Valery Grinevich, Shai Netser, Shlomo Wagner, Hala Harony-Nicolas

Background: Oxytocin (OXT), a neuropeptide synthesized in paraventricular (PVH), supraoptic (SON) and accessory nuclei (AN) of the hypothalamus is implicated in social behaviors including social recognition memory (SRM). However, the role of the 3 nuclei in modulating SRM is not fully understood. In this study, we addressed if PVH-OXT neurons are necessary for short and long–term SRM, and if OXT activity within a hypothalamic nuclei called supramammillary nucleus (SuM) is necessary for social recognition. The SuM send direct projections to the hippocampal CA2 region and is known modulate social memory, however the role of OXT in mediating this is unclear.

Methods: Using designer receptors activated by design drugs (DREADDs), we silenced OXT neurons (OT-hM4DGi) in the PVH of rats and assessed their short and long term SRM. We used immunohistochemistry and RNAscope to verify the presence of OXT fibers and receptors in the SuM respectively. We also blocked OXTR activity in the SuM to determine if this is necessary for social recognition memory.

Results: Silencing PVH-OXT neurons impairs both short and long-term SRM. This effect is specific for the social domain as object recognition remains intact. We also confirmed SuM to receive OXT projection fibers and confirmed that they originate from the PVH and not SON. We further confirmed that the SuM expresses OXT receptors which segregate into specific neural subtypes. Finally, we showed that blockade of OXTR activity affects long but not short-term social recognition memory.

Conclusions: These findings attribute a novel role for PVH-OXT neurons in SRM. We also determined that OXT modulation of SuM selectively affects specific forms of social recognition memory.

2022 Neuroscience Retreat abstract submission

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Talk Poster

EEG markers for tracking changes and predicting outcomes in substance use disorder abstinence and treatment: a systematic review

Authors: Bel-Bahar, Tarik; Khan, Anam; Parvaz, Muhammad A.

BACKGROUND: Substance use disorders (SUD) are complex, with high relapse rates and moderately successful treatments. Neuropsychological SUD implicate reactivity to substance-related cues and alterations in various brain systems as bases for craving, compulsive drug-taking, and relapse. Yet to date there are no established biomarkers for SUD treatment and outcome evaluation. There is now a growing interest in electroencephalography (EEG) biomarkers for indexing SUD treatment progression and outcomes. Therefore, this review advances our knowledge of the current state of the field by appraising extant findings on EEG biomarkers in SUD treatment.

METHODS: Literature search was conducted for publications between 2000-present using keywords associated with EEG and SUD treatment. Studies included cross-sectional and longitudinal work regarding 1) pre-treatment or initial abstinence 2) post-treatment, and 3) prediction of post-treatment clinical outcomes. Studies were reviewed in terms of findings, sample size, data quality, EEG signal processing, clinical utility, and external validation.

RESULTS: Identified studies mainly focused on abstinence in alcohol and cocaine use disorders during abstinence. As compared to non-using controls, patterns of interest in SUD included decreased event-related potential components (ERP) amplitudes, hyperactive resting-state spectral EEG, and decreased connectivity, which tended to normalize with extended abstinence and/or treatment. However, there is currently heterogeneity in terms of methods, findings, and samples, and a lack of longitudinal studies with multiple time points.

CONCLUSIONS: Overall, EEG markers in SUD treatment require further development and validation before they can be deployed in clinics, including enhancing reliability and links to biological and clinical end points. With continued research EEG biomarkers may assist in enhancing objective SUD diagnosis, treatment monitoring and prediction of outcomes.

Funding: NIH and ISMMS

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BCI-838 enhances adult hippocampal neurogenesis, behavior and regulates exercise-related molecular pathways in an Alzheimer's disease mouse model

Georgina Perez-Garcia, Mesude Bicak, Jacqueline Buros, Jean-Vianney Haure-Mirande, Gissel M. Perez, Alena Otero-Pagan, Miguel A. Gama Sosa, Rita De Gasperi, Mary Sano, Fred H. Gage, Carrolee Barlow, Joel T. Dudley, Benjamin S. Glicksberg, Yanzhuang Wang, Benjamin Readhead, Michelle E. Ehrlich, Gregory A. Elder, Sam Gandy

BACKGROUND: Physical exercise (PE) may delay, slow or prevent mild cognitive impairment or dementia due to Alzheimer's disease (AD). Beneficial effects of PE include the stimulation of adult hippocampal neurogenesis (AHNG). BCI-838 is an antagonist of the group II metabotropic glutamate receptor (mGluR2/3). We previously demonstrated that administration of BCI-838 to a mouse model of cerebrovascular accumulation of oligomeric AbE22Q ("Dutch") reduced learning behavior impairment and anxiety. The objective of the present study was to evaluate the effects of the administration of BCI-838, PE or both on learning behavior, AHNG and the transcriptome of the mouse model of amyloid pathology APPKM670/671NL/ PSEN1Δexon9 (APP/PS1) prior to the significant amyloid deposition in the form of plaques.

METHODS: Three-month-old APP/PS1 mice were treated with either BCI-838 (5 mg/kg daily), PE (running wheels) or a combination of both for 1 month. We performed Novel Object Recognition and Barnes Maze tests, biochemical analyses and generated transcriptomic profiles of the dentate gyrus (DG) of the APP/PS1 mice. Finally, we performed drug repurposing and chemogenomic enrichment analysis.

RESULTS: Our findings demonstrate that: (i) BCI-838, PE or their combination enhanced AHNG, (ii) BCI-838 alone or associated with PE led to improvement in both spatial and recognition learning behaviors, (iii) BCI-838 increased mRNA levels of BDNF, metabotropic glutamate receptors, PIK3C2A of the PI3K-MTOR pathway, and decreased EIF5A of ketamine-modulating mTOR activity in the hippocampal DG, (iv) qPCR results validated the statistical significance of the association between BCI-838 and increased levels of BDNF.

CONCLUSIONS: Our study points to BCI-838 as a safe and orally active compound capable of mimicking the beneficial effect of exercise on HNG, learning behavior and anxiety in a mouse model of AD neuropathology.

2022 Neuroscience Retreat

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Neuronal deletion of tRNA methyltransferase Nsun2 is associated with activation of the integrated stress response and alterations in addiction-related behaviors

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Background: NSUN2, a mammalian tRNA methyltransferase, is expressed at high levels in brain and has been linked to neurodevelopmental defects in humans and mice due to its regulatory role in protein synthesis. We recently showed that there is a potent effect of Nsun2 depletion, via loss of tRNA methylation, on codon-specific tRNA expression and amino acid levels, producing proteomic shifts that impair synaptic transmission, cognition, and depressive-like behavior. Because dysregulation of amino acids and tRNA expression are known to produce the integrated stress response (ISR), we sought to explore whether this may be a mechanism by which loss of tRNA methylation alters phenotypic outcomes, including addiction-related behaviors.

Methods: We used Cre-driven conditional knockout of Nsun2 in the postnatal mouse cortex to deplete tRNA methylation levels and used western blot to measure hallmarks of the ISR, including Atf4 and phosphorylated Eif2a protein expression. We also conducted behavioral testing, including morphine conditioned place preference, to assess addiction-related behavior after Nsun2 deletion.

Results: Nsun2 KO mice showed a marked increase in ATF4 expression and phosphorylated Eif2a expression compared to WT control mice. Further, Nsun2 KO mice also show impairments in reward-seeking behavior.

Conclusions: Data suggest that the ISR may be a crucial mediator between tRNA dysregulation and phenotypic outcomes, including impairments in reward-seeking related to addiction. Future studies will investigate reversal of the ISR via small molecular ISRIB as a potential rescue for our Nsun2 KO mediated phenotypes.

Funding: NIMH

2022 Neuroscience Retreat

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Potentially beneficial effects of cannabidiol (CBD) in EcoHIV infection in culture and mice.

Alejandra Borjabad, Jennifer Kelschenbach, Loreto Carvallo-Torres, Eran Hadas, Wei Chao, David J. Volsky

BACKGROUND: Cannabidiol (CBD), a non-psychoactive cannabis component, is freely available and widely used for relieving pain and anxiety commonly experienced by people living with HIV (PLWH) and it has been described as having several anti-inflammatory effects. However, its long-term effects on HIV infection and progression of HIV neurocognitive disease remain largely undetermined.
METHODS: Here, we use in vitro models and EcoHIV infected mice to investigate the effects of CBD on virus load, inflammatory markers, brain transcriptional profiles, and behavioral outcomes.
RESULTS: Following kinetic and dose optimization studies, our preliminary results show a reduction of EcoHIV viral load in monocyte/macrophage-derived RAW 264.7 and microglia-derived SIM-A9 cell lines and in primary murine macrophages pre-treated with CBD. Virus load was also reduced in the brain of EcoHIV infected mice pretreated with 30 mg/kg of CBD. This effect was accompanied by altered transcriptional signature in brain tissue compared to untreated infected mice that included down-regulation of immune-related genes TNF-α, CXCL10 and C3. However, CBD treatment of EcoHIV mice had no significant effect on neurocognitive disease in these animals.
CONCLUSIONS: Our data indicate that CBD can have beneficial effects in mitigating some HIV effects in vitro and in vivo.

FUNDING: Supported by grants R01 DA052844-01 and U01 DA053629 from the National institute on Drug Abuse (NIDA), NIH

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Measuring Optic Nerve Head Swelling Using Machine Learning

AUTHORS: Joseph Branco, Jui-Kai Wang, Elena Solli, Louis Pasquale, Mark Kupersmith

BACKGROUND: Convolutional neural networks (CNNs) can differentiate eyes with a swollen optic nerve head (ONH) due to intracranial hypertension from normal eyes, but the use of CNNs to estimate the descriptive Frisén grade or quantification of the ONH swelling has been limited. Our study explored: 1) if CNN models can predict Frisén grade using expert-labeled fundus photos, and 2) if we could train a model using fundus photos labeled with optical coherence tomography (OCT) measurements after 3D segmentation to predict retinal nerve fiber layer thickness (RNFLT), total retinal thickness (TRT), and optic nerve head volume (ONHV).

METHODS: We used a total of 430 fundus photos from 165 subjects (330 eyes) in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT). To increase the number of eyes with more severe swelling we added 24 subjects (43 eyes) taken from our clinic, and eight subjects (16 eyes) from the University of Iowa. We labeled photos according to expert-determined Frisén grade. We used 316 fundus photos from 88 subjects in the IIHTT and labeled them with their corresponding RNFLT, TRT, and ONHV values determined by 3D segmentation of OCTs. We trained one model each for prediction of Frisén grade, RNFLT, TRT, and ONHV using the Densely Connected Convolutional Neural Network "DenseNet161" base architecture.

RESULTS: We found a strong correlation between predicted and actual Frisén grades ($r=0.757$, $p<0.001$, MAE=0.691). We also found a strong correlation between the actual RNFLT ($r=0.861$, $p<0.001$, MAE=56 microns), TRT ($r=0.854$, $p<0.001$, MAE=73 microns), and ONHV ($r=0.788$, $p<0.001$, MAE=1.73 mm3) values and those predicted by the model.

CONCLUSIONS: A CNN model with supervised learning can estimate Frisén grade and OCT values for RNFLT, TRT, and ONHV with small data sets. We think that increasing the number of study eyes should increase the moderate correlations and improve accuracy.

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Transcriptional characterization of the secretome of APOE3 and APOE4 iPSC-derived mural cells

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Background

Vascular dysfunction and loss of blood-brain barrier integrity initiate at the earliest stages of Alzheimer's disease (AD) and is crucial in its pathophysiology. Pericytes, specialized mural cells surrounding brain capillaries, play an important role in the regulation of blood-brain barrier (BBB) integrity. Interestingly, patients carrying the APOE4 variant of apolipoprotein E gene, the highest genetic risk factor for AD, display accelerated BBB breakdown and pericyte dysfunction. However, the mechanisms through which APOE4 alters pericyte function and leads to BBB disruption is not fully understood.

Methods

Previously generated RNA-sequencing of iPSC-derived mural cells with pericyte-like properties (iMCs) was further analyzed. The secretome was extracted using the Human Protein Atlas and compared between iMCs with APOE3:3 and APOE4:4 genotype. Qiagen's Ingenuity Pathway Analysis and DAVID's Gene Ontology analysis were used for post-analyses and data interpretation.

Results

More than 1500 genes were identified as genes encoding for secreted proteins of which over 400 genes were differentially expressed between APOE3:3 and APOE4:4 iMCs. Post-analyses of the differentially expressed genes pointed towards extracellular matrix organization as the most significant biological process and the involvement of molecular functions such as binding of integrins, β-amyloid and transforming growth factor β. Canonical pathways with predicted increased activity included GP6 and LXR/RXR signaling pathways while the acute phase response signaling was predicted to be inhibited. Comparisons with publicly available datasets show overlapping pathways of interest in APOE4 AD carriers confirming their clinical relevance.

Conclusion

These preliminary results suggest that APOE4-induced alterations of the pericyte secretome could play an important role in dysregulating the local homeostasis of the BBB. Our future studies will focus on identifying and validating key players relevant to the pathogenesis of AD in order to potentially modulate APOE4-induced damage to the neurovascular unit.

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INPP5D limits plaque formation and glial reactivity in the APP/PS1 mouse model of Alzheimer's disease

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BACKGROUND: Late-onset sporadic Alzheimer's disease (LOAD) is the most common form of dementia, characterized by progressive memory decline. Inositol polyphosphate-5-phosphatase D (INPP5D) has been highlighted by multiple approaches as an AD risk gene, and its expression in brain is restricted to microglia. The role that INPP5D plays in either early or late disease, and the mechanism remain unknown.
METHODS: We used Inpp5d-flox mice crossed with an inducible Cx3cr1CreER/+ to assess pathological consequences of Inpp5d knockdown in AD mouse model APP(KM670/671NL)/PSEN1Δexon9 (PSAPP). To induce recombination, 3-month-old (mo) Inpp5d-flox/Cx3cr1CreER/+ mice, with and without the PSAPP transgenes, were injected for 5 consecutive days with either tamoxifen (TAM) or corn oil (CO). At 6mo, we utilized immunohistochemistry to characterize plaque pathology and microgliosis, with spatial transcriptomics to analyze brain region-resolved and peri-plaque gene expression patterns.
RESULTS: At 6mo, we found that Inpp5d knockdown in TAM-treated PSAPP/Inpp5d-flox/Cx3cr1CreER/+ mice significantly increased the percent area of 6E10+ deposits in the hippocampi by over 50% compared to CO-treated. Additionally, overall area and diameter of individual amyloid plaques were increased. We also found a significant spatially-constrained increase in microglia associated with Abeta-plaques due to Inpp5d knockdown. Our spatial transcriptomics analysis identified a plaque-specific expression profile, Cluster 26, which was extensively altered by the knockdown of Inpp5d. Finally, we projected the differential gene expression profiles of the Inpp5d knockdown mouse onto the INPP5D regulatory network from human AD and control brains in the Mount Sinai Brain Bank cohort - demonstrating significant overlap between our Cluster 26 signature with that of human AD gene networks.
CONCLUSIONS: These results demonstrate that conditional Inpp5d downregulation in the PSAPP mouse increases plaque burden and phagocytic microglial recruitment to plaques. Our spatial transcriptomics analysis highlights an extended DEG signature associated with plaques, and identifies a potentially highly specific marker of plaques in the AD brain.

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Interactions between peripheral myeloid cells and the brain in stress-impaired social behaviors

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Background: Chronic psychosocial stress is an important risk factor for major depressive disorder (MDD) and can lead to profound changes in the peripheral immune system. However, the mechanisms linking peripheral immune system activation and neuronal dysfunction in the Nucleus accumbens (NAc) and as a consequence, deficits in social reward processing, are still poorly understood.

Methods: In a murine model of chronic social defeat stress (CSDS), we applied mass cytometry, bulk and single-cell RNA-sequencing to characterize immune cells in circulation and the central nervous system. Using pharmacological and genetic strategies, we investigated the causal effects of the identified murine targets on stress-induced behavioral and electrophysiological changes.

Results: CSDS led to trafficking of peripheral pro-inflammatory monocytes to the vasculature of the NAc in stress-susceptible mice. Single-cell RNA-sequencing of brain infiltrating monocytes identified increased expression of the endopeptidase matrix metalloproteinase 8 (Mmp8) in susceptible vs. resilient or control mice. Susceptible mice showed abnormal extracellular matrix (ECM) ultrastructure, indicative of increased ECM remodeling. ECM abnormalities correlated positively with plasma levels of MMP8. Genetically depleting Mmp8 in leukocytes promoted resilience to CSDS, prevented stress induced ECM alterations and attenuated increased neuronal excitability.

Conclusions: Our findings provide mechanistic evidence that neuro-immune interactions are relevant to the etio-pathophysiology of stress-induced social behavior deficits. Targeting specific inflammatory molecules such as matrix metalloproteinases could constitute interesting novel therapeutic targets for stress-related neuropsychiatric disorders.

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Common and distinct cortico-striatal volumetric changes in cocaine and heroin use disorder

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Background: Drugs of abuse impact cortico-striatal dopaminergic targets and their morphology across substance types in common and unique ways. While the dorsal striatum drives addiction severity across drug classes, opiates impact ventromedial prefrontal cortex (vmPFC) and nucleus accumbens (NAcc) neuroplasticity in preclinical models, and psychostimulants alter inhibitory control, rooted in cortical regions such as the inferior frontal gyrus (IFG). We hypothesized parallel gray matter volume (GMV) changes in individuals with cocaine or heroin use disorder (CUD/HUD): decreased GMV of vmPFC/NAcc in HUD and IFG in CUD, and putamen GMV to be associated with addiction severity.
Methods: We quantified GMV in age/sex/IQ-matched individuals with CUD (n=20; 5 women), HUD (n=20; 6 women), and healthy controls (HC; n=20; 5 women), further replicated in an extended sample (combined n=96).
Results: Overall, addicted individuals had smaller vmPFC volumes than HC ($p<0.05$-corrected), driven by HUD ($p<0.05$-corrected; similar NAcc reduction). Right IFG reductions were specifically evident in CUD vs. HUD ($p<0.05$-corrected). Posterior putamen volume increased as a function of craving in CUD vs. HUD ($p<0.05$-corrected).
Conclusions: These results indicate compression of dopamine-innervated regions (in the vmPFC and NAcc) across cocaine- or heroin-addicted individuals, more severely in the latter. For the first time we demonstrate IFG compression specifically in CUD. This group also showed a unique association between craving and increased putamen volume, together indicating a signature of enhanced cue-sensitivity and habit formation. Results suggest common and substance-specific morphometry volumetric changes in human psychostimulant or opiate addiction, with implications for fine-tuning biomarker and treatment identification by primary drug of abuse.

