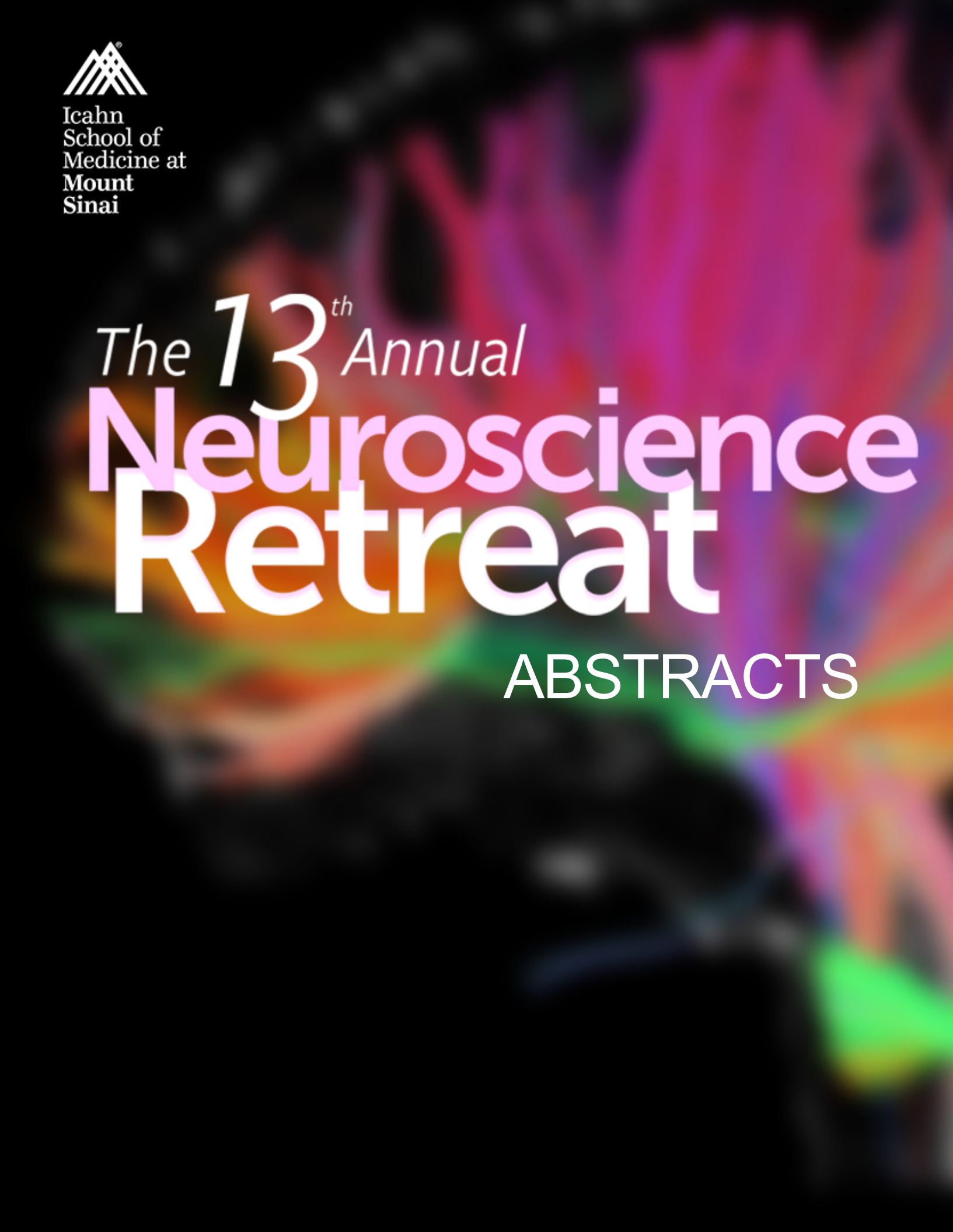
Icahn
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The 13th Annual
Neuroscience
Retreat
ABSTRACTS

| First Name | Last Name | Topic | Student/postdoc | Poster# | DataBlitz? |
|---|---|---|---|---|---|
| Yee Lam (Karen) | Lei | Molecular | Student | M1 | |
| AYAN | HUSSEIN | Molecular | Student | M2 | |
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| Christopher | Guevara | Molecular | Student | M5 | |
| Kelsey | Lucerne | Molecular | Student | M6 | |
| Shiyi | Pan | Molecular | Student | M7 | |
| Philip | Hwang | Molecular | Student | M8 | |
| Iya | Prytkova | Molecular | Student | M9 | |
| Yiqun | Wang | Molecular | Student | M10 | |
| Valerie | Marallano | Molecular | Student | M11 | |
| Xiaoting | Zhou | Molecular | Student | M12 | |
| Kristi | Niblo | Molecular | Student | M13 | |
| Lauren | Dierdorff | Molecular | Student | M14 | |
| Katherine | Meckel | Molecular | Student | M15 | |
| Randall | Ellis | Molecular | Student | M16 | |
| Lily | Sarrafha | Molecular | Student | M17 | |
| Farzanna | Mohamed | Molecular | Student | M18 | |
| Pamela | Del Valle | Molecular | Student | M19 | |
| Jennifer | Blaze | Molecular | Postdoc | M20 | Y |
| Adele | Mossa | Molecular | Postdoc | M21 | |
| Rebecca | Hofford | Molecular | Postdoc | M22 | |
| Chrystian | Junqueira Alves | Molecular | Postdoc | M23 | |
| Abhishek | Sahasrabudhe | Molecular | Postdoc | M24 | |
| Rukmani | Pandey | Molecular | Postdoc | M25 | |
| Swati | Gupta | Molecular | Postdoc | M26 | |
| Sivaprakasam | Ramamoorthy | Molecular | Postdoc | M27 | |
| Stephanie | Caligiuri | Molecular | Postdoc | M28 | |
| Catarina | Ferreira | Molecular | Postdoc | M29 | Y |
| Lauren | Wills | Molecular | Postdoc | M30 | |
| Hsiao-Yun | Lin | Molecular | Postdoc | M31 | |
| Rachel | Litke | Molecular | Postdoc | M32 | |
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| Amara | Plaza-Jennings | Genetics/Genomics | Student | G3 | |
| Samuel | Powell | Genetics/Genomics | Student | G4 | |
| Hadley | Walsh | Genetics/Genomics | Student | **G5** | |
| Zarmeen | Mussa | Genetics/Genomics | Student | G6 | Y |
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| Fatou | Mbaye | Genetics/Genomics | Student | G9 | |
| Casey | Fecko | Genetics/Genomics | Student | G10 | |
| Sanan | Venkatesh | Genetics/Genomics | Student | G11 | |
| Collin | Teague | Genetics/Genomics | Student | G12 | |
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| Andrew | Chan | Genetics/Genomics | Student | G14 | |
| Kumayl | Alloo | Genetics/Genomics | Student | G15 | |
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| Carole | Morel | Genetics/Genomics | Postdoc | G19 | |
| Kiran | Girdhar | Genetics/Genomics | Postdoc | G20 | |
| Susana Isabel | Ramos | Genetics/Genomics | Postdoc | G21 | |
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| George | Heaton | Genetics/Genomics | Postdoc | G29 | |

| First Name | Last Name | Topic | Student/postdoc | Poster# | DataBlitz? |
|---|---|---|---|---|---|
| Brianna | Agyapong | Cells/Systems | Student | S1 | |
| Michelle | Caizaguano | Cells/Systems | Student | S2 | |
| Taylor | Francisco | Cells/Systems | Student | S3 | |
| Sarah | Montgomery | Cells/Systems | Student | S4 | |
| Yu | Feng | Cells/Systems | Student | S5 | |
| Sherod | Haynes | Cells/Systems | Student | S6 | |
| Angelica | Minier-Toribio | Cells/Systems | Student | S7 | Y |
| Lauren | Vetere | Cells/Systems | Student | S8 | |
| Priscilla | Maccario | Cells/Systems | Student | S9 | |
| Alexa | LaBanca | Cells/Systems | Student | S10 | |
| Emily | Teichman | Cells/Systems | Student | S11 | |
| Yosif | Zaki | Cells/Systems | Student | S12 | |
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| Amanda | Leithead | Cells/Systems | Student | S14 | |
| Nick | Upright | Cells/Systems | Student | S15 | Y |
| Zhe | Dong | Cells/Systems | Student | S16 | Y |
| Brian | Sweis | Cells/Systems | Postdoc | S17 | |
| Feng-Kuei | Chiang | Cells/Systems | Postdoc | S18 | |
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| Lingxuan | Chen | Cells/Systems | Postdoc | S22 | |
| Keerthi | Thirtamaraa Rajamani | Cells/Systems | Postdoc | S23 | |
| Kenny | Chan | Cells/Systems | Postdoc | S24 | |
| Atsushi | Fujimoto | Cells/Systems | Postdoc | S25 | |
| Long | Li | Cells/Systems | Postdoc | S26 | |
| Joseph | Burnett | Cells/Systems | Postdoc | S27 | |
| Natalia | Biscola | Cells/Systems | Postdoc | S28 | |
| Anthony | Lacagnina | Cells/Systems | Postdoc | S29 | Y |
| Catherine | Elorette | Cells/Systems | Postdoc | S30 | |
| Marie | Barbier | Cells/Systems | Postdoc | S31 | |
| Flurin | Cathomas | Cells/Systems | Postdoc | S32 | |
| Chelsea | Brea | Computational/Clinical | Student | C1 | |
| Kayla | Leung | Computational/Clinical | Student | C2 | |
| Marishka Manoj | Mehta | Computational/Clinical | Student | C3 | |
| Kristen | Watkins | Computational/Clinical | Student | C4 | |
| Gabe | Marx | Computational/Clinical | Student | C5 | |
| Talia | Wigder | Computational/Clinical | Student | C6 | |
| Matthew | Schafer | Computational/Clinical | Student | C7 | |
| Denise | Croote | Computational/Clinical | Student | C8 | |
| Srinivasan | Anantha Ramakrishnan | Computational/Clinical | Student | C9 | |
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| Alara | Akyatan | Computational/Clinical | Student | C12 | |
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| Sarah | Barkley | Computational/Clinical | Student | C15 | |
| Bonnie | Lerman | Computational/Clinical | Student | C16 | |
| Katherine | Keller | Computational/Clinical | Student | C17 | |
| Jeenia | Zaki | Computational/Clinical | Student | C18 | |
| Faith | Adams | Computational/Clinical | Student | C19 | |
| Riaz | Shaik | Computational/Clinical | Student | C20 | |
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| Ahmet | Ceceli | Computational/Clinical | Postdoc | C27 | |
| Jihan | Ryu | Computational/Clinical | Postdoc | C28 | |
| Anastasia | Shuster | Computational/Clinical | Postdoc | C29 | |
| Elena | Solli | Computational/Clinical | Postdoc | C30 | |
| Ofer | Perl | Computational/Clinical | Postdoc | C31 | |

# 2021 Neuroscience Retreat abstract submission

Region specific engagement of actin nucleation mechanisms at the synapse

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FBI, Department of Neuroscience, Icahn School of Medicine at Mount Sinai, NY

BACKGROUND: There are two major actin nucleation mechanisms employed within the cell: Arp2/3-driven branched polymerization and Formin-driven straight polymerization. Multiple actin nucleators are expressed in neuronal cells but surprisingly there is no clear understanding of how or if their activity overlaps in different synaptic sub-domains across time.

METHODS: We used pharmacological and genetic tools to perturb the individual actin nucleators in cultured primary neurons followed by extensive image analysis to identify morphological and functional outcomes.

RESULTS: On the postsynaptic side, our pharmacological approach has revealed that both Arp2/3- and Formin-driven actin polymerization is essential for NMDA dependent spine volume expansion. However inhibiting formins had a greater impact on the pre-synaptic vesicle accumulation while Arp2/3 inhibition led to disorganization of the PSD. We are currently utilizing CRISPR/Cas9 mediated gene-knockout strategy to assess the contributions of individual Formins to the synaptic architecture.

CONCLUSIONS: There are distinct regional differences between the activity of different actin nucleators. While Arp2/3 is likely a dominant nucleator on the postsynaptic side, Formins play a greater role on the presynaptic side. These observations are crucial given that recent genomics studies have identified truncations in formin genes leading to non-syndromic intellectual disability in humans.

FUNDING: This work is funded by NINDS R01NS115469.

# 2021 Neuroscience Retreat abstract submission

The intellectual disability gene DDX3X in sex-specific neuronal morphogenesis

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BACKGROUND: DDX3X syndrome is a rare form of intellectual disability caused by mutations in the DDX3X gene. Most DDX3X mutations are de novo, lead to haploinsufficiency, and are found only in females. The few mutations found in males are inherited from healthy mothers. DDX3X regulates mRNA translation, but the mechanisms of action in neurons, the target genes, and the impact of clinical mutations have not been studied. Also, the influence of sex remains unknown.
METHODS: We generated a mouse with loxP sites around exon 2 of Ddx3x (Ddx3xflox mice). Using this model, we generate male (Ddx3xflox/y) and female (Ddx3xflox/+) cortical neurons and transfect with Cre and mCherry. With this strategy, we can model Ddx3x-haploinsufficient female neurons or Ddx3x-null male neurons (and respective controls). We also introduce sex-specific mutations in female and male neurons, also after manipulating Ddx3x dosage. We then examine morphogenesis, synaptogenesis, and translation of specific mRNAs.
RESULTS: DDX3X contributes to sex differences in neuronal morphogenesis. Sex-specific DDX3X mutations have differential impact, with female-pathogenic mutations being more severe.
CONCLUSIONS: Our data show lay the bases to understand the sex biases in the prevalence and severity DDX3X syndrome.
FUNDING: NIH/NICHD, Seaver Foundation, Fondation pour la recherché medicale.

# 2021 Neuroscience Retreat abstract submission

Cortico-striatal volume changes in human cocaine and heroin addiction

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ISMMS

Background: While all drugs of abuse share dopaminergic targets, differences in neural morphology between psychostimulant and opiate addiction remain largely unresolved. Compared to opiates, psychostimulant use accompanies increased impulsivity (via inferior frontal gyrus [IFG] and dorsolateral prefrontal cortex [dlPFC]) in humans, and, in preclinical models, enhanced cue-extinction (via ventromedial PFC [vmPFC]) and neuroplasticity (via nucleus accumbens [NAcc]). We hypothesized parallel neuroanatomical changes in individuals with cocaine or heroin use disorder (CUD/HUD): specifically, increased NAcc/vmPFC but decreased IFG/dlPFC volumes in CUD vs. HUD.

Methods: Voxel-based morphometry quantified gray matter volume differences via T1-weighted MRI in demographic/IQ-matched individuals with CUD, HUD, and healthy controls (HC; n=20 each).

Results: Overall, supporting prior literature, addicted individuals displayed smaller vmPFC volumes than HC ($p<0.05$-corrected)—an effect driven by HUD ($p<0.05$-corrected; similar NAcc trend, $p=0.051$). Importantly, as hypothesized, there were significant right IFG reductions in CUD vs. HUD ($p<0.05$-corrected); trends for midbrain/NAcc and vmPFC volume increases were further revealed in CUD vs. HUD (uncorrected).

Conclusions: Consistent with the literature, addicted individuals exhibited mesolimbic cortical/sub-cortical compression. IFG compression and NAcc/vmPFC expansion in CUD vs. HUD extend clinical/preclinical findings, offering for the first time a direct contrast between human CUD and HUD neuroanatomy. Overall, results suggest neurobiological conservation across species and mechanistic bases for substance-specific neuropsychological differences in humans, with implications for fine-tuning addiction treatment by primary drug of abuse.

Funding: NIH/NCCIH/NIDA

# 2021 Neuroscience Retreat abstract submission

Clinical and Neuropathological Features of COVID-19 in Pediatric Decedents

Alara Akyatan, Michelle Stram, Etty Cortez, Alan Seifert, John Crary, Rebecca Folkerth, Enna Selmanovic, Kristen Dams-O'Connor

Icahn School of Medicine at Mount Sinai, New York Office of the Chief Medical Examiner

BACKGROUND: Despite evidence that COVID-19 infection presents an increased risk of severe multisystem inflammatory syndrome in children (MIS-C), knowledge of the effects of SARS-CoV-2 on the nervous system at autopsy remains limited. Our aim was to characterize the clinical symptoms and postmortem neuropathology in a convenience sample of pediatric patients with confirmed COVID-19.

METHODS: Pediatric patients who expired following confirmed COVID-19 infection were evaluated as part of a public health surveillance effort in conjunction with the OCME. Clinical data were collected through medical record abstraction. We conducted ex-vivo 3T MRI and image-guided tissue sectioning in addition to standard sections of 22 brain regions. Tissue sections were stained with hematoxylin and eosin/luxol fast blue (H&E/LFB).

RESULTS: We examined 4 cases aged 5-15. Two were obese and had clinical diagnosis of asthma; one had a metabolic disease. Clinical evidence of systemic inflammation was present in all cases. Neuropathological features common across cases included thickening of the leptomeninges and evidence of compromise of microvessel walls, including dilation of perivascular spaces and macrophage infiltrates.

CONCLUSIONS: Postmortem neuropathology is suggestive of vascular disease, in the setting of multiple indicators of inflammatory response. Together with clinical data this series begins to inform the neurological implications of COVID-related MIS-C in children.

FUNDING: NIH/NINDS

# 2021 Neuroscience Retreat abstract submission

Title: Dissociable contributions of protein synthesis to traumatic memory recall and fear sensitization

Authors: Alexa R. LaBanca, Taylor R. Francisco, Zachary T. Pennington, Denise J. Cai

Affiliations: Department of Neuroscience, Mount Sinai

Background: As seen in PTSD patients, traumatic experiences have the ability to produce lasting enhancements in fear and anxiety. However, the extent to which the same regions support fear memory recall and stress sensitization is unknown. Here, we used targeted protein translation inhibitors to investigate this question.

Methods: Anisomycin was infused before/after trauma in either the dorsal hippocampus or basolateral amygdala, regions responsible for associative fear learning. One week later, memory of the traumatic experience was assessed. The next day, subjects were subjected to a loud auditory stimulus in a novel context to assess trauma-induced fear sensitization.

Results: While inhibiting protein synthesis in the dorsal hippocampus or basolateral amygdala disrupted memory of the trauma, subjects surprisingly still expressed fear sensitization, measured by heightened fear of the auditory stimulus. These results demonstrate that protein synthesis in the dorsal hippocampus and basolateral amygdala is required for trauma recall, but not subsequent fear sensitization.

Conclusions: These findings have implications for PTSD treatments aimed at reducing fear of trauma-associated stimuli, as they suggest that even if memory recall of a traumatic event were abolished, patients may still have increased anxiety post-trauma. Moreover, they highlight the need to look beyond canonical memory circuits for PTSD treatment.

Funding: NIMH, NIDA, Klingenstein-Simons Foundation, McKnight Foundation, One Mind Organization, BRF, Botanical Center, Friedman Brain Institute

# 2021 Neuroscience Retreat abstract submission

Characterizing glutamatergic inputs to oxytocin neurons in the hypothalamus

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BACKGROUND: Within the hypothalamus, glutamate influences cell firing and release of oxytocin (OXT), which regulates birth/lactation and social behavior. However, the contribution of glutamatergic inputs from extrahypothalamic brain regions to the hypothalamus has been understudied. We hypothesize that brain regions implicated in sensory processing of social stimuli send glutamatergic inputs to OXT neurons in the paraventricular nucleus (PVN) of the hypothalamus that are important for OXT neural activity and social behavior.

METHODS: To characterize glutamatergic inputs to the PVN in mice we combined viral retrograde tracing with immunohistochemistry for CaMKIIα, a protein kinase largely expressed in excitatory neurons. To further identify specific inputs to PVN-OXT neurons, we utilized a novel modified rabies virus system with specificity to OXT neurons.

RESULTS: We found that several brain regions send glutamatergic inputs to the hypothalamus, and some specifically project to OXT neurons. One region of particular interest is the posterior intralaminar complex of the thalamus, which we found to be activated following social interaction with a novel juvenile.

CONCLUSIONS: Our study identifies several possible glutamate-OXT circuits which will be targeted in our future studies to decipher their role in social behavior.

# 2021 Neuroscience Retreat abstract submission

CELL-TYPE SPECIFIC GENOMICS AND TRANSCRIPTOMICS OF HIV IN THE BRAIN

Plaza-Jennings, A.1, Benxia Hu2, Aditi Valada1, Callan O'Shea1,3, Benjamin K. Chen4, Lotje de Witte1, Hyejung Won2, Susan Morgello5, and Schahram Akbarian1

1Department of Psychiatry, ISMMS; 2UNC Neuroscience Center, UNC School of Medicine; 3Interdepartmental Neuroscience Program, Yale School of Medicine; 4Department of Medicine, ISMMS; 5Department of Neurology, ISMMS

BACKGROUND: Viral integration is a key step in establishing the HIV reservoir. The CNS is a large reservoir site with important functional implications, but integration has yet to be studied in the CNS.

METHODS: Using postmortem cortex of HIV-, HIV+, and HIV encephalitis (HIVE) donors we utilized flourescence activated nuclei sorting to isolate specific cell types and perform either integration site (IS) analysis or Hi-C. Unsorted nuclei were additionally submitted for single nucleus RNA-sequencing (snRNA-seq).

RESULTS: We identified 1,279 IS, predominantly from non-neuronal (NeuN-) nuclei of HIVE cases. NeuN- IS were found preferentially in active, gene dense regions. There was significantly less clonal and recurrent integration and more integration into Alu repeat elements than in T-cells. snRNA-seq of HIV- and HIVE brains revealed that IS are enriched in microglial genes and genes that are differentially expressed in HIVE microglia. Changes in microglial gene expression were accompanied by rewiring of the 3D-genomic landscape as assessed by Hi-C. Futhermore, sites of viral integration had undergone changes in cis-chromosomal contacts.

CONCLUSIONS: These findings link HIVE to changes in microglial gene expression and spatial genome organization that may influence integration site selection.

FUNDING: Supported by NIDA.

# 2021 Neuroscience Retreat abstract submission

Histone serotonylation: a novel regulator of stress-induced neuroplasticity
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Background: The field of neuroepigenetics has recently implicated chromatin phenomena in the etiology of major depressive disorder (MDD). While it has been demonstrated that dysregulation of histone posttranslational modifications may be involved in the deleterious transcriptional processes that promote physiological maladaptations in MDD, the field still has only a limited understanding of the underlying mechanisms contributing to this disorder. Data from our laboratory suggest potential alternative mechanisms of action for monoamines, where the presence of serotonin in the dorsal raphe nucleus (DRN) may directly mediate transcriptional responses related to various forms of serotonergic plasticity, and the subsequent mediation of mood.

Methods: Mice were subjected to chronic social defeat stress (CSDS) and behavioral response was analyzed via social interaction (SI), classified as either stress-susceptible or resilient. Each cohort was 1) sacrificed 48h post-CSDS, 2) subjected to 30 days of fluoxetine vs. water treatment, or 3) underwent viral surgery to block serotonylation. Human tissue were obtained from a brain bank.

