Innovators in Neuroscience: From Molecules to Mind

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Tuesday, May 25, 2021

Poster Session 1

T1. Astrocyte-Specific Expression of the Extracellular Matrix Gene HtrA1 Regulates Susceptibility to Stress in a Sex-Specific Manner

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Category: Brain Disease and Disorders

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.

T2. Plexin-B2 Regulates Migratory Plasticity of Glioblastoma Cells in a 3D-Printed Micropattern Device

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Category: Brain Disease and Disorders

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.

Methods: 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).

Conclusions: 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.

T3. Pathoanatomical Mapping of Differential MAPT Expression and Splicing in Progressive Supranuclear Palsy
Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized by pathological accumulation of the 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 alternative pre-mRNA splicing of exon 10 cause familial PSP through accumulation of tau with four microtubule binding domain repeats (4R). 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. Gene levels were normalized to cell population estimates derived from deconvolution analysis. Data was visualized with ggplot2. Findings were validated on a single-cell level using novel tau isoform-specific mRNA in situ hybridization (ISH) probes.

Results: 5,039 genes were differentially expressed in the neocortex, and 7,753 genes in the cerebellum. 2,764 genes overlapped. In both brain regions, total levels of MAPT and 4R tau were increased in cases compared to controls. MAPT levels positively correlated with 4R tau in the cerebellum. Whole transcriptome regressions identified gene candidates that may influence tau splicing.

Conclusions: 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.

T4. Behavioral Variability in Response to Chronic Stress and Morphine in BXD and Parental Mouse Lines

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.

T5. Thyroid-Stimulating Hormone Receptor Regulates Anxiety

Dysregulation of thyroid hormones is associated with mood disorders in humans. For example, subclinical hypothyroidism, defined as a state in which serum thyroxine (T4) levels are in a normal range, but thyroid-stimulating hormone (TSH) is elevated, which increases anxiety. Subclinical hypothyroidism, as well as
anxiety disorders, are much more common in females compared to males. TSH is released from the anterior pituitary gland and binds to the TSH receptor (TSHR) on thyroid follicular cells. This binding induces the production of T4 and triiodothyronine (T3), which play an essential role in metabolism. Previous studies revealed TSHR gene expression in non-thyroid tissues, including the brain. However, the functional role of TSHR in the brain is not characterized. The objective of this study is to examine the contribution of brain TSHR to anxiety.

**Methods:** First, we examined TSHR expression throughout the brain using RNAscope. Following the quantification of TSHR signals, we investigated the receptor's role in anxiety states using systemic administration of MS438, a small-molecule TSHR agonist in the elevated plus-maze (EPM) test.

**Results:** TSHR positive signals were detected in areas that play a role in modulating anxiety, including the bed nucleus of the stria terminalis (BNST), amygdala, hippocampus, nucleus accumbens, and substantia innominata (SI). EPM test revealed that an anxiogenic, dose-dependent response of MS438 was observed in female wild-type mice. At the highest dose tested (50 μg/mouse; n=6/group), MS438 attenuated time spent in the open arms compared to the vehicle-treated mice throughout the entire 15-min EPM test. Lower doses (6.26-25 μg/mouse; n=6/group) generally enhanced anxiety-like behavior during the first 5-min of the EPM test.

**Conclusions:** We verified the TSHR expression in the brain regions that are known to facilitate anxiety. We also observed that TSHR agonist administration induced anxiogenesis in a dose-dependent manner. Collectively, these results suggest that TSHR regulates anxiety. We are currently testing whether direct stimulation of the TSHR in the BNST and SI regulates anxiety-like behavior in mice.

**T6. Drugs That Inhibit Microglial Inflammation Also Ameliorate Aβ1-42 Induced Toxicity in C. Elegans**

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Abstract not Included

**T7. Phosphodiesterase 1b is an Upstream Regulator of a Key Gene Network in the Nucleus Accumbens Driving Addiction-Like Behaviors**

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**Category:** Brain Disease and Disorders

**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.

**T8. Reduced Gap Effect in Children With FOXP1 Syndrome and Autism Spectrum Disorder**
Background: FOXP1 syndrome is a rare, genetic neurodevelopmental disorder characterized by intellectual disability and speech and attention deficits. Moreover, FOXP1 is a risk gene for autism spectrum disorder (ASD), which is associated with poor socialization and abnormal eye-contact and reciprocal gaze. Previous eye-tracking studies in idiopathic ASD (iASD) suggest that visual attention deficits are more attributed to global delays in reorienting of attention than to particular deficits in socialization. No studies have tested whether attentional deficits in FOXP1 syndrome follow this same paradigm.

Methods: We investigated whether children with FOXP1 syndrome a) show similar patterns of visual attention engagement and disengagement to those we previously observed in iASD and b) are impacted by the social versus non-social nature of visual stimuli. Eye-tracking data were collected from age- and sex-matched groups of individuals with FOXP1 syndrome (n=8) and typically developing (TD) controls (n=17), ages 3-17. The FOXP1 cohort received consensus ASD diagnoses based on gold-standard diagnostic assessments (ADOS-2, ADI-R), DSM-5 criteria, and clinical impressions of licensed psychologists and psychiatrists. During the eye-tracking task, a central stimulus was presented for 1s, followed by presentation of a peripheral stimulus on the left or right. The central stimulus either remained on screen (“overlap”) or disappeared 250ms before the peripheral stimulus appeared (“gap”). Central and peripheral stimuli were either social (20 child faces) or non-social (20 objects, e.g., ball, globe) and were presented in grayscale. We measured saccade latency to the peripheral stimulus and calculated gap effect (difference between average “overlap” and “gap” saccade latencies) for each participant overall and for each social/non-social condition. Reduced gap effect reflects deficits in engagement of visual attention.