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Longitudinal changes in default mode network with subcallosal cingulate deep brain stimulation for treatment-resistant depression

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BACKGROUND: Subcallosal cingulate deep brain stimulation (SCC DBS) has been investigated as a novel treatment option for severe and chronic treatment-resistant depression (TRD). The aim of this study is to characterize the longitudinal brain changes in default mode network (DMN) with SCC DBS using 15O-water PET and test in a new cohort of subjects in18F-FDG PET.

METHODS: The first dataset (n=17) collected at Emory University was used to examine the longitudinal brain changes with ongoing chronic stimulation using 15O-water PET. The second dataset (n=5) from ISMMS was used to test brain changes in individual patients using an alternative PET. All patients received bilateral SCC DBS and were stimulated for 6 months. Serial PET scans were acquired at 4-time points: baseline, 1 month after surgery, and 1 and 6 months of chronic stimulation. The average cerebral blood flow (CBF) or glucose metabolism in the DMN was calculated. A linear mixed-model analysis was conducted to examine the differential trajectory of brain changes over time in the first cohort. In addition, the relationship between changes in DMN and depression severity was assessed independently of time.

RESULTS: A significant differential trajectory of CBF with SCC DBS was found in the DMN: 1) early change induced by initial stimulation, and 2) delayed changes induced by chronic stimulation. In addition, the CBF changes in the DMN correlated with depression severity. Furthermore, the responders showed a significantly increased rCBF change with 6-month chronic stimulation in DMN, whereas nonresponders did not. This differential trajectory pattern between responder and nonresponders was also seen in the second cohort with FDG-PET.

CONCLUSIONS: The trajectory of CBF changes with SCC DBS is not linear, consistent with the chronology of therapeutic effects. The DMN changes suggest showing a biphasic pattern that will be further explored as a readout to track clinical improvement with ongoing treatment.

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Title: Mechanisms contributing to behavioral plasticity following pregnancy and postpartum experience in female mice

Authors: Jennifer C Chan, Giuseppina Di Salvo, Ashley Cunningham, Ian Maze

Background: Stress experienced during windows of dynamic brain plasticity has been associated with altered risk for developing neurological and neuropsychiatric disorders. Prenatal and early postnatal periods, for example, represent critical windows of neurodevelopment during which stress can disrupt highly organized neurotransmitter, hormone, and metabolite signaling. Pregnancy, parturition, and nursing are experiences unique to childbearing people that similarly encompass complex signaling cascades. Despite observations that reproductive experience and parity are associated with changes in brain disorder risk, the molecular mechanisms underlying the long-term impact of these important lifetime experiences on the brain is not well understood.

Methods: To examine whether reproductive experience influences the brain long-term, bulk RNA sequencing and behavioral assessments were conducted on age-matched adult female mice that 1) previously had one healthy pregnancy and postpartum experience (control primiparous), 2) previously had one pregnancy and were separated from pups for 3 hours per day from postpartum days 10-20 (stress primiparous), or 3) had carried no pregnancies to term (nulliparous).

Results: Bulk RNA sequencing analysis of the dorsal hippocampus show >2000 differentially expressed genes in control primiparous vs. nulliparous animals, which were disrupted by postpartum stress. Deconvolution of cell type proportions from these data suggest increased oligodendrocyte precursor cell and microglia populations specifically in control primiparous brains. Assessment of these animals on the object location memory task and in a context-dependent fear conditioning paradigm further support that healthy reproductive experiences in female mice impact behavioral plasticity long after parturition and offspring weaning, and that stress during this dynamic window disrupts these changes.

Conclusions: These data suggest that pregnancy and postpartum experiences encompass dynamic neuroplasticity that influences hippocampal cellular organization and behavior in female mice long-term.

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Chronic social defeat stress increases intestinal permeability and endotoxemia in mice

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BACKGROUND: Major depressive disorder (MDD) represents the leading cause of disability, affecting >300 million people worldwide. Largely characterized behaviorally, it is critical to identify biological changes associated with MDD. Emerging literature recognize a correlation between MDD and inflammation; however, it is not fully known how this inflammation initiates. Recently, several chronic inflammatory conditions have been associated with increased intestinal permeability. We hypothesize that chronic stress compromises the gut barrier, allowing translocation of gut microbial byproducts into circulation, triggering inflammation associated with depression-like behavior.

METHODS: To model depression-like behavior in mice, a 10-day chronic social defeat stress (CSDS) model was used. Following CSDS, mice were separated into 'susceptible' or 'resilient' groups based on social avoidance, and compared with control mice, which never encountered aggressor mice.

RESULTS: To test intestinal permeability following CSDS, mice were orally-gavaged with FITC-labelled dextran, with its concentration measured in circulation 1-4 hours later. At all time points, blood FITC levels were elevated in susceptible mice. Moreover, circulating bacterial endotoxins, possibly arising from gut bacteria, were greater in susceptible mice. Additionally, several tight junctions, including claudins-4, 8, and 12 were downregulated in the intestines from defeated mice. Evaluating gut inflammation, IFNγ+ T cells were upregulated, and IL4+ T cells were downregulated in susceptible mouse colons.

CONCLUSIONS: Collectively, these results reveal that CSDS induces intestinal barrier breakdown, which may promote systemic inflammation.

Funding: NIH, CIHR

2022 Neuroscience Retreat

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Neuronal and synaptic alterations underlying cell-type specific hyperexcitability in the medial entorhinal cortex in a mouse model of Alzheimer's disease pathology

Lingxuan Chen, Zoé Christenson Wick, Lauren Vetere, Denise Cai, Tristan Shuman

BACKGROUND: Alzheimer's disease (AD) is a disorder characterized by memory loss and progressive cognitive impairments. In mouse models of AD pathology, there has been extensive work characterizing neurophysiological changes in the hippocampus, but little is known about cellular and synaptic changes in the medial entorhinal cortex (MEC), which is the primary input into the hippocampus and an early site of AD pathology. In order to understand how circuit and memory deficits emerge in AD, it is critical to examine cellular and synaptic alterations in MEC during the progression of AD pathology.

METHODS: We performed in vitro whole-cell patch clamp recording in the 3xTg mouse model of AD pathology at ages before (3 months) and after (10 months) the onset of memory impairments.

RESULTS: In 3xTg mice at 3 months of age, MEC layer II stellate cells have a depolarized resting membrane potential, but with more synaptic inhibition, the current-evoked firing remains normal. By 10 months of age, MEC layer II stellate cells in 3XTg mice have both an increased neuronal excitability and a higher excitation to inhibition (E/I) ratio at the synaptic level, leading to overall hyperexcitability at this later time point.

CONCLUSIONS: Intrinsic and synaptic plasticity work together to regulate network activity. While early hyperexcitability in MEC layer II stellate cells is compensated by increased inhibition, loss of the balance between intrinsic excitability and synaptic E/I ratio during the progression of AD may lead to local and downstream circuit changes and memory deficits at a later time point.

FUNDING: NIH

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Prefrontal modulations of gamma and beta bursts in a self-ordered working memory task.

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Cognitive strategies used in working memory tasks have been associated with different population codes in primate lateral prefrontal cortex (LPFC). The oscillations of local field potentials (LFP) in sequential working memory tasks have also revealed that gamma (45-100 Hz) and beta (20-35 Hz) play distinct roles in an anti-correlated way across task epochs. However, how those gamma and beta oscillations change during strategy-based behaviors remain unknown. To assess this, we have collected local field potentials from lateral prefrontal cortex in behaving monkeys while they performed a sequential self-ordered target selection task in which they moved their eyes between a central fixation and one of six targets, in any order, on the screen. Juice reward was delivered when they selected each individual target the first time, so that monkeys had to use WM to track which targets had been visited and prepare for the next target selection. Additionally, six blocks of 40 trials with the same configuration were arranged in each recording session and allowed us to identify how consistently the sequencing strategy used to improve target selections. Only correct responses were included in analyses of LFP signals and beta/gamma burst activities. Preliminary data revealed the higher power activity of beta and gamma showed in fixation and reward epochs, respectively, but these didn't change with strategy used. Further, beta bursts increased during central fixation, and gamma bursts increased in reward epoch. These results suggest LFP signals in LPFC are dynamically modulated during a series of responses within trials.

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Neurobiological Underpinnings of Cannabidiol's Action in Attenuating Opioid Relapse

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Background: Drug addiction is a chronic relapsing disorder characterized by cycling periods of compulsive drug use, abstinence, and relapse. Cannabidiol (CBD) is currently under investigation as an anti-relapse treatment. Previously, our laboratory has demonstrated that CBD attenuates cue-induced heroin-seeking in an animal model of relapse. Clinically, CBD attenuates craving and anxiety induced by drug-associated cues in individuals with heroin use disorder. The exact mechanisms by which CBD exerts its anti-relapse effects are not well understood. The objective of the current study was to assess the effects of CBD treatment on heroin-seeking in conjunction with transcriptomic profiling in the prelimbic cortex, nucleus accumbens core and basolateral amygdala.

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

Results: Both doses of CBD attenuated heroin-seeking during the drug-seeking test compared to vehicle controls. Acute CBD treatment increased CBD, 7-OH-CBD, anandamide and arachidonic acid levels. Initial transcriptomic analyses reveal CBD administration that reduces heroin seeking behavior is associated with alterations of transcripts relevant to cytoskeletal structure, cytokine signaling and 'response to morphine'.

Conclusions: These findings suggest that the anti-relapse potential of CBD is linked to alterations in endocannabinoid levels and genes previously implicated in addictive-like behaviors.

2022 Neuroscience Retreat

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Understanding the molecular heterogeneity in Alzheimer's Disease progression to reveal novel mechanisms and potential targets

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Background: Alzheimer's disease (AD), the most common neurodegenerative disorder, causes progressive cognitive impairments and is remarkably heterogeneous clinically, exemplified by a wide range of rates of cognitive decline. We hypothesize that the clinical progression heterogeneity observed among AD patients may be due to the presence of distinct misfolded tau strains with specific seeding and prion-like propagation properties.
Methods: Using biochemical and cell-based assays, we performed a detailed characterization of tau across two brain regions (inferior temporal gyrus BA20 and prefrontal cortex BA9) in post-mortem human brain tissue from individuals with different rates of progression of cognitive decline. Immunoblot and ELISA analyses were used to assess tau levels in the human brain extracts. To characterize the physical properties of tau in the brain extracts, a protease-sensitivity digestion assay was used. Tau prion-like seeding activity was measured by using the Forster resonance energy transfer (FRET)-based biosensor. We performed immunodepletion experiments using an anti-tau antibody to ensure that seeding activity was specific to tau. To assess aggregate morphology semi quantitatively within biosensor cells seeded with human brain lysates, various aggregate phenotypes were delineated according to a previously established system that grades the morphology of prion-like strains of tau aggregate conformers.
Results: We found patient-to-patient heterogeneity in the levels of both hyperphosphorylated, high molecular weight (HMW) tau (oligomers and aggregates) and low molecular weight (LMW) forms of tau (monomers and proteolysis products). Altered levels of the tau isoforms with four microtubule-binding domains repeats (4R) and three (3R) signatures were observed across patients. Pathogenic HMW and LMW phospho-tau and 3R and 4R tau isoforms correlated with rates of disease progression. Increased tau seeding and accumulation of HMW tau species were found in more aggressive clinical manifestations of the disease. The reduction of pathological forms of tau significantly suppressed tau seeding bioactivity.
Conclusion: This dataset provides critical insights into molecular mechanisms underlying clinical heterogeneity in AD patients. Future work will explore differential gene expression changes and their implications on disease progression.

2022 Neuroscience Retreat

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ATP13A2 loss of function mutations in midbrain organoids reveal astrocytes' critical role in Parkinson's Disease pathogenesis.

Elena Coccia, Gustavo Morrone Parfitt, Lily Sarrafha, Peter Vangheluwe, Tim Ahfeldt, Joel Blanchard.

Parkinson's disease (PD) is the second most common neurodegenerative disease, it has a complex etiology in which an interplay of environmental and genetic factors leads to the loss of dopaminergic neurons (DN). Even though the degeneration is selective for DN in the substantia nigra, it is becoming clear that other cell types, such as astrocytes, are also altered and have an essential contribution to neurodegeneration. The mechanisms behind the pathology onset and progression are poorly understood, but the familial cases, caused by highly penetrant genetic variants, point to lysosomal and mitochondrial pathway disfunction. ATP13A2 loss of function genetic variants cause early-onset PD and Kufor-Rakeb syndrome, with an age of onset around 15yo. ATP13A2 was recently established as a lysosomal exporter of polyamines, which have protective anti-oxidant and autophagy regulator roles. The transporter dysfunction disrupts cellular polyamine distribution, induces lysosomal dysfunction and cell death. We differentiated isogenic hPSC lines harboring ATP13A2 into midbrain organoids and analyzed quantifiable phenotypes in whole organoids, DN and midbrain patterned astrocytes. We found that ATP13A2 variants deplete the DN population in the organoid, and alter astrocytic functions, which would further damage neuronal populations. Astrocytes presented increased activation, impaired lysosomal activity, and consequently, clearance capacity and α-synuclein accumulation.
Overall, we developed a model that recapitulates hallmark signatures of PD in vitro enabling future studies and screens to elucidate and target the mechanisms of PD pathogenesis. We discovered that ATP13A2 has a critical role in astrocytic lysosomal function highlighting astrocytes as a new therapeutic target in PD.

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Neuronal loss and progressive spatial memory deficits in pilocarpine-induced chronically epileptic mice

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Background: Temporal lobe epilepsy (TLE) causes pervasive memory impairments which highly impact patients' quality of life. Pilocarpine-treated epileptic mice show cell loss and memory deficits but a detailed characterization of cell-type specific cell loss and spatial memory deficits at different stages of epileptogenesis remains unexplored. Therefore, we tested whether spatial memory deficits were progressive across epileptogenesis, and also how distinct cell types were affected in TLE.

Methods: We investigated spatial memory using novel object location, and tested anxiety levels using a light-dark box test in epileptic and control mice. To investigate cell type-specific cell death, we stained for neurons and parvalbumin-positive interneurons using immunohistochemistry, and we stained for ongoing apoptosis using Fluoro-Jade C staining at 3 different time points: 2days, 3 weeks, and 8 weeks post pilocarpine injection.

Results: We identified progressive spatial memory deficits that emerge between 3 and 8-wk following pilocarpine status epilepticus. Results from the light-dark box test show that 8-wk mice showed heightened anxiety levels in comparison to 3-wk epileptic mice. Preliminary immunohistochemistry analysis shows severe ongoing cell death that only occurred 2 days after pilocarpine injection in the EC layer 3 as well as in the hippocampus CA1 region.

Conclusions: Together, this data reveals a progressive impairment in spatial memory through the development of epilepsy, which was predicted by the progressive spatial coding deficits we previously reported. Immunohistochemistry staining confirms that most cell death occurs during the early stage of TLE development which leads to the idea that cognitive or memory deficits may be driven by some other mechanism that remains to be explored.

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2022 Neuroscience Retreat

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TITLE: Locus coeruleus PAC1 receptors regulate stress induced metabolic changes in a sexually dimorphic manner

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BACKGROUND: The locus coeruleus (LC) is the main source of norepinephrine in the brain and a sympathetic nervous system regulator. In patients with post-traumatic stress disorder (PTSD), the LC has been shown to modulate stress responses such as enhanced arousal potentially by utilizing energy resources in the body. In addition to altered fear response and hypervigilance, patients with PTSD demonstrate metabolic dysregulation with comorbid obesity and diabetes. The LC has a high concentration of neurons expressing the receptor PAC1 which is modulated by pituitary adenylate-cyclase-activating-polypeptide (PACAP). Research has demonstrated the neuropeptide PACAP modulates fear, stress, and metabolism, but its role in LC neuronal functions is poorly understood. Our goal was to test the hypothesis that LC-PAC1 mediates stress-induced fear behavior and metabolic functions.

METHODS: To test our hypothesis, male and female PAC1-floxed mice were injected with either rAAV/hSyn-eGFP-Cre or rAAV/hSyn-eGFP into the LC to locally ablate PAC1 receptors and exposed to an acute stress or non-stress paradigm. Energy metabolism was then measured by indirect calorimetry.

RESULTS: Results showed no significant effect of LC-PAC1 ablation on freezing behavior. However, males with LC-PAC1 deletion exhibited significant increase in energy expenditure, oxygen consumption, carbon dioxide production, and respiratory exchange ratio following acute stress. This effect was not observed in females. However, non-stressed females with LC-PAC1 deletion showed a significant reduction in oxygen consumption, carbon dioxide production, and respiratory exchange ratio.

CONCLUSIONS: These results suggest neuronal LC-PAC1 regulates metabolic activity in a sexually dimorphic manner. Neuronal LC-PAC1 could be important for regulating stress-induced metabolic response primarily in males. However, PAC1 receptors appear to be vital for respiratory control in non-stressed females but not in males. Given the known sexually dimorphic role of LC in regulating stress-related functions, our results are important for elucidating novel therapeutic targets for treating stress and energy dysregulation.

2022 Neuroscience Retreat

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Role of Fragile-X mental retardation protein in neurodevelopment and network activity in iPSCs neuronal models.

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Background: Fragile X Mental Retardation protein (FMRP) is a neuronal RNA-binding protein shown to regulate neuronal differentiation and synaptic plasticity. The loss of FMRP is among the top genetic causes of autism and intellectual disability. The FMRP-KO mouse model exhibits autism relevant phenotypes including deficits in synaptic plasticity and neuronal excitation. However, limited success of therapies developed from animal models emphasize the need for human models. This study examines how the absence of FMRP influences cellular differentiation and neuronal network formation using human induced pluripotent stem cell (iPSCs) - derived 2D and 3D models.