Results: We detected a decrease in serotonylation and an enrichment in ubiquitin pathways in MDD patients and male/female mice 48h post-CSDS. Serotonylation levels were significantly increased 30 days post-CSDS, an effect that is reversed with fluoxetine treatment. Blocking serotonylation resulted in significantly higher SI than control groups.

Conclusion: Globally blocking serotonylation in DRN promotes a resilient response to CSDS, and there is an accumulation of serotonylation that promotes a long-term vulnerability to stress, possibly through ubiquitination.

# 2021 Neuroscience Retreat abstract submission

THE IMPACT OF SOCIAL NORMS AND PSYCHIATRIC PROFILE ON DISHONESTY

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BACKGROUND: Social norms are powerful signals guiding decision-making. However, norms' strength varies between scenarios, and people vary in their sensitivity to them. Here, we characterize the influence social norms have on moral decision-making and its relationship with psychiatric traits.

METHODS: We used a Message game, in which participants send either a deceitful (yet profitable) or truthful (and less profitable) message to their partner. Payoffs varied for both players, conflicting one's own benefit with another's loss. After completing a series of choices, participants were presented with social information regarding the choices of others and chose again.

RESULTS: Overall, participants conformed to norms when presented with social information, switching truthful responses to deceitful ones or vice versa. Although overall, conforming to lying was as likely as to truth-telling, participants required a stronger consensus to do so. We also discovered inter-participant variation in conformity: First, extremely honest or dishonest individuals were less likely to conform. Second, individuals high on psychopathy lied more often, and were more likely to conform to lying. Conversely, autistic traits were associated with higher honesty, but no relationship with conformity.

CONCLUSIONS: Using a novel task, we study complex social decision-making, showing individual differences relating to psychiatrically-relevant traits. These findings may help elucidate the normative components of pro- and anti-social behaviors and have broader implications on mental health.

FUNDING: ISMMS

# 2021 Neuroscience Retreat abstract submission

Region-specific microglial responses to peripheral influenza infection

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Departments of Immunology, Microbiology, and Neuroscience, ISMMS

BACKGROUND: Microglia, the tissue-resident macrophages of the CNS, are important regulators of neuronal activity through their dynamic surveillance of neuronal health. These highly responsive cells are not only activated by local cues such as tissue damage and injury, but also by distant insults to tissue homeostasis such as peripheral inflammation. While microglia play a key role in debris removal and tissue repair during local injury, the nature and functional consequences of their activation in response to peripheral infections is unclear. We propose that microglia sense peripheral inflammation in order to convey this information to neurons and to modulate region-specific neuronal circuits, acutely influencing sickness behaviors associated with infections.

METHODS: We comprehensively characterized immune and behavioral responses to a physiological model of peripheral infection using a sublethal challenge with mouse-adapted influenza A virus. Using TRAP-seq, we performed cell-type specific transcriptional profiling of microglia at different timepoints following influenza infection.

RESULTS & CONCLUSIONS: We observed that microglia respond early and in a region-specific manner following peripheral infection. We plan to test the contributions of region-specific microglia populations using microglial depletion models developed in the lab. We also identified important transcriptional networks and responses and microglia and in other CNS cell types, and we will test their function using genetic knockout mouse models.

FUNDING: NIAID, NIH

# 2021 Neuroscience Retreat abstract submission

The impact of social stress on approach-avoidance behaviors

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BACKGROUND:  Healthy individuals balance their decisions towards the most favorable outcomes under approach-avoidance scenarios. However, depressed individuals display deficits in these decision-making processes. Here, we adapted a novel platform-mediated avoidance (PMA) task to assess decision-making under approach-avoidance conflict in mice previously exposed to chronic social defeat stress (CSDS).

METHODS: CSDS mice were classified as resilient (RES) or susceptible (SUS) based on their social interaction. Subsequently, they were trained in the PMA task whereby they learn to avoid a tone-signaled shock, at the cost of losing access to a saccharine-water reward. Time on platform and lever presses were recorded as avoidance and approach learning, respectively. After ten days of acquisition, mice underwent four days of extinction training (no shocks).

RESULTS: While we did not observe significant differences in the acquisition of avoidance or pressing among groups, we found that RES mice show reduced time on platform and increased lever pressing, suggesting facilitation of extinction learning. In contrast, SUS mice show elevated avoidance and reduced lever pressing.

CONCLUSIONS: Together, our results suggest that RES mice balance their behavior towards approach when contingencies change (i.e., extinction), whereas SUS mice balance their behavior towards avoidance. This is consistent with growing evidence suggesting that resilience is not the absence of susceptibility, but rather an active response to stress involving a unique phenotype which might reveal novel neurobiological markers to treat depression.

FUNDING: NIMH

# 2021 Neuroscience Retreat abstract submission

Influence of immunity on tumor hypoxia and hypoxia-induced immunosuppression during glioblastoma progression

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Background: Glioblastoma (GBM) is the most lethal brain cancer. Hypoxia (low oxygen) within cancers, especially GBM, is linked to worse patient outcome.

Method: We tracked tumor hypoxia in intracranial GBM transplant models (in mice) with GBM cells that we had engineered with a fluorescent hypoxia reporter protein. We performed single-cell RNA sequencing to understand the molecular changes in hypoxic GBM cells. We also analyzed virally-induced autochthonous GBM tumors to reveal the relationship between tumor hypoxia and immunity.

Results: We found that hypoxic GBM cells showed NF-kB cytoplasmic retention and expressed many anti-inflammatory cytokines and factors that influence chemotaxis of tumor-associated microglia/macrophages (TAMs). Conversely, attenuated cancer immunity in GBM-bearing hosts with immunodeficiency or IL1β-deletion greatly reduced hypoxia. Strikingly, in immunocompetent hosts, hypoxic GBM cells displayed a spatiotemporal transition into pseudo-palisading patterns, coinciding with influx and gradual confinement of CD68+ TAMs and CD8+ cytotoxic T cells in hypoxic zones, thus likely contributing to hypoxia-induced immunosuppression by limiting inflammatory spread.

Conclusion: Contrary to the model that hypoxia arises solely from insufficient angiogenesis, we identified cancer immunity as a driving force of hypoxia in GBM. We also found that sequestering of immune cells into necrotic areas is an active process by hypoxic GBM cells.

Funding: NIH R01

# 2021 Neuroscience Retreat abstract submission

Hippocampal somatostatin interneurons implicated in fear extinction memory retrieval

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Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai

BACKGROUND: Fear extinction is a process where defensive responses to a conditioned stimulus diminish when the stimulus no longer predicts a threat. While plasticity in prefrontal-hippocampal-amygdala circuits has been implicated in extinction learning, much less is known about the mechanisms of extinction retrieval.

METHODS: We first identified brain regions associated with extinction retrieval by mapping expression of the activity-related gene c-Fos in mice retrieving a contextual fear extinction memory. Once areas and cell-types exclusively activated by extinction retrieval were identified, we combined intersectional activity-dependent tagging and projection-specific optogenetic silencing to investigate their role in memory.

RESULTS: We found that both fear and extinction retrieval similarly engaged many cortical, hippocampal, and thalamic regions. However, extinction retrieval was associated with elevated c-Fos expression in the stratum oriens layer of ventral hippocampal area CA1 (vCA1), which occurred predominantly in interneurons co-expressing somatostatin (SST-INs). An extinction-specific recruitment of SST-INs in vCA1 was confirmed using an intersectional genetic strategy to tag SST-INs active during fear conditioning or extinction retrieval. Additionally, silencing excitatory projections from vCA1 to prelimbic medial prefrontal cortex or basolateral amygdala did not affect fear retrieval but prevented extinction retrieval.

CONCLUSIONS: Our results suggest extinction retrieval may be mediated by activity in vCA1 SST-INs, which could regulate the output of particular hippocampal ensembles projecting to cortical and amygdalar regions.

FUNDING: NIH

# 2021 Neuroscience Retreat abstract submission

TITLE: Interaction between decision-making and interoceptive representations of bodily arousal in frontal cortex

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AFFILIATIONS: (1) Icahn School of Medicine at Mount Sinai (2) National Institute of Mental Health

BACKGROUND: How bodily arousal states influence decision-making has been a central question in psychology, but the neural mechanisms are unclear.

METHODS: We recorded heart rate, a measure of bodily arousal, while simultaneously monitoring neural activity in orbitofrontal cortex (OFC) and dorsal anterior cingulate cortex (dACC) of macaques making reward-guided decisions.

RESULTS: In intact macaques higher HR was associated with shorter reaction times. Concurrently, the activity of a set of neurons in OFC and dACC selectively encoded HR. Following amygdala lesions, HR generally increased and now the relationship between HR and reaction times was reversed. At the neural level, the balance of encoding in dACC shifted towards signaling HR.

CONCLUSIONS: Taken together, the present results provide insight into how bodily arousal and decision-making are signaled in frontal cortex. Our findings may shed light on the neural mechanisms underlying some psychiatric disorders linked to amygdala dysfunction that are characterized by heightened arousal and deficits in decision-making.

FUNDING: NIH, BBRF, Takeda Science Foundation

# 2021 Neuroscience Retreat abstract submission

Gut-Derived Acetate in Autism-Related Behaviors
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Background:  Signaling via microbially produced Short Chain Fatty Acid (SCFA) acetate is a possible mechanism linking
gut microbiome with Autism Spectrum Disorder (ASD). Here, we combined antibiotic (Abx) depletion of the microbiome with acetate supplementation in a Shank3KO model of ASD. Biological samples from Phelan McDermid Syndrome (PMS) patients, hemizygous for the Shank3 gene were also analyzed.

Methods: Shank3KO mice and wild-type (Wt) littermates were treated with Abx, acetate or acetate + Abx from weaning. On postnatal day 60, behavioral testing using three-chambered social interaction and open field was conducted. Caecal content was collected for 16S sequencing and metabolomic profiling and medial prefrontal cortex (mPFC) for gene expression profiling and western blot analysis. Targeted SCFA analysis on PMS patients and control serum was conducted.

Results: Shank3KO alters microbiome composition and levels of acetate – effects exacerbated by Abx. Behaviorally, control KO mice displayed decreased social interaction, an Abx exacerbated deficit. RNA-sequencing showed marked gene expression changes in Abx KO mice compared to Wt, while western blot analysis demonstrated altered histone acetylation in mPFC of Abx KO mice. Acetate or Abx + acetate in KO animals reversed social deficits and acetylation of specific histone marks. Clinical data revealed sex specific alterations in acetate levels, inversely correlated with behavior.

Conclusions: Acetate supplementation in Shank3KO mice 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.
Funding: Seaver Family Foundation

# 2021 Neuroscience Retreat abstract submission

Altered striatal-dependent learning in mice expressing a single point mutation associated with Parkinson's Disease

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BACKGROUND: Parkinson's disease (PD) is diagnosed clinically by motor symptoms, but non-motor cognitive symptoms (deficits in executive processes controlling goal-directed behavior and attention) are prevalent and can manifest earlier in the disease. The LRRK2-G2019S mutation is a major genetic cause of late-onset PD. LRRK2 is enriched in striatum and cortex, with onset of expression that parallels postnatal corticostriatal development. We have previously established that G2019S alters baseline properties of corticostriatal synapses by 3 postnatal weeks, while striatal projection neurons are unable to express LTP. The early postnatal onset of such synaptic abnormalities suggests that circuit-dependent cognitive functions would be impaired later in life.

METHODS: To test this, we compared the performance of adult WT and G2019S knockin mice in goal-directed learning or the 5-choice serial reaction time task (5CSRTT) of attention.

RESULTS: The data show a significant deficit in goal-directed learning in mutants that could not be attributed to differences in motivation since their progressive ratio breakpoint was similar to WT. Additionally, mutant mice showed a deficit in sustained attention when required to respond to randomized, short stimulus durations.

CONCLUSIONS: These data suggest that early and persistent alterations in corticostriatal synaptic plasticity may significantly impair goal-directed action-outcome associations and attention in young adulthood, which may contribute to non-motor cognitive symptoms in PD.

FUNDING: NIH, NSF

# 2021 Neuroscience Retreat abstract submission

Analyzing the role of ethnicity in the treatments of schizophrenia and depression

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Background:In healthcare, there are many disparities in the treatment of patients of color, including mental health treatment. African Americans have higher rates of diagnosis of schizophrenia and psychotic disorders. Treatments of the same illness can vary greatly based on patients' characteristics and symptoms, and the clinician. We aim to examine the variations in the treatment of schizophrenia and depression across patients of different ethnicities.

Methods:We will collect patient data from the Mount Sinai Hospital System. We will analyze differences in the treatments of schizophrenia and depression among patients of different ethnicities. Data will be analyzed utilizing R software. The requested data is separated into three categories: Individual-level demographics, clinical data and pharmaceutical data.

Results:We will use ordinal regression models to test self-reported race as a predictor of the types of medication prescribed for both illnesses. We expect a higher amount of first-generation antipsychotics in non-white patients compared to white Americans. Linear regression models will be used to test race as a predictor for medication dosages. If patients of color are over-diagnosed with schizophrenia, we expect lower dosages of respective medications. We will control for covariates such as age, gender, and comorbidities.

# 2021 Neuroscience Retreat abstract submission

Gross Motor Profile of Children and Adolescents with DDX3X Syndrome

Lerman, B., Levy, T., Tang, L., Frank, Y., Halpern, D., Zweifach, J., Foss-Feig, J.H., Siper, P.M., Grice, D.E.

BACKGROUND: DDX3X syndrome is a rare genetic disorder associated with intellectual disability, developmental delays, autism spectrum disorder, and various medical comorbidities. The motor phenotype in individuals with DDX3X syndrome has yet to be comprehensively examined.

METHODS: 24 individuals (23 female) with DDX3X syndrome, ages 3-16yrs (7.97±3.94) participated. Motor milestones, gait ratings, and standardized gross motor testing were obtained. The cohort was divided by: (i) protein-truncating variants (PTV; nonsense, frameshift, splice site) or (ii) missense (including in-frame deletions), and exploratory associations were assessed.

RESULTS: Motor milestones were delayed in 91.3% for sitting, 91.7% crawling, and 95.8% walking. Average age of first walking was 24.9 months. Three participants could not walk independently (ages 5-6yrs). Gait abnormalities were present in 95%, as measured by neurological exam. Ataxic/wide-based gait (29.2%) and toe-walking (20.8%) were most common. Average Vineland-3 gross motor subdomain scores fell 2-3 standard deviations below the population mean. The missense group was less likely to walk independently (p=0.028) and showed greater gross motor deficits (p=0.033) than the PTV group.

CONCLUSIONS: The DDX3X syndrome motor phenotype is characterized by delays in the attainment of early motor milestones and continued gross motor delays throughout childhood and adolescence. Gait abnormalities were present in the majority of participants. Those with missense variants displayed a more severe motor phenotype compared to those with PTV variants.

FUNDING: Seaver Foundation.

# 2021 Neuroscience Retreat abstract submission

Genetic modifiers of Alzheimer's risk conferred by age, sex and APOE genotype

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Background: The main predictors of sporadic Alzheimer's Disease (AD) are age, sex and the APOE locus. Although there are several large case-control genome-wide association studies (GWAS) of AD risk, none have explored genetic modifiers of age, sex and APOE risk. We have undertaken this modifier GWAS, which has the potential to identify novel loci that could lead to drug targets for the prevention of AD.

Methods: Using data from the Alzheimer's Disease Genetics Consortium (ADGC), we have generated a Kaplan-Meier survival model for AD, stratified by sex and APOE genotype, which we use to generate risk priors for each individual. This prior is the phenotype in a control-only GWAS. Controls with a low prior are presumed to have low burden of protective genetic modifiers, and controls with a high prior are presumed to have high burden of protective genetic modifiers. Significant loci are protective against AD.

Results: We have generated GWAS results in ADGC (N=11,768), the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study (N=3055), and in multiple member studies of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium (N>12,207). There are 27 suggestive loci (P<1e-5) in ADGC and A4 with minimal inflation. We will present results of the full meta-analysis.

Conclusions: The loci identified in this study are potential novel targets for therapeutic intervention.

Funding: JPB Foundation 0266-A409

# 2021 Neuroscience Retreat abstract submission

Resilience versus susceptibility to stress differentially alters two distinct forms of regret in mice

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BACKGROUND: Regret describes the phenomenon in which individuals recognize that alternative actions could have led to better outcomes. Regret-related behavioral and neurophysiological processes have only recently been discovered in rodents using a novel neuroeconomic decision-making paradigm, termed “Restaurant-Row.” Animal models of depression have yet to capture higher-order affective processes observed in humans struggling with emotional dysregulation.

METHODS: Following exposure to chronic social-defeat stress, a well-established model for depression, we separated 32 male C57BL/6J mice into non-defeated, defeated-susceptible, and defeated-resilient phenotypes defined by a post-stress social-interaction test and then assessed them on Restaurant-Row. Mice foraged for their sole source of food with varying delays (1-30s cued by tone pitch) while on a limited time-budget (60min).

RESULTS: We found that individual differences in response to stress relate to unique ways in how mice react to distinct economically disadvantageous scenarios. Stress-susceptible mice were uniquely sensitive to opportunity costs following risky decisions with poor outcomes (skipping a low-cost offer followed by a high-cost offer), whereas stress-resilient mice were hypersensitive to change-of-mind decisions when correcting past mistakes (quitting while waiting after rapidly accepting a high-cost offer).

CONCLUSIONS: These data reveal behavioral insights into how distinct forms of counterfactual thinking and emotion-cognition interactions are related to adaptive versus maladaptive stress responses.

FUNDING: NIMH, Friedman Brain Institute

# 2021 Neuroscience Retreat abstract submission

Effect of Different Carbohydrate Diets on Islets and Nerve Populations in Murine Pancreas

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Background: Many diet induced diseases affect millions of people, namely diabetes. The effect of diet composition on the physical structure of the pancreas is unknown. Here we take a look at the islets and neurons of the pancreas in mice in relation to diets made of different portions of carbohydrates.

Methods: 18 mice were fed a baseline diet (40% carbohydrate) for 1 week and were then split into 3 groups (n=6/group). One group had a low carbohydrate diet (2%), one continued the normal diet (40% carbohydrate) and one had a high carbohydrate diet (80%) for 2 weeks. Their pancreas samples were cleared using iDisco+ and stained for insulin to identify islets and for neurofilament 200 to identify nerves. These samples were imaged using a confocal microscope and analyzed using Imaris.

Results: There is significant increase in exocrine nerve volume and in islet density. There is no significance between islet size and insulin intensity.

Conclusions: The results show changes in islet and nerve makeup. There should be more insight on the long term effects and the holistic lifestyle of people since many factors go into metabolism.

Funding: NIH, ADA

# 2021 Neuroscience Retreat abstract submission

Blood-borne regulation of microglial function in aged hippocampus

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The brain exhibits diminished functioning 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 lessen the impact of risk factors for the disorder. Emerging evidence revealed rejuvenation of the CNS by exposure to young blood factors, raising the possibility that CNS function can be restored or improved by targeting pathways in the systemic environment. No studies have yet evaluated how microglia serve as sensors for youth-associated plasma factors to alter functional states in the context of aging or AD. Using a heterochronic parabiosis model, 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. Transcriptomic differences were observed between primary microglia from TIMP2 KO and WT mice by RNA-seq, suggesting that TIMP2 may be important for normal microglial functioning. Our current results argue that microglia are responsive to youth-associated plasma proteins and may regulate aging-relevant phenotypes. Characterization of blood-CNS communication facilitate development of therapies to target detrimental aging processes to limit AD onset.

NIA/NIH-R01AG061382, BrightFocusFoundation, Katz-MartinFBIScholarAward

# 2021 Neuroscience Retreat abstract submission

Fine mapping and characterization of neurological disease-associated regulatory elements human neurons

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MSSM

Disorders of the brain affect nearly one-fifth of the world's population. Although genome-wide association studies have identified many genetic variants strongly linked to psychiatric disorders, functional interpretation is challenging. Most common disease risk distributes to non-coding regions. Besides, evidence indicates that dysregulation of neuronal activity-regulated gene transcription may contribute to the molecular basis of autism and schizophrenia. However, activity-regulated enhancers that control this program are not possible to identify from post-mortem tissue. Here, we used homogeneous human neurons generated from pluripotent stem cells and characterized functionally distinct cis-regulatory elements (CREs) in two neuronal types tightly associated with neuropsychiatric disorders - the glutamatergic excitatory neurons and GABAergic inhibitory neurons at resting state and after membrane depolarization based on biochemical modifications. We determined the impact of disease-associated enhancers on gene expression and activity-dependent neuronal signaling networks by combining whole transcriptomic analysis (RNA-seq) with epigenomics and chromatin landscape analysis (ATAC-seq and CUT&RUN). We observed that disease risk genes can be differentially expressed or regulated by activity in different neuronal types and the neuronal CREs are enriched for genomic variants of multiple psychiatric disorders. These observations underscore the cell-type-specific expression and regulation of disease-associated genes and the importance of interrogating the activity-dependent transcriptional regulation in different disease relevant cell types. Moreover, our data will enable improved fine mapping of disease-associated variants within CREs and lay the foundation for future work to uncover new aspects of human gene regulation in diseases.

NIH

# 2021 Neuroscience Retreat abstract submission

Behavioral variability in response to chronic stress and morphine in BXD and parental mouse lines

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Background: Drug addiction is a multifactorial syndrome in which genetic predisposition and environmental stress constitute major risk factors for early onset, escalation and relapse of addictive behaviors. While it is well-known that both social and non-social stressors play a key role in drug addiction, the genetic factors that make certain individuals particularly sensitive to stress and thereby more vulnerable to addiction are unknown.

Methods: In an effort to map a complex set of G x E interactions, specifically Gene x Chronic Stress, here we leveraged a systems genetics resource—BXD recombinant inbred mice and C57BL/6J and DBA/2J parental lines— and investigated their vulnerability to prolonged exposure to social or non-social stressors and subsequent drug exposure.

Results: We first show that DBA/2J and BXD22 male and female mice are more susceptible to chronic social and non-social stressors than C57BL/6J mice. Further, we observe sexual dimorphism in response to stress amongst the BXD lines tested. Finally, we identify that DBA/2J and C57BL/6J mice pre-exposed to prolonged stress displayed differences in morphine sensitivity.

Conclusions: Our results support the hypothesis that genetic variations in predispositions to stress responses influence sensitivity to drugs of abuse, specifically morphine. Characterization of the genetic, neurobiological and environmental factors that mediate addiction risk will fundamentally provide highly useful information for the development of new treatments.

Funding: NIH, NIDA

# 2021 Neuroscience Retreat abstract submission

Generating and Testing Signature Matrices for Mouse Brain Cell Types and Use with CIBERSORTx

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Background: Gene Expression Omnibus (GEO) and Sequence Read Archive (SRA) are databases of raw or processed genetic data. Much of the murine brain RNA datasets available are bulk RNA-seq instead of single cell RNA-seq. The goal is to assess the relative contribution of each brain based cell type in preexisting murine brain RNA-seq datasets.

Methods: We used the NGS Data Charmer to process murine brain RNA-seq data from GEO and SRA and to perform quality control. We then differentiated individual cell types of the murine brain RNA-seq data using CIBERSORTx. CIBERSORTx is a tool which uses machine learning to generate signature matrices and impute cell fractions of given mixture files using those signature matrices.