Methods: An isogenic conditional-KO line was used to create WT and FMRP-KO cells by addition of either Cre or mutant-Cre. Dorsal organoids were created using a mixture of WT and FMRP-KO cells as previously described in Velasco et al (2019). Organoids were analyzed using immunostaining and single-cell RNA sequencing (scRNA-Seq). Excitatory and inhibitory neuronal cultures were also generated via lentiviral induction with Ngn2 and Ascl1/Dlx2, respectively. Neuronal activity was analyzed via multielectrode array.

Results: Using previously described methods, we generated mixed WT and FMRP-KO dorsal forebrain organoids that expressed markers for neural stem cells, cortical neurons, astrocytes and oligodendrocytes. Preliminary scRNA-Seq data confirms the presence of these various cell types and suggests possible abnormalities in neuronal differentiation in FMRP-KO cells. This result will be confirmed in single genotype organoids. The absence of FMRP also reduces the formation of synapses in inhibitory neurons in 2D cultures as evidenced by reduced Synapsin-1 and VGAT puncta. Lastly, preliminary results suggest that FMRP-KO inhibitory neurons are less effective in reducing firing rate and bursting of excitatory neurons in co-cultures.

Conclusions: Altogether, these results suggest cell type specific roles for FMRP in both differentiating and mature neurons. The use of these IPSCs-derived models potentially increase our understanding of disease mechanisms involved in autism and intellectual

disability.

2022 Neuroscience Retreat

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Title: Peripheral and Central Effect of Physical Exercise on Diet-induced Metabolic Syndrome during Midlife in a Mouse Model

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Abstract
Despite national and international efforts for the prevention of metabolic syndrome and its underlying diseases/disorders, its prevalence is still rising, especially in middle aged population. In this study, we explore the effect of western diet, initiated at 12 months of age - equivalent to middle age in human, on the development of metabolic syndrome and to evaluate the potential benefits of voluntary physical exercise on periphery as well as brain cognitive function. We found that metabolic syndrome developed at middle age significantly impairs cognitive function and the impairment is associated with gene dysregulation in metabolic pathways that are largely affecting astrocytes in the brain. Eight-week voluntary wheel running not only improves peripheral glucose control but also significantly improves learning and memory. The improvement of cognitive function is associated with restoration of gene expression involved in energy metabolism in the brain. Our study suggests that voluntary physical exercise is beneficial for metabolic syndrome-induced peripheral as well as cognitive dysfunction and can be recommended as therapeutic intervention for metabolic syndrome and associated diseases.

2022 Neuroscience Retreat

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Title: Altered resting-state functional connectivity after chemogenetic silencing of amygdala in macaques

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Background: Despite widespread use of fMRI resting state functional connectivity (FC), how transient activity changes in local structure affects brain-wide FC remains unclear. To address this issue, we combined resting state fMRI and manipulation of neural activity using chemogenetics in non-human primates. DREADDs, designer receptors exclusively activated by designer drugs, are a chemogenetic system allowing for selective, reversible manipulation of neural activity via systemic administration of a synthetic ligand.
Methods: We injected inhibitory DREADD construct AAV5-SYN1-hM4Di-HA bilaterally into the amygdala in two rhesus macaques. We evaluated the effects of systemic administration of highly-selective DREADD activating ligand deschloroclozapine (DCZ, 0.1 mg/kg), clozapine-n-oxide (CNO, 10 mg/kg) which has been used as a DREADD actuator despite many off-target actions, or vehicle during resting state fMRI. Whole brain functional images were acquired on a 3T scanner (1.6mm isotropic). Using ROIs derived from cortical, subcortical, or whole brain atlases, we compared changes in FC after drug injection.
Results: Compared to vehicle, DCZ increased whole brain FC, and specifically FC between the amygdala and the striatum, hippocampus, and contralateral amygdala ($p<0.05$). In contrast, CNO depressed FC throughout subcortical regions.
Conclusions: These findings show a direct link between local neural manipulation and brain-wide functional connectivity, but also illustrates the importance of selectivity in chemogenetic actuators. Further experiments will assess how inactivating amygdala efferent pathways alters functional connectivity in specific circuits.

Funding: NIH

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Exploring the effects of TREM2 and TYROBP on microglial homeostasis and activation

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BACKGROUND: Microglia, the primary immune cell in the brain, have multiple activation phenotypes involved in broad functions in the brain, including in neurotoxicity and release of inflammatory cytokines, in neuroprotection and release of anti-inflammatory cytokines, in cell survival, proliferation, and phagocytosis. TREM2 and TYROBP form a transmembrane complex in microglia that leads to intracellular signaling networks, and these proteins are important regulators of the transition from homeostatic microglia to its activation states. Recent findings have shown a TYROBP-dependent and TREM2-independent molecular signature that is involved in the early transition step from homeostatic to disease-associated microglia (DAM). Interestingly, the sequential step of DAM activation is TREM2-dependent. However, the underlying mechanisms of how TREM2 or TYROBP regulate these downstream phenotypes are largely unknown.

METHODS: Here, we isolate primary microglia from wild-type, Trem2 KO and Tyrobp KO mice and stimulate them with Alzheimer's disease (AD)-relevant provocations, such as amyloid beta oligomers, or 'inflammatory' stimuli, such as Lipopolisaccharides (LPS). We further explored protein and gene expression in the presence or absence of inhibitors within the TREM2/TYROBP downstream signaling pathway.

RESULTS: Our results have shown that stimulating primary microglia with either amyloid beta oligomers or LPS lead to differential signal transduction as well as gene expression outcomes in cells lacking either TREM2 or TYROBP.

CONCLUSIONS: The dysregulated downstream signaling in the absence of TREM2 or TYROBP suggests their important role in both microglial homeostasis and activation. Future goal is to dissect the differential roles of these proteins in the mechanisms underlying microglial activation in a disease context, and to ultimately identify potential therapeutic targets that could contribute to the delay or treatment of AD pathology.

2022 Neuroscience Retreat

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Title: Cannabidiol alleviates cue-induced anxiety linked to alterations in the lipidome and transcriptome within the nucleus accumbens shell

Authors: JMN Ferland, RJ Ellis, AM Chisholm, JA Landry, JE Callens, YL Hurd

Background: Anxiety disorders affect ~18% of the US population every year. Cues previously associated with a fearful event have been shown to precipitate acute anxiety experiences, especially for conditions like post-traumatic stress disorder. Cannabidiol (CBD), a non-psychoactive constituent of cannabis, has been shown to reduce stress-induced social anxiety and cue-induced drug-seeking and craving, suggesting it may be effective in mediating behavioral responses to cues. However, clinical and preclinical results indicate mixed efficacy of CBD for anxiety, and few address the neurobiological mechanisms underlying these effects.

Methods: To test the efficacy of CBD on cue-precipitated anxiety-like behavior, adult Long-Evans rats underwent a footshock protocol with the presence of a distinct lemon oil or control, neutral odor cue. Light/dark box and open field were used to assess anxiety-like behavior in the presence of the cue associated with the shock. Rats were given either 10 mg/kg CBD or vehicle 1hr prior to the behavioral tests.

Results: CBD did not reduce anxiety-like behavior in rats in the neutral condition or reduce encoding of the cue, but reversed the heightened avoidance behavior in animals exposed to the lemon oil cue associated with the repeated shock-pairings. A multi-omics approach of the lipidome and transcriptome of the nucleus accumbens shell, a region involved in the extinction of fear, revealed CBD altered N-acylethanolamine levels and transcripts related to endocannabinoids, glutamatergic transmission, and synaptic plasticity.

Conclusions: These results suggest that CBD may be uniquely suited to alleviate cue-induced anxiety via multiple biological pathways linked to synaptic regulation in the nucleus accumbens shell.

2022 Neuroscience Retreat

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TITLE: Causal contribution of amygdala input to primate frontal cortex in encoding the timing of reward outcomes

AUTHORS: Davide Folloni, Elisabeth A. Murray, Peter H. Rudebeck

BACKGROUND: Interaction between amygdala and prefrontal cortex (PFC) is essential for adaptively guiding learning and decision-making based on reward (Murray and Fellows 2021). The amygdala plays a key role not only in representing the reward-value of outcomes following reward-guided choices, but it is also critical in tracking when rewards start and end. Here we investigated how parts of frontal cortex represent the timing of reward delivery both before and after excitotoxic lesions of amygdala in two distinct tasks.

METHODS: Macaque monkeys performed a two-alternative forced-choice task for fluid reward while neural activity was recorded from areas 11 and 13 in the orbitofrontal cortex (OFC) and the dorsal bank of the anterior cingulate cortex (dACC) both before and after bilateral amygdala lesions. In one task monkeys made choices between familiar stimuli (object discrimination) whereas in another they chose between novel stimuli (learning).

RESULTS: Neurons in both OFC and dACC showed an outcome-related encoding signal associated with the timing of the end of reward. Before lesions of amygdala more neurons in OFC, but not dACC, encoded when rewards ended in the object discrimination task compared to the learning task. This pattern was altered after amygdala lesions; more neurons in ACC signaled the reward end in the object discrimination task. Notably, this higher proportion of reward timing encoding neurons in the object discrimination task was largely preserved in OFC after amygdala lesions.

CONCLUSIONS: Amygdala inputs to PFC are crucial in valuation and learning. Here we show that they also play a crucial role in signaling the timing of reward in frontal cortex and critically this role differs depending on the familiarity of stimuli chosen from.

2022 Neuroscience Retreat

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Title: Brainwide correlates of probabilistic choice for novel and familiar options in macaque monkeys.

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Background

Identifying the best course of action requires exploiting the value of known options but also learning about the value of novel options to maximize rewards. Despite this, the distinct brain mechanisms that support these processes are poorly understood. Recent studies suggested that ventro-lateral prefrontal cortex (vlPFC) is critical for learning reward values, but it is unclear how this area represents new and known values. Using fMRI we assessed how vlPFC and other areas interact during choices between options that were novel or familiar in macaque monkeys.

Methods

We trained four adult female macaque monkeys (Macaca mulatta) to perform a probabilistic choice task, in which they were required to choose between two visual stimuli that were associated with either 90%, 50% or 30% of juice reward. Monkeys underwent whole brain fMRI scans while performing the task in blocks of trials with familiar or novel stimuli.

Results

All four monkeys performed at a very high level in Familiar block (> 82%). Performance in the Novel block varied across monkeys (62-76% in the latter half of a block) and all animals showed distinct learning curves. Whole-brain fMRI analysis showed that several areas including bilateral vlPFC were activated in both Novel and Familiar blocks in all four monkeys. Other areas such as lateral prefrontal cortex and dorsal striatum reflected differences in performance in Novel blocks.

Conclusions

Our data suggest that vlPFC tracks the value of novel and familiar options, while lateral frontal cortex and dorsal striatum play a distinct role learning about novel stimuli. Thus, common and different neural circuits are involved in novel and familiar choices.

2022 Neuroscience Retreat

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Title: The brain wide effects of subcallosal ACC deep brain stimulation in macaques

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Background: Deep brain stimulation targeting subcallosal anterior cingulate cortex and adjacent white matter (scACC-DBS) is a promising therapy for treatment resistant depression. However, the brain-wide mechanisms through which scACC-DBS works is still unknown. Prior work has reported alterations in brain-wide resting-state networks, such as the default mode network (DMN), in people who recover from depression following scACC-DBS. Here we tested the hypothesis that scACC-DBS specifically alters connectivity within the DMN using a translationally relevant in vivo neuroimaging approach in non-human primates.

Methods: Following the paradigm successfully used in patients, we implanted two rhesus macaques with a scACC-DBS electrode to establish the brain-wide effects of 6 weeks of continuous stimulation. Electrodes targeted the confluence of the cingulum bundle, forceps minor, and uncinate fasciculus based on diffusion tractography, as previously done in human patients. Whole brain resting-state functional MRIs were acquired before surgery and following 6 weeks of stimulation, and were analyzed using a seed-based comparative-connectome analysis.

Results: scACC-DBS stimulation specifically decreased functional connectivity (FC) between scACC and multiple areas, including bilateral medial and dorsolateral frontal lobe and ipsilateral hippocampus. Notably, the biggest change in FC was with posterior cingulate cortex, a major node in the DMN. In contrast, the FC with the anterior insular cortex was increased. Additionally, there was no obvious global change in brain-wide FC.

Conclusions: Chronic scACC-DBS changes brain networks which are connecting to scACC, especially the DMN. Our data reveal the specific effects of scACC-DBS on brain-wide functional connectivity, information essential for optimizing this treatment for patients with depression, and establishing the neural mechanisms of pathology in depression.

2022 Neuroscience Retreat

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Impact of ethanol on neuronal excitability and AMPA-R/NMDA-R ratio in populations of human glutamatergic neurons.

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BACKGROUND: Alcohol use disorder (AUD) is a chronic and relapsing disease affecting over 283 million people worldwide. Glutamatergic inputs from the frontal cortex play a key role in the reward circuit, and growing evidence from slice and single-cell electrophysiology studies shows that glutamate receptors (Glu-R), particularly NMDA-R, are negatively affected by ethanol. However, the study how ethanol affects Glu-R mediated neuronal activity in a population of human neurons simultaneously had not yet been achieved.

METHODS: We used a 2D model of human cortical glutamatergic neurons: hiPSCs-derived NGN2 excitatory neurons, co-cultured with mouse glia. We examined their neuronal excitability utilizing a high-throughput electrophysiological approach: GCaMP6f-based calcium imaging in cell populations. To evaluate how ethanol affected Glu-R mediated neuronal activity, NGN2 neurons were exposed to ethanol following a chronic intermittent exposure paradigm (7 days of exposure to 17 mM ethanol, ≈ 0.08 BAC). To determine the AMPA-R and NMDA-R mediated neuronal activity and their ratio in each neuron in the population, we optimized an experimental protocol using glutamate stimulation in the presence of the antagonists NBQX (AMPA-R) and AP-V (NMDA-R).

RESULTS: NGN2 neurons chronically exposed to ethanol showed a substantial decrease in their spontaneous activity, from 0.3 to 0.13 spikes/neuron/min, compared to naïve neurons. No differences were observed in the extent of NBQX blockade of glutamate response between naïve and ethanol exposed neurons, while the application of NBQX and AP-V exerted a stronger blockade of the glutamate response the ethanol exposed. The AMPA-R/NMDA-R ratio calculated from this blockade showed a 2-fold increase in ethanol exposed neurons, from 4.8 to 9.2, indicating a decrease in NMDA-R mediated neuronal activity.

CONCLUSSIONS: 7 days of exposure to low-intoxicating concentrations of ethanol notably decreases the spontaneous and NMDA-R mediated neuronal activity in populations of NGN2 neurons. The calcium imaging experimental approach developed here overcomes the limitations of single-cell electrophysiology, and can be extended to the study of the effects of ethanol and other drugs on glutamatergic and other types of human neurons.

2022 Neuroscience Retreat

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Frontal white matter microstructure recovery with abstinence during inpatient treatment in individuals with opiate use disorder

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BACKGROUND: Addiction is not only associated with functional brain impairments but also gray and white matter (WM) structural abnormalities. Few studies assessed abstinence-related WM changes in individuals with opiate use disorder (iOUD) and did not detect specific longitudinal effects. This study aimed at assessing longitudinal WM microstructure differences after 12-weeks of abstinence (and 8-weeks of standardized group therapy) during inpatient treatment in iOUD as compared to demographically matched controls (CTL).

METHODS: Diffusion MRI was acquired twice (Time1/Time2: 12.2±3.7 weeks apart) in 20 inpatient iOUD (42.1±9.7yo, 5W) on medication-assisted treatment and 15 CTL (42.5±10.8yo, 6W). Tract-Based Spatial Statistics permitted whole-brain/voxel-wise analyses of diffusion coherence metrics [FA-fractional anisotropy, MD-mean diffusivity, RD-radial diffusivity, AD-axial diffusivity]. Permutation statistics (p<.05-corrected) were used to compare changes from Time1 to Time2 between groups.

RESULTS: Group differences showed reduced FA and increased MD, RD, and AD in iOUD vs. CTL at both times (p<.05). However, as compared to Time1, significant group-differences at Time2 were less extensive (average 65%) throughout the brain. Group × time analyses showed significantly higher FA increases and RD decreases from Time1 to Time2 in iOUD when compared to CTL, specifically frontally and encompassing the genu/body of the corpus callosum and anterior corona radiata (p<.05).

CONCLUSIONS: Corroborating previous reports of structural recovery with abstinence in prefrontal cortical regions affected by chronic drug use, these results suggest longitudinal WM recovery (at least partial) in iOUD after 12-weeks of abstinence in an inpatient treatment program. Potential mechanisms may include reduced neuroinflammation, fiber

reorganization, and/or myelin restoration, as remains to be ascertained.

FUNDING: NCCIH

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Impairment in adaptive down-scaling in striatal projection neurons expressing Parkinson's disease associated Lrrk2-G2019S mutation

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive motor decline. Using a preclinical mouse model expressing one of the most common pathogenic PD mutations, Lrrk2G2019S, our lab has documented behavioral responses to stress and cognitive deficits that correlate with altered glutamatergic synaptic function and the absence of corticostriatal bi-modal Hebbian plasticity. An equally important, but understudied form of synapse plasticity is homeostatic scaling, a process by which synaptic strengths scale multiplicatively by regulating AMPAR number, to control network activity while retaining strength relationships. To address whether homeostatic scaling occurs in striatum and to assess whether it may be disrupted by Lrrk2G2019S, we compared basic metrics of AMPAR biology using biochemical, super-resolution imaging and electrophysiological approaches in mutant and WT striatal projection neurons (SPNs). The data reveal an abnormal accumulation of synaptic GluA1 containing calcium permeable AMPARs in D1R Lrrk2G2019S expressing SPNs under baseline conditions, which is due in part by a failure to internalize and recycle GluA1 subunits. Consistent with this impairment, in response to 48h incubation with bicuculline, AMPARs in cultured SPNs neurons from Lrrk2G2019S mice fail to reduce their AMPAR content (scale-down) compared to wildtype neurons while both mutant and wildtype neurons similarly increase their AMPAR content (scale-up) in response to 48h incubation with TTX. On-going experiments are probing molecular mechanisms that normally drive homeostatic adaptation or down-scaling in the striatum, they will determine how Lrrk2G2019S selectively disrupts this process, and they will test pharmacological approaches that can restore a normal dynamic range for synapse plasticity. In parallel, using chemogenetic approaches, we are developing an in vivo tool to study and manipulate homeostatic scaling in striatal circuits that can be examined electrophysiologically.