Results: We were able to use CIBERSORTx to perform in silico deconvolution of bulk RNA-seq samples into different neuronal cell types such as oligodendrocyte, astrocyte, and endothelial cells.

Conclusions: The preliminary samples used suggest that CIBERSORTx, along with the use of appropriate signature matrices, can effectively perform in silico deconvolution of bulk brain RNA-seq samples into its constituent cell types.

# 2021 Neuroscience Retreat abstract submission

TIMP2 regulates hippocampus-dependent cognitive function

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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 LTP, yet its mechanism of action and how it 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 expression is largely restricted to hilar mossy cells, and its deletion alters hippocampi expression in genes related to synapse organization, memory, and neurogenesis. TIMP2KO mice exhibit altered DG granule cell intrinsic membrane properties, increased gliosis, and reduced hippocampal neurogenesis with concomitant impaired hippocampus-dependent cognition. TIMP2KO hippocampi display altered levels of TIMP2's target MMP2, suggesting that it may exert its role through extracellular matrix regulation. Finally, peripheral and hippocampal TIMP2 levels were reduced in mouse models of AD pathology, phenocopying deficits observed in aging and suggesting interactions with pathology. Together with new tools we developed, these data will 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 Friedman Brain Institute Scholar Award

# 2021 Neuroscience Retreat abstract submission

Chemogenetic silencing of amygdala alters resting state functional connectivity in macaques

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Functional connectivity measures are widespread in human neuroimaging where they have been used to discern brain connectivity in health and disease. To specifically probe the neural basis of functional connectivity, 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. We injected inhibitory DREADD construct AAV5-SYN1-hM4Di-HA bilaterally into the amygdala in three rhesus macaques (concentration 1.7*1013 GC/ml, 18μl per hemisphere). We systemically administered DREADD activating ligand deschloroclozapine (DCZ, 0.1mg/kg IV, 1ml; Nagai et al. 2019) or vehicle (1ml IV) during resting state fMRI. Whole brain functional images were acquired on a Siemens MAGNETOM Skyra 3T scanner (TR/TE 2100/16ms, voxel size 1.6x1.6x1.6mm). Injections of DCZ altered the pattern of functional connectivity seen after vehicle injection; using bilateral amygdala as a region of interest, we observed altered connectivity with prefrontal cortex and insula ($p < 0.05$, clustered at >10 voxels). These findings show a direct link between neural activity and functional connectivity. Further experiments will assess how inactivating amygdala efferent pathways alters functional connectivity in specific circuits.

Funding: NIH

# 2021 Neuroscience Retreat abstract submission

Automated Model for Detecting Differences Between Females and Males in Aggressive Behavior

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*equal contribution

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Background: Female aggression in mice is understudied relative to males. Manually scoring behavior is notoriously tedious, subjective, and error-prone, thus limiting experimental capabilities. This deficiency emphasizes the need to study female aggression more broadly and develop an automated behavioral scoring model.

Methods: Data were collected from 5-minute resident-intruder test trials using male CD-1 resident and female Swiss Webster resident mice, paired with C57BL/6 intruder mice. We manually scored behaviors in resident and intruder mice, then created a computer model to automate behavior scoring by implementing manual scoring results from JWatcher into DeepLabCut and Simple Behavioral Analysis (SimBA).

Results: Manual scoring results revealed differences in aggression between male and female mice, with females displaying less aggressive behavior than males. Further analysis revealed a strong positive correlation between male, but not female, resident aggression and intruder response behaviors. The SimBA model supported this result.

Conclusions: Studying female aggression unveils sex differences in aggression highlighting the importance of examining aggressive behaviors in both sexes. This preclinical model can be applied to other experiments and studies, such as social reward-seeking behavior and the study of neural circuits related to aggression.

Funding: NIMH

# 2021 Neuroscience Retreat abstract submission

Vagal tone mediates the effects of maternal prenatal anxiety on child anxiety at 5-years-old

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Queens College, CUNY1, Icahn School of Medicine at Mount Sinai2

Background:
Previous research indicates that in-utero exposure to maternal anxiety has consequences on child mental health. However, the mechanism of action underlying this association is still elusive. This study tests autonomic modulation (vagal tone) as a possible mechanism of action.

Method:
A longitudinal study of mother-child dyads measured maternal anxiety during the second trimester of pregnancy (self-reported via STAI-S) and subsequent child anxiety (maternal-reported via BASC-II) and vagal tone (high frequency band of HRV power spectrum) at 5-years-old. Mediation analysis was conducted to test whether child vagal tone mediates the relationship between prenatal anxiety and child anxiety.

Results:
Prenatal anxiety was a significant predictor for vagal tone ($\beta$=-0.009, $p<0.001$) and child anxiety ($\beta$=-0.009, $p=0.002$). Vagal tone predicted child anxiety accounting for prenatal anxiety ($\beta$=-4.7441, $p=0.026$). After controlling for vagal tone, prenatal anxiety was no longer associated with child anxiety ($\beta$=0.0753, $p=0.148$). Mediation analysis using bootstrapping procedure revealed that vagal tone mediated the relationship between prenatal anxiety and child anxiety ($\beta$=0.044, 95% CI [0.007, 0.085], $p<0.05$).

Conclusions:
Results indicate that in-utero exposure to maternal anxiety influences the child's autonomic nervous system development. Importantly, changes in vagal tone from prenatal anxiety is driving the relationship between prenatal anxiety and child anxiety. Autonomic markers can contribute to a multidimensional model to identify children at risk for subsequent anxiety.

Funding: NIMH

# 2021 Neuroscience Retreat abstract submission

Altered synaptic and intrinsic membrane properties associated with Parkinson's disease LRRK2-G2019S mutation following acute stress

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1Nash Family Department of Neuroscience at Mount Sinai

The G2019S-mutation in the LRRK2 gene is the most common genetic cause of late-onset Parkinson's Disease (PD) and is prevalent in idiopathic PD patients. PD is associated with cognitive and psychiatric (depression) non-motor symptoms that appear early, are independent of dopamine neuron loss and are poorly understood. The risk for both PD and depression is increased by stress. To probe the relationship between PD mutation, stress, and neural circuits, we examined synaptic function in the nucleus accumbens an area enriched in LRRK2 and known to regulate stress and depression-like responses-from wildtype (WT) and G2019S mice following acute stress. We subjected G2019S and WT mice to either acute social defeat stress or variable stress, then probed for behaviorally driven adaptations in cellular and/or synaptic plasticity. Stressed G2019S-mice displayed behavioral differences in comparison with WT mice, along with underlying synaptic and intrinsic excitability differences. These data suggest that mice expressing G2019S mount entirely distinct behavioral and adaptive cellular plasticity responses to acute stress. Ongoing experiments target identifying dysregulated circuits mediating these alterations, alongside mechanisms regulating trafficking of relevant glutamate receptors and membrane channels. Ultimately the data may reveal novel targets for ameliorating mood-related and cognitive symptoms associated with PD.

Funding: R01NS107512,T32MH087004

# 2021 Neuroscience Retreat abstract submission

Plexin-B2 regulates migratory plasticity of glioblastoma cells in a 3D-printed micropattern device

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Affiliation: ISMMS

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 gain invasiveness are unclear. As tumor cells frequently usurp developmental pathways, we suggest that the Plexin axon guidance receptors may regulate GBM invasiveness.

Method: In a collaboration with Azeloglu Lab at Mount Sinai, we have established a novel in vitro paradigm that utilizes a 3D-printed micro-grid pattern to investigate the capability of GBM cells to move when they are physically confined in a small space with narrow exit channels.

Results: Wild-type GBM cells showed very active locomotion and constantly extend cellular processes to probe gateways. These cells also demonstrate propensity to squeeze through the narrow gateways by nuclear translocation (nucleokinesis). During the saltatory movement, GBM cells accumulate high concentrations of F-actin at the rear, driving posterior cell contractility to squeeze the nucleus through narrow gateways. In contrast, Plexin-B2 knockout cells failed to ‘infiltrate’ through narrow gateways. Intriguingly, cells overexpressing Plexin-B2 showed reduced propensity to extend cellular processes and high contractile projections of cell membrane (blebs).

Conclusion: Plexin-B2 provides biomechanical plasticity and regulates the cytoskeletal dynamics for GBMs facing the challenge of negotiating through tight spaces in a 3D-printed micropattern device.

Funding: NIH-NINDS.

# 2021 Neuroscience Retreat abstract submission

Phosphodiesterase 1b is an Upstream Regulator of a Gene Network in the Nucleus Accumbens Driving Addiction-Like Behaviors

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Background: Cocaine use disorder (CUD) is a serious public health issue with no effective pharmacotherapies. Treatments for CUD are hindered in part by an incomplete understanding of the coordinated changes in gene expression that drive addiction-like behaviors.

Methods: We conducted gene network analysis on a published RNA sequencing dataset from 6 brain regions of animals that underwent cocaine self-administration. We ranked gene modules by their fold enrichment in genes whose expression is correlated with the “Addiction Index” (AI) ¬– a composite score developed by machine learning to capture maladaptive, addiction-like behaviors during cocaine self-administration.

Results: We identify phosphodiesterase 1b (Pde1b), a Ca2+/calmodulin-dependent enzyme that catalyzes hydrolysis of cAMP and cGMP, as the strongest regulator of a gene network in the nucleus accumbens (NAc) that shows the highest enrichment in AI-associated genes of all gene modules in this region. Our data demonstrate that chronic cocaine regulates Pde1b expression in the NAc and that Pde1b overexpression potentiates the locomotor response to cocaine.

Conclusions: To further investigate the role Pde1b in regulating addition-like behaviors, we will overexpress Pde1b in the NAc and perform conditioned place preference and self-administration for cocaine. This work may present a novel therapeutic target for the treatment of CUD.

# 2021 Neuroscience Retreat abstract submission

Circadian clock drives axon growth in neuroregeneration

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Circadian rhythm impacts cell renewal in regenerating tissues such as liver, pancreas, yet its contribution to regeneration of post-mitotic neurons is currently unknown. Here, we show that peripheral sensory neurons display circadian rhythmicity in intrinsic regeneration capacity, peaking in the active phase and troughing in the resting phase. Active phase is associated with injury independent induction of TET3 and global 5hMC. Injury in the resting phase upregulated global 5hMC marks, while injury in the active phase maintained 5hMC levels. Unbiased analysis of TF binding sites in regeneration associated DhMRs identified enrichment of circadian clock components, supported by evidence of physical interaction between TET3 and BMAL1. Pathway enrichment analysis of circadian regulated DhMRs implicated cAMP and CREB1 signaling. Analysis of CREB1 phosphorylation revealed injury independent circadian regulation peaking in the active phase. Phospho-CREB was maintained after active phase injury, but not induced after resting phase injury suggesting diurnal differences in injury induced DhMRs. Finally, Bmal1 knockdown impaired axon growth of hESC-induced sensory neurons after replating injury. Our data unveil a novel role for the circadian clock in gating DNA hydroxymethylation in neuroregeneration and indicate that circadian timing of injury has broad impact on the injury response and regeneration of adult neurons.

# 2021 Neuroscience Retreat abstract submission

A Map for Goals in the Human Brain

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Center for Computational Psychiatry

Often in different psychiatric disorders there is an impairment in goal setting. For example in addiction, there is an extreme focus on a certain goal (drug seeking) at the cost of other goals (job, family) and in depression apathy towards setting any goals for the future. Yet, we do not know how the brain encodes future goals more broadly. In this project we explore whether the hippocampus creates a cognitive map of goals, mapped based on their relevance and the time left to achieve them. We hypothesized that we would observe increasingly anterior activation as the temporal distance to a goal lengthened. To test this, we sent participants on a 'Mission to Mars' during 7.0T fMRI (n=31). While on Mars, participants kept track of goals that they needed to accomplish in the current Mars' year, in the near future, in the distant future, and goals that they had already accomplished. We found evidence for a temporal gradient in the left hippocampus, where current goals activated the medial and mental time traveling goals (i.e. past/future goals) activated the anterior sub-region of the hippocampus. Whole brain analyses further revealed a dissociation, with time traveling goals activating frontal and current goals activating posterior regions of the brain. Multi-voxel pattern analyses are ongoing to more resolutely examine how the brain maintains an updated representation of a goal's temporal proximity.

# 2021 Neuroscience Retreat abstract submission

Title: AI Analysis of Visual Fields in Optic Nerve Disorders Reveals Unrecognized Deficits and Predictions

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Affiliations:
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Background: AI has exploded as a method to evaluate medical images for diagnosing. Recent studies show AI is useful to monitor visual field (VF) deterioration of glaucoma but it has not been utilized to study non-glaucomatous optic neuropathies, which in contrast to glaucoma, often fluctuate, worsen and improve.

Methods: We used archetype analysis (AA), a form of unsupervised machine learning, to prospective treatment trial datasets, on optic neuritis (ON) and papilledema (IIH). Wegenerated 2 sets of disease specific archetypes (ATs, quantitative patterns), such that every VF within the dataset could be described as weighted sum of its component ATs (total=1.0). We compared resulting ATs to conventional study measures for treatment effects and outcomes.

Results: For 3892 VFs for ON and 2862 VFs for papilledema, AA showed AT patterns typical for each disorder, but AA showed additional regions of dysfunction not recognized in the trial datasets. Changes in the AT weighting reflected improvement and worsening. For IIH, AA identified treatment failures. Select baseline AT weights were associated with visual outcome and treatment benefit. AA showed residual VF loss in eyes considered normal at each study outcome.

Conclusion: Archetype weighting changes accurately reflect treatment failure, and improvement. AA revealed unrecognized residual optic neuropathy in both disorders. AA identifies quantifiable, disease-specific VF defects.
Funding: NYEEI FDN

# 2021 Neuroscience Retreat abstract submission

DK-AH-269 Analogs Inhibit Ih Current and Reduce Firing Rate of VTA Dopamine Neurons

Emily Teichman, Jianping Hu, Romain Durand, Scott Russo, Jian Jin, Ming-Hu Han

Background: Depression is a devastating disease, associated with a variety of neurotransmitter and neurophysiological alterations. Previous studies have shown that Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel upregulation in ventral tegmental area (VTA) dopamine neurons is associated with depressive-like symptomology in mice, and that the inhibition of these channels by DK-AH-269 can alleviate those symptoms.

Methods: In an attempt to improve inhibition efficacy, 12 analogs of HCN inhibitor DK-AH 269 (also known as cilobradine) 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 DK-AH 269. Compounds 10 and 12 were chosen for further study based on their strong inhibition of Ih. DK-AH 269 caused a 66% reduction in firing rate of VTA dopamine neurons, while compounds 10 and 12 led to 91.5% and 92.4% reductions, respectively.

Conclusions: Our results demonstrate that minimal changes to the DK-AH-269 scaffold can alter, and even improve, its inhibitory effect on VTA dopamine neurons. Our results also characterize the use of local, extended application of compounds in slice electrophysiology.

Funding: Supported by Pharmacology T32 grant

# 2021 Neuroscience Retreat abstract submission

Clinical and Neuropathological presentation of Lewy body pathology

Enna Selmanovic et al.

Icahn School of Medicine at Mount Sinai, NY Office of the Chief Medical Examiner

There is growing scientific interest in the associations of single traumatic brain injury (TBI) and/or repetitive head injury (RHI) with neurodegenerative disease. Epidemiological studies suggest particular risk for Lewy body disease and associated α-synucleinopathies, but few detailed case studies exist.

We report in-vivo clinical and ex-vivo multimodal autopsy data for 2 cases from the Late Effects of TBI (LETBI) project. Clinical data were collected through record abstraction and/or interview. Postmortem data include ex-vivo 3T MRI and image-guided brain dissection followed by a network-based sampling protocol. Tissue sections were stained with hematoxylin and eosin/luxol fast blue (LHE) and Bielschowsky. Paired helical filament (PHF) tau, (AT8) TDP43, α-synuclein, β-amyloid (4G8) were performed on select regions.

Case 1 is a 46 y.o male with RHI +2 mild TBIs; gross pathology was unremarkable but microscopy reveals limbic Lewy body disease with secondary hypoxic-ischemic encephalopathy and cerebrovascular disease. Case 2 is a 69 y.o male with 1 severe TBI +4 mild TBIs and no RHI; neocortical Lewy body disease was evident alongside Alzheimer's disease neuropathological changes. Clinical characteristics consistent with Lewy body dementia were evident for both cases; psychiatric and motor symptoms predominated in Case 1 and 2, respectively.

Lewy body pathologies co-exist with multiple pathological processes in individuals with extensive head trauma exposure; antemortem clinical phenotypes are overlapping with, but distinct from, common clinical sequelae of TBI.

NIH/NINDS

# 2021 Neuroscience Retreat abstract submission

Astrocyte-Specific Expression of the Extracellular Matrix Gene Htra1 Regulates Susceptibility to Stress in a Sex-Specific Manner.

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Background: While the underlying pathophysiology of major depressive disorder (MDD) is poorly understood, convergent evidence from pre-clinical and clinical research supports the notion that MDD is related to impaired structural plasticity in key limbic regions. The extracellular matrix (ECM) of the brain represents a novel domain for study as it not only provides structural support, but also is intimately involved in regulating synaptic plasticity and remodeling.

Methods: We analyzed transcriptional profiles of ECM-related genes from the nucleus accumbens (NAc) in postmortem brain tissue of humans with MDD as well as in mice exhibiting a depression-like phenotype after exposure to chronic variable stress (CVS).

Results: We identified Htra1, an astrocyte-enriched secreted serine protease, as being significantly down-regulated in the NAc of males and up-regulated in females across species. We found that selective manipulation of the Htra1 gene in astrocytes within the mouse NAc increases susceptibility to stress in a sex-specific manner.

Conclusions: Our findings reveal a pivotal role of astroglia as well as the brain's ECM in mediating stress vulnerability that is impacted in a sex-specific manner.

Funding: NIMH and HDRF

# 2021 Neuroscience Retreat abstract submission

Title: Positive and negative urgency aspects of impulsive trait are associated with problematic alcohol exposure (sipping) in adolescents

Faith Adams1, Ariella Wagner, Lauren Lepow, Muhammad A Parvaz

Icahn School of Medicine at Mount Sinai

Background: Impulsivity has shown to be a risk factor for onset of alcohol use in adolescents and young adults. We have recently shown that impulsiveness increases with increasing alcohol use in initially alcohol-naïve adolescents. However, it is unclear which specific aspects of impulsive trait are associated with alcohol use initiation. Here, we leverage data from the Adolescent Brain Cognitive Development (ABCD) study (N=11,875; 9–11-year-olds) and compare different aspects of impulsivity (assessed via the UPPS-P scale) between problematic and non-problematic alcohol sipping children.

Methods: Among the entire ABCD sample, 2673 (23%) reported alcohol exposure (sipping), of whom 259 (13%) displayed problematic sipping behavior. Mixed effects modeling was performed to study the association between problematic sipping and impulsivity.

Results: The mixed effects modeling suggested that problematic sippers showed greater positive ($F(1,1758) = 4.6972$, $p = 0.030$; and $t(1758) = 2.013$, $p = 0.030$) and negative ($F(1,1757) = 6.0076$, $p = 0.014$; $t(1757) = 2.451$, $p = 0.0014$) than non-problematic sippers, even after controlling for sociodemographic variables.

Conclusion: These findings point to the importance of different aspects of impulsivity (e.g., negative urgency and positive urgency) in determining early problematic alcohol sipping. Further analyses will address other predisposing factors associated with alcohol use and explore differences in underlying neurobiology assessed via resting state function connectivity.

Funding: NIDA

# 2021 Neuroscience Retreat abstract submission

Clinical observations have shown that patients with psychiatric disorders, like Post-Traumatic Stress Disorder (PTSD), may develop metabolic syndromes such as Type II Diabetes and obesity in their lifetime. Empirical evidence from both systems neuroscience and endocrinology have suggested a mechanistic link between psychological stress and metabolism. Our laboratory has been focused on characterizing the relationship between traumatic stress and metabolism by investigating the role of the neuropeptide Pituitary Adenylate Cyclase-Activating Peptide (PACAP) and its receptor PAC1. Previous findings in the laboratory have shown that PACAP innervates the brown adipose tissue (BAT), a metabolically active type of fat tissue. PACAP receptor PAC1 is also abundant in BAT. These two findings suggest a role for PACAP and PAC1 in BAT thermogenic regulation, a key aspect of energy metabolism. We also found that the locus coeruleus (LC), a major source of norepinephrine (NE) in the forebrain, is rich in PAC1 expression. LC can modulate aspects of traumatic stress and metabolism via the sympathetic pathway, which innervates the BAT and various brain areas. Our hypothesis is that traumatic stress enhances metabolism on the short term for high energy demand, but in the long run can lead to decreased metabolism, thereby inducing metabolic syndromes. To answer our questions, we use mice (males and females aged between 3-4 months) with floxed PAC1 receptors and employ a range of techniques, including viral-mediated knockdown, the stress-enhanced fear learning assay for traumatic stress, immunohistochemistry, in situ hybridization, and qRT-PCR. Upon knockdown of PAC1 receptors in BAT, we found that expression of UCP1 (uncoupling protein 1), a critical BAT-specific mitochondrial protein, increased. We have also observed that viral-mediated knockdown of PAC1 receptors in the LC led to enhanced fear expression in SEFL, decreased fat mass and enhanced expression of UCP1 acutely. After a chronic time-point, fear expression in SEFL was still enhanced, but fat mass increased. Taken together, our results indicate that PACAP/PAC1 is an important neuropeptidergic system in the sympathetic node that links the brain and the body to regulate traumatic stress and associated metabolic changes.

# 2021 Neuroscience Retreat abstract submission

Understanding the Protective Mechanisms of Phenothiazine Compounds in a C. elegans Model of Alzheimer's Disease Using Bioinformatics Tools

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Background:
Alzheimer's Disease (AD), the most prevalent type of dementia, is characterized by age-related irreversible damage through neuronal loss. Our project aims to screen compounds for their protective effects in a model of AD and assess their mechanisms.

Methods:
First, we conducted a paralysis assay to assess the ability of tricyclics to delay Abeta toxicity in a C. elegans model of AD. Wells containing the worms exposed to drugs were filmed for 90sec on Day 15 and videos were analyzed blinded by students. Then, to assess the mechanisms of the best compounds, bioinformatics tools L1000 and CMap were used to identify gene signatures induced by the best drugs. Orthologs of highly regulated genes were then found using BLAST.

Results:
In CMap, 4 novel targets were identified. In L1000, gene signatures in NPC/NEU cell-lines of the top 20 protective tricyclics produced 953 upregulated genes. 11 genes were common to 3 of the tricyclics, 1 gene was common to 4 tricyclics. Search for C. elegans orthologs of these common genes was successful in BLAST.

Perspectives: We plan to knock down genes common to all signatures in C. elegans with RNAi.

# 2021 Neuroscience Retreat abstract submission

Prefrontal oscillations underlying information updating in a self-ordered working memory task.

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Working memory (WM) is the ability to hold information temporarily in mind, allowing it to be manipulated for cognitive processes such as planning and reasoning, e.g. planning possible steps before each move in chess or GO game. Prefrontal lesions cause significant impairments in WM tasks in human and non-human primates. However, how prefrontal areas manipulate and update the information online remain unclear. To assess this, we have trained monkeys to perform a sequential self-ordered target selection task with chronic implants of two 64-channel microelectrode arrays on dorsolateral prefrontal cortex (DLPFC). Monkeys learned to move their eyes, in any order, between a central fixation and one of eight targets on the screen. Monkeys received a juice reward the first time they selected each individual target, but repeat selections were not rewarded. Therefore, monkeys had to use WM to track which targets had been visited and prepare for the next target selection. Preliminary data revealed theta (4-8 Hz) activity, but not alpha/beta (10-25 Hz), in DLPFC was stronger at the reward epochs and late fixation epochs after a correct target selection, suggesting that theta activity is important for updating target-reward contingencies held in mind. These results indicate LFP signals in DLPFC can dynamically modulate the information updating process in a series of responses within trials.

Funding: R01 MH121480, FBI Seed Funds.

# 2021 Neuroscience Retreat abstract submission

Interactions between peripheral monocytes and the brain in stress-related neuropsychiatric disorders

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1Icahn School of Medicine at Mount Sinai

Background: Chronic psychosocial stress, an important risk factor for major depressive disorder (MDD), induces profound changes in the immune system associated with behavioral alterations relevant to MDD. However, the mechanisms linking peripheral immune activation and brain alterations remain to be elucidated.

Methods: Using the murine chronic social defeat stress (CSDS) model and applying a combination of mass cytometry and cell-type specific bulk and single-cell RNA-sequencing, we performed high dimensional characterization of immune cells in blood and brain.

Results: In blood, stress altered leucocyte subpopulation frequencies of both the myeloid and lymphoid lineage, though there were no differences between stress-susceptible and resilient mice. In the brain, however, CSDS led to the selective accumulation of pro-inflammatory Ly6chigh monocyte, specifically in susceptible mice. Using the tissue clearing method iDISCO+ revealed increased monocyte trafficking to the neurovasculature of brain regions of the limbic system and the meningeal space. Single-cell RNA-sequencing of brain infiltrating monocytes revealed increased gene expression of matrix metalloproteinases (MMPs). The increase in MMPs was further validated in both plasma of susceptible mice and human patients with MDD.

Conclusions: Investigating the mechanisms underlying interactions between the peripheral immune system and CNS will yield important insights into the etio-pathophysiology of MDD and could lead to potential novel therapeutic targets.

Funding: NIMH, SNSF

# 2021 Neuroscience Retreat abstract submission

Title: This Tangle Does Not Exist: Analysis of Neurofibrillary Tangle Morphology via Deep Generative Modeling

Authors: Gabe Marx1,2,5,6, Andrew McKenzie1,2,3,5,6, Kurt Farrell1,2,5,6, Daniel Koenigsberg1,2,5,6, Young Joon Kwon4, Benjamin Rapoport4, Anthony Costa4, Maxim Signaevsky1, Marcel Prastawa1, Jack Zeineh1, Gerardo Fernandez1, John Crary1,2,5,6

Departments of 1Pathology, 2Neuroscience, 3Psychiatry, 4Neurological Surgery, 5Friedman Brain Institute, 6Ronald M. Loeb Center for Alzheimer's Disease, Icahn School of Medicine at Mount Sinai

Background:
Neurofibrillary tangles (NFT) are a hallmark histopathological feature of Alzheimer's disease and other neurodegenerative diseases. NFT undergo a morphological progression that correlates with disease severity. Improved approaches for measurement and quantification of the evolution of NFT using machine learning would facilitate diagnosis and disease staging.

Methods:
We deployed a novel method to analyze NFT morphometry by investigating the latent space of a generative adversarial network (GAN). We trained StyleGAN2 using 537,455 images of immunohistochemically-labeled NFT derived from 526 slides from post-mortem human brain tissue from patients detected using a pre-trained model. Detection of semantically meaningful latent directions was also performed.

Results and Conclusions:
Our GAN achieved an Fréchet inception distance score of 8.76. Qualitative assessment of generated NFTs showed the model captured a wide spectrum of NFT morphology. Analysis of the latent space revealed several meaningful latent directions that correlated to tau inclusion density, color, size, and neurite loss. We proposed that when combined, these directions can be used to stage neurofibrillary degeneration.

Funding Tau Consortium

# 2021 Neuroscience Retreat abstract submission

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

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Background
Chronic inflammation and the gut-brain axis are 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. Intriguingly, the recent identification of LRRK2 variants associated with both PD and Crohn's disease, a subtype of inflammatory bowel disease (IBD), has provided genetic basis to link these two disorders. This raises the question of whether certain type of PD and IBD share the same disease origin and mechanism of progression.

Methods
We have developed a knock-in mouse model of the LRRK2-N2081D Crohn's-Parkinson's disease risk variant. In order to validate this model, 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 harbouring 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.

# 2021 Neuroscience Retreat abstract submission

Exacerbated Worsening of Positive and Negative Mood in Underage Drinkers during the COVID-19 Pandemic

Gopi K. Neppala, Muhammad A. Parvaz, Ph.D. et. al.

Funding/Affiliations: ISMMS

Background: This study sought to evaluate the impact of the COVID-19 pandemic on mood for underage alcohol drinkers versus non-drinkers.

Methods: An online survey was conducted in individuals ages 21 and younger [non-drinkers (n=162); drinkers (n=58)]. The survey included questions regarding positive and negative mood (prior to and during the COVID-19 pandemic), anxiety, alexithymia, anhedonia, and resilience. The effect of the pandemic on negative and positive mood and its association with alexithymia, anhedonia, and resilience were assessed.

Results: Participants showed a worsening of negative and positive mood from prior to during the pandemic, which was exacerbated in alcohol users compared to non-users. Anxiety regarding the pandemic significantly mediated the relationship between alcohol use and changes in mood while the difference in time spent outdoors mediated the relationship with changes in positive mood. Across both groups, lower increase in negative mood was associated with greater alexithymia, and greater decrease in positive mood was associated with greater anhedonia. Interestingly, drinkers with higher resilience showed lower increase in negative mood.

Conclusions: Underage drinkers showed exacerbated worsening of mood during the COVID-19 pandemic, and these changes in mood were mediated by anxiety related to the pandemic (negative and positive mood) and outdoor activity (positive). Mood changes were also associated with alexithymia (negative) and anhedonia (positive), and remarkably, drinkers with greater resilience showed less worsening of negative mood over time.

# 2021 Neuroscience Retreat abstract submission

Differential expression and splicing of MAPT in progressive supranuclear palsy

Authors:
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Background
Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized by accumulation of hyperphosphorylated microtubule-associated protein tau. While rare kindreds harbor autosomal dominant mutations in the tau gene (MAPT), the majority of cases are sporadic. MAPT mutations that increase splicing of exon 10 cause familial PSP through accumulation of four-repeat (4R) tau. Here we explore if this mechanism plays a role in sporadic PSP.

Methods
Publicly available RNA-seq data (n=164, cerebellum and neocortex) were analyzed alongside a novel replication cohort (n=40, neocortex). Data were trimmed, aligned, and assessed using STAR, Trimmomatic, FASTQC, and Picard. Differential gene expression was performed using RSEM, and splicing analysis was conducted using LeafCutter. Data was visualized with ggplot2.

Results
5,039 genes were differentially expressed in the neocortex, and 7,753 genes in the cerebellum. 2,764 genes overlapped. Total levels of MAPT and 4R tau were significantly increased in cases compared to controls. MAPT levels positively correlated with 4R tau in the cerebellum. Whole transcriptome regressions illuminated a variety of gene candidates that may influence tau splicing.

Conclusion
These findings indicate that sporadic PSP is associated with increased levels of 4R tau mRNA that may play a role in driving the accumulation of pathological tau protein aggregates in this disorder.

# 2021 Neuroscience Retreat abstract submission

Sex-specific peripheral and central responses to stress-induced depression

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Background
Women are about twice as likely as men to develop major depression, the molecular mechanism underlying the sex difference in regulation of stress response remain poorly understood. Our previous study revealed complex patterns of sex dimorphism in peripheral system in response to stress. Here, we report a brain region-specific regulation of stress response in a sex-specific manner.
Methods
In this study, female chronic social defeat stress (CSDS) model was used to evaluate depression-like behavior in mice. Peripheral cytokines were measured by multiplex ELISA and gene profile were validated by qPCR in prefrontal cortex (PFC).
Results
As microglia orchestrators the first defense response to the stress in the brain, microglia morphology was evaluated. We found that susceptible mice show a primed or phagocytic microglia phenotype characterized by a ramified morphology, reduced branching length in PFC region compare to resilient and control mice. Elevated CC chemokine receptor 5 (Ccr5) expression in microglia was also found in susceptible mice.
Conclusions
Together our findings reveal the importance of studying sex-specific therapeutic approaches to combat stress-related disorders

Funding
JJPVAMC NCCIH NIH

# 2021 Neuroscience Retreat abstract submission

Title: Impact of KCNJ6 expression and ethanol on function of human excitatory neurons
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Affiliations: 1Nash Family Department of Neuroscience, Friedman Brain Institute, ISMMS 2Ronald M. Loeb Center for Alzheimer's Disease, ISMMS 3Department of Genetics and Genomic Sciences, Icahn Institute of Genomics and Multiscale Biology, ISMMS 4Department of Cell Biology and Neuroscience, Rutgers University, Piscataway, New Jersey

BACKGROUND: Alcohol Use Disorder (AUD) is highly heritable, affecting adults and adolescents worldwide. Single nucleotide polymorphisms (SNPs) within KCNJ6 have a genome-wide association with an electrophysiological endophenotype for AUD risk. Some of these SNPs are hypothesized to result in elevated KCNJ6 mRNA. KCNJ6 encodes GIRK2, a subunit of a G protein-coupled inwardly-rectifying potassium channel, which regulates neuronal excitability and is directly activated by alcohol.
METHODS: We utilized NGN2 overexpression to model glutamatergic cortical neurons in a cohort of human induced pluripotent stem-cells (hiPSCs) derived from healthy individuals. We then upregulated KCNJ6 expression using either CRISPRa or lentiviral vector, and treated the neurons with 17mM ethanol for one week. Patch clamp and calcium imaging were used to assess neuronal function.
RESULTS: After a week of daily exposure to an intoxicating concentration of ethanol, neurons exhibited an increased sensitivity to glutamate; however, the effect was diminished when KCNJ6 was upregulated.
CONCLUSIONS: KCNJ6 expression attenuates ethanol’s effects on excitatory neuron function.
FUNDING: Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship; National Institute on Alcohol Abuse and Alcoholism

# 2021 Neuroscience Retreat abstract submission

TITLE: Neural Processes Associated with Agency Discrimination in Misophonia
AUTHORS: Jacqueline Beltrán, Sarah Banker, Jennifer Foss-Feig
AFFILIATION: Psychiatry, Icahn School of Medicine at Mount Sinai

BACKGROUND: Misophonia is an underinvestigated neurobehavioral syndrome in which people experience decreased tolerance and distress to sounds such as other's chewing and repetitive pen tapping. Previous research suggests the greatest intolerance occurs with socially-generated sounds. Therefore, neural processes associated with agency discrimination during sound processing may be important for understanding misophonia.

METHODS: (N=15) answered a series of survey questions measuring severity of misophonia symptoms and assessing aspects of personality, behavior, and mood. Electroencephalogram (EEG) was then recorded as they participated in a self-agency sound task that involved listening, in separate runs, to a pure tone and common misophonic trigger, produced, in separate blocks, passively, by the participants, and by a social other. We hypothesized that misophonia symptoms would be associated with socially-generated sounds in comparison to those generated by the self and passively.

RESULTS: Results for the pure tone indicated a significant difference in P2 latency between the active condition and both social and passive conditions. P2 latency to self-generated tones also showed a strong, positive, linear relationship with the misophonia symptoms.

CONCLUSIONS: Together these results suggest that people with more misophonia symptoms may experience greater difficulty with differentiating self-generated sounds from those they hear through passive listening or from a social other.

FUNDING: The Ream Foundation.

# 2021 Neuroscience Retreat abstract submission

Title: Adolescent THC affects stress and cognition via likely recruitment of the tripartite synapse.

JMN Ferland, YL Hurd, et al.

Background: Cannabis is the most commonly used drug amongst adolescents in the United States. Despite the belief that cannabis is relatively harmless, exposure during adolescence is associated with increased risk of developing addiction, depression, and cognitive deficits in adulthood. In addition to the high levels of use amongst teenagers, delta-9-tetrahydrocannabinol (THC) potency has increased more than fourfold compared to twenty years ago. Determining the impact of adolescent THC exposure, especially high dose THC, on behaviors relevant to psychopathologies observed clinically is essential to determine neural networks and molecular mechanisms underlying the development of psychiatric conditions.

Methods and Results: I leveraged a translational model of adolescent drug exposure to assess the protracted behavioral and molecular effect of adolescent THC exposure. While low dose THC influenced reward value and susceptibility to self-administer heroin, high dose THC led to greater sensitivity to stressful conditions and re-exposure to THC later in life. RNA sequencing of the basolateral amygdala, a region linked to reward processing, stress, and cognition, revealed that stressed rats with prior history of THC exposure had significant downregulation astrocyte-specific genes, which was paired with upregulated genes of excitatory and inhibitory neurons. Furthermore, Gfap expression directly correlated with the cognitive deficits after adult re-exposure to THC.

Conclusions:These data indicate that astrocytes, and possibly the “tripartite synapse,” are affected by adolescent THC experience, conferring greater susceptibility to stress and drug in adulthood.

Funding: NIDA

# 2021 Neuroscience Retreat abstract submission

Effects of Postnatal Cannabis Use and Environmental Trauma on Child Heart Rate Recovery

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Queens College1, Icahn School of Medicine at Mount Sinai2

Background:
Previous research indicates that prenatal exposure to cannabis and psychosocial trauma are associated with dysregulated heart rate (HR) during childhood. The roles of postnatal cannabis exposure (PNCBE) on child HR and the possible moderating role of prenatal exposure to natural disaster on associations between PNCBE and HR measures have been explored.

Method:
Child HR recovery (HR-R) was measured during a startle paradigm (ages 2-5 years). HR-R was measured via the difference in post-startle and startle HR. A moderation analysis tested if prenatal Superstorm Sandy exposure (SSE) enhances association between PNCBE and HR-R. Post-hoc univariate GLM was used to assess directionality.

Results:
PNCBE was not significantly correlated with HR-R ($p=0.20$). However, moderation analysis revealed a strong interaction between PNCBE and SSE on HR-R ($p=0.003$). Post-hoc testing revealed significant differences in overall mean HR-R ($p=0.028$). Pairwise comparisons demonstrated that PNCBE and SSE significantly lowered HR-R ($M=-1.55$) as compared to only SSE ($M=3.62$, $p=0.007$), only PCBE ($M=4.44$, $p=0.007$), or neither ($M=2.76$, $p=0.023$).

Conclusions:
Co-exposure to Sandy and postnatal CB was associated with a substantially blunted effect on child HR-R. As HR-R dysregulation is highly associated with future cardiovascular dysfunction, cannabis exposure during cardiovascular development in children who were exposed to disaster-related trauma, may contribute to later cardiovascular disease

Funding:
NIMH

# 2021 Neuroscience Retreat abstract submission

Neuronal Nsun2 deficiency is associated with codon-specific epitranscriptomic dysregulation of Gly-tRNAs and corresponding proteomic shift impacting synaptic signaling and behavior

Blaze, J.(1), Navickas, A.(2) , Phillips, H.L.(3), Heissel, S.(4), Plaza-Jennings, A (1), Haghighi, F.(1), Akbarian, S.(1) et al.

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(4) The Rockefeller University

Background: RNA cytosine methylation is most abundant in tRNAs and plays a regulatory role in protein synthesis.  NSUN2, a mammalian tRNA methyltransferase, is expressed at high levels in brain and has been linked to neurodevelopmental defects in humans and mice, but its role in the adult brain is unexplored.

Methods: We used viral overexpression and Cre-driven conditional knockout of Nsun2 in the postnatal mouse cortex to alter tRNA methylation levels and measured resulting tRNA expression, proteomic outcomes, synaptic transmission, and behavior.

Results: We report that depressive and cognitive behaviors are highly sensitive to bi-directional changes in Nsun2 in prefrontal cortex neurons. Nsun2-deficient mutant cortex showed a selective deficit in glycine tRNAs, resulting in codon-specific shifts in translational efficiencies, a 200% increase in glycine amino acid levels, and a distorted proteomic landscape with deficits in glycine-rich neuronal proteins associated with synaptic signaling.

Conclusions: tRNA methylation is a critical process for regulating synaptic plasticity and behavior through proteomic changes in the mature cortex, and we uncovered here another mechanism by which glycine could critically regulate brain function and complex behaviors, suggesting potential for novel therapeutic avenues in psychiatry.

Funding: NIMH, JJPVAMC-CSR&D

# 2021 Neuroscience Retreat abstract submission

Title: Patient's Response in Trust Game Predicts Psychotherapeutic Relationship

Authors: Jihan Ryu, Soo Jung Na, Matt Heflin, Xiaosi Gu

Affiliations: Center for Computational Psychiatry

Background: Strong patient-therapist alliance drives successful outcomes in psychotherapy treatment. We aimed to develop a novel application of Trust Game (King-Casas, 2005) paradigm previously studied in social neuroscience research in clinical setting to identify quantitative markers descriptive of therapeutic alliance.

Methods: After completing Working Alliance Inventory scale post-psychotherapy session, patients and psychotherapists in the IRB-approved Mount Sinai psychiatric clinic separately played trustees in the ten-round economic exchange task after being instructed to mentalize the investor as their therapy partner. Individual average repayment fraction, a proxy index for trustworthiness of investor, was computed and regressed on clinical alliance and attachment trait scores.

Results: In the Trust Game played by N=26 pairs (patient mean age=40, ~73% female, ~70% personality disorder), patients' average repayment fraction was positively associated with alliance (r=0.45, p= 0.02) driven by emotional bond subscore (p=0.005), despite being smaller in absolute amount compared to therapists' (95% CI -0.29, -0.07). Average repayment fraction was not associated with closeness attachment trait (p=0.42). Therapists' data were not significant (p=0.24).

Conclusions: Patients and therapists behaved differently in the economic exchange task, indicating their different social norms in the real-life clinical setting. Patients' repayment behavior to investment by therapists explained treatment-specific therapeutic alliance, especially the emotional bond. Quantitative paradigm to describe interpersonal trust can be utilized in clinically-oriented social neuroscience studies.

Funding: 2019 New York County Psychiatric Society Resident Fellow Grant

# 2021 Neuroscience Retreat abstract submission

Neural Network Mechanisms of Acute Stress-Provoked Aggression

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Background: Aggressive behavior serves as an adaptive behavior in many species, but commonly presents as a symptom of psychiatric disorders in humans. Pathological aggression often results from traumatic experiences during childhood or adolescence. Furthermore it manifests as reactive aggression, a symptom that is well-characterized in patient populations but mechanistically poorly understood. Inconsistences exacerbate this problem due to differences in methodology and reported results in preclinical rodent models. We propose a new model of traumatic adolescent social experience that leads to aberrant social behaviors, especially after acute stressors during adulthood.

Methods: We multiplexed juvenile stressors – chronic social defeat stress (CSDS) and isolation housing – to create a traumatic juvenile stress model. During adulthood we compared social interactions before and after an acute stress experience. We characterized behavior and underlying neurophysiology specific to this experience by assessing immediate early gene expression and circulating factors.

Results: Exposure to chronic social defeat stress during adolescence can exacerbate aggressive behavior in C57 male mice but not in females. We also observed brain-wide engagement during social behavior as measured by alterations in Fos expression provoked by adult social interactions after acute stress.

Conclusions: This may provide a beneficial model for understanding neural circuits and physiology uniquely underlying adolescent trauma-induced social deficits, especially aggressive behavior, that are symptomatic of many disorders.

Funding: NIMH

# 2021 Neuroscience Retreat abstract submission

Differential Pathways to Externalizing Behavior in ASD and TD

Keller, K., McLaughlin, C., Barkley, S., Grosman, H., Layton, C., Guillory, S., Thakkar, K., Foss-Feig, J.H.

Background: Children with ASD display externalizing behaviors, including aggression, rule-breaking, and oppositionality. In non-ASD populations, these behaviors associate with perspective taking and empathy deficits. This study explores these relations in ASD and TD and whether, in ASD, externalizing behaviors also associate with clinical features.

Method: Child Behavior Checklist was used to measure externalizing behaviors in 39 ASD (28 males; M=8.10years) and 39 TD (23 males; M=8.05years) participants. The Reading the Mind in the Eyes Test and Empathy Questionnaire for Children and Adolescents measured perspective taking and empathic ability, respectively. Core ASD symptoms were assessed via the Autism Diagnostic Observation Schedule and the Sensory Experiences Questionnaire.

Results: ASD children displayed significantly more externalizing behaviors than TD (p=.007). In TD, more externalizing behavior associated with lower empathy (r=-.35, p=.047) and weaker perspective taking (r=-.36, p=.025). In ASD, externalizing behaviors were unrelated to empathy or perspective taking. Rather, externalizing behaviors correlated with multisensory processing difficulties (r=.348, p=.043).

Conclusion: Results show externalizing behaviors are associated with deficits in perspective taking and empathy in TD, but not ASD. In ASD, increased externalizing behavior did not associate with empathy or perspective taking deficits, but rather with multisensory processing difficulties. This may indicate externalizing behaviors reflect distress response following overwhelming sensory experiences. Therefore, in ASD targeted treatment of sensory behaviors and modulating the sensory environment may reduce externalizing behaviors.

Funding: NIMH

# 2021 Neuroscience Retreat abstract submission

Microbial metabolites modulate cocaine-seeking and transcriptional homeostasis

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Background: Psychostimulant addiction represents a public health crisis leading to tremendous morbidity. Emerging evidence suggests gut bacteria and their metabolites significantly affect brain and behavior in models of psychiatric disease. Our research examines the effects of the microbiome in models of cocaine use disorder.

Methods: Depletion of gut bacteria and their metabolites was induced in Sprague-Dawley rats via addition of antibiotics in their drinking water and compared to untreated 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: Microbiome depletion enhanced motivation for low dose cocaine in a behavioral economics task and increased cue-induced cocaine-seeking following prolonged abstinence. Microbiome-depleted animals exhibited significantly altered gene expression in networks known to affect synaptic signaling and plasticity. Supplementation with bacterial metabolites short-chain fatty acids (SCFAs) reversed these behavioral and molecular effects.

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

Funding: NIDA, NARSAD

# 2021 Neuroscience Retreat abstract submission

Interpretable connectivity-based decoding models for chronic marijuana use

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AFFILIATIONS: ISMMS, CU Boulder, GSU, UT Dallas

BACKGROUND: Psychiatric neuroimaging typically proceeds with encoding models which aim to model neural mechanisms, and decoding models which aim to predict clinical features from brain data. In this study, we combine these aims by developing interpretable decoding models that offer both accurate prediction and novel neural insight.