2022 Neuroscience Retreat

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Title: Accelerated global and local brain ageing differentiate cognitively impaired from cognitively spared patients with schizophrenia

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Background:
Accelerated ageing has been proposed as a mechanism underlying the clinical and cognitive presentation of schizophrenia. The current study extends the field by examining both global and regional patterns of brain ageing in schizophrenia, as inferred from brain structural data, and their association with cognitive and psychotic symptoms.
Methods:
Global and local brain-age-gap-estimates (G-brainAGE and L-brainAGE) were computed using a U-Net Model from T1-weighted structural neuroimaging data from 84 patients (aged 16 to 35 years) with early-stage schizophrenia (illness duration <5 years) and 1169 healthy individuals (aged 16 to 37 years). Multidomain cognitive data from the patient sample were submitted to Heterogeneity through Discriminative Analysis (HYDRA) to identify cognitive clusters.
Results:
HYDRA classified patients into a cognitively impaired cluster (n=69) and a cognitively spared cluster (n=15). Compared to healthy individuals, G-brainAGE was significantly higher in the cognitively impaired cluster (+11.08 years) who also showed widespread elevation in L-brainAGE, with the highest deviance observed in frontal and temporal regions. The cognitively spared cluster showed a moderate increase in G-brainAGE (+8.94 years), and higher L-brainAGE localized in the anterior cingulate cortex. Psychotic symptom severity in both clusters showed a positive but non-significant association with G-brainAGE.
Conclusions:
In this study, we found differential patterns of accelerated brain ageing in early psychosis patients based on their cognitive performance, with greater global accelerated brain ageing, and more widespread local accelerated brain ageing in patients with impaired than those with spared cognition. Accelerated ageing in schizophrenia can be detected at the early disease stages and appears more closely associated with cognitive dysfunction rather than clinical symptoms.

2022 Neuroscience Retreat

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Characterization of distinct LRRK2 variants linked to Parkinson's and Inflammatory bowel disease in mouse models of colitis

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Background
Chronic inflammation and the gut-brain axis have been suggested to play a critical role in the pathogenesis of Parkinson's disease (PD). Mutations in the LRRK2 gene represent the largest known cause of heritable PD, occurring in up to 40% of select patient populations. The LRRK2-G2019S mutation is the most prevalent in PD patients. Intriguingly, the recent identification of the LRRK2-N2081D variant, which is associated with both PD and Crohn's disease, a subtype of inflammatory bowel disease, has provided genetic basis to link these two disorders. This raises the question of whether certain type of IBD and PD may share the same disease origins and mechanism of progression.

Methods
We have developed a knock-in (KI) mouse model of the LRRK2-N2081D Crohn's- disease risk variant. We have characterized both LRRK2-N2081D and LRRK2-G2019S KI models to understand their relevance to disease. We have employed an inducible colitis model. In our experiments, dextran sulphate salt (DSS) is added to the drinking water, causing progressive destruction of epithelial tissues leading to inflammation and weight loss that characterizes inflammatory bowel disease.

Results
We have observed that mice carrying the N2081D mutation demonstrate an increased sensitivity to induced colitis, resulting in elevated intestinal inflammation, worsened symptoms and increased mortality.

Conclusions
We present a novel, pathogenically validated LRRK2 knock-in disease model. Deeper characterization of these phenotypes and investigation into the mechanistic underpinnings of these observations will offer insight into the pathogenesis of IBD and PD.

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Treatment reduces drug-biased reactivity in heroin use disorder suggested by preliminary results – an fMRI study

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Background: Enhanced cortico-striatal reactivity to drug-cues coupled with blunted reactivity to non-drug-reinforcers is a core characteristic of drug addiction. Cognitive reappraisal of drug-cues and savoring of non-drug-reinforcers have decreased drug cue-reactivity; however, the neural mechanisms mediating these effects in heroin use disorder (HUD), and potential changes via abstinence during treatment, remain unresolved.

Methods: Twenty-five individuals with HUD (iHUD) (age=42.31±9.18, women=5) were scanned twice, before and after 8-weeks of standardized group therapy (abstinence: before/after=201.28±239.91/268±261.30 days). Twenty-five healthy controls (HC; age=40.45±10.96, women=9) were scanned at similar time intervals. During fMRI, participants passively viewed heroin, food, and neutral images, separately reappraising heroin and savoring food images. Craving was assessed immediately before and after the task.

Results: Before treatment and compared to HC, iHUD exhibited higher ventromedial prefrontal cortex (vmPFC) and nucleus accumbens (NAcc) activity when passively viewing drug vs. neutral images; the vmPFC cue-reactivity predicted post-task drug craving within iHUD ($p<0.05$-corrected). Both groups showed increased inferior frontal gyrus (IFG) and dorsolateral prefrontal cortex activity during (drug) reappraisal and (food)savoring (controlling for passively viewing the respective images). Compared to the HC group, the ventral caudate, anterior cingulate cortex, and IFG showed higher (drug) reappraisal than (food) savoring activity in iHUD. Preliminary results suggest reduced drug cue-reactivity and enhanced savoring in iHUD after treatment and as a function of abstinence length.

Conclusions: Before treatment, iHUD exhibited heightened cortico-striatal activation during drug cue-reactivity and reappraisal at the expense of non-drug reward savoring. Preliminary results suggest reduced drug cue-reactivity and enhanced savoring in iHUD after treatment, suggesting the normalization of cortico-striatal function with abstinence.

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Title: Blau Center: Bridging psychosis research with clinical services

Authors: Gavin Hynes and Nicole Simons on behalf of the Blau Center

Background: Severe mental illness ranks among the leading causes of disease burden worldwide. Over the past 15 years, a new understanding of its pathogenesis has emerged particularly through genetics and epidemiology. However, there have been few breakthroughs in diagnosis, prevention, or treatment. Here we present an overview of the newly formed Blau Center within the Department of Psychiatry at Icahn School of Medicine at Mount Sinai, which aims to fill these gaps through combining excellent clinical care with groundbreaking clinical research and data science. We will study the presentation, treatment, and course of psychotic illness in our psychiatric patients, participate in the development of new treatments, and optimize Sinai's existing clinical services.

Methods: Patients receiving psychiatric care within Mount Sinai inpatient and outpatient service areas are being enrolled into a broad, exploratory clinical research protocol. This protocol involves clinical interviews, blood collection, CSF collection, audio/video recording, and medical record review. To inform our clinical research and clinical care, we will also be employing data science approaches to improve and augment psychiatric care delivered to Sinai patients.

Results: The center aims to achieve several clinical, research, and data science goals. The Blau Center Clinic will provide consultation and specialized treatment for patients with psychosis. Through our research, we will survey MSHS psychiatric patients, run clinical trials for new psychiatric treatments, and facilitate collaboration between researchers. Using patient data from research encounters and electronic medical records we will investigate treatment patterns in the health system, identify new targets for treatment, and create new platforms to house and summarize aggregate patient data.

Conclusion: The Blau Center will standardize psychiatric care within the health system and inform clinical care for our patients through providing specialized services to those with psychotic disorders. To this end, we hope to better improve patients' prognoses and quality of life.

2022 Neuroscience Retreat

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Shifts in local neuroplasticity in World Trade Center responders with post-traumatic stress disorder

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Introduction: World Trade Center (WTC) responders have high prevalence (23%) of persistent, clinically significant WTC-related post-traumatic stress disorder (PTSD). Recent structural magnetic resonance imaging (MRI) studies demonstrate anatomical differences between WTC responders with and without PTSD. We used resting state functional (rs-fMRI) to investigate neural mechanisms underlying WTC-PTSD and identify changes in local brain areas associated with WTC exposure.

Methods: Using graph theory analysis of rs-fMRI data, we calculated eigenvector centrality (EC) to measure connectivity in 111 brain areas in WTC responders with PTSD (WTC-PTSD, n = 45) and matched responders without PTSD (non-PTSD, n = 51). Permutation statistics quantified EC differences; partial least squares discriminant analysis (PLS-DA) modeled the divergence in EC values between groups. Associations between WTC-exposure duration (months on site) and EC in identified brain areas were examined using general linear model (GLM) regression, adjusting for medication usage and comorbid depression. Generalized weighted quantile sum (WQS) regression was used to examine associations between an index of PTSD symptoms and EC values.

Results: PLS-DA analysis of EC values enabled effective discrimination (auc: 0.749 (0.651-0.847)) of WTC-PTSD from non-PTSD; EC in nine brain regions (right/left anterior inferior temporal gyrus, right superior parietal lobule, right anterior parahippocampal gyrus (PHG), right anterior/posterior temporal fusiform cortex, right caudate nucleus, left amygdala (AMG) and brainstem) differed significantly and contributed the most to differentiate functional neuro-profiles between groups. The association between exposure duration and EC differed significantly between WTC-PTSD and non-PTSD in PHG and AMG (p= 0.010, 0.005, respectively). Within WTC-PTSD, the index of PTSD symptoms was positively associated with EC values in PHG and brainstem.

Conclusions: Our results confirm hypotheses about key brain areas associated with PTSD

and extend our understanding of neural mechanisms linking WTC exposure with PTSD. Better understanding of neural mechanisms leading to WTC-PTSD would help guide intervention and treatment.

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Diabetes Affects Astrocyte and Integrity of the Anterior Commissure in a Sex-Dependent Manner.

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Background: Diabetes is a complex metabolic disorder which correlates with genetic and environmental factor. Alteration in structure and function of the brain from neuronal death to inflammation under diabetic conditions represents in behavioral level. Upon reports diabetes increases comorbid mood disorders (e.g., depression). Clinical studies showed integrity of white matter is decreased in psychiatric disorders. Anterior commissure (AC) is the most conserved white matter structure and connected to different regions of the brain which controls emotion and social interaction. Astrocytes are the largest population of glial cells in the central nervous system and control energy homeostasis, immune response, and synaptic plasticity. Studies showed diabetes induces astrocyte activation in hypothalamus and hippocampus. But the influences of the diabetes and hyperglycemia on astrocytes of the AC are unknown. Here, we show how astrocytes in AC respond to diabetes upon sex dependent manner. Methods: Male and female C57BL/6J mice were injected intraperitoneally of streptozotocin (STZ; 50-60 mg/kg) in HBSS for 5 consecutive days. Blood glucose was monitored by using glucometer weekly. After 6 weeks, mice were perfused with 4% paraformaldehyde (PFA) fixative. After preparing 40-µm-thick coronal tissue sections, primary antibodies against GFAP and NeuN were used for immunohistochemistry.

Results: Our results show that in AC size is decreased only in male mouse with diabetes. In addition, our findings show the size and number of astrocytes only decrease in the AC of diabetic male mice. Skeleton analysis of astrocyte morphology shows in male diabetic model total length of processes, numbers of endpoint and junctions in AC. While in female diabetic mice astrocyte skeleton has no changes.

Conclusion: Our finding suggests that diabetes influences astrocyte and integrity of the AC in a sex-dependent manner.

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Glioblastoma cell migration requires membrane tension and endocytosis regulated by Plexin-B2

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Background: Infiltrative growth is a major cause of high lethality for the malignant brain tumor glioblastoma (GBM). To initiate invasion, GBM cells face the challenge of negotiating through tight interstitial space inside the brain. The mechanisms of how GBM cells regulate invasiveness are unclear. As tumor cells frequently usurp developmental pathways, we suggest that the Plexin axon guidance receptors may regulate GBM invasiveness.

Method: We have established a novel in vitro paradigm that utilizes a 3D-printed microchannel device to investigate the capability of GBM cells to migrate through constrictions of different sizes. We speculated that the GBM cell migration may be through endocytosis, which is a major regulator of signaling events and has been shown to be regulated by membrane tension. We interfered with GBM cell migration using drugs known to inhibit endocytosis. Next, we deleted Plexin-B2 in GBM cells by lentiviral CRISPR-Cas9. We probed membrane tension using live fluorescent membrane tension probe and optical tweezers. We also investigated the endocytosis dynamics using fluorescent labeled dextran, plasma membrane-targeting dyes, and membrane-attached intracellular fluorescent proteins in live GBM cells.

Results: Wild-type GBM cells showed active locomotion, high velocity, and forward motility through the constrictions. In contrast, Plexin-B2 knockout cells extend long cellular processes, displayed plasma membrane rupture, and failed to 'infiltrate' through narrow constrictions. It was associated with low uptake of cytoplasmic dextran, reduced endocytosis of membrane-attached intracellular proteins, and low membrane tension. Similar phenotypes were observed after treating WT GBM cells with endocytosis inhibitors.

Conclusion: Plexin-B2 regulation of membrane tension and endocytosis provides biomechanical plasticity for GBMs facing the challenge of negotiating through tight spaces during cancer invasiveness.

2022 Neuroscience Retreat

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Morphine dependence accelerates HIV-associated neurocognitive impairment in EcoHIV infected mice.

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BACKGROUND: Antiretroviral therapy (ART) has shifted HIV from a fatal disease to a chronic, survivable HIV infection. Despite this success, HIV patients on ART frequently suffer chronic HIV-related diseases, including neurocognitive impairment (HIV-NCI). HIV-NCI can range from mild to severe affecting quality of life, medication adherence, and independent living. Environmental factors including opiate use disorder (OUD) may facilitate HIV-NCI pathogenesis. Here, we tested this hypothesis in mice using EcoHIV, a chimeric mouse-tropic HIV that can chronically infect conventional immunocompetent mice causing HIV-NCI like disease.

METHODS: To induce morphine dependence, 25 mg morphine pellets were implanted subcutaneously once a week in male C57BL/6J mice, and placebo pellets served as controls. Three days after implantation, mice were inoculated intraperitoneally with EcoHIV or PBS, 10 days later animals were assessed for cognitive deficits using the radial arm water maze (RAWM) test, then mice were euthanized, spleens, peritoneal macrophages, and portions of the brain were collected for virological analysis while prefrontal cortex (PFC) was collected for snRNAseq analysis.

RESULTS: EcoHIV infected C57BL/6J mice manifested spatial learning and working memory deficits in RAWM starting at 4 weeks after infection. EcoHIV infected morphine dependent, but not infected placebo-implanted mice, developed these cognitive deficits only 10 days after virus infection. This disease in morphine dependent, infected mice, but not placebo mice was associated with elevated HIV burdens in the spleen, peritoneal macrophages, and a trend towards increased burdens in the brain accompanied by extensive gene dysregulation in neuronal and other cellular populations in the PFC.

CONCLUSION: Morphine dependence accelerates HIV brain disease in EcoHIV infected mice, potentially modeling acceleration and/or worsening of NCI in HIV patients with OUD. We attribute this acceleration to increased HIV replication in the presence of chronic morphine and a potential convergence of neuropathogenic effects of HIV and morphine in the brain.

2022 Neuroscience Retreat

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Title
A comprehensive statistical and functional fine-mapping pipeline applied to bipolar disorder GWAS risk loci

Authors
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Background
Recent genome-wide association studies (GWAS) have implicated an abundance of common variant risk loci associated with bipolar disorder (BD). However, identifying the causal variants and genes within these linkage disequilibrium (LD) windows of association, and the underlying molecular mechanisms of disease, is a major challenge.

Methods
Here, we conducted statistical and functional fine-mapping of 64 BD risk loci identified by the largest BD GWAS to date, published by the Psychiatric Genomics Consortium (PGC3). First, we conducted a stepwise conditional analysis of each locus using GCTA-COJO, based on LD information from the Haplotype Reference Consortium (HRC) reference panel, which indicated one association signal in each locus. Fine-mapping analyses were conducted via the echolocatoR pipeline that uses a suite of Bayesian tools, including ABF, FINEMAP, SuSiE, PAINTOR and PolyFun. Functional annotations were incorporated to compute prior causal probabilities (priors) and included: brain epigenomic, LD-related annotations, genic and variant consequence annotations.

Results
Preliminary analyses highlight several GWAS lead SNPs which also harbor the highest PIP values across methods, indicating a putative causal effect for these variants. Interestingly, amongst the prioritized risk genes after genomic clumping are TRANK1, THSD7A and MACROD1. Concordance was also observed with regards to the number of consensus SNPs across different functional and non-functional fine-mapping methods, when using the HRC and UK Biobank reference panels, as well as when narrowing the fine-mapping window. LD information from the HRC, the UK Biobank, and the PGC3 BD cohorts is currenly

implemented to examine the impact of LD structure on fine-mapping.

Conclusions

Herein, we present a detailed pipeline for performing robust statistical and functional fine-mapping, optimized for BD, for the rapid, scalable and cost-effective prioritization of likely causal SNPs and genes, as promising candidates for functional follow-up experiments. We hope that this pipeline will be established as a comprehensive statistical and functional fine-mapping framework applied across psychiatric disorders.

2022 Neuroscience Retreat

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Effects of abstinence during treatment on shared Nucleus Accumbens reactivity and craving in response to a drug-related movie in heroin addiction

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Background
Drug addiction is associated with heightened mesolimbic cortico-striatal reactivity to drug-related stimuli over alternative reinforcers. However, the extent of this biased processing in real-world settings, its relationship to craving, and its dynamics with abstinence and treatment are not fully established, especially in opioid addiction.

Methods
We collected fMRI during the first 17 minutes of watching the engaging, heroin-related, movie "Trainspotting" in 29 inpatients with heroin use disorder (iHUD; 40.4±10.3 years, 23 Male, 19 White) before and after 8 weeks of standardized group therapy (74.69±43.74 days abstinence). Sixteen healthy controls (HC; 43.8±10.3 years, 10 M, 11 W) were scanned at similar time intervals. Using a reverse correlation approach, we identified movie scenes that elicited synchronized responses in the Nucleus Accumbens (NAc), a major processing hub for motivational salience attribution, reward anticipation, and craving.