METHODS: Chronic marijuana users (n=195) and non-using controls (n=128) completed a cue-elicited craving task, consisting of marijuana and control cues. Linear machine-learning algorithms were used to classify group status based on task-evoked, whole-brain functional connectivity. Novel interpretation methods, including prediction of continuous clinical severity scores, and graph theoretical measures, were used to elucidate whole-brain regional and network involvement.

RESULTS: We obtained high accuracy (~80% out-of-sample) models, demonstrating that whole-brain functional connectivity can successfully differentiate chronic marijuana users from non-users. Model-derived confidence scores were highly associated with clinical severity scores. Subsequent network analysis revealed key predictive regions that are often found in neuroimaging studies of drug use disorders. Novel communities of brain regions were also revealed that contributed to successful classification.

CONCLUSIONS: Our dual aims of accurate prediction and interpretability were successful, producing a neurobiological description that corroborated existing drug use disorder models, and suggested other neural processes. This novel approach may complement other approaches for a more complete understanding of neural mechanisms in drug use disorders.

FUNDING: NIDA

# 2021 Neuroscience Retreat abstract submission

Automated Model for Detecting Differences Between Females and Males in Aggressive Behavior

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Background: Female aggression in mice is understudied relative to males. Manually scoring behavior is notoriously tedious, subjective, and error-prone, thus limiting experimental capabilities. This deficiency emphasizes the need to study female aggression more broadly and develop an automated behavioral scoring model.

Methods: Data were collected from 5-minute resident-intruder test trials using male CD-1 resident and female Swiss Webster resident mice, paired with C57BL/6 intruder mice. We manually scored behaviors in resident and intruder mice, then created a computer model to automate behavior scoring by implementing manual scoring results from JWatcher into DeepLabCut and Simple Behavioral Analysis (SimBA).

Results: Manual scoring results revealed differences in aggression between male and female mice, with females displaying less aggressive behavior than males. Further analysis revealed a strong positive correlation between male, but not female, resident aggression and intruder response behaviors. The SimBA model supported this result.

Conclusions: Studying female aggression unveils sex differences in aggression highlighting the importance of examining aggressive behaviors in both sexes. This preclinical model can be applied to other experiments and studies, such as social reward-seeking behavior and the study of neural circuits related to aggression.

Funding: NIMH

# 2021 Neuroscience Retreat abstract submission

Title
Role of Hypothalamic Paraventricular Oxytocin Neurons in Social Recognition Memory
Authors
Keerthi Thirtamara Rajamani1,2, Kristi Niblo1,2, Valery Grinevich6, Hala Harony-Nicolas1,2,3,4,5
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Background: Oxytocin (OXT) is a neuropeptide synthesized in the paraventricular (PVN), supraoptic and accessory nuclei of the hypothalamus. OXT is implicated in social behaviors including maternal care, social bonding, and social recognition memory (SRM). Despite a clear role of OXT in SRM it is still unclear which of the three nuclei is necessary for this form of memory.

Methods: Using designer receptors activated by design drugs (DREADDs), we silenced OXT neurons (OT-hM4DGi) in the PVN of rats and assessed their short and long term SRM.
Results: Silencing of OXT neurons in the PVN resulted in impairment of both short and long-term SRM. In order to account for nonspecific effects of CNO, animals were injected with a control virus (OT-mcherry) which lacks the DREADD. We found no effect of CNO, indicating that the impairment in SRM in the test group are a result of silencing of OXT neurons in the PVN.
Conclusions: These findings attribute a novel role for PVN OXT neurons in SRM. Future studies are aimed at identifying the downstream targets of PVN-OXT neurons and their ability to modulate SRM.
Funding
Beatrice and Samuel A. Seaver Foundation

# 2021 Neuroscience Retreat abstract submission

The role of GM-CSF in behavioral and molecular responses to cocaine

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Background: Evidence shows the gut microbiome markedly effects behavioral and neurobiological responses to cocaine. Here we investigate the potential role of the immune system as a mechanism underlying gut-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. Mice with intact or depleted microbiomes, receiving daily injections of GM-CSF (10μg/kg) or vehicle, underwent a cocaine conditioned place preference (CPP) assay to measure preference for cocaine. Quantitative polymerase chain reaction (qPCR) and RNAscope in-situ hybridization quantified GM-CSF receptor expression in the nucleus accumbens (NAc) following cocaine treatment. NAc tissue from GM-CSF+cocaine treated animals was used for RNA-sequencing.

Results: Multiplex analysis identified granulocyte-macrophage colony-stimulating factor (GM-CSF) to be significantly increased by chronic cocaine only in animals with an intact gut microbiome. On the CPP test, GM-CSF treatment normalized cocaine preference in microbiome-depleted animals, and significantly attenuated cocaine preference in microbiome-intact animals. qPCR and RNAscope showed cell-type specific cocaine-induced increases in GM-CSF receptor 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 neuroimmune signal in cocaine use.

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# 2021 Neuroscience Retreat abstract submission

Chronic social defeat stress increases intestinal permeability and inflammation in mice

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1ISMMS

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. We subsequently measured gut inflammation by flow cytometry, and intestinal permeability by orally gavaging mice with FITC-Dextran.

RESULTS: Following CSDS, intestinal permeability was elevated in stressed mice. Moreover, circulating bacterial endotoxins were greater following CSDS. Additionally, expression of several tight junctions was downregulated in the intestines from defeated mice. Evaluating gut inflammation, IFN$\gamma$+ T cells were upregulated, and IL4+ T cells were downregulated in the colon after CSDS. Using ITG$\beta$7-deficient mice, which have impaired immune cell migration to the gut, we find that gut inflammation precedes permeability and behavioral defects during stress.

CONCLUSIONS: Collectively, these results reveal that CSDS induces intestinal inflammation and barrier breakdown, which may promote systemic inflammation associated with depression-like behavior.

FUNDING: NIMH, CIHR

# 2021 Neuroscience Retreat abstract submission

Regulation of Nicotine Intake by the Gut Hormone Cholecystokinin

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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 stimulation 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 animals. 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, conditioned place preference, and food self-administration. Finally, we used Targeted Recombination in Active Population (TRAP) mice to identify nicotine-activated neurons.

Results: Nicotine increases postprandial, but not fasting plasma CCK concentrations. CCK-8 decreases nicotine self-administration without impairing food responding or nicotine place preference. Finally, we identified nicotine-reactive population in the nucleus of the solitary tract, a primary target of vagal afferents and critical hub for nicotine aversion neurocircuitry.

Conclusions: Peripheral CCK receptors regulate nicotine intake, likely due to actions on aversive, not hedonic, neurocircuitry including vagal sensory afferents. Future studies will aim to characterize molecular mechanisms of nicotine intake regulation by vagal neurons.

Funding: NIH

# 2021 Neuroscience Retreat abstract submission

Title: Neuronal Chromatin Organization in Prefrontal Cortex of Subjects with Schizophrenia
Authors: Kiran Girdhar, Gabriel E Hoffman, Jaroslav Bendl, Panos Roussos, Schahram Akbarian
Funding: NIMH

Chromosomal architecture includes kilo- to mega-base scaling functional domains, but little is known about modular chromatin organization in schizophrenia and related psychiatric disease. Here, we profile cell-type specific histone H3K27ac acetylation and H3K4me3 methylation landscapes in prefrontal cortex (PFC) from
572 cases and controls, with correlational structuring from 821 ChIP-seq datasets assigning % of neuronal histone acetylome and methylomes into sequential arrays of histone peaks (CRD cis-regulatory domains) encompassing 6% of linear genome and strongly constrained by chromosomal conformations. Diseased PFC neurons, while showing complete preservation of histone methylation profiles, were selectively affected by 11,471 dysregulated H3K27ac CRDs, with hypoacetylated domains showing strong co-regulation of inhibitory interneuron-specific histone peaks and hyperacetylated chromatin strikingly enriched for regulatory sequences
associated with projection neurons and prenatal development and heritability.

# 2021 Neuroscience Retreat abstract submission

Title: Establishing reproducibility of cluster analysis across Parkinson's disease cohorts
Authors: Kristen Watkins,1 Julia Greenberg,2 Towfique Raj,3 Giulietta Riboldi2,3
Affiliations: MSH[1], NYU[2], Friedman Brain Institute[3]

Background: Cluster analysis of clinical cohorts in Parkinson's Disease (PD) is a valuable tool for characterizing phenotypic variability and correlating phenotypes with biomarkers. However, data collection methods often differ between clinical and research settings, limiting the ability to obtain significant results from less characterized cohorts and to compare studies. Establishing reproducibility of clinical cluster analysis across different studies/centers would greatly enhance their research potentials. We compared cluster analysis of a gold standard multi-center PD bioregistry (Parkinson's Progressive Marker Initiative (PPMI)) and the PD cohort at our centers (NYU/MSMD cohort).

Methods: Non-hierarchical kmeans clustering by phenotype of subjects in the NYU/MSMD (n=175) and PPMI cohorts (n=371) were performed via Principal Component Analysis (cohort-based clusters). Eigenvectors of clustering in the PPMI cohort were identified and utilized to re-cluster the NYU/MSMD cohort (PPMI-based clusters). Overlap in cluster membership between cohort-based clusters and PPMI-based clusters of the NYU/MSMD cohort was assessed.

Results: Clustering of subjects in the PPMI cohort revealed two clusters. The first four principal components, accounting for 31% of the variability, were driven by dementia, depression, anxiety, age at diagnosis, urinary symptoms, constipation, and gender. After re-clustering the NYU/MSMD cohort, 94% of subjects remained in their original cluster.

Conclusions: We successfully leveraged cluster analysis of PD patients from a gold standard cohort study to validate reproducibility of cluster analysis in smaller cohorts.

Funding: Parkinson's Disease Foundation, MJFF

# 2021 Neuroscience Retreat abstract submission

NOS1 in the Interpeduncular Nucleus Mediates Tolerance to Aversive Effects of Oxycodone
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Background: Previously we demonstrated that nitric oxide synthetase 1 (NOS1) in the interpeduncular nucleus (IPN) is upregulated by chronic nicotine and disrupting Nos1 in the IPN abolishes place preference for nicotine. Our data suggests that nitric oxide inhibits presynaptic glutamate release, reducing aversion and leading to the development of tolerance. Our current studies are focused on whether development of tolerance to other drugs, specifically oxycodone, coincides with an increase in NOS1 in the IPN.

Methods: For forced chronic nicotine exposure, mice were given 2% saccharin +/- 500mg/L nicotine-tartrate in drinking water for 6 weeks. For voluntary chronic nicotine exposure, mice underwent IV self-administration of escalating doses of nicotine over 8 weeks. Forced chronic opioid exposure mice were implanted with minipumps containing saline or oxycodone for 10 days. Voluntary chronic opioid exposure mice underwent IV self-administration of escalating oxycodone doses. NOS1 levels were measured via immunohistochemistry.
To visualize NO in behaving animals via fiber photometry, we are developing an Cre-dependent AAV encoding a fluorescent NO-sensor.
To test tolerance, mice were given water or oxycodone in drinking water and underwent conditioned placed preference for oxycodone.

Results: Chronic drug exposure increases IPN NOS1 and chronic oxycodone exposure results in reduced aversion to high dose oxycodone.

Conclusions:  Chronic exposure to nicotine and oxycodone results in upregulation of IPN NOS1, suggesting a common pathway for development of tolerance for multiple drugs of abuse.

Funding: FBI

# 2021 Neuroscience Retreat abstract submission

Common genetic variation in humans impacts in vitro susceptibility to SARS-CoV-2 infection

AUTHORS
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The world is in the midst of an ongoing pandemic caused by the novel and highly contagious SARS-CoV-2. There is marked inter-individual variability in both the tissues affected as well as the severity of response to SARS-CoV-2. It is unclear why some otherwise healthy individuals experience profound clinical complications to SARS-CoV-2 and others do not. We hypothesize that, in addition to viral load and host antibody repertoire, host genetic variants also impact vulnerability to infection. Here we apply human induced pluripotent stem cell (hiPSC)-based models shRNA-mediated knock-down and CRISPR-engineering to explore the host genetics of SARS-CoV-2. Using alveolospheres, intestinal organoids and NGN2-neurons as model, we demonstrate the importance of FURIN in SARS-CoV-2 infection of these different cell types. Furthermore, we determine that a single nucleotide polymorphism (rs4702), common in the population at large, and located in the 3'UTR of the protease FURIN, impacts alveolar and neuron infection by SARS-CoV-2 in vitro. Thus, we provide a proof-of-principle finding that common genetic variation can impact viral infection, and so potentially contribute to clinical heterogeneity in SARS-CoV-2. Ongoing genetic studies will help to better identify high-risk individuals, predict clinical complications, and facilitate the discovery of drugs that might treat disease.

# 2021 Neuroscience Retreat abstract submission

Parkinson's Disease-Linked LRRK2-G2019S Mutation Promotes Behavioral Maladaptations to Acute Stress

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Nonmotor symptoms of Parkinson's Disease (PD) can be as debilitating as motor symptoms and may appear many years earlier. Even so, studies to date have focused mostly on motor control; far less is known about the underlying mechanisms driving nonmotor disorders. This asymmetry emphasizes the need to design therapeutics for prominent symptoms outside of the ones currently defining PD. In this study, we explore how two PD risk factors—the LRRK2-G2019S (GS) mutation and stress—interact to promote depression and anxiety, common nonmotor symptoms. Applying an Acute Variable Stress paradigm to young-adult GS and wildtype (WT) mice of both sexes, we find significant differences in depressive-like behaviors between stressed GS and WT mice, without changes across anxiety-like behaviors or sexes. Further analysis reveals a significant, positive correlation between anxiety-and depressive-like behaviors for WT mice post-stress, but a surprising lack of this relationship for GS mice. These and previous data indicate that altering stress type alters behavior in mice expressing a PD-associated gene mutation. This variance—suggesting underlying complexity—further unveils principles important for PD detection, classification, and treatment.

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# 2021 Neuroscience Retreat abstract submission

Cellular and Molecular Characterization of a New Mouse Model for DDX3X Syndrome

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Background: DDX3X syndrome is a rare X-linked form of intellectual disability (ID) that accounts for ~2% of cases in females and is co-morbid with behavioral problems, motor deficits, and brain malformations. Mutations in the DDX3X gene, which encodes an RNA helicase, have emerging effects in corticogenesis and synaptogenesis.

Methods: Using a Ddx3x haploinsufficient mouse (Ddx3x+/−) with construct validity for DDX3X loss-of-function mutations, a standardized battery was performed to assess developmental milestones and adult behaviors, as well as immunostaining of cortical projection neurons to capture early postnatal changes in brain development.

Results: We observed neurodevelopmental delays and adult behavioral changes that are accompanied by deficits in cortical lamination, indicating that Ddx3x regulates the balance of glutamatergic neurons in the developing cortex.

Conclusions: These data shed new light on the developmental mechanisms driving DDX3X syndrome and support face validity for a novel pre-clinical mouse model.

Funding: NIH/NICHD, Beatrice and Samuel A. Seaver Foundation, Friedman Brain Institute, Fundación Alfonso Martín Escudero, Fondation pour la recherché medicale.

# 2021 Neuroscience Retreat abstract submission

Prenatal Drug Exposure Potentiates the Effect of Childhood Trauma on Emotion Reactivity in an ABCD Sample

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MSSM, Psychiatry

BACKGROUND: Prenatal exposure to drugs of abuse is known to alter neurodevelopment and predispose to psychopathologies of emotion processing. The “two-hit hypothesis” suggests prenatal environmental exposure disrupts brain development and establishes a vulnerability to a second hit. With Adolescent Brain Cognitive Development (ABCD) data, we test whether prenatal drug exposure (PDE) exacerbates the effects of childhood trauma (CT) on emotion reactivity.

METHODS: The ABCD cohort of 10-year-olds was stratified into groups based on PDE and CT (PDE-/CT-, n=3269); (PDE-/CT+); (PDE+/CT-); and (PDE+/CT+). Linear mixed models examined the interactive effect of PDE and CT on mean reaction time (MRT) for the emotional valence contrast of the EN-back task. The emotional Stroop was examined for convergent validity.

RESULTS: Emotional valence showed a significant PDE*CT interaction ([POSITIVE–NEGATIVE]: $\beta$= 43.49, p< 0.001) driven by higher MRT for CT+ vs CT- within the PDE+ group ($\beta$=30.65, p=0.045). The Emotional Stroop task corroborated this finding with a trend-level main effect of CT ($\beta$= -4.06, p= 0.088) and a significant interaction effect PDE*CT ($\beta$= 36.32, p= 0.026).

DISCUSSION: The two-hit hypothesis is supported by the PDE*CT interaction such that CT only influences emotion reactivity in children exposed to PDE. Results suggest prenatal drug exposure confers vulnerability to later environmental insults such as traumatic experiences and affects the processing emotional social stimuli.

FUNDING: NIDA

# 2021 Neuroscience Retreat abstract submission

Entorhinal-hippocampal synchronization in a mouse model of Alzheimer's disease pathology

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1Department of Neuroscience

Background: Alzheimer's disease (AD) is a devastating neurodegenerative disease characterized by memory loss and progressive age-related cognitive decline. While leading hypotheses have posited that accumulation of amyloid-beta (Aβ) and tau proteins drives neurodegeneration, simply reducing pathological proteins without preventing or reversing functional changes may be insufficient to alleviate cognitive decline. Therefore, it is critical to understand circuit-level changes in memory networks. Impairments in hippocampal processing and memory are well established in AD, but it is unclear whether this is driven by local changes or abnormal inputs, such as those from medial entorhinal cortex (MEC).

Methods: To understand how AD pathology impacts communication within and between brain regions that are critical for memory, we performed in vivo silicon probe recordings to simultaneously record from 512 channels throughout MEC and hippocampus in a 3xTg mouse model of AD pathology. By recording before and after the onset of memory impairments, we can determine how and when synchrony of individual cells and local field potentials breaks down.

Results: Our data suggests that synchronization between MEC and hippocampus is impaired in 3xTg mice prior to the onset of hippocampal-dependent memory impairments. Possible explanations for early entorhinal dysfunction include hyperexcitability of entorhinal stellate cells or loss of entorhinal parvalbumin interneuron function.

Conclusions: These findings support the hypothesis that entorhinal degeneration precedes and may contribute to hippocampal changes.

Funding: NIA

# 2021 Neuroscience Retreat abstract submission

Nicotine Addiction – The Role of IL-18 in the Medial Habenula

Lauren Wills, Zuxin Chen, Xin-an Liu, Paul J. Kenny et al.

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

# 2021 Neuroscience Retreat abstract submission

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

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BACKGROUND: Drug addiction represents an enormous healthcare burden. To better understand the 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 indicates that astrocytes are also involved in disorders of the nervous system, including addiction. Indeed, 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 been investigated.
METHODS: We utilized whole cell sorting of astrocytes and RNA-sequencing to investigate the astrocyte transcriptome in key brain regions involved in reward-processing, including the NAc and mPFC, following exposure to cocaine.
RESULTS: Gene ontology analysis revealed a variety of pathways, including synaptic regulation, and GPCR and calcium signaling in both brain regions as being prominently regulated by cocaine. Additional analysis revealed several deduced upstream regulators of this abnormal transcription, such as CREB and several members of the STAT family. Furthermore, our analysis indicates a robust regional-specific response of astrocytes following exposure to cocaine.
CONCLUSIONS: Current studies are directed at extending our findings utilizing cocaine self-administration in mice to establish the astrocyte transcriptome in response to drugs of abuse and to study the role of specific transcripts in contributing to the pathophysiology of addiction.

FUNDING: NIDA

# 2021 Neuroscience Retreat abstract submission

Investigating cell-type vulnerability in Parkinson's Disease using an in vitro genetic model
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ISMMS-Nash-Loeb-FBI-CDRB-BFSCI

Parkinson's Disease (PD) is a common neurodegenerative disorder characterized by loss of dopaminergic neurons (DNs) in the substantia nigra of the midbrain. Although the etiology of PD is unknown, about 10% of cases are familial. Parkin is a familial PD gene which encodes a protein that mediates mitophagy and causes mitochondrial dysfunction in DNs upon its loss of function. While nigral DNs degenerate in PD, DN subtypes in the ventral tegmental area of the midbrain undergo less degeneration and those in the hypothalamus are relatively spared. Although cell-type vulnerability has been observed in all forms of PD, its causes are still unclear. Human pluripotent stem cells (hPSCs) can be differentiated into different DN subtypes, serving as a useful model for studying cell-type vulnerability in PD. Using reporter knock-in isogenic control and Parkin-/- lines, we derived midbrain and hypothalamic organoids and analyzed emerging DNs. We use high-throughput imaging and flow cytometry to compare oxidative stress and cell death in different DN subtypes using several genetic markers. We leverage single-cell RNA sequencing to identify the molecular pathways that lead to cell-type vulnerability. Our preliminary results show that midbrain, but not hypothalamic, Parkin-/- DNs undergo cell death. Results from this study will elucidate the molecular pathways that are differentially dysregulated in nigral and hypothalamic DNs and help in identifying the cell-autonomous causes of vulnerability in PD, leading to novel therapeutic approaches.

Funding: NIH, MJFF, ASAP, ISMMS-Illumina

# 2021 Neuroscience Retreat abstract submission

Spatial coding and entorhinal-hippocampal circuit deficits 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. The hippocampal circuit has been extensively studied in AD because memory is often impaired in AD patients. Deficits in hippocampal cellular excitability have been reported in various models of AD pathology. However, relatively little attention has been paid to 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 deficits in hippocampal memories emerge in AD, it is critical to examine alterations in the spatial coding and intrinsic excitability in each part of the MEC-hippocampus circuit during the progression of the disease.

METHODS: We used in vitro whole-cell patch clamp and in vivo calcium imaging with Miniscopes in the 3xTg mouse model of AD pathology.

RESULTS: In 3xTg mice, we have found that MEC layer II stellate cells are hyperexcitable at 3 months of age, prior to the onset of memory impairments. We have also found CA1 spatial coding deficits at 10 months of age.

CONCLUSIONS: The abnormalities of intrinsic excitability appeared much earlier in the MEC than the onset of hippocampal-dependent memory impairments in the 3xTg model. We hypothesize that hyperexcitable MEC stellate cells may lead to local and downstream circuit changes and affect spatial coding during the progression of AD pathology.

FUNDING: NIH

# 2021 Neuroscience Retreat abstract submission

Traumatic social experience engages lateral septum neurotensin circuitry to occlude social reward.

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Background: In humans, social stress can elicit feelings of social isolation and reduce responses to the rewarding aspects of social behavior, both at the behavioral and neural levels. Chronic social defeat stress (CSDS) as a depression model, has been used to understand how reward circuitry mediates social interaction behavior. However, social stress-induced deficits in social reward or preference and the underlying mechanisms remain unknown.

Methods: We used conditioned place preference (CPP) assay to test the social reward in defeated mice. And used iDISCO+ whole brain cfos mapping to identify the differentially regulated brain regions during social behavior after CSDS. Then we use chemogenetics and optogenetics tools to manipulate these pathways and identify their functions in CSDS depression model.

Results: We found susceptible mice show greater avoidance and significantly less time interacting with same-sex juvenile intruders compared to control or resilient mice; we found only susceptible (both females and males) mice fail to develop a preference for the context paired with the juvenile target. Activating/silencing of LSNT neurons and their downstream circuits (LS-AHN, LS-NAc but not LS-PAG) reduces/increases social investigation and increases/ reduces social avoidance behavior in defeated mice.

Conclusions: In both females and males, the traumatic social experience leads to social reward impairment in susceptible mice. LS neurotensin population plays an important role in regulating depressive-like behaviors.

Funding: R01 MH090264 (Russo PI)

# 2021 Neuroscience Retreat abstract submission

Proteomic profiling of FMRP translational networks involved in homeostatic synaptic plasticity in PSC-derived isogenic human neurons

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BACKGROUND: The RNA-binding protein FMRP regulates neuronal translation and is a common genetic cause of autism and intellectual disability. A previous study using human pluripotent stem cell-derived neurons demonstrated that loss of FMRP impairs homeostatic synaptic plasticity. Network silencing increased excitatory (EPSC) and decreased inhibitory postsynaptic current (IPSC) amplitudes in control (WT) but not FRMP-null (KO) neurons.

METHODS: To examine whether aberrant protein synthesis is involved in this impairment, we used biorthogonal noncanonical amino acid tagging. Cells were transduced with mutant methionyl-tRNA synthetase that incorporates the methionine surrogate azidonorleucine (ANL) in nascent translated proteins. ANL-tagged proteins were purified and analyzed via mass spectrometry in WT and KO neurons at baseline and after synaptic scaling.

RESULTS: Our analysis identified ~300 unique proteins upregulated in WT neurons during synaptic scaling, demonstrating that induction of synaptic plasticity involves increased protein translation. In contrast, we observed a significant defect in the translation of a subset of transcripts during synaptic plasticity in KO. We identified aberrant translation of FMRP targets, synaptic proteins, and autism-associated genes. Robust targets will be confirmed using western blot, and RNA levels examined to verify translation dependent increase.

CONCLUSION: Overall, our model examines global changes of FMRP-translational network during synaptic plasticity and offers new insights toward synaptic defects associated with autism and intellectual disability.

# 2021 Neuroscience Retreat abstract submission

Studying the impact of Shank3-deficiency on neural circuits of social reward

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Background: Clinical studies have implicated the mesoaccumbens reward circuit in autism spectrum disorder. However, the causality between alterations in this system and social deficits has not been established. We hypothesize that Shank3 mutation impacts neural activity in the mesoaccumbens system leading to impairments in processing social reward.

Methods: We used fiber photometry to record from the ventral tegmental area (VTA) of a rat model for ASD, the Shank3-deficient rat, during a social reward paradigm. In this paradigm we introduced two rewarding stimuli, social and food, during satiety and food deprivation and examined investigation time for each reward during the two conditions. To control for attentional deficits, we used the same paradigm, but replaced the social stimuli with a moving toy rat. To rule out reduced motivation to food or impairment in food consumption, we assessed food consumption.

Results: We found that Shank3-deficient rats have deficits in processing social reward that are associated with perturbation in VTA neural activity and an intact attention and food consumption.

Conclusions: Our study demonstrates that Shank3-deficient rats have a specific deficit in processing social reward and provides a first step toward understanding the role of Shank3 in the reward system, and how Shank3-deficiency may leads to social deficits.

# 2021 Neuroscience Retreat abstract submission

Comparing Multi Echo Denoising Approaches in Ultra-High Field Resting State fMRI

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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. In this project, we aim to compare the predominant ME preprocessing pipelines: AFNI and MEICA, and analysis of individual echo images using SE AFNI preprocessing. We evaluate the quality of the denoised BOLD signal using global and regional temporal Signal-to-Noise Ratio (tSNR) and functional connectivity measures in healthy individuals (N=9). Comprehensive results of various AFNI and MEICA based pipelines will be presented and discussed in terms of findings the optimal ME preprocessing pipeline.
Funding: The project is funded by the National Institute of Mental Health.

Keywords: Multi Echo, fMRI, Denoising, MEICA, AFNI

# 2021 Neuroscience Retreat abstract submission

The hippocampus represents place in social space: encoding and decoding evidence in independent samples

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Background: Evidence suggests that the brain organizes social information into a multidimensional map, similar to that of physical space. In this framework, individuals can be thought of as occupying an abstract social place, based on their location along social dimensions.

Methods: To search for such a neural representation, functional magnetic resonance imaging (fMRI) was measured in two samples of healthy individuals while they completed a naturalistic role-playing game that models change in social relationships as movement in an abstract two-dimensional social space.

Results: Hippocampal fMRI signals consistent with this representation were seen in both ROI-based and searchlight representational similarity regression as well as a decoding probability analyses, and in two independent samples. This was not explained by other measures of task behavior or other kinds of categorical or continuous social information in the task.

Conclusions: Our findings suggest that ‘social place’ along two abstract social dimensions is represented in the human brain. Future work will aim to answer how social places are combined into maps and used for flexible behavior - social navigation.

Funding: NIDA

# 2021 Neuroscience Retreat abstract submission

The Effect of Lesioning MeA→VMH Neurons on Mouse Behavior

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Background
Violence and aggression have a severe impact on society. This project aimed to understand the neurobiological circuits involved in aggressive behaviors. Using viral techniques, we lesioned medial amygdala (MeA) neurons that project to ventromedial hypothalamic (VMH) neurons and tested whether the lesion had any effect on aggressive or social behavior in male mice.
Methods
In our experiment, we injected AAV2/retro-CAG-Cre or AAV2/retro-CAG-EGFP (control) into the VMH of male mice. Next, we injected AAV8-EF1-mCherry-DIO-DTA into the MeA to lesion the MeA→VMH neurons. Finally, we conducted a resident intruder test for periods of 10 minutes daily over the span of 5 days.
Results
Although mice with lesioned MeA→VMH neurons did show differences in aggressive behaviors compared to control mice, the lesioned mice had increased investigative behavior such as sniffing towards the intruder mice than the control mice.
Conclusions
In this study, we found that lesioning MeA→VMH neurons increased investigative behavior in male mice without affecting aggression. Future studies will investigate the neuronal cell type responsible for this behavior to better understand possible treatments for aggressive behavior in humans.
Fundings
American Diabetes Association

# 2021 Neuroscience Retreat abstract submission

Detrusor Underactivity is Associated with Metabolic Syndrome in Aged Primates

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Background: Lower urinary tract (LUT) dysfunction is responsible for significant morbidity, compromised quality of life, and markedly rising health care costs worldwide in a rapidly growing elderly population. Both overactive and underactive forms of bladder dysfunction may develop with aging, but mechanisms for these detrusor impairments are not well understood.

Methods: We evaluated adult (n=27) and aged (n=20) female rhesus macaques by urodynamic studies and metabolic chemistry markers.

Results: Filling cystometry and pressure flow studies showed increased bladder capacity and compliance in aged subjects, whereas peak pressure and voiding efficiency were similar between the groups. Several metabolic indicators were significantly increased in the aged subjects, including weight, triglycerides, lactate dehydrogenase, alanine aminotransferase (ALT), and high sensitivity C-reactive protein.  Aspartate aminotransferase (AST), cholesterol, and glucose were not different between the cohorts, and the AST/ALT ratio was significantly decreased in the aged group.

Conclusions: Collectively, the metabolic markers suggest the presence of metabolic syndrome in a subset of aged animals. This association was independent history of prior pregnancies, live births, and menopause onset in aged primates. Our findings have implications for the direction of future clinical studies and for the development of new strategies to prevent and treat LUT dysfunction in the elderly.

Funding: AMRF, CIRM, NIH

# 2021 Neuroscience Retreat abstract submission

Pathway-specific chemogenetic neuromodulation enhances working memory in rhesus monkeys

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Background: Acetylcholine plays a critical role in promoting neuronal plasticity. Although systemic pro-cholinergic drugs and electrical deep brain stimulation of the basal forebrain improve memory in nonhuman primates and humans, it has yet to be shown whether circuit-specific activation of a cholinergic neuromodulatory system can improve cognitive performance.

Methods: Using a dual-viral intersectional approach with DREADDs (designer receptors exclusively activated by designer drugs), we reversibly activated projections from the basal forebrain to the dorsolateral prefrontal cortex. We tested whether circuit activation could overcome deficits in a spatial-delayed response task caused by the muscarinic antagonist scopolamine or by presentation of a distractor in two young male rhesus monkeys. Working memory performance was assessed after combined intramuscular injections of either scopolamine and vehicle, the DREADD actuator deschloroclozapine (DCZ) and vehicle, or a combination of scopolamine and DCZ.

Results: Monkeys showed significant working memory deficits following scopolamine. Notably, monkeys showed significant memory improvement after scopolamine plus DCZ injection compared to scopolamine alone, indicating that activation of the target circuit could offset scopolamine-induced memory impairment. In the distractor paradigm, monkeys showed significant improvement in the distractor condition following DCZ injection compared to performance after vehicle.

Conclusions: These findings may provide a novel potential neurotherapeutic approach for circuit-specific treatment of cognitive impairments seen in aging and disease that result from deficits in cholinergic neuromodulation.

Funding: NIH and NIA

# 2021 Neuroscience Retreat abstract submission

Intracranial Signatures of Social Norm Encoding in Human Substantia Nigra and Globus Pallidus

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The ability to dynamically detect and adapt to deviations from norms is imperative to an individual's social functioning. Neuroimaging studies highlighted roles for both midbrain and cortical areas in these processes. However, responses of dopaminergic neurons – the drivers of learning processes – to social rewards and norm-based prediction error, have not been directly measured in humans.

We capitalized on microelectrode recordings during DBS surgery to study neuronal activity intracranially in the human substantia nigra (SN) and globus pallidus (GP) while patients engaged in a social exchange game. Patients (10 sessions in 5 cases) played 30 rounds of the ultimatum game, in which they were offered a split of $20 which they could either accept or reject. Notably, all offers were disadvantageous for the responder (<=$9) thus driving in-session adaptation to suboptimal social rewards.

Accepted offers drove higher population firing rate than rejected ones, in both SN and GP, observable within a timewindow of 250-750 msec post-event. This change in firing rate was proportional to offer size in SN (r=0.198 p=0.009) and GP (r=0.21, p=0.035). Behavioral modeling revealed activity in both SN and GP was negatively correlated with the magnitude of norm-based prediction-error per trial (r=-0276 p=0.005). Taken together, our results imply central roles for these structures in adaptation to violation of social norms.

Funding: NIH

# 2021 Neuroscience Retreat abstract submission

The Long Noncoding RNA, FEDORA, is a Cell-Type and Sex-Specific Regulator of Mood

Issler O, et al.

Nash Family Department of Neuroscience and Friedman Brain Institute

Background: Major depressive disorder, one of the leading causes of disability worldwide, strikes women twice as often as men, yet the molecular mechanisms contributing to this sex difference are poorly understood.

Methods: We performed a bioinformatic analysis of our brain RNA-sequencing (RNA-seq) dataset of human depression. We developed cell-type-specific viral tools to express long noncoding RNA (lncRNA) in mice prefrontal cortex (PFC). Such mice of both sexes were comprehensively phenotyped. Additionally, we tested the blood levels of the lncRNA.

Results: We found a lncRNA (RP11-299D21.1) which is upregulated in multiple brain regions in depressed females only; therefore, we named it FEDORA (FEmale DepressiOn lncRnA). FEDORA is enriched in the brain and is expressed in oligodendrocytes and neurons. We found that expressing FEDORA in the PFC in both cell types promotes depression-like behaviors in females only, which mirrored the human sex-specific phenomenon. However, this phenotype was associated with cell-type-specific transcriptional, electrophysiological, and morphological changes. Furthermore, we found that circulating FEDORA levels are elevated in depressed women-only compared to controls.

Conclusions: Together, these findings support our hypothesis that FEDORA lncRNA plays a key role in depression and contributes to the sex differences in this disorder. Moreover, we suggest FEDORA as a potential sex-specific biomarker for a depression diagnosis. These translational findings provide a new view of molecular adaptations that contribute to depression risk.

Funding: NIMH, HDRF

# 2021 Neuroscience Retreat abstract submission

NEURAL MECHANISMS DRIVING COMORBID PARKINSON'S AND MELANOMA

PAMELA DEL VALLE, JULIE DI MARTINO, GEORGE W HUNTLEY, J JAVIER BRAVO CORDERO, DEANNA L BENSON

DEPT OF NEUROSCIENCE & FBI, HEMATOLOGY AND ONCOLOGY & TISCH CANCER INSTITUTE; GRADUATE SCHOOL OF BIOMEDICAL SCIENCES, MOUNT SINAI

BACKGROUND: Epidemiological studies have shown that people with Parkinson's disease (PD) have a significantly higher risk of developing melanoma and vice-versa. However, research on this comorbidity is sparse. One possible point of convergence lies in the sympathetic nervous system. Studies show that activating sympathetic axons residing in breast adenocarcinomas increases cancer growth and metastasis. Therefore, we hypothesize that a PD environment produces an altered melanoma response 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. The data show that the extent and pattern of melanoma growth is altered significantly in GSKI mice and that tumors have altered patterns of innervation and macrophage infiltration. These and additional data will be used to establish conditions and timing for testing whether LRRK2-G2019S-mediated alterations in melanoma growth lie downstream of local sympathetic axonal activity, and to ascertain whether positive results can be reversed by LRRK2 kinase inhibition, which is significantly elevated with the G2019S mutation.

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

FUNDING: NINDS and Michael J Fox Foundation

# 2021 Neuroscience Retreat abstract submission

Age associated changes to microglia-adenosine based neuromodulation

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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 dysfunction in the aging brain. In support of this idea, we found that microglia are able to regulate neuronal activity 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 this mechanism. Using microglia specific knockout of the rate-limiting enzyme for adenosine generation (CD39), I will investigate the microglial role on adenosine generation in multiple brain regions using in vivo recordings in addition to investigating their impacts on physiological functions such as learning and memory as well as sleep. 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.

Funding: T32AG049688-06

# 2021 Neuroscience Retreat abstract submission

Whole-brain white matter microstructure abnormalities in human cocaine-use disorder

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BACKGROUND: The symptomatology of addiction arises from abnormal functioning of corticostriatal connectivity including in executive control, reward processing and salience attribution networks. Although fMRI studies commonly show functional connectivity impairments in individuals with cocaine-use disorder (iCUD), substantially fewer studies have assessed structural connectivity, especially of white matter (WM) tracts. Our study aimed at using state-of-the-art diffusion MRI analyses to assess whole-brain WM integrity in iCUD.

METHODS: 3T diffusion MRI was acquired in 47 iCUD (current users[N=24]/abstinent users[N=23]) and 47 healthy controls. Diffusion tensors were computed and Tract-Based-Spatial-Statistics was used for whole-brain/voxel-wise analyses of metrics assessing the coherence of water diffusion along specific orientations [FA-fractional anisotropy, MD-mean diffusivity, AD-axial diffusivity, and RD-radial diffusivity]. Permutation statistics (p-corrected) were used for group comparisons and correlations with cocaine-use variables.

RESULTS: Compared to controls, iCUD showed increased AD, MD, and RD ($p<.05$) in all major WM tracts. These results were driven by current users (urine positive>urine negative in AD/MD, $p<.05$). Unexpectedly, RD positively correlated with age of first use ($p<.05$; AD/MD: $p=.05$), whereas AD and MD negatively correlated with days of abstinence ($p<.05$; RD: $p=.07$).

CONCLUSIONS: iCUD showed whole-brain WM impairments defined by less diffusion directionality and increased diffusivity thought to reflect axonal packing attenuation and demyelination. WM association with cocaine-use variables, especially recency, suggests structural connectivity impairments with cocaine use, but also potential adaptation of anatomical networks with abstinence.

FUNDING: NIDA/CIHR

# 2021 Neuroscience Retreat abstract submission

Developmental Trajectory of Attentional Behavior in Mice Revealed by Accelerated Protocol
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Background:Attention is a cognitive process that facilitates the detection of task-relevant sensory information. In psychiatric disorders such as autism spectrum disorder, attention deficits manifest as early as childhood, suggesting a disruption in the underlying neural circuitry during development. However, due to the short developmental window in rodents and lengthy training for operant attention tasks, it has been a challenge to capture the development of attentional behavior using rodent models. In this study, we aim to establish an accelerated attention behavior training protocol to elucidate the developmental trajectory of attentional performance from adolescence to adulthood in male and female wild-type mice.
Method:Using an accelerated protocol, male and female mice are trained to perform a freely-moving attentional task, 5-choice serial reaction time task(5CSRTT), with a translational automated touchscreen system and are tested at adolescence(~p35) and adulthood(~p74).
Results:Male mice show an improvement in attentional behavior from adolescence to adulthood whereas the behavior of female mice remains stable. However, the developmental difference in male mice is no longer visible when a light distractor is introduced during an anticipatory attention period. Notably, adult male performance is particularly vulnerable to the distractor immediately after error trials.
Conclusion:An accelerated 5CSRTT protocol revealed late maturation of attentional behavior in male mice but not in females. Future studies will examine mouse models of neuropsychiatric disorders across development in attentional behavior.
Funding:NIH

# 2021 Neuroscience Retreat abstract submission

Phenothiazines to treat Alzheimer's disease

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Neuroscience ISMMS

BACKGROUND: Current treatments of Alzheimer's Disease (AD) are largely ineffective and do not address underlying pathophysiological processes. The model organism Caenorhabditis elegans has been successfully used to discover compounds to treat human diseases, some now in clinical trials.

METHODS: To develop novel drugs and explore pathways to treat AD, we took on a forward pharmacological approach with a C. elegans model for AD, completed with studies to expand results to lifespan as well as healthspan. We screened 2560 drugs from the Microsource Spectrum library for their ability to delay proteotoxicity (indicated by paralysis) in an Abeta transgenic C. elegans muscle model of AD (CL2006) in liquid medium.

RESULTS: Among the most protective drugs were phenothiazines, which are orally active and cross the blood-brain barrier, desirable properties of drugs to treat AD. 80 phenothiazines congeners were further assessed; 60% were protective in CL2006 worms. 9/20 tested phenothiazines increased lifespan in N2 worms and 2/3 phenothiazines tested promoted significantly higher pharyngeal pumping rates compared with control till day 10 of adulthood in N2 worms. 2 of the drugs were protective in the C. elegans neuronal model of AD.

CONCLUSIONS: This phenotypic screening approach led to the discovery of potential drugs to treat AD. These studies suggest the utility of C. elegans to discover drugs to treat human diseases. Future studies will assess molecular mechanisms mediating the protective effects of these compounds.

FUNDING: NIH

# 2021 Neuroscience Retreat abstract submission

Machine learning identifies SHISA7 as a translational target of heroin abuse directly relevant to drug-seeking and reversal learning

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

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BACKGROUND: Opioid use disorder (OUD) kills 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.

METHODS: Here, we used a machine learning approach with RNA-seq data obtained from human post-mortem OFC tissue to classify subjects as either belonging to the heroin overdose or control group based on the expression of 1-100 genes. We used a translational rodent model of opioid use disorder to study the relationship of identified transcripts to heroin-related and cognitive behaviors.

RESULTS: Three feature (gene) importance metrics from machine learning analyses highlighted SHISA7, an auxiliary subunit of the GABAA receptor, predictive of heroin users. SHISA7 was reduced in the human OFC and in the OFC of rats that self-administered heroin. Further, viral overexpression of SHISA7 in OFC after heroin self-administration training augmented heroin-seeking, along with sucrose reversal learning, demonstrating the direct relevance of this transcript to heroin-related and cognitive behaviors.

CONCLUSIONS: SHISA7, identified using a machine learning-based workflow, represents a novel, translational neurobiological target related to addiction and cognition with particular relevance to heroin-seeking behavior.

FUNDING: NIDA, F31 DA051183; T32 GM062754-19

# 2021 Neuroscience Retreat abstract submission

Machine learning identifies SHISA7 as a translational target of heroin abuse directly relevant to drug-seeking and reversal learning

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

Addiction Institute of Mount Sinai, Icahn School of Medicine at Mount Sinai, New York, NY, USA

BACKGROUND: Opioid overdoses kill more than 47,000 Americans per year. Failure to develop novel treatments for opioid use disorder (OUD) is a result of a lack of understanding the molecular pathophysiology of OUD, a complex disorder that involves dysregulation of reward and neurocognitive processes.

METHODS: Here, we used a machine learning approach with RNA-seq data obtained from human post-mortem OFC tissue to classify subjects as either belonging to the heroin overdose or control groups based on the expression of 1-100 genes. We used a translational rodent model of OUD to study the relationship of identified transcripts to heroin-related and cognitive behaviors.

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FUNDING: NIDA, F31 DA051183; T32 GM062754-19

# 2021 Neuroscience Retreat abstract submission

Microbiome knockdown reduces opioid reward and histone acetylation in an age-specific manner

Rebecca S. Hofford, Drew D. Kiraly

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Background: Adolescence is a period of significant development and corresponds to a time of high rates of onset of mental health disorders. In addition to maturation of several crucial brain areas, there are major changes occurring in organ systems throughout the body – including major shifts in the composition of the gut microbiome. New data suggests that the microbiome and its metabolites the short-chain fatty acids (SCFA), can affect drug reward. Yet it is unknown if perturbation of the microbiome might influence opioid reward in an age-dependent manner.

Methods: To test this, adolescent and adult mice were given a cocktail of broad-spectrum antibiotics (Abx) in their drinking water to reduce gut microbial bulk and diversity. After five days of Abx, mice underwent morphine conditioned place preference (CPP) and their medial prefrontal cortex (mPFC) were collected for measurement of histone acetylation using Western blot.

Results: Abx-exposed adolescent mice showed reduced morphine reward. This period of microbiome knockdown did not significantly alter morphine CPP in adult mice at any dose. Additionally, adolescent mice with microbiome knockdown had reduced levels of H3K27 acetylation and adolescents had lower levels of in H3K9 acetylation regardless of treatment.

Conclusion: Together, this suggests that adolescents are more sensitive to the behavioral and neurobiological effects of gut microbiome reduction and suggest that SCFA might be an important mediator of gut-brain signaling in adolescents.

Funding: NIDA and BBRF

# 2021 Neuroscience Retreat abstract submission

Auditory Mismatch Negativity Deficits in Individuals at Clinical High Risk for Psychosis Their Correlation Symptom Severity and Cognitive Dysfunction

Riaz Shaik1, Muhammad Parvaz1, Zarina Bilgrami1, Shaynna Herrera1, Cansu Sarac1, Agrima Srivastava Srivastava1, Shalaila Haas1, Javier Lopez-Calderon1, Cheryl Corcoran1

Background: Sensory processing deficits are core features of schizophrenia, reflected in impaired generation of EEG-derived event-related potentials such as the auditory mismatch negativity (MMN), a robust predictor of psychosis onset in clinical high-risk (CHR) cohorts. We examined auditory MMN in two CHR cohorts, collected at Columbia University and Mount Sinai, and assessed MMN deviants and their association with prodromal symptom severity and cognition.