Results
Strikingly, before treatment the left NAc was synchronized during drug scenes in iHUD, but mostly non-drug scenes in HC (iHUD: 40/8, HC: 25/40 drug/non-drug; $\chi 2(1)=20.95$, $p=0.0000047$). This left NAc signal also predicted stimulus-induced heroin craving in iOUD. Preliminary results suggest a reduction in this drug-biased NAc reactivity with treatment and abstinence as associated with reduced craving, increased treatment adherence (prospectively measured), and better drug use outcomes at 3 months follow-up.

Conclusions
Our results open a window into the neurobiology underlying shared drug-biased processing of naturalistic stimuli and cue-induced craving in opiate addiction in the real world as applicable to novel treatment biomarker identification.

2022 Neuroscience Retreat

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Hippocampal somatostatin interneurons mediate retrieval of conflicting threat and safety memories

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Background: Fearful experiences create enduring negative associations with the surrounding context. Emotional responses to these contextual cues can be alleviated in the absence of threat, a process known as extinction. Fear and extinction memories appear to be represented by competitive, orthogonal neural ensembles. However, very little is known about the mechanisms governing the switching between these conflicting memories. Understanding neural circuits underlying the gating of emotional memory expression can provide crucial insights for developing novel therapeutics for treating disorders of pathological fear.

Methods: Brain-wide c-Fos mapping, contextual fear conditioning, optogenetics, activity-dependent ensemble tagging, intersectional genetics.

Results: Using brain-wide c-Fos mapping, we identified activity in somatostatin interneurons (SST-INs) in ventral hippocampal CA1 (vCA1) as uniquely correlated with extinction retrieval. An extinction-specific recruitment of vCA1 SST-INs was confirmed using an intersectional genetic tagging strategy. Additionally, fear and extinction retrieval reactivate distinct ensembles of excitatory vCA1 neurons. Optogenetically silencing vCA1 SST-INs impaired extinction retrieval, while stimulating these cells, either broadly or in an activity-dependent manner, prevented fear relapse.

Conclusion: Our results suggest that retrieval of conflicting memories of contextual threat and safety is mediated by vCA1 SST-INs. We hypothesize the vCA1 SST-INs gate the activity of orthogonal excitatory ensembles to suppress the activity of the fear-related ensemble and promote the retrieval of the extinction ensemble.

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Rab12 accelerates synaptic vesicle exocytosis and causes hyperactivity in mice

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Background: Rab12 is a poorly characterized small GTPase with no report of its function in neurons. Recent evidence (including our work) showed that Rab12 is a physiological substrate of protein kinase LRRK2, which is linked to the most common inherited form of Parkinson's disease. LRRK2 regulates multiple cellular and neuronal functions including synaptic vesicle (SV) trafficking. Therefore, we propose to investigate if RaB12 plays a role in regulating SV trafficking and LRRK2-mediated modification may alter the related functions.

Methods: We established Rab12 knockout (Rab12KO) mice, and applied genetically encoded probe vGlut1/VMAT2-pHluorin, electrophysiological and molecular biology, and animal behavioral tests to the characterization of Rab12 function.

Results: Immunofluorescent staining indicated that mCherry-Rab12 was partially localized in synaptic terminals. Synaptosome fractionation of mouse cortex further suggested endogenous Rab12 was enriched in synaptosome fraction. PHluorin assay revealed that overexpressing Rab12 in neurons dramatically repressed the release of SVs, while exocytosis was accelerated both in Rab12KO cortical and dopamine neurons. Electrophysiological examination on mouse dorsal striatum brain slices showed that the frequency of spontaneous and miniature excitatory postsynaptic currents were increased significantly while the pair pulse ratio was decreased in Rab12KO spiny neurons. Moreover, we showed that that Rab12KO mice were hyperactive in open field test. Interestingly, they were able to maintain longer on accelerated rotarod and displayed stronger grip strength. We are currently investigating if LRRK2-mediated phosphorylation of Rab12 alters the above functional characteristics.

Conclusions: Rab12 inhibits SV exocytosis; deletion of Rab12 in mice causes neuronal hyperexcitability and behavioral hyperactivity.

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A novel compound which is highly protective in animal models of Alzheimer's Disease and stroke, inhibits microglial cytokine secretion, is highly concentrated in brain after oral delivery, and increases lifespan with no evidence of toxicity. R. Litke, J. Vicari, D. Gonzalez, B.T. Huang, C. Kellner, J. Jin, and C. Mobbs.

Alzheimer's Disease and related dementias are among the most expensive in the American health system, and stroke is not far behind. Although there are FDA-approved treatments for these conditions, the clinically efficacy is minimal. To develop better treatments we carried out an unbiased screen of 2500 compounds from the Microsource Spectrum library in a C. elegans model of Alzheimer's disease. Among the most prominent protective were several phenothiazines. Using congeners from the NCI chemical library, we carried out structure-activity relationship studies for inhibition of microglial TNF-alpha and IL-6 secretion, implicated in driving many neurological conditions, including Alzheimer's and stroke. From these studies we predicted and synthesized novel compounds which were even more protective and less toxic. The lead compound from this study was highly protective in animal models of Alzheimer's Disease and stroke, was highly effective in inhibiting TNF-alpha and IL-6 in mouse and human myeloid cells, was highly concentrated in brain after oral delivery, and increased lifespan with no evidence of toxicity. This and related novel compounds (patents pending) are now being developed for clinical trials.

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Neuroimmune insights through single-cell transcriptomics of paired brain and blood from living human subjects

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Background: The intricate interactions between the central nervous system (CNS) and the peripheral immune system play a key role in health and disease, yet the exact nature of these communications remains unclear. This study aims to characterize the cellular and molecular basis of the CNS-periphery interaction, by analyzing the single-cell transcriptomes profiled on matched brain-blood specimens from living human subjects.

Methods: The prefrontal cortex and peripheral blood were sampled simultaneously from each patient during neurosurgical procedures, and were processed together on the same day for droplet-based single-cell RNA sequencing. Immune cells in the brain were sorted by CD45+CD11b+ fluorescence activated cell sorting. Following quality control, data on 13 brain-blood pairs from ten individuals were analyzed. Immune cell populations in the CNS and the periphery were compared with respect to cell type composition and cell transcriptional states, and were correlated for gene expression across the 13 pairs.

Results: The brain immune cell populations contained microglia, resident macrophages, and peripheral immune cells (PICs) including T cells, B cells, natural killer (NK) cells, and monocytes. Brain PICs displayed different cell type proportions compared to the same four cell classes in the blood. Brain PICs tended to take on more activated transcriptional phenotypes than those of their peripheral counterparts, displaying an up-regulation in pathways including immune signaling (NFKBID, JUND), chemokines (CCL4, CXCR4), stress response (Heat Shock Protein family) and metabolism (SCL2A3, NABP1). Clustering brain and blood cells together identified both shared and unique transcriptional states. Across 13 brain-blood pairs, the cell types that showed the highest average gene-wise correlation with microglia were blood NK and CD4+ T cells. Negatively correlated genes between brain and blood were enriched in cellular stress response and immune activation.

Conclusions: There are widespread differences and correlation between the CNS and the peripheral immunity at the cellular and molecular level. These insights highlight the potential to extract molecular information about the brain via a routine blood draw.

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FUNCTIONAL CURE OF HIV BRAIN DISEASE IN CHRONICALLY EcoHIV INFECTED MICE BY THERAPEUTIC VACCINATION WITH GAG-POL MOSAIC VACCINE.

Shuhui Liu, Eran Hadas, Hongxia He, Alejandra Borjabad, Jennifer Kelschenbach, Wei Chao, Edmund G. Wee, Tomáš Hanke, David J. Volsky, Mary Jane Potash

Introduction. Antiretroviral therapy in HIV infected people controls virus replication and partially restores immune competence but fails to prevent chronic HIV diseases including HIV-associated neurocognitive impairment. Therapeutic vaccination has been shown to improve anti-HIV immune responses but its effects upon chronic HIV complications are unknown. We tested this therapeutic approach in conventional mice infected by chimeric HIV, EcoHIV, that develop anti-HIV T cell responses, but like HIV infected people, can neither clear virus nor control HIV brain disease.
Methods. To boost T cell responses in chronically EcoHIV-infected mice, we used mosaic DNA vaccines expressing widely conserved regions of HIV Gag and Pol, pSM2.HIVconsv1+ pSM2.HIVconsv2. EcoHIV burdens in T cells, macrophages, and microglia were determined by QPCR, anti-HIV T cell responses by Elispot to HIV Gag and Pol peptides, brain gene dysregulation by RNAseq, synaptodendritic damage by confocal microscopy, HIV localization in the brain by RNAscope, and cognitive function by radial arm water maze.
Results. Chronically EcoHIV infected mice receiving control plasmid had anti-HIV T cell responses in periphery and brain, but they carried viral DNA and RNA in lymphocytes, macrophages, and microglia; showed broad dysregulation of genes involved in immune, neuronal, and metabolic functions in striatum, showed reduced dendritic arbors in hippocampus and cortex, and exhibited impaired memory. Vaccination of cognitively impaired mice with pSM2.HIVconsv1+ pSM2.HIVconsv2 enhanced HIV-specific T cell responses, reduced HIV burdens systemically and in the brain including in isolated microglia, and reversed HIV brain disease at the levels of gene dysregulation, synaptodendritic injury, and cognitive impairment.
Conclusions. These findings indicate that therapeutic pSM2.HIVconsv1+ pSM2.HIVconsv2 vaccination induced protective T cell responses in chronically infected mice that reduced HIV below pathogenic levels and allowed recovery from chronic brain disease. To our knowledge, this is the first demonstration that functional cure of HIV chronic brain disease through therapeutic vaccination is feasible.

2022 Neuroscience Retreat

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HIV-I Nef expression is essential for induction of HIV-associated neurocognitive impairment, in part through dysregulation of the endocannabinoid system.

Xiaokun Liu, Wei Chao, Hongxia He, Jennifer Kelschenbach, and David J. Volsky

Background: Antiretroviral therapy (ART) preserves immune competence but allows development of brain disease in 50% of HIV infected patients. Tat and gp120 are neurotoxic in various model systems, but the role of Nef in brain disease is not clear. Here we used EcoHIV, which can infect and cause HIV-neurocognitive impairment (NCI) in conventional mice, to investigate how Nef contributes to cognitive disease.
Methods: We employed EcoHIV, EcoHIVΔnef, two point-mutants in EcoHIV nef, and MLV expressing nef gene to infect conventional mice and primary adult mouse microglia (MG). NCI was assayed in radial arm water maze (RAWM) and fear conditioning tests. HIV expression in brain and MG was tested by QPCR and RNAscope; expression of M1 and M2 markers by QPCR; phenotypic M1 and M2 transitions relative to nef expression by confocal microscopy and RNAScope; and endocannabinoids and enzymes involved by ELISA and QPCR, respectively. Interventions included treatment of EcoHIV infected mice with the 2-arachidonoylglycerol (2-AG) or its inhibitor JZL184 daily prior to RAWM.
Results: EcoHIV associated NCI in mice was eliminated by deletion of Nef or selected point mutations in EcoHIV nef despite similar replication of parental and mutant viruses in peritoneal macrophages, spleen and brain. EcoHIV but not Δnef virus increased expression of neuroinflammation- and wnt pathway-related genes and microgliosis in mouse brain, and increased M1 marker expression in MG in vitro. MLV-Nef infection of mice reproduced EcoHIV effects. Treatment of mice with 2-AG or JZL184 during infection prevented the development of HIV-NCI.
Conclusion: We show that Nef is essential for induction of HIV-NCI in an animal model, thus supporting its role as a major HIV pathogenic protein. We propose that Nef acts, at least in part, through dysregulation of the endocannabinoid system by reducing 2-AG activation of M2 microglia. This identifies HIV Nef as a potential therapeutical target for controlling HIV-NCI in patients on ART.

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AI software detection of large vessel occlusion stroke on CT angiography: a real-world prospective diagnostic test accuracy study

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Background:
Artificial Intelligence (AI)-software is increasingly applied in stroke diagnostics. However, the actual performance of AI tools for identifying large vessel occlusion (LVO) stroke in real-time in a real-world setting is not fully studied.
Objective: To determine the accuracy of an AI software in a real-world, three-tiered multi-hospital stroke network.

Methods:
All consecutive head and neck computed tomography angiography (CTA) scans performed during stroke codes and run through an AI software engine (Viz LVO) during the period of May 2019 to October 2020 were prospectively collected. CTA reads performed by radiologists served as the clinical reference standard test and Viz LVO output served as the index test. Accuracy metrics were calculated.

Results:
Of a total of 1,822 CTAs performed, 190 occlusions were identified; 142 of which were internal carotid artery terminus (ICA-T), middle cerebral artery M1, or M2 locations. Accuracy metrics were analyzed for two different groups: ICA-T and M1±M2. For the ICA-T/M1 vs. the ICA-T/M1/M2 group, sensitivity was 93.8% vs. 74.6%, specificity was 91.1% vs. 91.1%, negative predictive value was 99.7% vs. 97.6%, accuracy was 91.2% vs. 89.8% and area under the curve was 0.95 vs. 0.86, respectively. Detection rates for ICA-T, M1, and M2 occlusions were 100%, 93%, and 49%, respectively. As expected, the algorithm offered better detection rates for proximal vs. mid/distal M2 occlusions (58% vs 28%, p=0.03).

Conclusions:
These accuracy metrics support Viz LVO as a useful adjunct tool in stroke diagnostics. Fast and accurate diagnosis with high negative predictive value mitigates missing potentially salvageable patients.

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Title: Breakdown of past neuronal ensembles supports memory-updating

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Background: The brain uses memories to guide future behavior, but updating these memories is equally important for adapting behavior to dynamic environments. We know that neuronal ensembles form the foundation of memories, but we know less about how they change when a memory must be modified. The present study investigates the dynamics of hippocampal ensembles during memory-updating.

Methods: We used in vivo calcium imaging with head-mounted Miniscopes to study the neural basis of memory-updating. Using a hippocampus-dependent spatial reversal task and a computational method for grouping together co-active neurons, we identified and tracked the activity of neuronal ensembles in dorsal CA1.

Results: Hippocampal ensembles encoded spatial location and lick port identity during the task. During the reversal phase, the mice updated their memories by learning to navigate to new goal locations. As the mice learned, a subset of hippocampal ensembles decreased their activation strength over trials, and their prevalence correlated with behavior. We propose that these "fading" ensembles are a result of ensemble remodeling to support memory-updating. Within these fading ensembles, we also observed that weakly-connected neurons were the most likely to drop out of the ensemble. These effects were not seen in aged mice (16-19 mo), who were impaired in spatial reversal.

Conclusions: We have identified a mechanism where the hippocampus breaks down ensembles to support memory-updating. Ensemble remodeling is impaired in aged mice who also suffer from poor memory-updating. These results help paint a more complete picture of how memory functions across a lifespan.

2022 Neuroscience Retreat

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Comparing Denoising Approaches in Ultra-High Field Resting State fMRI

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Background: One of the biggest challenges in functional Magnetic Resonance Imaging (fMRI) research has been parsing brain activation (BOLD signal) from artifact noise. Multi-echo (ME) acquisition of fMRI data facilitates BOLD separation by capturing every slice at multiple echo times. The use of ME 7 Tesla data allows examination of more detailed signal at a high spatial resolution. Currently there are several mathematical approaches to combining and denoising ME data to obtain BOLD signal but the optimal method for high-resolution data is unknown.
Methods: In this project, we aim to compare the predominant ME preprocessing pipelines: AFNI and MEICA. We also analyze individual echo images using SE AFNI preprocessing approach. We evaluate the quality of the denoised BOLD signal using global and regional temporal Signal-to-Noise Ratio (tSNR), functional connectivity and stationarity measures in healthy individuals (N=17).
Results: Our preliminary data suggest that with minimal processing with smoothing a 6 mm full width at half maximum (FWHM) kernel in the MNI space, there was significant effect of combining and denoising method on the whole-brain tSNR [$F(8,164) = 75.35$, $p<0.001$] and functional connectivity of key nodes of the motor network [$F(8,164) = 3.09$, $p= 0.003$].
Conclusion: Our preliminary results suggests that denoising and multi-echo combining approaches significantly impact the pre-processed BOLD signal. We observed that MEICA and AFNI differently impact BOLD signal quality measures. This may suggest that reliance on either tSNR or functional connectivity as data quality measures may not be sufficient. Through this exploratory study, specially by using simulations and recoverability analysis, we aim to highlight the differences in data quality measures such as tSNR, functional connectivity and time series stationarity and propose a weighted composite score as global measure for signal quality of ME resting state (rs)-fMRI data.

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RECONSTRUCTION OF HUMAN BRAIN TISSUE IN VITRO TO DISSECT THE MECHANISMS UNDERLYING SYNUCLEIN PATHOLOGY

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Background: Intracellular aggregation of synuclein is a hallmark of Parkinson's disease (PD), dementia with Lewy bodies (LBD) and multiple system atrophy (MSA). Animal models of synucleinopathies have not successfully translated their findings to human disease, and conventional 2D cell culture systems fail to recapitulate the complex cellular interactions in the human brain. As a result, we have limited insight into the mechanisms that govern the initiation and severity of synuclein pathologies, hindering the development of effective therapeutics and diagnostics.

Methods: To address this, we developed the multi-cellular integrated brain (miBrain), an iPSC-derived human brain tissue that contains anatomically correct cerebrovasculature, physiologically active neuronal circuits, myelination, and a neuroinflammatory system. We applied the miBrain to dissect cell-autonomous and non-cell-autonomous mechanisms underlying alpha-synuclein pathology, including synuclein aggregation, accumulation, and neurotoxicity.

Results: Vascular networks present in the miBrain expressed platelet endothelial cell adhesion molecule and were associated to platelet-derived growth factor receptor beta-expressing pericytes and S100B-expressing astrocytes, forming a functional blood brain barrier. Neurons within miBrain expressed neurofilament and were enwrapped by myelin basic protein expressed by oligodendrocytes. TMEM119 expressing microglia are present throughout the miBrain tissue in a grid-like pattern similar to the human brain. Using live imaging, we observed that iPSC-derived astrocytes readily take up synuclein monomer, which leads to intracellular aggregation and accumulation. Mitochondrial dyes revealed that synuclein uptake coincided with changes in mitochondrial morphology. Neurons exposed to synuclein have increased levels of phosphorylated synuclein within 1 week.

Conclusions: These results demonstrate that the miBrain system is suitable to study synuclein pathology. We are further developing the model and applying it to dissect the molecular mechanisms underlying genetic risk factors associated with synuclein pathology.

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Human iPSC-derived microglia for modeling central nervous system (CNS) HIV-1 infection in vitro and in humanized mice.

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Background
The persistence of latent viral reservoir is a key barrier to achieving a cure against HIV-1 infection. Microglia are thought to constitute the main HIV-1 viral reservoir in the central nervous system (CNS). Understanding the biology of HIV-infected microglia could shed light on the mechanisms underlying viral reservoirs. We propose human induced pluripotent stem cells (iPSCs)-derived microglia (iMG) as a powerful tool for modeling CNS HIV-1 infection in vitro and in humanized mice.

Methods
We generated hematopoietic progenitor cells (HPC) from genetically modified human induced pluripotent stem cells (iPSCs) that harbor Cre-recombinase dependent dual fluorescent dsRed-to-GFP reporter switch cassette. HPCs are then used: 1) to differentiate into microglia (iMG) in vitro; and 2) to transplant into the brains of transgenic neonatal immunodeficient mice that express human csf1 gene and allow reconstitution of iMG xenograft. We infect iMG cells with Cre recombinase-expressing M-tropic HIV-1 JRFL CreI and infection is verified through FACS and DNA/RNA FISH.

Results
Cortical sections of humanized mice brain demonstrated dsRed-expressing iMG xenograft. Engraftment was validated by staining for microglia-specific antibodies, IBA1 and P2RY12. We infected iMG cells in vitro with HIV-1 JRFL CreI that induced the dsRed-to-GFP color switch. HIV-1 infection was further verified using HIV-1 specific DNA and RNA FISH probing of the iMG cells.

Conclusion
The iMGs and humanized microglia xenograft mice model are powerful new tools for studying CNS HIV-1 infection. Our dual reporter switch system allows lineage tracing of HIV-infected iMGs that will be useful for single cell profiling and downstream identification of therapeutic targets against cells of the viral reservoir.

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TITLE: α5* nicotinic acetylcholine receptors modulate cholinergic transmission in cocaine reward

AUTHORS: Janna K Moen, Astrid Stoker, Brian Lee, Stephanie Caligiuri, Paul J Kenny

BACKGROUND: Cocaine enhancement of dopamine transmission in the nucleus accumbens (NAc) contributes to its rewarding properties. Cocaine also modulates cholinergic transmission in the NAc, and accumulating evidence suggests neuronal nicotinic acetylcholine receptors (nAChRs) regulate cocaine reward. Allelic variations in the gene that encodes for the α5 subunit are protective against developing cocaine dependence in humans, making α5-containing (α5*) nAChRs of particular interest. Striatal cholinergic interneurons (CINs) are a major source of cholinergic transmission in the NAc and modulate dopamine signaling. Cocaine produces a transient increase then persistent decrease in CIN activity, which is important for its reinforcing properties. We hypothesized that α5* nAChRs enhance GABAergic signaling onto CINs to pause their activity and subsequently enhance cocaine reward.

METHODS AND RESULTS: Using intravenous self-administration and intracranial self-stimulation paradigms, we found that α5 knockout (KO) mice exhibit decreased sensitivity to the rewarding effects of cocaine. Whole-cell slice electrophysiology data show that accumbal CINs of α5 KO mice are markedly hyperactive and insensitive to the inhibitory actions of cocaine, suggesting that α5* nAChRs are important for driving GABAergic transmission onto CINs. Finally, a viral tracing approach was employed to identify sources of input to the NAc which express α5* nAChRs, where we found a discrete population of locally-projecting GABAergic interneurons in the NAc that may express the α5 subunit.

CONCLUSIONS: Our behavioral data showcase the importance of α5* nAChR expression on cocaine responses, and our slice electrophysiology data suggest this effect is mediated through enhanced GABAergic drive onto CINs. Our preliminary viral tracing data brings up the intriguing possibility that a discrete population of GABAergic interneurons in the NAc may express α5* nAChRs to impact CIN activity and subsequent motivational responses to cocaine. Future studies will further investigate the relationship between acetylcholine release, CIN activity, and α5* nAChR-expressing neurons in response to cocaine.

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Ventral Tegmental Area Integrity Measured with High-Resolution 7-Tesla MRI Relates to Motivation Across Diagnoses

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The ventral tegmental area (VTA) is one of the major sources of dopamine in the brain and has been associated with reward prediction, error-based reward learning, volitional drive and anhedonia. However, precise anatomical investigations of the VTA have been prevented by the use of standard-resolution MRI, reliance on subjective manual tracings, and lack of quantitative measures of dopamine-related signal intensity-based MRI. Here, we combine ultra-high field 400-µm3 quantitative MRI for dopamine-related signal mapping, with a mixture of machine learning and supervised computational techniques to delineate the VTA in a transdiagnostic sample of subjects with and without depression and anxiety disorders. Subjects also underwent cognitive testing to measure intrinsic and extrinsic motivational tone. Fifty-one subjects were scanned in total, including healthy control (HC) and depression/anxiety (DA) subjects. DA subjects had significantly larger VTA volumes compared to HC but significantly lower signal intensity within VTA compared to HC, indicating reduced structural integrity of the dopaminergic VTA. Interestingly, while VTA integrity did not significantly correlate with self-reported depression or anxiety symptoms, it was correlated with an objective cognitive measure of extrinsic motivation, whereby lower VTA integrity was associated with lower motivation. This is the first study to demonstrate a computational pipeline for detecting and delineating the VTA in human subjects with 400-µm3 resolution. We highlight the use of objective transdiagnostic measures of cognitive function that link neural integrity to behavior across clinical and non-clinical groups.

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PARK7 LOSS OF FUNCTION INDUCES LYSOSOMAL AND PROTEOSTASIS DISRUPTION IN MIDBRAIN ASTROCYTES

Gustavo Morrone Parfitt, Elena Coccia, Camille Goldman, Ricardo Reyes, Kristen Whitney, Lily Sarrafha, John Crary, Alban Ordureau, Tim Ahfeldt, Joel Blanchard

Non-cell autonomous contribution to dopaminergic cell death in Parkinson's disease (PD) remains poorly understood and essential for the full understanding of the pathology progression. Astrocytes although more resilient to cell death display damage in PD with deleterious consequences for neuro-astrocytic function. Loss of function variants in DJ1 (PARK7) cause autosomal recessive early onset PD by mechanisms that are not fully understood. Glycation and Advance glycation product (AGES) formation are a deleterious process that erodes cellular function overtime. DJ1 was recently identified as a deglycase in eukaryotic cells acting in early glycation products in DNA, RNA, and proteins or degrading glycating agents. However, the deglycase DJ1 function was not put in the context molecular mechanism of PD neurodegeneration nor the main cell types affected were identified. Here, using iPSC midbrain organoids model, we show that loss of DJ1 function causes the accumulation of advanced glycation products (AGEs) concomitantly with the increase in alpha-synuclein phosphorylation. These phenotypes are independent of glycolysis levels or accumulation of toxic glycolytic intermediaries. Prevention of AGE formation by the dicarbonyl scavenger aminoguanidine treatment decreased alpha-synuclein phosphorylation. Proteomics experiments in purified midbrain astrocytes showed increase reactivity related proteins and pro-inflammatory cytokines. Our results show that astrocytes lacking DJ1 activity display impairment in lysosomal proteolysis causing accumulation of aggregated proteins, alpha-synuclein, and AGEs. In addition, mix-genetic astrocytic co-cultures reverse the proteolysis deficits observed in DJ1-KO midbrain neurons. In conclusion, astrocyte inability to clear toxic damaged proteins are detrimental for neuronal function and contribute to neurodegeneration observed in PD. The pathological mechanisms described involving astrocytes in this early onset PD model highlight new therapeutic targets for PD.

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Title: Longitudinal tracking of depression recovery with DBS in an interactive naturalistic environment

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Background: Deep brain stimulation (DBS) of the subcallosal cingulate (SCC) is an experimental treatment for depression. Clinicians currently rely on rating scales to make important clinical decisions when tuning stimulation parameters. A better approach would combine objective real time brain readouts and multi-dimensional behavioral measures to guide clinical decisions and thus improve treatment outcomes of patients with ongoing DBS.

Methods: Multimodal data was collected monthly at 8 time points during a series of naturalistic tasks performed in a fully immersive interactive environment, built in collaboration with Studio Elsewhere at the Center for Advanced Circuit Therapeutics at Mount Sinai West. We collected resting state electroencephalography (EEG) recordings, biometric data measuring affect, arousal, effort and patient physical and sleep activity captured via wristband and real time video collection. Twice a day local field potential, video diaries, mood/arousal ratings and continuous actigraphy data were also collected at home during treatment.

Results: Across modalities, we find that our metrics demonstrate robust changes over time, but with both early and late effects. Traditional voice acoustic features and performance on simple motor tasks change with initiation of DBS therapy. Facial action units that correlate with expressions of happiness, measures of physical activity and power distribution of the resting EEG (increasing central Cz beta band power) correlate with phases of recovery.

Conclusions: This is the first proof-of-concept study exploring multimodal naturalistic and objective assessments of depressive state in DBS implanted patients. These results demonstrate behavioral and physiological correlates of sustained plastic changes induced by the therapy. This study will help develop classification methods quantifying the recovery of the patients over time. We hope to expand this research into more comprehensive studies of a variety of neuropsychiatric disorders.

2022 Neuroscience Retreat

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Role of autism risk genes in frontal-thalamic projections underlying social processing in mice

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BACKGROUND: Challenges in social processing are associated with autism spectrum disorders (ASDs), yet little is known about the link between mutations in ASD risk genes and neural circuits underlying social processing. Recent genetic and transcriptomic studies have shown that many ASD risk genes are enriched in fetal and infant prefrontal cortical (PFC) layer 5/6 projection neurons. Based on our recent finding that the posterior paraventricular thalamus (pPVT) is the most prominent projection target of PFC L5/6 neurons that is preferentially recruited by social interaction (Yamamuro et al., Nat. Neurosci., 2020), we aim to examine the impact of different ASD risk genes on PFC L5/6 projection neurons to the pPVT and social behavior.

METHODS: We assessed the electrophysiological functions of medial PFC neurons projecting to the pPVT (mPFC→pPVT neurons) of adult mice harboring mutations in multiple ASD risk genes (Fmr1-KO, Tsc2-Ht and Pten-Ht) by whole-cell patch clamp recording. In adult Fmr1-KO mice, we also examined to what extent the optogenetic stimulation of mPFC-pPVT projections mitigates social behavior deficits.

RESULTS: Patch clamp recordings revealed electrophysiological dysfunction of adult mPFC-pPVT neurons (decline of excitability and/or increment of inhibitory drive) in all of the three ASD mouse models we tested. Of note, an optogenetic simulation of mPFC-pPVT projections acutely reversed social behavior deficits in adult Fmr1-KO mice.

CONCLUSIONS: These findings support that the frontal-thalamic projection to pPVT, essential for social processing, is not only a key converging circuit vulnerable to multiple ASD risk genes, but also a promising therapeutic target for circuit cure of social processing deficits in ASD.

***Equal contributions**

282/300 words

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Acetate Mediates Gut-Brain Signalling in the Shank3KO Mouse Model of ASD

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Background: Evidence demonstrates a role for the gut microbiome in Autism Spectrum Disorder (ASD), with signaling via the Short Chain Fatty Acid (SCFA) acetate proposed as a mode of communication. To investigate this, we combined antibiotic (Abx) depletion of the microbiome with acetate replenishment in a genetic model of ASD (Shank3Δ4-22KO). Moreover, to begin assessing the clinical relevance of findings from the mouse model, we also carried out targeted serum SCFA metabolomic analysis in human Phelan McDermid Syndrome (PMS) patients who are hemizygous for the Shank3 gene.

Methods: Shank3Δ4-22KO mice and wild-type (Wt) littermates were divided into control, Abx depletion, acetate replenishment and acetate + Abx groups at weaning. On postnatal day 60, animals were subjected to behavioral testing using three-chambered social interaction. Caecal content was collected for 16S sequencing and metabolomic profiling and medial prefrontal cortex (mPFC) for transcriptomic profiling and western blot analysis. Serum from PMS patients and controls was collected for targeted SCFA analysis.

Results: Shank3Δ4-22KO significantly alters microbiome composition and levels of acetate – effects exacerbated by Abx treatment. Behaviorally, control KO mice displayed decreased social interaction, an Abx exacerbated deficit which was rescued by acetate or Abx + acetate treatment. RNA-sequencing showed unique gene expression changes in KO mice following Abx, acetate or combination treatment with an upregulation of genes involved in cholesterol metabolism in the presence of acetate. Western blot analysis demonstrated robust gene by microbiome and metabolome on levels of H3K27ac in KO mice. Clinical data revealed sex specific alterations in acetate levels, inversely correlated with behavior.

Conclusions: Acetate supplementation in the Shank3Δ4-22KO model reverses social deficits possibly via epigenetic mechanisms. Clinical data corroborate altered acetate levels in PMS and add sex differences as a variable for further investigation.

2022 Neuroscience Retreat

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Title: Coordinated multi-region activity during choice behavior revealed by human intracranial recordings

Authors: Jacqueline Overton, Matthew Stickle, Karen Moxon, Ignacio Saez

BACKGROUND: Decision-making requires coordinated activity across multiple brain regions involved in evaluation, comparison, and choice. Contrary to notions that assign compartmentalized and sequential roles for individual brain regions, the associated neural activity is likely represented across multiple brain regions in a parallel and distributed fashion (e.g., Hunt & Hayden, 2017; Hunt et al. 2018). Understanding neural activations underlying choices therefore requires examination of distributed neural activity.

METHODS: Here, we probed activity across multiple brain regions involved in valuation and choice using intracranial electroencephalography (iEEG) in human neurosurgical patients (n=20) while they played a gambling game designed to probe value-based decisions. On each trial, participants chose between a certain reward and a risky gamble of varying win probability. We recorded iEEG activity from orbitofrontal cortex (OFC), lateral prefrontal cortex (LPFC), cingulate cortex (CC), amygdala, hippocampus, insula, parietal cortex, and pre- and post-central gyri. We analyzed iEEG local field potential data across six canonical frequency bands and nine regions during deliberation (1s prior to choice).

RESULTS: By comparing pre-choice activity to a pre-stimulus baseline, we found significant widespread task-related power modulations across multiple power bands and regions. Specifically, lower frequency (<30Hz) activity increased in all regions except pre- and post-central gyri and parietal regions, whereas higher frequencies were more likely to decrease, particularly in LPFC, OFC and CC. Next, we examined power modulations related to patient choice (gamble or safe bet) and found that low (30 to 70 Hz) and high gamma (70 to 200 Hz) were associated with decisions taken, particularly in OFC, LPFC, and precentral gyrus.

CONCLUSION: These results describe critical neural components underlying human decision-making and demonstrate that widespread and multi-frequency neural activity underlies human choices under uncertainty.

2022 Neuroscience Retreat

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Cell type-specific nuclei isolation and single cell transcriptomics inform glial pathology in human temporal lobe epilepsy

Balagopal Pai, Jessica Tome-Garcia, Wan Sze Cheng, German Nudelman, Anne Schaefer, Robert Sebra, Dalila Pinto, Elena Zaslavsky, Nadejda M. Tsankova.

Background: Epilepsy is one of the most common and disabling neurological disorder with diverse clinical characteristics, but its pathophysiology is poorly understood due to the complexity of underlying networks of cells. Current strategies for treatments have mostly focused on contributions of neurons and their hyperexcitability in epilepsy whereas role of glial cells is less explored.

Methods: Fluorescence-activated nuclei sorting (FANS), single-cell RNAseq (scRNAseq), single-nuclei RNAseq (snRNAseq).

Results: In this study we validated the method of FANS in simultaneously isolating neuronal (NEUN+), astrocyte (PAX6+NEUN-), and oligodendroglial progenitor cells (OPC) (OLIG2+NEUN-) enriched nulcei from cortical tissue of patients with drug resistant temporal lobe epilepsy (TLE) and age-matched human autopsy temporal cortex (TL). Nuclear RNA-seq confirmed robust cell type specificity and informed distinct pathways associated with TLE in each cell type. Gene set enrichment analysis indicated upregulation of development-associated genes and downregulation of mature astrocytic markers in epileptic astrocytes and OPCs, compared to normal TL samples. To gain further insight into the heterogeneity of glial cells involved, we performed scRNAseq on four additional human TLE samples. Integration and dimensionality reduction analysis revealed a subset of glia clustering between the reactive astrocytes and OPCs that showed an interesting hybrid signature of both the cell types. Comparison to previously published normal human temporal lobe scRNAseq dataset confirmed the presence of this unique hybrid glia in TLE samples. Pseudotime analysis using Monocle3 revealed cell transition trajectories stemming from this hybrid population towards both the OPCs and the reactive astrocytes, indicating a dual lineage. Finally, we corroborated the presence of these rare GFAP+OLIG2+ hybrid cells in-vivo, in mouse model of pilocarpine-induced status epilepticus.

Conclusions: Advanced transcriptomic analysis at single-cell level combined with validated cell-type specific isolation from surgical samples unraveled rare hybrid population of TLE

glial cells.

2022 Neuroscience Retreat

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Dual Specificity Phosphatase 4 (DUSP4) overexpression reduces ß-amyloid load and improves memory deficits in the 5xFAD Alzheimer's disease mouse model

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Abstract

Background: Hyperphosphorylation of tau and amyloid precursor protein in Alzheimer's disease (AD) is associated with dysregulation of phosphatase and kinase activities. Dual specificity phosphatase 4 (DUSP4) has recently been identified as a potential key driver in AD pathogenesis and progression. DUSP4 dephosphorylates both phospho-tyrosine and phospho-serine/phospho-threonine residues, negatively regulating members of the mitogen-activated protein kinase (MAPK) pathway. Importantly, DUSP4 gene expression is downregulated in the postmortem brains of AD subjects, but the role of DUSP4 in AD has not been well studied.