Methods: Participants included fifty-two CHR and 27 healthy controls who completed an auditory MMN paradigm with deviants in duration, frequency, intensity, frequency modulation, and change of location (right and left). Clinical symptom severity in CHR assessed using the SIPS and Cognition measured by MATRICS. Group differences assessed by multivariate analysis of covariance and MMN association with clinical symptoms were determined using partial correlations, with sites as covariates.

Results: Significantly reduced MMN in CHR for the duration (p=.009) and Right location (p=.023). Among CHR patients, MMN duration is correlated with higher SIPS total positive (p=.006), Negative Symptoms (p=.006), MMN Right location with negative symptoms Social Anhedonia (p=.041).

Conclusion: Duration and Right location MMN significantly reduced in CHR patients. Duration MMN is among the most replicated biomarkers of psychosis risk; current results extend our understanding regarding MMN to other deviants and their association with more severe clinical symptoms.

FUNDING: R01MH107558(CMC), R01MH49334(DCJ)

# 2021 Neuroscience Retreat abstract submission

## Pancreatic Neural Circuitry in Obesity and Diabetes

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

Diabetes Institute & Neuroscience

BACKGROUND: Pancreatic islets are richly innervated. 2D immunohistochemistry and the use of extreme models of obesity and diabetes have limited our understanding of pancreatic nerve anatomy. Additionally, our knowledge of the roles of pancreatic nerves in regulating pancreatic function is incomplete. Determining how high-fat diet (HFD) impacts pancreatic nerve structure and function will provide novel insights into the mechanisms and pathophysiology of diabetes.

METHODS: To test the hypothesis that HFD causes structural changes in pancreatic innervation, C57Bl6 mice were randomized to HFD or low-fat diet (LFD) groups. Metabolic phenotyping was determined. Pancreata were cleared and immunolabeled using iDISCO+ and imaged by lightsheet microscopy.

To test the roles of pancreatic parasympathetic nerves on islet hormone release and the effects of HFD, cre-dependent hM3D(Gq)-mCherry or mCherry viral constructs were injected into the pancreatic duct of ChAT-IRES-cre mice. ChAT-cre mice were fed a LFD or HFD and the effects of neuromodulation were assessed.

RESULTS: HFD significantly impairs glucose tolerance and insulin sensitivity. Within islets, 4 week HFD increases sympathetic nerve volume and reduces parasympathetic nerve volume.

Targeted activation of pancreatic parasympathetic nerves improves insulin secretion and glucose tolerance.

CONCLUSIONS: HFD remodels pancreatic innervation and these changes may contribute to insufficient insulin release to maintain normoglycemia. Targeted activation of pancreatic parasympathetic nerves improves glycemic control. Future studies will assess pancreatic nerve structure and function with long-term HFD-induced diabetes.

FUNDING: NIH, ADA

# 2021 Neuroscience Retreat abstract submission

Regulation of Striatal Circuit Architecture by Cadherin-8

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The corticostriatal network is necessary for a diversity of motor and executive tasks and is vulnerable to developmental disorders. Yet, the systematic mapping of the establishment of mPFC-Striatal connections at early postnatal stages, and the molecules guiding such development, remain to be clarified. By visualizing the axons of virally-tagged mPFC projection neurons in WT mice, axonal innervation and striatal topographic patterning in striatum were quantified at different postnatal stages (P7-P56) using a combination of stereological approaches, immunofluorescence and a novel clustering algorithm. Our results suggest that mPFC axons target correctly the dorsomedial striatum at the earliest ages examined, with subsequent directed growth of terminal fibers through later ages. We previously showed that Cadherin-8 (Cdh8), an autism-linked gene and type II classical Cadherin, is enriched in corticostriatal neurons and in striatal spiny projection neurons (SPNs). We hypothesized that ablation of Cdh8 would alter axon targeting to, and functional connectivity with, the striatum. Preliminary work in a pre-synaptic (cortical L5) Cdh8 conditional knockout (cKO) mouse model reveals a profound deficit in axon innervation of the striatum by P56. Functionally, presynaptic Cdh8-cKO reduced sEPSC frequency recorded from dorsomedial SPNs at P21. These data may contribute to behavioral deficits observed in Cdh8 haploinsufficient patients with autism.

Funding: 1R01MH104491; F31MH115541; Autism Speaks#10544

# 2021 Neuroscience Retreat abstract submission

Inhibition of gamma-secretase and PS1 FAD mutant decrease VEGF-induced angiogenesis in brain endothelial cells

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Abstract
Background: Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder. Accumulating evidence shows microvascular abnormalities and reduced vascular density in human AD brains suggesting impaired angiogenesis. Vascular Endothelial Growth factor (VEGF), is the most important angiogenic factor which acts via its receptor VEGFR2, a type I transmembrane protein (TMP). We found that VEGFR2 is proteolyticaly processed by Presenilin 1 (PS1)/γ-secretase in primary cortical endothelial cells (pCEC) and that a PS1 mutant linked to Familial AD (FAD), decreases this processing. We hypothesize that PS1 FAD mutants decrease the VEGF-induced angiogenic functions of pCEC.
Methods: pCEC were cultured from wild type (WT) and PS1 M146V mutant knockin mouse brain, a "humanized" FAD mouse model. In vitro angiogenesis assays (sprouting, migration and tube formation) were performed. VEGFR2 processing was detected by western blot.
Results: We found that VEGFR2 is processed by γ-secretase and that VEGF-induced angiogenic functions decrease by inhibition of γ-secretase and in PS1 M146V pCEC.
Conclusions: The effects of PS1 FAD mutant on the angiogenic functions of pCEC occur in the absence of amyloid plaques and neurofibrillary tangles indicating that these mutants affect angiogenesis independently of the neuropathological hallmarks of AD. Targeting brain angiogenesis could have therapeutic value in AD.
Funding: NIH 0255-1814 and 02-55-9314

# 2021 Neuroscience Retreat abstract submission

Modeling the Impact of Schizophrenia Risk Variants in the 3D Genome with hiPSC-Derived Neuronal Subtypes

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Background: Genetic risk loci for schizophrenia are overrepresented among non-protein-coding regions of the genome, including those involved in 3D chromatin structures that regulate gene expression. The impact of these loci on the 3D genome (3DG) remains largely unknown. We sought to map the 3DG in dopaminergic, GABAergic, and glutamatergic neurons and test potential functional roles of risk locus-anchored chromatin structures using CRISPR-based techniques.

Methods: Dopaminergic, GABAergic, and glutamatergic neurons were successfully generated from hiPSCs. RNA-sequencing and in situ Hi-C were employed to profile gene expression and chromatin structure, respectively, genome-wide. Chromatin loop reorganization using CRISPR-dCas9 (CLOUD9) enabled the rearrangement of chromatin interactions for functional analyses.

Results:  Each subtype of neuron exhibited differential gene expression among biological pathways corresponding to its cell type identity. Specifically expressed genes in dopaminergic, GABAergic, and glutamatergic neurons showed heritability enrichment in multiple psychiatric disorders. Hi-C assays demonstrated 3DG structures that were unique to each neuronal subtype; mapping schizophrenia risk loci to the 3DG revealed potential gene targets. Preliminary results using CLOUD9 demonstrate its feasibility for experimentally testing the functions of risk loci overlapping 3DG structures.

Conclusions: Specific subtypes of neurons show unique gene expression and 3D chromatin profiles. Hi-C provides structural evidence of putative gene targets of risk loci participating in 3DG structures.

Funding: NIMH, NIDA.

# 2021 Neuroscience Retreat abstract submission

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

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BACKGROUND: Most neuropsychiatric disorders are moderately heritable but characterized by many genetic risk variants with weak effects. Despite the ease in gathering genetic data from humans, genetic data does not easily explain mechanistic effects. Gene expression on the other hand, can more easily explain mechanistic effects, but is harder to gather, especially in brain regions which 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 three hundred thousand European individuals in the Million Veteran Program (MVP).

METHODS: We use EpiXcan (based on PrediXcan) to develop machine learning models. We use custom scripts to impute individual GREx and perform a variety of downstream association analyses, including PCA, GREx PheWAS, and Transcriptome Wide Association Studies (TWAS).

RESULTS: Results show an overlap in Schizophrenia genes identified by TWAS and those identified by GWAS. Single gene imputation efforts confirm clinical results obtained from COVID-19 positive individuals.

CONCLUSIONS: 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.

FUNDING: NIH, US Department of Veterans Affairs, Brain & Behavior Research Foundation

# 2021 Neuroscience Retreat abstract submission

Title: A Psychological and Computational Characterization of Misophonia

Authors: Sarah M. Banker, Soojung Na, Jennifer Foss-Feig, Xiaosi Gu, Daniela Schiller

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Background: Misophonia is a syndrome in which specific sounds lead to strong negative physical and/or emotional responses. Individuals with misophonia typically show the greatest intolerance to sounds produced by social others, such as chewing or clicking a pen. To date, misophonia is largely uncharacterized.

Methods: Herein, we use large-scale online assessment to characterize misophonia. A total of 1,175 participants completed questionnaires assessing symptoms of misophonia and 13 other psychiatric conditions. A factor analysis including each individual question from the surveys was used to identify latent constructs underlying these symptoms. Additionally, an interactive social controllability task probed the role of control within social environments.

Results: Three dissociable factors were extracted from the data, which we labeled “Mood”, “Social Withdrawal”, and “Misophonia/Obsessive Compulsive Behavior” based on the individual items that loaded most highly. Participants were divided into two groups based on the lowest and highest quartile of scores on the “Misophonia/Obsessive Compulsive Behavior” factor (n=261 per group). Linear regression probed group differences in task performance. Compared to individuals in the lowest quartile, those in in the highest quartile reported a higher level of perceived control during the condition in which they were actually unable exert control ($t=3.832$, $p<0.001$).

Conclusions: These results suggest misophonia and OCD symptoms may represent a latent psychiatric dimension characterized by maladaptive exertion of control.

Funding: The Ream Foundation.

# 2021 Neuroscience Retreat abstract submission

Resting State EEG Power Abnormalities in DDX3X Syndrome

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Background: DDX3X syndrome is a rare genetic disorder associated with developmental delay, intellectual disability, and autism spectrum disorder (ASD). While previous research has characterized the behavioral and phenotypic profile of this syndrome, there is a lack of clinical research examining underlying neural systems that may account for these symptoms.

Method: This study aimed to characterize neurobiological markers of DDX3X syndrome by examining resting-state electrophysiological (EEG) data. EEG was recorded for 5 minutes from DDX3X (N= 5) and typically developing (TD) (N= 13) participants seated in a dark room watching a silent video of their choice.

Results: Relative power was calculated for delta (.4-4hz), theta (4-8hz), alpha (8-12hz), beta (12-30hz), and gamma (30-50hz) frequency bands from an average of 22 electrodes evenly distributed across the scalp. Compared to TD, the DDX3X group showed significant reduction of power in the alpha ($t=3.12$, $p=.02$) and beta ($t=2.81$, $p=.02$) bands, and significantly enhanced delta power ($t=-2.48$, $p=.04$). No significant between-group differences were found in theta or gamma bands.

Conclusions: Results suggest that individuals with DDX3X syndrome differ from TD controls in baseline neural power across several frequency bands. This finding highlights the potential for resting EEG data to characterize neurophysiological processes of this syndrome and their convergence and divergence from idiopathic ASD and other related genetic disorders.

Funding: Beatrice and Samuel A. Seaver Foundation

# 2021 Neuroscience Retreat abstract submission

Prefrontal-Habenular Track Abnormalities Associated with Drug-Seeking and Recent Use in Cocaine Addiction

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BACKGROUND: Addiction encompasses impairments in reward valuation contributing to preference for drugs over alternative rewards. The lateral habenula(Hb) conveys reward-related information from the prefrontal cortex(PFC) to subcortical limbic system, and its functional impairment predicts drug-use and drug-seeking in preclinical addiction models. We performed high-resolution diffusion-tractography in 31 individuals with cocaine-use disorder(CUD; 15 urine-negative/16 urine-positive for cocaine) and 29 controls(CTL) and evaluated self-reported drug-use and objective choice-bias for drug versus alternative reinforcers.

METHODS: PFC-Hb track reconstruction was performed and fractional anisotropy(FA) computed to evaluate diffusion coherency in PFC white matter and subcortical fiber bundles, including stria medullaris(SM) and internal capsule-anterior limb(ALIC). A subset (22 CUD/24 CTL) performed a task measuring preferences for viewing cocaine and alternative high-value (food) and low-value (threat) salient cues over a neutral image to measure drug-seeking.

RESULTS: Compared to CTL, right-hemisphere track FA was reduced overall in CUD (p=.001), driven by reductions in SM (p=.030) and ALIC (p=.018). FA reductions were driven by urine-positive CUD in SM, and urine-negative CUD in ALIC. In right SM, FA reductions correlated with increased drug-versus-food preference (driven by CUD: r=-0.45, p=.035) and more recent cocaine use (r=-0.46, p=.009) in CUD.

CONCLUSION: Prefrontal-habenular white matter showed microstructural abnormalities in CUD. In SM, deficits were driven by shorter abstinence/more recent drug-use and drug-seeking, whereas in ALIC these abnormalities may reflect longer-term/predisposing factors.

FUNDING:NIH/NIDA

# 2021 Neuroscience Retreat abstract submission

Mesolimbic circuit dynamics underlying individual alcohol drinking

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Background: Harmful alcohol use remains a serious public health issue, resulting in 3 million deaths globally per year. A hallmark of the progression of Alcohol use disorder (AUD) is the dysfunction of dopamine (DA) neurons projecting from the ventral tegmental area to the nucleus accumbens (VTA-NAc), a neural circuit critical to encoding the rewarding properties of both drug and naturalistic stimuli. However, the mechanisms underlying why one individual will succumb to AUD while another will not remain vague.
Methods: Utilizing cell- and circuit-specific fiber photometry in freely moving mice and in vivo electrophysiology, we performed longitudinal assessments of the neural and behavioral signatures that predict low or high voluntary alcohol drinking behavior and how these signatures adapt following alcohol consumption.

Results: We show that unique behavioral responses to natural reward and the associated temporal dynamics of the VTA-NAc DA circuit predict the future development of alcohol drinking phenotype. Further, we see divergent neuroadaptations across individuals consecutive to the emergence of individual alcohol drinking phenotype.

Conclusions: By assessing mesolimbic circuit dynamics before and after alcohol drinking, this study will provide novel insight into the neural and behavioral risk signatures for the future development of alcohol misuse, as well as uncover novel mechanisms harnessed by individuals that are resilient to consuming high levels of alcohol.
Funding: NIAAA F31

# 2021 Neuroscience Retreat abstract submission

Title: Extended Amygdala Gates the Affective Consequences of Chronic Psychological Stress

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Background: Chronic Stress is a key risk factor for the development of Major Depressive Disorder (MDD) and one's capacity to cope is compounded by the deleterious effects of stress accumulation. While studies have examined individual differences in stress vulnerability, very little is known regarding the substrates that underlie the psychological capacity to manage continuous and unrelenting stress exposure.

Methods: We used Repeated Social Defeat Stress, patch-clamp electrophysiology, chemo- and optogenetics, combined with fiber photometry to observe and mimic neuroadaptive changes in male c57/bl6j mice.

Results: We observed that the neuronal excitability of CRF neurons of the BNST changed concomitantly as mice developed either susceptible or resilient phenotypes. Cell-type-specific chemo- and optogenetics produced resilient/susceptibility in a robust bidirectional manner thereby reproducing the effect. Fiber photometry revealed that BNSTovCRF neuroadaptive changes were specific to social context. Lastly, optical real-time place preference showed that BNSTovCRF neuroadaptation was correlated with a shift in aversive to appetitive states.

Conclusions: We uncovered that the behavioral display of resiliency may be a consequence of an alteration in the emotional experience of stressful contexts as being less aversive, via neuroadaptation in BNSTovCRF neurons.

Funding: This work is funded by the NIH (F31MH114624) and (R01MH120637)

# 2021 Neuroscience Retreat abstract submission

Autophagy Kinase ULK1 Modulates Mutant Huntingtin Aggregate Clearance and Offers Neuroprotection in HD Mouse Model

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Background: Huntington's Disease (HD) is a neurodegenerative disease caused by the expression of mutant Huntingtin (mHTT). mHTT triggers proteotoxic stress in brain and cause neurotoxicity. Autophagy clears protein aggregates, including mHTT aggregates, offering neuroprotection. Autophagy thus emerges as therapeutic targets for human diseases associated with protein aggregates (proteinopathies). However, the exact mechanism for the clearance of protein aggregates through autophagy degradation is poorly understood. ULK1 is autophagy protein kinase that regulates initiation of autophagy. ULK1 modulates clearance of toxic protein aggregates by phosphorylating autophagy proteins p62 and Atg14.

Methods: We crossed Q175 HD models to ULK1KO (knockout) and ULK1TG (overexpression transgenic) mouse lines, respectively, to study the effect of loss of function and over-expression of ULK1 in mHTT clearance and neuroprotection. We performed mouse behavior, brain pathology, transcriptomics and Western blot in the striatum and cortex.

Results: Loss of ULK1 causes a reduction of the body weight, impairment of grip strength, worse striatal atrophy, and increase of mHTT protein in the striatum and cortex. Overexpression of ULK1 results in a decrease of mHTT levels and enhancement of autophagy activity.

Conclusions: ULK1 plays a critical role in modulating mHTT aggregate clearance through autophagy regulation, thus offering neuroprotection. Enhancing ULK1 levels and activity should be investigated as a therapeutic strategy for the treatment of Huntington's disease.

Funding: CHDI Foundation, NIH

# 2021 Neuroscience Retreat abstract submission

Title: Neurotoxic astrocytes secreted glypican-4 drives Alzheimer's tau pathology

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Background: Apolipoprotein E4 (APOE4) is the most crucial genetic risk factor of late-onset Alzheimer's disease (AD). However, the exact mechanisms through which APOE4 induces AD risk remains unknown. Here, we report that the astrocyte-secreted protein glypican-4 (GPC-4), a novel binding partner of APOE4, drives tau pathology.

Methods: We have taken genetic mouse models, astrocytes and neuronal culture, and biochemical approaches to demonstrate the role of GPC4 in tau pathology.

Results: GPC-4 selectively interacts with APOE4 isoform and regulates APOE4-mediated cellular surface trafficking of APOE receptors. The astrocyte-secreted GPC-4 induced both tau accumulation and propagation in vitro and in vivo. Further, GPC-4 is necessary for APOE4-mediated tau uptake and propagation. APOE4-carring AD patients display higher levels of GPC-4, primarily in neurotoxic astrocytes, and NF-κB signaling pathway regulates the expression of GPC-4.

Conclusion: Together, our data comprehensively demonstrate that one of the key APOE4-induced AD risks is directly mediated by GPC-4.

# 2021 Neuroscience Retreat abstract submission

Impaired Arbitration Between Decision-Making Strategies In Alcohol And Cannabis Users: A Preliminary Computational Modeling Study

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Background:  Recent advances in reinforcement learning dissociate between habitual (model-free) processing and goal-oriented (model-based) planning, whereby the reliance of model-based control is increased under high stakes conditions. However, it remains to be studied how addicted individuals arbitrate between model-free and model-based control under higher stakes of reward.

Methods: Thirty-eight (median age: 25–30 years; 83% females) performed a decision-making task tracks the arbitration between model-based and model-free strategies (Kool, et al., 2016) under different reward conditions. Participants were grouped by AUDIT and CUDIT scores [substance users (n=18) and non-users (n=20)]. A dual-system reinforcement-learning model was used to assess the degree of model-based control (weighting parameter 0 to 1) between the low, high stakes.

Results: A significant stakes by group interaction (F=4.44, p=.042) was observed, driven by a significantly increased model-based control for high compared to low reward stakes in non-users (t=2.49, p=.022), and not in substance users (p=.561).

Conclusion: The results show unlike non-users, alcohol and cannabis users did not engage in greater goal-oriented control when the stakes were higher, and instead used the less cognitively taxing, but more error-prone, habitual approach. Such lack of model-based control may underpin maladaptive decision-making in alcohol and cannabis users. Work is in progress to further characterize this behavior by examining the role of impulsivity and reward sensitivity in substance users.

# 2021 Neuroscience Retreat abstract submission

The bitter taste receptors regulate the addictive properties of nicotine

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The taste system guides ingestive behaviors to ensure survival, ie: reinforcing intake of sweet, salty, and umami flavors, which represent carbohydrates, electrolytes, and protein respectively, while avoiding strongly sour and bitter tastes which through evolution often represented spoiled or poisonous compounds. This gustatory system may not only apply to ingestive behaviors, but general consummatory behaviors which include substances of abuse. The relevance of the taste system to substance use is supported by many addictive drugs being plant alkaloids with a strongly bitter taste; taste receptors are not only expressed in the oral cavity, but systemically, and may respond to circulating drugs. Here, we provide evidence that drugs of abuse like nicotine, cocaine, oxycodone, and caffeine increase intracellular calcium in an alpha-gustducin-bitter taste receptor (Gnat3-T2R) dependent manner. With pharmacological antagonism, global KO, or ventricular-oral CRISPR mediated knockdown of the Gnat3-T2R complex, measures of nicotine aversion reduced, nicotine preference and nicotine taking behavior enhanced. These behavioral findings were accompanied by reduced neuronal recruitment in the nucleus of the tractus solitarius and altered cholinergic expression. These data suggest that the bitter taste receptor complex may influence nicotine taking behavior, and moreover that the gustatory system may not only guide ingestive behavior, but consumption of substances via different routes.

Funding: NIH and CIHR

# 2021 Neuroscience Retreat abstract submission

An atlas of human cortical glial lineage specification resolved by single nucleus transcriptomics

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Background: Single-cell transcriptomics have provided insight into the cellular diversity of the adult neocortex and contributed to our understanding of fetal corticogenesis. As these studies have thus far have been limited to earlier stages of development (up to 28 gestational weeks [GWs]), a primarily neurogenic period, we have yet to resolve the diversity of glial cell types in the late gliogenic period.

Methods: We collected human fetal cortices, ranging from 17 and 41 GWs in age, and isolated >180,000 nuclei from the germinal matrix and cortical plate. For comparison, we isolated >25,000 nuclei from the subventricular zone and cortex of the adult cortex and performed parallel single-nuclei RNA-seq analyses to ascertain spatiotemporal transcriptomic changes and reconstruct gliogenic lineages during corticogenesis.

Results: Our cell type proportion analysis reveals a neurogenic to gliogenic switch at mid-gestation. Using lineage reconstruction methods, we identify a gliogenic intermediate progenitor cell (g-IPC) with bipotent potential that differentiates into astrocytes and oligodendrocyte precursors. g-IPCs are highly proliferative and transient, as their transcriptomic signature is no longer detected in the adult neocortex.

Conclusions: g-IPCs are functionally analogous to their neurogenic counterpart (n-IPCs). Further experimentation will be required to validate their bipotency in situ and their contribution to third trimester cortical expansion.