Methods: To determine potential effects of DUSP4 in AD-associated pathologies, we first investigated whether DUSP4 involved in the development of learning behavior impairment and neuropathology in the 5xFAD amyloidopathy mouse model using Adeno Associated Virus (AAV5)-mediated overexpression of DUSP4. Then, the effects of DUSP4 on AD-associated amyloid load were assessed utilizing immunohistochemistry, western blotting, and ELISA assay. Finally, RNA-seq was used to identify potential pathways involved in AD-associated regulation by DUSP4.

Results: Overexpression of DUSP4 in dorsal hippocampus (dHc) rescued impaired Barnes maze performance in female 5xFAD but had no effect in male 5xFAD. To investigate whether DUSP4 overexpression exerted sex-specific effects on AD-associated pathologies, we determined that DUSP4 overexpression significantly reduced amyloid loads in both female and male 5xFAD mice. Intriguingly, RNA-seq analysis identified a plethora of differentially expressed genes (DEGs) in dHc of 5-month-old mice in female 5xFAD, but not in male 5xFAD mice. The majority of DEGs from female 5xFAD were upregulated compared to WT, and most of these upregulated DEGs were found to be downregulated by DUSP4 overexpression. Further analysis of downregulated DEGs in female 5xFAD mice showed that these genes were involved in inflammatory-associated, interferon signaling, PD-1/PD-L1 and ERK/MAPK

pathways.

Conclusions: These results provide evidence that DUSP4 involved in regulation of AD-associated pathologies, potentially through suppression of neuroinflammation, interferon signaling, PD-1/PD-L1 and ERK/MAPK pathways.

2022 Neuroscience Retreat

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Presenilin1 FAD mutants and γ-secretase inhibitor decrease VEGFR2 cleavage, signaling and block angiogenic functions of brain endothelial cells

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Background: Cerebral microvasculature abnormalities contribute substantially to neuronal dysfunction and loss that lead to Alzheimer disease (AD). Brain angiogenesis is a reparative function in response to toxic insults and is regulated by endothelial cells (ECs) and VEGF/VEGFR2 system; impairment in this function would render the brain vulnerable to insults. In the present study, we examine the effects of Presenilin 1 (PS1)-Familial AD (FAD) mutants and γ-secretase in the VEGF-induced angiogenic signaling and functions of brain endothelial cells.

Method: Primary cortical EC (pCECs) of wild-type (WT) and knock-in (KI) mouse (PS1 M146V or PS1 I213T FAD) brains were isolated and cultured. We performed the in vitro angiogenesis assays sprouting on beads, cell migration and tube formation. Processing of VEGFR2 was detected in HEK293 cells overexpressing VEGFR2 and in pCECs in the presence or absence γ-secretase inhibitor (RO4929097) by western blotting (WB). VEGF-induced phosphorylation of signaling molecules downstream of VEGFR2 such as p38 kinase and PLCγ1 was also examined in WT and PS1 M146V mutant pCECs by WB. VEGF-induced complexes between VE-cadherin and Rok-α kinase were detected in the presence or absence of RO4929097 in BAMEC with immunoprecipitation.

Result: We found that VEGFR2 is processed by γ-secretase and this processing together with VEGF-induced sprouting, tube formation, migration and VE-cadherin angiogenic complexes are decreased in the presence of γ-secretase inhibitor or by PS1 FAD mutants. Furthermore, the VEGF-induced phosphorylation of p38 and PLC1 is decreased in PS1 FAD mutant pCECs.

Conclusion: Our findings suggest that VEGFR2 is processed by γ-secretase, which promotes VEGF-induced angiogenic functions of brain ECs through activation of VEGF-VEGFR2 downstream signaling. Our data also show that a PS1 FAD mutants decrease both the processing of VEGFR2 by γ-secretase and the VEGF-induced signaling and angiogenic functions of pCECs, providing a mechanism via which FAD mutants affect brain angiogenesis.

2022 Neuroscience Retreat

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Title: Prioritized encoding of unexpected rewards enhances memory by suppressing noise during recall

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Background: How does our decision-making influence what, and how, we remember? Prior work has demonstrated that reward-prediction error (RPE), a critical signal for reinforcement learning, also enhances memory. Identifying how, specifically, RPEs enhance memory is crucial to understanding the linkage between decision-making processes and memory.

Methods: Here, we tested the idea that encoding information about surprising rewards enhances memory by providing a source of information about past events that is more robust to noise during recall processes than perceptual features of the stimulus alone. We designed an experiment in which participants performed a gambling task in which they bet on specific images of faces, and were required to learn the value associated with different faces in order to maximize their reward. Then, the same face stimuli were presented in a recognition memory task along with novel face images, and participants had to indicate which images they had seen before. We computed the trial-by-trial RPE in the gambling task using reinforcement-learning models, and tested how these RPEs modulated subsequent recognition memory.

Results: We show that the presence of positive RPEs (pRPE) enhances subsequent memory for the stimuli associated with them, compared to those associated with negative RPEs or no RPE. In line with this finding, when examining individual participants' memory performance we found that participants who relied more heavily on pRPEs than the perceptual features of the stimulus exhibited better memory than those who relied more heavily on perceptual features. However, this improved memory performance was primarily driven by significant improvement at rejecting novel lures.

Conclusions: These results suggest that pRPEs enhance memory by providing a recognition signal that is more robust to noise (and thus false recognition) than the intrinsic perceptual features of a stimulus alone. Prediction errors are tightly bound to midbrain dopamine release, which modulates hippocampal plasticity. By showing that pRPEs minimize the interference of noise in recognition memory, we can begin to converge on a more specific role for dopamine in hippocampal memory processes.

2022 Neuroscience Retreat

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Oxytocin Modulation of the Paraventricular Nucleus and Supramammillary Nucleus Differentially Regulates Social Recognition Memory

Keerthi Thirtamara Rajamani, Marie Barbier, Kristi Niblo, Nick Cordero, Valery Grinevich, Shai Netser, Shlomo Wagner, Hala Harony-Nicolas

Background: Oxytocin (OXT), a neuropeptide synthesized in paraventricular (PVH), supraoptic (SON) and accessory nuclei (AN) of the hypothalamus is implicated in social behaviors including social recognition memory (SRM). However, the role of the 3 nuclei in modulating SRM is not fully understood. In this study, we addressed if PVH-OXT neurons are necessary for short and long–term SRM, and if OXT activity within a hypothalamic nuclei called supramammillary nucleus (SuM) is necessary for social recognition. The SuM send direct projections to the hippocampal CA2 region and is known modulate social memory, however the role of OXT in mediating this is unclear.

Methods: Using designer receptors activated by design drugs (DREADDs), we silenced OXT neurons (OT-hM4DGi) in the PVH of rats and assessed their short and long term SRM. We used immunohistochemistry and RNAscope to verify the presence of OXT fibers and receptors in the SuM respectively. We also blocked OXTR activity in the SuM to determine if this is necessary for social recognition memory.

Results: Silencing PVH-OXT neurons impairs both short and long-term SRM. This effect is specific for the social domain as object recognition remains intact. We also confirmed SuM to receive OXT projection fibers and confirmed that they originate from the PVH and not SON. We further confirmed that the SuM expresses OXT receptors which segregate into specific neural subtypes. Finally, we showed that blockade of OXTR activity affects long but not short-term social recognition memory.

Conclusions: These findings attribute a novel role for PVH-OXT neurons in SRM. We also determined that OXT modulation of SuM selectively affects specific forms of social recognition memory.

2022 Neuroscience Retreat

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Single nucleus (sn) multi-omics landscapes of murine pituitaries, human pituitaries, and pituitary neuroendocrine tumors (PitNETs)

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Background
The pituitary, the “master gland” of the endocrine system, is a complex tissue regulating key physiological functions including reproduction, metabolism, and the stress response.

Methods
We characterized pituitary cell types (PCT) and their underlying gene regulatory programs using sn multi-omics assays of snap-frozen adult murine and of pediatric, adult, and aged archived post-mortem human pituitaries from both sexes. Specifically, we performed paired snRNAseq and snATACseq in all samples, sn methylation of male murine pituitaries, and sn same-cell multiome for validation [1,2]. We also applied these approaches to characterize the epigenetic gene regulatory landscape (EGRL) of PitNETs.

Results
Analyses of these datasets facilitated robust identification of the PCTs and enabled us to characterize the transcriptome and epigenetic landscapes of murine and human pituitaries. We refined the identification of human pituitary stem cell (PSC) subtypes and their changes during aging. Using latent variable pathway analysis, we uncovered previously unreported coordinated gene expression and epigenetic programs for each major PCT and an age-specific module. We identified clusters corresponding to naive and committing PSCs in both species. Linear modeling of multiome data identified putative transcription factor (TF) regulators and regulatory domain accessibility sites that were significantly associated with PSC gene expression. PitNETs within a given type are heterogeneous and suggest the EGRL may contribute to tumor aggressiveness.

Conclusions
Our data suggest that: 1) transcriptional and epigenetic programs can be distinguished in PCT subtypes, 2) promoter and enhancer accessibility is central in shaping cell-defining

transcriptional programs, 3) human pituitaries contain uncommitted PSCs and committing progenitor cells at all ages, 4) multiome data identify regulatory domains and TFs associated with the expression of specific genes, and 5) EGRL may contribute to the varied clinical behavior of PitNETs. These multi-omics pituitary maps are an important resource for elucidating PCT-specific processes in health and disease.

1 Ruf-Zamojski, NatComm 2021
2 Zhang, CellReports 2022

2022 Neuroscience Retreat

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Title: Patient's Response to Therapist's Reciprocity in Trust Game Predicts the Closeness in Psychotherapeutic Relationship

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Background: Patient-clinician alliance is a key transdiagnostic factor for mental health treatment success across domains of intervention, including psychotherapy. Yet, the conceptual and methodological challenges of its assessment in objective measures deterred investigation of mechanisms underpinning successful dyadic interactions. Here, using a social neuroeconomics paradigm, we identified parameters embedded in quantitative behavioral interaction descriptive of treatment alliance.

Methods: A cross-sectional sample of patients and therapists in outpatient clinics (n=37 pairs) rated their alliance using Working Alliance Inventory and separately played a trustee in the 10-round Trust Game, where one reciprocates to the partner's economic investment, while incentivized to maximize self profits. They were instructed to mentalize the investor as their real-life therapy partner. Behavioral indices were analyzed using pearson's correlation and linear mixed effects model.

Results: Despite being smaller (0.40) compared to therapists' (0.57) (95% CI: -0.26, -0.08, $p<0.05$), patients' mean repayment fraction ratios were positively correlated with therapeutic alliance scores with their investors ($r=0.48$, $p=0.003$), unlike therapists ($r=0.23$, $p=0.15$). Patients' changes in repayment to the investors' benevolent signals (mean delta=0.04, n=105) were significantly higher than to malevolent signals (mean delta=-0.03, n=130) ($t=2.1$, $p=0.03$), unlike therapists' ($t=0.55$, $p=0.58$). Reciprocity of the investors significantly predicted the momentary change in repayment behavior by patients in the top 50% alliance (n=107, $\beta=6.2e02$, $p=0.003$), but not in the bottom 50% alliance (n=124, $\beta=4.7e-03$, $p=0.78$).

Conclusions: Patients and therapists behave differently in the economic exchange task, indicating their different social norms in the clinical setting. Quantitative paradigm to describe interpersonal trust provides insights into the mechanism of therapeutic alliance

operation.

2022 Neuroscience Retreat

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CAPTURING, TRACKING, AND PROFILING COCAINE-RECRUITED NEURONAL ENSEMBLES IN THE NUCLEUS ACCUMBENS.

Marine Salery, Arthur Godino, Yu Qing Xu, John F. Fullard, Panos Roussos and Eric J. Nestler

BACKGROUND: Learned associations between the rewarding effects of drugs and the context in which they are experienced are decisive for precipitated drug-seeking and relapse in addiction. These associative memories are stored in sparse and highly discriminative populations of concomitantly activated neurons defining drug-recruited neuronal ensembles.

METHODS: In this study, we explore the dynamics and molecular mechanisms of both the recruitment of these ensembles upon initial drug exposure and their contribution to the encoding, strengthening and ultimately expression of drug-associated memories. Additionally, we explore the intrinsic and acquired cellular properties favoring the allocation of specific cells to these ensembles and/or predicting their further reactivation. Capitalizing on the activity-dependent labeling in Arc-CreERT2 mice (Denny et al., 2014), we captured and permanently tagged (fluorophores, channel-rhodopsin) cocaine-activated cells in the nucleus accumbens for further characterization, optogenetics, and nuclei sorting.

RESULTS: We identified subsets of neurons activated at both early and late stages of drug exposure and show that the reactivation of an initial ensemble correlates with behavioral sensitization. Similarly, re-exposure to a cocaine-paired context in a conditioned place preference (CPP) paradigm triggered cocaine ensembles' reactivation. Using optogenetics-mediated artificial reactivation, we found that populations recruited at early versus late stages of drug exposure had opposite roles in CPP expression. Single nucleus RNA Sequencing was then performed on FACS-isolated tagged neurons, and we successfully isolated a cluster of reactivated cells within the initially activated ensemble.

CONCLUSIONS: Together, this ensemble-specific approach represents a pivotal step in identifying highly specific cellular processes involved in the encoding of pathological memories associated with drug addiction.

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Spatial patterning and immunosuppression of glioblastoma immune contexture in hypoxic niches

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Background: Glioblastoma (GBM), a highly lethal brain cancer, is notorious for its immunosuppressive microenvironment, yet current immunotherapies are ineffective. Thus, understanding the immune contexture and governing factors of immunosuppression is crucial.

Methods: We used a sensitive fluorescent reporter to track tumor hypoxia and single cell RNA sequencing analysis to identify hypoxic GBM cells and tumor-associated macrophages (TAMs) populations. Immunofluorescence and genetically engineered mice were used to validate bioinformatic findings and to perform mechanistic studies respectively.

Results: Here, we identified a highly dynamic temporospatial patterning of TAMs corresponding to vascular changes in GBM: as tumor vessels transition from an initial dense regular network to later scant engorged vasculature, CD68+ TAMs shift away from perivascular regions to poorly vascularized areas. We revealed that hypoxic niche controls immunosuppression by at least two mechanisms: first, attracting and actively sequestering activated tumor-associated macrophages (TAMs) in hypoxic zones, and second, reprograming entrapped TAMs towards an immunotolerant state. Indeed, entrapped TAMs also experience hypoxia and upregulate phagocytic marker Cd68 and immunotolerant genes Mrc1 and Arg1, thereby facilitating debris clearing, inflammatory containment, and immunosuppression in hypoxic zones. Remarkably, this process is heavily influenced by the immunocompetency of host animal, as tumor vessels in immunodeficient hosts remained dense and regular while TAMs evenly distributed. Mechanistically, we identified Ccl8 and IL-1β as two hypoxic niche factors released by TAMs in response to cues from hypoxic GBM cells, functioning to reinforce TAM retainment.

Conclusion: Mutual communication between tumor and immune cells in the hypoxic niche plays a determining role in sculpting the immune landscape, limiting inflammatory spread and inducing an overall tolerogenic/immunosuppressive microenvironment.

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Ependymal cells-CSF flow Regulate Stress-induced Depression

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Background: Major depressive disorder (MDD) is a severe, common mood disorder. While reduced cerebrospinal fluid (CSF) flow adversely affects brain metabolism and fluid balance in the aging population and during development, only indirect evidence links aberrant CSF circulation with many diseases including neurological, neurodegenerative and psychiatric disorders, such as anxiety and depression.
Methods: We use comprehensive approaches, including molecular, cellular, genetic, imaging, MRI, bioinformatic and behavior.
Results: Here we show a very high concentration of p11 as a key molecular determinant for depression in ependymal cells, which is significantly decreased in patients with MDD, and in two mouse models of depression induced by chronic stress, such as restraint and social isolation. The loss of p11 in ependymal cells causes disoriented ependymal planar cell polarity (PCP), reduced CSF flow, and depression-like and anxiety-like behaviors. p11 intrinsically controls PCP core genes, which mediates CSF flow. Viral expression of p11 in ependymal cells specifically rescues the pathophysiological and behavioral deficits caused by loss of p11. A cross-species ependymal cell-specific functional network reveals that ependymal cells, CSF flow and p11 control depression.
Conclusions: Taken together, our results identify a new role and a key molecular determinant for ependymal cell-driven CSF flow in mood disorders and suggest a novel strategy for development of treatments for stress-associated neurological, neurodegenerative and psychiatric disorders.

Keywords: Ependymal cells, CSF, Stress, Depression.

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Title: Acute hypoxia induces CA1-specific inflammasome activation, autophagic flux and synaptic changes

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Background: Individuals who have been exposed to acute hypoxia suffer from various cognitive deficits including learning and memory. The hippocampus is one of the brain regions that are most sensitive to hypoxic insults. CA1 neurons, specifically, are more vulnerable to hypoxia compared to other hippocampal regions (i.e. CA3). Understanding the underlying molecular mechanisms of selective vulnerability of CA1 neurons to hypoxia will be critical for the development of new therapeutic approaches.

Methods: To investigate the transcriptional changes of CA1 and CA3 neurons caused by acute hypoxia, we utilized Translating Ribosome Affinity Purification (TRAP) with mice expressing Cck-EGFP/Rpl10a and Gprin3-EGFP/Rpl10a, respectively, followed by RNA sequencing. Mice were exposed to 6% hypoxia for 5 consecutive hours in a custom-made hypoxic chamber. At two different time points (0hr and 24hr post hypoxia), mice were sacrificed for TRAP, immunohistochemistry and western blot.