Funding: NIH

# 2021 Neuroscience Retreat abstract submission

Altered AMPA receptor trafficking associated with Parkinson's disease LRRK2-G2019S mutation in the striatum

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Parkinson's disease (PD) is the fastest growing neurological disorder and despite its first description in 1817, etiology and treatments remain elusive. Although PD in humans is predominantly sporadic, identification of multiple pathogenic gene loci has prompted the use of animal models to study PD pathogenesis. Studies in humans and PD animal models show altered excitatory corticostriatal pathways and have implicated vesicle trafficking defects. Thus, we have been examining whether PD-associated increases in LRRK2 activity caused by the common G2019S variant disrupts AMPAR subunit composition and activity-dependent trafficking at identified cortico-striatal projection neuron (SPNs) synapses. Under resting conditions, surface GluA1 levels are significantly and selectively increased in the striatum of Lrrk2G2019S mice (KI) compared to WT. Total levels are unchanged. These results are corroborated by whole-cell patch recordings in D1 SPNs, which show increased sensitivity to a calcium-permeable AMPAR (lacking GluA2 subunit) blocker in KI compared to WT. Consistent with deficient LTP in KI mice, surface GluA1 levels fail to increase in KI compared to WT cortico-striatal cultures following chem-LTP. On-going experiments will identify the role of Lrrk2 phosphosubstrate Rab8, an endosomal protein that can regulate activity-dependent synaptic AMPAR trafficking and rescue altered AMPAR biology at the synapse using pharmacology.

Funding: R01NS107512

# 2021 Neuroscience Retreat abstract submission

Stem Cell Culturing Robot

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Background: Differentiating stem cells is a challenging, time-consuming process that requires researchers to treat cells with exact measurements of fluids at specific times daily. Because of these rigid requirements, it is a difficult task that is subject to human error. Thus, our objective is to automate this process with a low-cost robot.

Methods: This stem cell culture robot is designed using computer modeling software (Fusion360) and is being built from off-the-shelf and custom parts made by 3D printing (Ultimaker 3).

Results: Fitting within a standard incubator, the robot holds 70 culture plates stacked on shelves. Plates are selected and transported around the incubator by a conveyor belt, electromagnet, H-Bot mechanism, and ball screw. Plates travel to a culturing section inside the incubator where two needles move to each well using a 5 bar parallel mechanism and a lead screw to take liquid in or out. The liquid is pulled in from selectable aliquots in a nearby refrigerator. The plate can also move to a microscope section inside the incubator, so researchers can remotely view the progression of their cells.

Conclusions: This project has the potential to help bridge the gap between industrial and academic stem cell research because it will offer a cheaper and smaller alternative to the large, complex, and expensive cell culture robots used in the pharmaceutical industry.

Funding: NIH, NSF-CASIS

# 2021 Neuroscience Retreat abstract submission

Title: Crem Isoform Dysregulation in the Nucleus Accumbens Mediates Impulsivity and Heroin Self-Administration Vulnerability
Authors: Tanni Rahman, Yanhua Ren, Joseph Landry, Yasmin L. Hurd
Affiliations: Departments of Psychiatry and Neuroscience, Addiction Institute, Icahn School of Medicine at Mount Sinai.

Background: Impulsivity, mediated partly by the nucleus accumbens core (NAcC) and shell (NAcS), has demonstrated to be a risk factor for addiction. We previously linked the cAMP Response Element Modulator (Crem) gene to impulsivity and heroin addiction. However, limited information exists regarding the function of Crem isoforms, CremT and Icer, in these behaviors.

Methods: We utilized a rodent ADHD model, comprising the spontaneously hypertensive rats (SHRs) and Wistar Kyoto rats (WKYs). Impulsive behavior and sub-regional Crem isoform expression were studied.

Results: While CremT mRNA was reduced in the SHR's NAcC, NAcS, and dorsal striatum (DS), no correlations were observed between CremT and impulsive choice. Next, Crem isoforms were measured in relation to impulsive action by dichotomizing the behavior into low or high impulsive action groups. Icer was reduced in the NAcC, but not the NAcS or DS, of rats in the high impulsive action group. Interestingly, results also highlighted individual differences in impulsive action in WKYs; SHRs had high variability of impulsive action. Moreover, Icer expression in the NAcC negatively correlated with impulsive action in WKYs. Subsequent over-expression of Icer in the NAcC neurons of WKYs reduced impulsive action.

Conclusions: Future directions will investigate Icer's role in heroin self-administration behavior and differences in neural activity with in-vivo fiber photometry.

Funding: NIH

# 2021 Neuroscience Retreat abstract submission

Title: Trauma has differential effects on aversive and non-aversive stimulus association learning
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Background: Post-traumatic stress disorder is highly comorbid with substance use disorder. Despite this phenomenon being well documented, little is known about the mechanisms that support the interaction between these two disorders. Acute traumatic events are known to sensitize aversive learning systems, and to predispose individuals to develop PTSD. Since there are overlapping brain regions that support both aversive and appetitive stimulus associations, we asked whether an acute trauma can enhance both aversive and appetitive learning.

Methods: Mice experienced either an acute traumatic or neutral experience. We then tested whether trauma altered subsequent learning to associate an aversive stimulus (loud auditory noise) or an appetitive stimulus (cocaine) paired with a context.

Results: As expected, the trauma enhanced subsequent aversive learning (higher freezing in the context paired with the loud noise). Interestingly, the trauma did not alter appetitive learning (as measured by the preference for the chamber paired with cocaine).

Conclusions: In our model of acute trauma, we found long-lasting enhancement on subsequent aversive but not appetitive learning. However, further studies are needed to validate and characterize the effects of trauma on different forms of associative learning.

Funding: DC's NIH with diversity supplement, FBI, Mount Sinai, One Mind Rising Star Award, NARSAD, McKnight Foundation, Brain Research Foundation.

# 2021 Neuroscience Retreat abstract submission

Examining the role of hypoxia induced genes, CXCR4 and NXPH4, in cell invasion in glioblastoma patient derived stem cells

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Hypoxia has been associated with adverse effects in tumor biology by exaggerating the capability of invasion, proliferation, and survival of tumor cells within the tumor microenvironment. Our studies are focused on the implication that hypoxia induced genes, CXCR4 and NXPH4, are being upregulated due to exposure to hypoxia in order to allow glioblastoma patient derived stem cells, SD3, to become more aggressive and resistant to conventional forms of therapies. This glioma stem cell line will be transduced with a Lenti-virus-CXCR4-Dox inducible knockdown or a Lenti-virus-NXPH4-Dox inducible KD and test for reduced invasion and overall tumor burden in SCID mice after intracranial injections.

3D invasion assays, RNA sequencing analysis, Western blots, orthotopic intracranial injections in SCID mice, Lenti-virus-CXCR4-Dox inducible KD, Lenti-virus-NXPH4-Dox inducible KD, histology, and quantification of invasion, growth

Our hypothesis, based on preliminary data, suggests that our glioma patient derived stem cell, SD3, relies on CXCR4 and NXPH4 to be able to upregulate their invasive/migratory ability that is triggered when responding to hypoxic stress.

National Institute of Neurological Disorders and Stroke

# 2021 Neuroscience Retreat abstract submission

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 medium spiny neurons (MSNs) 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 RIMS 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. 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 regulate mitochondrial-mediated bioenergetics. Currently, we are exploring the role for circRIMS2 in regulating mitochondrial function with respect to stress-induced behavioral abnormalities.
Conclusions: circRIMS2 levels in the NAc are highly responsive to stress, and circRIMS2 acts in this area to regulate depression-related behavioral abnormalities.
Funding: NIH

# 2021 Neuroscience Retreat abstract submission

Microbiome knockdown alters cortical transcriptomic response to morphine in adolescent and adult mice

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BACKGROUND: Adolescence is a time when substance use disorders often present. As the medial prefrontal cortex (mPFC) is undergoing rapid development during this time, it may be critical for development and maintenance of drug abuse during this time. Peripherally, the gut microbiome is also undergoing dynamic changes during adolescence in ways that alter gut-brain signaling. Since both the microbiome and the brain are undergoing drastic changes during this time of life, gut-brain signaling may be particularly important in adolescents.

METHODS: To test effects of the microbiome adult and adolescent mice were given an antibiotic cocktail in their drinking water (Abx) or remained on regular water ($H_2O$). After 5 days, mice received injections of 15 mg/kg morphine or saline for 5 days. Using RNA-sequencing of the mPFC, we compared gene expression of adult and adolescent mice receiving $H_2O$ or Abx and saline or morphine.

RESULTS: Adolescent Abx+Morphine mice had 2,732 differentially expressed genes compared to controls. Adult Abx+Morphine mice had 918 differentially expressed genes compared to controls, suggesting that the combination of Abx and Morphine had a greater effect on brain transcriptomics in adolescents than adults. Using Gene Ontology analysis, we found that adolescent Abx+Morphine mice had an increased number of regulated genes related to transcription and to histone modification.

CONCLUSIONS: These results suggest adolescents are particularly susceptible to effects of gut-brain signaling following opioids.

FUNDING: NIDA

# 2021 Neuroscience Retreat abstract submission

Ensemble activity patterns underlying spatial navigation and reversal learning in aged and young adult mice

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BACKGROUND: Aging is often accompanied by cognitive decline. The hippocampus is particularly afflicted during aging, resulting in impaired memory functions in rodents, non-human primates, and humans. In rats, aging reduces the reliability of hippocampal activity patterns possibly contributing to deficits in spatial navigation and reversal learning. Here, we sought to investigate the neural signatures of memory persistence and reversal learning in aged versus young adult mice.

METHODS: We used calcium imaging with head-mounted Miniscopes to study stability of hippocampal activity patterns in aged and young adult mice navigating to spatial goal locations for rewards. After multiple days of this training, mice are forced to ignore the old goal locations and navigate to new ones for reward (reversal learning). We applied computational analyses to calcium traces of hundreds of simultaneously recorded neurons during task running to detect co-activations of cell populations comprising neuronal ensembles.

RESULTS: Mice consistently learn the task and slowly learn the new goal locations during reversal learning. Preliminary evidence suggests that repeatable ensemble activations observed during the task may be associated with memory retrieval and reversal learning.

CONCLUSIONS: We are characterizing differences in aged versus young adult mice in the rate of reversal learning and patterns of ensemble activation. We expect reduced persistence of ensemble activity in aged compared to young adult mice.

FUNDING: NIA

# 2021 Neuroscience Retreat abstract submission

The Landscape of Autophagy Degradation and Regulation in Neurons

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Autophagy is a fundamental lysosomal degradation pathway that declines over aging and is often disrupted in neurodegenerative diseases. Regulation of autophagy in CNS neurons, particularly human neurons, remains poorly defined. The mechanism on how autophagy is involved in neurodegenerative disease remains unclear.

To study neuron-type specific vulnerability to autophagy deficiency, we firstly focused on one of the major neuronal types - the glutamatergic neurons in the brain and generated human neurons from pluripotent stem cells. To enrich autophagy cargo, we suspended autophagy in neurons using CRISPR-inhibition technology to knockdown ATG7, ATG14.  Floxed Atg7 and Atg14 mice were crossed with Synapsin::Cre mice to generate neuron-specific ATG7 or ATG14 conditional knockout (cKO) mice. To enrich autophagosomes in autophagy-deficient mice, we obtained brain tissues from GFP-LC3-expressing ATG7 cKO mice. Quantitative mass-spectrometry analysis was performed to identify proteins in ATG7 or ATG14-deficient human or mouse neurons.

Accumulations of known autophagy-associated proteins were observed in autophagy-deficient neurons. Intriguingly, novel autophagy cargoes and adaptors involved in pathways including ER-phagy (FAM134B and TEX264), synaptic function (Neurexins and Synaptophysin), and neurodegenerative diseases (VPS35) were identified.

Our work revealed the landscape of autophagy degradation and regulation in mouse and human neurons and has identified novel autophagy cargoes and adaptors related to specific pathways. It sheds light and provides the foundation for future work on the physiological functions of autophagy in neurons and the mechanisms for neuroprotective function of autophagy.

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# 2021 Neuroscience Retreat abstract submission

Exploring a novel method of D1 or D2 MSN-specific protein expression with AAV vectors

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Background: Expression of proteins in a specific population of cells is important to explore the molecular mechanisms of behavior in animals. Transgenic animals have been used extensively as a tool to achieve this goal. Recently, a new methodology based on using natural microRNA (miR) profiles in different cell populations has been proposed in other models. Here, we are testing its feasibility by inducing EGFP as a marker in D1 versus D2 medium spiny neurons in the ventral striatum.

Methods: We injected two AAV viral vectors (AAV2 and AAV9) that carry a miR-recognition site on the 3'-UTR region of EGFP. To examine cell-specific expression, we use mRNA labeling (RNAscope). Confocal images were analyzed by Fiji (ImageJ) software for quantification.

Results: Our preliminary results show a preferential expression in D1 MSNs with AAV2 vector. A similar pattern was observed with AAV9 vector with no statistical significance.

Conclusions: The preferential expression of the marker protein in D1 MSNs is promising, but reaching cell-type-specificity that is required for experiments requires further testing. Our preliminary data suggest that AAV2 may be a slightly better vector than AAV9 in this data set.

Funding: NIH

# 2021 Neuroscience Retreat abstract submission

Conditional deletion of Ahr in neurons promotes peripheral neuroregeneration

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Ahr is a ligand-binding transcription factor belonging to the bHLH-PAS family. Ahr is a regeneration-associated gene which contains DhMRs mediated by Tet3 in dorsal root ganglia (DRG) after peripheral lesion. However, the physiological and pathological role of Ahr in axon growth and neuroregeneration remains unclear. Here we provide evidence that Ahr and its target genes are upregulated in DRG after sciatic nerve injury. Conditional knock-out of Ahr upregulates 5hmC in uninjured DRG and promotes neuroregeneration after sciatic nerve crush and DRG neurite outgrowth in vitro. Interestingly, we show that Ahr knock-out mice present sensory and motor dysfunction suggesting the indispensability of Ahr in nervous system. Ahr agonists/antagonists also modulate neurite outgrowth of human EB-derived neurons. Ongoing experiments will use Arnt conditional knock-out mice to demonstrate whether Ahr impairs neuroregeneration through Ahr/Arnt pathway. Our data suggest that Ahr potentially maintains homeostatic function in normal peripheral nerve but plays a deleterious role which represses regeneration capacity when over-activated by severe injury. Disengagement of Ahr enables axon growth through DNA hydroxymethylation at regulatory regions of RAGs, thus defining a new target regulon for gene repression which could be possibly manipulated by small-molecule antagonists.
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# 2021 Neuroscience Retreat abstract submission

Sex differences in the human brain transcriptome of cases with schizophrenia

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BACKGROUND: While schizophrenia differs between males and females in age of onset, symptomatology and the course of the disease, the molecular mechanisms underlying these differences remain uncharacterized.
METHODS: To address questions about the sex-specific effects of schizophrenia, we performed a large-scale transcriptome analysis of RNA-seq data from 437 controls and 341 cases from two cohorts from the CommonMind Consortium.
RESULTS: Analysis across the cohorts identifies a reproducible gene expression signature of schizophrenia that is highly concordant with previous work. Differential expression across sex is reproducible across cohorts and identifies X- and Y-linked genes. Intriguingly, the sex expression signature is also enriched for genes involved in neurexin family protein binding and synaptic organization. Differential expression analysis testing a sex-by-diagnosis interaction effect did not identify any genome-wide signature after multiple testing corrections. Gene co-expression network analysis was performed to reduce dimensionality and elucidate interactions among genes. We found enrichment of co-expression modules for sex-by-diagnosis differential expression signatures, which were highly reproducible across the two cohorts and involve a number of diverse pathways, including neural nucleus development and neuron projection morphogenesis.
CONCLUSIONS: Our results indicate that the effect size of sex differences in schizophrenia gene expression signatures is small and underscore the challenge of identifying robust sex-by-diagnosis signatures, which will require future analyses in larger cohorts.
FUNDING: NIH

# 2021 Neuroscience Retreat abstract submission

Ensemble reactivation after learning links memories encoded close in time

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Background: The compilation of memories, aggregated across a lifetime, defines our human experience. How are memories dynamically updated and integrated across time and experience? Our study suggests that a shared neural ensemble may link distinct memories encoded close in time.

Methods: Using in vivo calcium imaging (with open-source Miniscopes in freely behaving mice), an activity-dependent cell tagging system, chemogenetics, and novel behavioral designs, we tested how hippocampal networks temporally link memories separated across hours to days.

Results: We found that contextual memories encoded close in time are linked by directing storage into overlapping hippocampal ensembles, such that the recall of one memory can trigger the recall of another temporally-related memory. Increasing the negative valence of a memory extends the temporal window for linking memories retrospectively. This transfer of fear from an aversive memory to a previously formed safe memory can be abolished by inhibiting the reactivation of the neural ensemble of the safe memory during the consolidation of the aversive memory.

Conclusions: Current work is focused on uncovering network dynamics that support fear learning and give rise to context-specific retrieval of memory. These results shed light on the neural substrates underlying how memories are integrated in the brain.

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# 2021 Neuroscience Retreat abstract submission

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). However, it remains unclear whether these synchronization deficits are limited to HPC or, rather, reflect impaired inputs from upstream entorhinal cortex (EC). Cognitive processes require precise communication between circuits, which suggests that altered timing between HPC and EC may underlie epilepsy-associated cognitive deficits.

METHODS: We have performed simultaneous in vivo electrophysiology with 512-channel silicon probes in HPC and EC of epileptic and control mice running in virtual reality.

RESULTS: Preliminary analysis using multiunit activity and local field potential (LFP) coherence measures revealed that epileptic mice had severely altered synchronization between the MEC and HPC. Epileptic mice show reduced theta phase coherence between MEC and CA1, and reduced phase locking of MECII spiking to CA1 (but not local) theta oscillations.

CONCLUSIONS: Together, these data indicate a specific impairment in the timing of MEC inputs into HPC, 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 excitatory and inhibitory neurons are specifically altered in epileptic mice.

FUNDING: NIH

# 2021 Neuroscience Retreat abstract submission

Brain-wide mapping of trauma-induced stress sensitization

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BACKGROUND: Traumatic experiences predispose individuals to an array of anxiety disorders. Although numerous studies have identified persistent trauma-induced changes in brain regions of interest (amygdala, hippocampus, etc.), it remains unclear whether these changes underlie the observed anxiety-related phenotypes. To investigate how network activity across multiple brain regions contribute to subsequent anxiety, we used an unbiased, whole-brain, cFos mapping approach to find brain regions whose activity covaries with heightened stress responses in the wake of trauma.

METHODS: 10 days after initially experiencing a traumatic experience or a control experience, mice were exposed to a novel stressor and brain-wide cFos counts were compared between trauma animals and controls using the iDISCO method.

RESULTS: We identified several subcortical structures that show heightened cFos activity in trauma animals relative to controls. As expected, trauma animals displayed heightened behavioral responses to the novel stressor.

CONCLUSIONS: Although identified structures are known to regulate stress responses, they are not included in canonical fear circuit diagrams. These findings highlight the potential utility of unbiased approaches for treatment discovery. Current work using site-specific protein synthesis inhibitors at the time of trauma is now underway to address whether the identified brain regions represent an origin for trauma-induced behavioral alterations.

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# 2021 Neuroscience Retreat abstract submission

Title: Single nuclei transcriptomics relates glioblastoma heterogeneity to fetal neurodevelopment.

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Introduction: Glioblastoma (GBM) recurrence is thought to be driven by therapy-resistant, invasive populations that recapitulate development. Comparisons of GBM to glial populations during human neurodevelopment are lacking due to limited data from late gestation, when gliogenesis accelerates.

Methods: We generated a single-nuclei RNA sequencing dataset of ~200,000 nuclei from the germinal matrix and cortical plate of 15 fetal samples, ranging from 17-41 gestational weeks, and the subventricular zone and cortex of three adult samples, enabling high spatiotemporal resolution of fetal gliogenesis. We then sequenced ~62,000 nuclei from the core and infiltrative edge of six surgically resected GBM samples with diverse genomic alterations.

Results: Clustering identified cell types within each sample and subclustering analysis of glia resolved developmental cell type signatures absent in the adult brain. Trajectory inference reconstructed glial lineages, identifying a common glial progenitor (gIPC) preceding both oligodendrocyte progenitor and astrocyte lineages. Clustering of tumor nuclei revealed distinct neoplastic and non-neoplastic populations within each sample. Projecting our signatures onto GBM clusters revealed enrichment of neurodevelopmental cell states within each tumor. A gIPC-like signature predominated in all tumors, and was consistently enriched in the infiltrative edge, with smaller contributions from other signatures.

Conclusions: The high resolution of the generated atlas dissects GBM intratumoral heterogeneity into distinct developmental states driven by potentially targetable regulatory networks.

Funding: NIH

# 2021 Neuroscience Retreat abstract submission

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

AUTHORS: Zhe Dong, William Mau, Yu (Susie) Feng, Lauren Vetere, Lucia Harley, Tristan Shuman, Denise Cai, et al.

AFFILIATIONS: Nash Family Department of Neuroscience, Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY

BACKGROUND: Context memory is thought to be stored in a stable neural ensemble in the hippocampus and other brain regions. However, recent findings suggest that firing pattern of the hippocampal ensemble may change across time, despite no change in the context (i.e., “representational drift”). Hence, we ask how a context memory can be stably represented in the hippocampus in the presence of representational drift.

METHODS: We used Miniscopes to record hippocampal activity while mice ran on either a linear or a circle track. We then used a dimensionality reduction technique called Laplacian Eigenmap to reduce the neural activity space into low dimensional space. Finally, we carry out analysis on simulated data to study the relationship between the tuning characteristic of the population and the extracted low-dimensional representation.

RESULTS: Despite patterns of neural activity changing from day to day (representational drift), the low-dimensional representation of the neural dynamics is stable across days. Interestingly, the topology also reflects the physical shape of the context (i.e., a linear vs circle track).

CONCLUSION: Laplacian eigenmap is an unsupervised learning technique to extract neural correlates that relate to behavior, and has potential to reveal how context representations may be preserved across time.

FUNDING: NIH

# 2021 Neuroscience Retreat abstract submission

Closed-loop control of spike timing

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BACKGROUND: The precise timing of neuronal spiking relative to the brain's endogenous oscillations (i.e., phase locking) has long been hypothesized to be involved in information processing and excitatory-inhibitory homeostasis. However, due in part to the considerable challenges of modulating single unit activity within just milliseconds of the brain's real-time oscillations, this hypothesis has never been thoroughly tested.

METHODS: Thus, we developed a closed-loop optogenetic system for low latency cell-type specific stimulation of single units during precise phases of endogenous oscillations. We performed in vivo silicon probe recordings in head-fixed mice navigating a virtual track to identify the baseline phase preference of specific interneurons within the hippocampus and applied our closed loop system to control their phase locking to hippocampal theta.

RESULTS: This system uses online signal processing to detect the target phase in real-time and deliver stimulation within milliseconds; it is capable of targeting any phase of theta with high precision. Using this system in awake behaving mice, we have succeeded in precisely altering the phase locked firing of hippocampal parvalbumin-expressing interneurons.

CONCLUSIONS: This closed-loop system outperforms existing tools and will enable us to investigate the causal role of precise single-unit phase locking to network-wide oscillations. Future experiments will apply this tool to investigate the role of precise timing of interneuron spiking in maintaining excitatory-inhibitory balance and mediating information processing in the healthy and epileptic brain.

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