Results: TRAP data revealed distinct transcriptional changes in CA1 and CA3 neurons after acute hypoxia. More specifically, hypoxia induced inflammation and inflammasome pathways in CA1 neurons compared to CA3 neurons. Western blot analyses showed elevated levels of NLRP3, cleaved caspase-1 and cleaved IL-1β. We also observed increased autophagic flux in CA1 neurons compared to CA3 neurons 24 hours post-acute hypoxia. Super-resolution microscopy revealed reduced colocalization of Homer1 and Bassoon synaptic markers in CA1 compared to CA3 after acute hypoxia.

Conclusion: CA1 neurons display distinct transcriptomic expression pattern compared to CA3 neurons in response to acute hypoxia. Specifically, NLRP3 may play an important role in CA1-selective vulnerability, including synaptic dysfunction and autophagy pathways.

2022 Neuroscience Retreat

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DIFFERENCES IN SLEEP PROBABILITY DEPENDING ON LIGHTING VARIABILITY IN HOSPITAL PATIENTS

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BACKGROUND: Sleep during inpatient admission to any hospital is disrupted for a variety of reasons, including lighting exposure that is typically fixed at constant intensity and spectra. This study aimed to test the hypothesis that customized lighting that promotes entrainment of the endogenous circadian rhythm by exposing subjects to blue-augmented lighting during the morning and blue-suppressed lighting evening would improve sleep timing and duration.

METHODS: Two Mount Sinai hospital rooms (with 2 beds each) were outfitted with Eight Mattress sensors that use a combination of movement, breathing, heart rate, and temperature variables to estimate wake and sleep vigilance states in 30-second epochs. One room contained customized lighting between 7 am and 11 pm, while the other room contained standard hospital lighting.

RESULTS: The current analysis includes 33 participants (18 in the control room and 15 in the custom lighting room), who were matched for time-of-year hospital admission date. The probability of sleep during any given 30-second epoch within the 24-hour day was determined by summating the incidences of sleep for that epoch across all patient-days and dividing by all valid sleep/wake outputs. The number of valid observations per 30-second epoch ranged from 11 to 55. The average number of 24-hour periods for a patient in the lighting condition was 5.47 ± 4.93 while the average number 24-hour periods for a patient in the control group was 5.11 ± 3.23. The probability distribution of sleep across the 24-hour cycle was significantly different between the custom lighting and control conditions ($p < 0.001$, 95% confidence interval [-0.13, -0.09]).

CONCLUSIONS: Given the results, there is an apparent increased probability of between approximately 8:30 pm and 9:00 am in the custom lighting condition. Future work will evaluate differences in sleep duration, continuity, and timing at the participant level between lighting conditions

2022 Neuroscience Retreat

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Stress-resilient mice optimize subjective value and food security on an economic foraging task

AUTHORS:
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BACKGROUND: Economic stress can often serve as a "second-hit" for those who have already accumulated a history of stressful experiences. This can precipitate significant changes in behavior that may be adaptive or maladaptive depending on one's unique stress-response predispositions. How an individual recovers from a setback is a core feature of resilience but is seldom captured in animal studies.

METHODS: Here, we challenged mice in a novel two-hit stress model by first exposing animals to chronic social defeat stress (first hit) – a protocol known to separate individual differences in stress-resilient versus stress-susceptible phenotypes. Mice were then tested longitudinally across two months on the neuroeconomic task termed "Restaurant Row" during which mice foraged daily for their sole source of food while on a limited time budget.

RESULTS: An abrupt transition into a reward-scarce environment on this task elicits an economic crisis (second hit) precipitating a massive drop in food intake that mice must respond to in order to survive. We found that stress-resilient mice mounted the most robust behavioral response to this economic challenge and readily renormalized food intake back to baseline levels faster compared to stress-susceptible and non-defeated control mice. This was achieved through an efficient increase in effort expenditure and a redistribution in how time was allocated among competing opportunities. Interestingly, stress-resilient mice learned to accomplish this while simultaneously maximizing subjective value by re-establishing flavor preferences that approximated yield previously obtained in a reward-rich environment.

CONCLUSIONS: These findings suggest that a resilient individual's capacity to "bounce back" following economic stress while foraging entails the development of a multi-pronged strategy that not only ensures food security necessary for survival but also prioritizes other aspects of well-being including subjective value, highlighting a motivational balance that may be impaired in depression.

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2022 Neuroscience Retreat

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Our survival depends on our ability to assign motivational value to neutral stimuli. This associative learning is encoded by the mesocorticolimbic dopaminergic pathway. Before learning, dopamine (DA) neurons in the VTA are activated by unpredicted reward. After learning, the conditioned stimulus predicts reward, and DA neuron are activated by the reward-predicting stimulus. The release of DA in the NAc controls the activity of two two subpopulations of medium spiny neurons (MSNs) D1 and D2. The classic view sustains D1 MSN promotes reward, while D2 MSN encodes for aversion. Drugs, including Alcohol, induce large DA elevations in the NAc. In contrast, high concentrations of ethanol dampen dopamine. Ethanol's low specificity and potency has likely contributed to the lack of a clear understanding of how alcohol alters the reward circuitry. Using in vivo fiber photometry, we simultaneous record genetically encoded fluorescent DA and calcium sensor in the NAc Core in freely moving female and male mice during alcohol-mediated behaviors; conditioned place preference (CPP) and 2-bottle Choice (2BC). Cross-hemisphere synchrony permits simultaneous comparison of DA and D1 signals. A Time-log cross-correlation analysis revealed a tight sub-second DA-D1 interplay. As expected, acute ethanol exposure during conditioning increased DA transients and baseline levels. Interestingly, ethanol dramatically affected D1-MSN activity inducing a characteristic burst-like inhibition (not observed under acute Cocaine administration). As a consequence, DA and D1 signals became uncoupled. Females showing a more robust alcohol preference than males presented a specific DA and D1 elevations in response to ethanol-paired contextual cues and voluntary ethanol-drinking. Together, these data elucidate distinct temporal DA and D1-MSNs signatures in the NAc in response to acute ethanol and to ethanol-associated stimulus.

2022 Neuroscience Retreat

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Role of Histone 3.3 Lysine 27 Methylation in Conferring Enduring Stress Susceptibility

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Background
Depression is a prevalent psychiatric disorder characterized by heterogeneous symptoms that can last a lifetime. Vulnerability to depression is associated with long-lasting changes in the transcriptional profile of the nucleus accumbens (NAc), a brain region involved in reward and mood regulation.

Methods
Here, we characterized the enduring changes in histone modifications in the NAc of mice exposed to chronic social defeat stress (CSDS), a validated model for the study of depression-like behaviors. Tissue from the NAc of control (CON), susceptible (SUS), and resilient (RES) mice was collected either 24 hr or 4 weeks after the SIT and processed for histone profiling via mass spectrometry. In parallel, we mapped the genome-wide enrichment of the most changed histone modifications using CUT&RUN and assessed for chromatin accessibility using ATAC-Seq.

Results
CSDS alters the methylation (me) dynamics of lysine (K) 27 of the histone variant H3.3. Specifically, we observed an increased abundance of H3.3K27me1 and a decreased abundance of H3.3K27me2 in the NAc of SUS mice. Indeed, H3.3K27me1 is primarily enriched in gene bodies and proximal promoters, suggesting its crucial role in determining stress-induced transcriptional profiles, while H3.3K27me2 is weakly deposited across intergenic regions. Using bioinformatics we are identifying changes in chromatin accessibility and functional regulatory elements that coincide with H3.3K27me1/me2 enrichment.

Conclusions
Our results suggest that H3.3K27me1 and H3.3K27me2 are important chromatin “scars” that mediate enduring susceptibility to stress in the NAc. Understanding the molecular basis of these adaptations and identifying the genomic regions affected will shed new light on persisting forms of stress-induced pathology.

2022 Neuroscience Retreat

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Nicotine Addiction – The Role of IL-18 in the Medial Habenula

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The habenula-IPn circuit was recently identified as a critical brain system that regulates the motivational properties of nicotine. Our premise is that nicotine-induced alterations in the activity of the habenula-IPn system play a central role in the development and persistence of the tobacco smoking habit. A unique feature of mHb neurons is their expression of interleukin-18 (IL-18), a cytokine heavily implicated in neurodegenerative processes. IL-18 is induced in mHb, but not in other brain sites, by acute and chronic stress. Given the unique expression of IL-18 in mHb neurons, we hypothesize that this cytokine regulates excitotoxic effects of nicotine. Consistent with this hypothesis, we find that Il18-/- mice are far more sensitive than wild-type mice to excitotoxic effects of self-administered nicotine. Furthermore, baseline and nicotine-induced increases in Fos were markedly higher in the IPn of Il18-/- mice compared with wild-type mice. As nicotine activates Fos in the IPn by stimulating habenular inputs this suggests that IL-18 deficiency renders mHb neurons hyper-responsive to nicotine. The mechanisms by which IL-18 regulates these changes are unclear. A major action of IL-18 in the brain is to control microglia activity. In preliminary experiments, we find that microglia numbers are far lower in mHb of Il18-/- mice than wild-type mice. These data suggest the relationship between IL-18 and microglia may play a role in the development of nicotine addiction.

Funding: NIH

2022 Neuroscience Retreat

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How does the brain sense peripheral infection and inflammation?

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Upon peripheral infection, the brain co-ordinates well-characterized sickness behaviors (reduced motor activity, anhedonia, fever, etc.) that aid in pathogen clearance and recovery from the infection. However, the nature and route of the signal that alerts the brain of a peripheral infection are not fully understood. While it is known that both direct neuronal signaling from the periphery via the vagus nerve as well as cytokine signals from the blood (such as interferon) play a role, their relative contribution and interactions are unknown. Downstream of that, it is also unclear which cells are the first to respond and how those signals are propagated through the brain. Given that microglia are the resident immune cells of the CNS we hypothesized that they may be among the first to sense or propagate the peripheral signals to the rest of the brain.

Using the viral mimetic Poly I:C as a model of peripheral infection in mice, we employ a combination of interferon reporter mice, immunostaining and in-situ analysis to assess interferon responses and neuronal activation across the brain. We find that brain responses to peripheral inflammation lead to a rapid activation of specific neuron populations in the circumventricular organs (Fos+) and is associated with the activation of the interferon response in macrophages in the choroid plexus and microglia in the circumventricular organs. These findings raise the question if and how neuron and microglia responses are coordinated and regulate each other. To address this question, we are combining different approaches that include targeted vagotomy or chemical inactivation of vagus nerve signaling with cell-type specific deletion of the interferon receptor.

2022 Neuroscience Retreat

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The Living Brain Project: A Multiscale, Data Driven Investigation of the Living Human Brain

Authors: Kimia Ziafat on behalf of the LBP Team

Background:

The Living Brain Project (LBP) was formed nearly a decade ago at Mount Sinai as a means to construct a more comprehensive knowledge of the living human brain by studying a large cohort of living participants using approaches traditionally limited to the postmortem setting. Here, we present an overview of the current LBP protocol.

Methods:

Patients receiving Deep Brain Stimulation (DBS) at Mount Sinai West were enrolled. Left and right hemisphere brain samples from the pial surface of the prefrontal cortex along with paired blood samples and electrophysiological recordings were collected during each of the cortical procedures. A skin biopsy was collected during the neurostimulator implantation procedure. Additional clinical information was collected from patient charts.

Results:

A total of 296 participants are currently enrolled in the study, from whom 502 cortical biopsies, 446 blood samples, and 257 skin biopsies were collected. The sample consists of 65% male, 85% white, 88% not hispanic or latino, and has a mean age of 61.2 years (SD 12.7). The majority of enrolled patients have Parkinson's Disease (N= 221) with a mean baseline UPDRS motor score of 37.6 (SD 18.6) in the off and 14.7 (SD 12.5) in the on medication states. Data generated from the brain samples include RNA sequencing (N=319), single-cell RNA sequencing (N=35), neuropathology staining (N=284) and multiomics (N=253). Data generated from the blood samples include RNA sequencing (N=241), and whole genome sequencing (N=159). Data generated from the skin samples include whole genome sequencing (N=83 samples). Additional data have been generated from Electrophysiological recordings using micro local field potential (N=453), as well as neuroimaging data (N=284), using CT scans, sMRI and DTI. Additional clinical data include

prescribed medications and baseline neuropsychological assessments. Ongoing analyses include single-cell transcriptomics and proteomics. Data is stored and managed on Minverva, REDCap and Data Ark.

Conclusions:

The comprehensive dataset for this study can be used to paint a more complete picture of the neurobiology, structure and function of the living human brain.

2022 Neuroscience Retreat

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TIMP2 remodeling of the extracellular matrix regulates hippocampus-dependent cognitive function and plasticity

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Aging is the major risk factor for neurological disorders such as Alzheimer's disease (AD), and exposure to youthful-blood factors counteracts age-related decline. The blood-borne youth-associated factor, tissue inhibitor of metalloproteinases-2 (TIMP2), was shown to revitalize aged mouse hippocampus, while its depletion impairs long-term potentiation, yet its mechanism of action and how its function relates to age-related disorders remains unclear. To define how TIMP2 regulates hippocampal function, we characterized its source of expression and putative cellular targets. We find that TIMP2 is expressed by adult hippocampal neurons and its deletion alters hippocampal expression in genes related to synapse organization, memory, and neurogenesis. Mice in which TIMP2 is deleted exhibit impaired dendritic spine plasticity and reduced adult hippocampal neurogenesis, with concomitant deficits in hippocampus-dependent cognition. TIMP2-deficient hippocampi exhibit altered levels of TIMP2's target MMP2 with a corresponding accumulation of extracellular matrix (ECM) proteins in contact with synapses, arguing for dysregulated ECM turnover adjacent to synapses. We report that migration of immature neuroblasts is also impaired in the absence of TIMP2, likely as a result of stiffness imparted by dysregulated ECM. Finally, peripheral and hippocampal TIMP2 levels are decreased in mouse models of AD pathology, phenocopying deficits observed in aging and suggesting interactions with pathology. Loss of TIMP2 exacerbates amyloid pathology, and TIMP2 gain-of-function mitigates AD-associated deficits in cognition. Together with new tools we developed, these results help define mechanisms through which TIMP2 regulates hippocampus-dependent function to potentially inform novel therapies for aging and AD-associated therapies.

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2022 Neuroscience Retreat

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Closed-loop control of inhibitory theta phase locking: Investigating a modulator of seizure activity and cognition

Zoe Christenson Wick*, Paul Philipsberg*, Sophia Lamsifer, Tristan Shuman

Background: The precise timing of single-unit spiking relative to network-wide oscillations (i.e., phase locking) has long been thought to maintain excitatory-inhibitory homeostasis and coordinate cognitive processes. We recently found that epileptic mice with spontaneous seizures and cognitive deficits show altered inhibitory theta phase locking in the dentate gyrus, but the causal influence of this phenomenon has never been determined. Thus, we aimed to causally test the hypothesis that inhibitory theta phase locking can bidirectionally control seizures and cognitive performance in control and epileptic mice.

Methods: To test these hypotheses, we developed a low-latency closed-loop optogenetic system to bidirectionally control inhibitory phase locking to theta in head-fixed control and epileptic mice navigating a virtual track. Using opto-tagging strategies, we first identified the preferred firing phase of parvalbumin+ and somatostatin+ dentate interneurons in control and epileptic mice. We then applied our closed-loop system to lock the spiking of these dentate interneurons to their preferred or non-preferred phase of theta while measuring seizure activity and accuracy of navigation.

Results: Our data suggests that, in epileptic mice, re-aligning inhibitory spiking to the preferred phase of theta diminishes seizure activity compared to stimulating at a non-preferred phase of theta. Further, preliminary data suggests that enforcing preferred dentate inhibitory neuron spiking improves performance on a navigation task while locking their firing to a non-preferred phase impairs performance.

Conclusions: Theta phase locking of inhibitory spiking seems to play an important and causal role in the two most concerning elements of epilepsy: seizures and cognitive deficits. Gaining deeper insights into the impacts of inhibitory theta phase locking may reveal its potential as an epilepsy therapeutic uniquely capable of treating both seizures and cognitive deficits.

Neuroscience Graduate Training Program

This year marked a slow return--at least a lurch in the right direction--towards normalcy. Classes, seminars, WIPs, thesis proposals, thesis defenses, scientific meetings in far-away lands... these were once again held in-person, though in some cases with a hybrid option for those who preferred or needed to remain remote. It cannot be stressed enough how important this is for our trainees (and all of us, really) to be able to socialize, to interact with faculty and fellow students, and to attend meetings.

That said, at the height of Omicron in early January, Covid bedeviled the admissions process once again, forcing for a second year a remote Admissions experience. I think without an in-person venue, we lose our best asset, which is to show (rather than simply state over a computer screen) how collegial, vibrant, stimulating and productive the training and research environment is for our trainees and faculty. One difference between this year and last was our ability to bring applicants here for an in-person visit with faculty and students in the weeks before final decisions were due, and this undoubtedly helped to some extent. In the end, we welcome 11 outstanding new students who represent a variety of research backgrounds, interests and life-experiences. I am ever grateful for the hard work of Mark Baxter, Betsy Cropper, Vanna Zachariou, Daniela Schiller, Nan Yan, Silvia De Rubeis, Xiaosi Gu and Ki Goosens--our Admissions screening team extraordinaire, and Chris Guevara, who sacrificed an entire day to slog by Zoom through the Institution-wide Admissions meeting with me. I am also grateful to the many faculty and students who, on a moment's notice, met with, dined, entertained and otherwise worked hard to recruit our re-visiting students, and am particularly indebted to Vena Persaud, who coordinated all travel and hotel arrangements.

The flip side to welcoming new students is that we say goodbye to those who successfully defended their spectacular thesis work. In the interval between last year's and this year's retreat, 19 PhD or MSTP students defended their thesis work, with several more to follow later this summer. What a banner year! Best of luck to our new colleagues.

Finally, we are re-tooling our Core course sequence such that all four Cores will run sequentially, starting in August and ending by mid-April. New material is being added to Core 3 to introduce principles of computational neuroscience, and Mark Baxter and Denise Croote are working on generating a new Neuroscience Biostatistics course that would be taught in the Fall.

George Huntley

Image by Andrew Varga & Juliet Varga

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Notes

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