Results: A Mann-Whitney U-test revealed a lower gap effect in FOXP1 relative to TD participants, with results approaching significance (p=0.091) and of large effect size (Cohen's d=0.86). Average saccade latency in the gap condition was higher in FOXP1 compared to TD (p=0.027), whereas saccade latencies in the overlap condition did not differ (p=0.38). There was no group-by-condition interaction for gap effect (p=0.56), suggesting attention engagement was not differentially affected by the social or non-social nature of stimuli. Interestingly, a Mann-Whitney U-test revealed that there was no difference in gap effect between FOXP1 participants with (n=3) and without (n=5) consensus ASD diagnoses (p=0.39).

Conclusions: We found a trend toward reduced gap effect in FOXP1 individuals compared to TD individuals, driven by slower latencies in the gap condition. Mirroring our previous findings in iASD, these results suggest that deficits in attention in FOXP1 may be driven by delays in the anticipation or reorientation of attention. As in iASD, there were no differences in engagement with social versus non-social stimuli among FOXP1 individuals, demonstrating that deficits in visual attention in FOXP1 are independent of stimulus type. These findings lend support to the notion that attentional deficits in FOXP1 may be similar to those in iASD, despite only ~25% of FOXP1 individuals receiving formal ASD diagnoses. This work provides important insight into shared mechanisms of attentional differences across idiopathic and genetic forms of ASD.


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Category: Brain Disease and Disorders

Background: Autism spectrum disorder (ASD) is a heterogenous disorder characterized by restrictive/repetitive behaviors and interests, social communication deficits, and sensory differences. Baseline electroencephalogram (EEG) data provides a means for understanding neural systems underlying ASD pathophysiology, as it captures the brain’s spontaneous oscillatory rhythms at rest. However, resting-state EEG findings have been largely inconsistent across autism research, perhaps due to heterogeneous clinical profiles within iASD samples, including wide ranges of IQ and overall functioning levels.

Methods: This study aimed to characterize neurobiological markers of a particular ASD group, idiopathic autism (iASD) without intellectual disability (ID), by examining resting-state EEG data. EEG was recorded for 5 minutes without intellectual disability (ID), by examining resting-state EEG data. EEG was recorded for 5 minutes.
from iASD participants without ID (N= 10) and typically developing (TD) (N= 12) participants seated in a dark room watching a silent video of their choice. 

**Results:** Absolute power was calculated for delta (.4- 4 hz), theta (4-8 hz), alpha (8-12 hz), beta (12-30 hz), and gamma (30-50 hz) frequency bands from an average of 22 electrodes evenly distributed across the scalp.

Compared to TD controls, the iASD group showed significantly enhanced power in the theta (t=−3.46, p=.003), delta (t=−2.98, p=.008), alpha (t=−3.03, p=.007), beta (t=−2.81, p=.01) and gamma (t=−2.50, p=.03) bands. There was also a significant increase in absolute total power in the iASD group compared to TD controls (t=−3.36, p=.003).

**Conclusions:** These results suggest that individuals with iASD differ from TD controls in baseline neural power, with enhanced power across every frequency band. This increase in spectral power in the iASD group suggests an elevated excitatory/ inhibitory ratio, reflecting neural disinhibition that may account for altered cognitive processing and clinical symptoms seen in ASD. Understanding these neurophysiological processes is essential in developing informed treatments for neurodevelopmental disorders.

**T10. The Intellectual Disability Gene DDX3X in Sex-Specific Neuronal Morphogenesis**

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**Category:** Brain Disease and Disorders

**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.

**T11. Bacterially Derived Metabolites Modulate Transcriptional Control and Cocaine-Seeking Behaviors**

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**Category:** Brain Disease and Disorders

**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.

**T12. 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 lead to social deficits.

**T13. Defining GM-CSF in Behavioral and Molecular Responses to Cocaine**

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**Background:** Recent work demonstrates the gut microbiome has profound effects on 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. 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.

**Conclusions:** These data suggest that GM-CSF participates in cocaine-induced behavioral and molecular plasticity, poising it as a novel neuroimmune signal in cocaine use. Ongoing research is working to clarify the molecular mechanisms through which GM-CSF acts to affect brain and behavior.
T14. Regulation of Nicotine Intake by the Gut Hormone Cholecystokinin

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Category: Brain Disease and Disorders

Background: Nicotine addiction in the form of habitual tobacco use is the leading cause of premature death in the United States. 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 identified nicotine-activated neurons in Targeted Recombination in Active Population (TRAP) mice.

Results: Nicotine increased postprandial, but not fasting plasma CCK concentrations. CCK-8 decreased nicotine self-administration without impairing food responding or nicotine place preference. Finally, we identified nicotine-reactive population vagal neurons and the nucleus of the solitary tract, a primary target of vagal afferents.

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.

T15. Spatial Coding and Entorhinal-Hippocampal Circuit Deficits in a Mouse Model of Alzheimer's Disease Pathology

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Category: Brain Disease and Disorders

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.

T16. Cortico-Striatal Volume Changes in Human Cocaine and Heroin Addiction

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Category: Brain Disease and Disorders

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 [dPFC]) 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.

T17. Mesolimbic Circuit Dynamics Underlying Individual Alcohol Drinking

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Abstract Not Included

T18. Behavioral and Cellular Characterization of a New Mouse Model for DDX3X Syndrome

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Category: Brain Disease and Disorders

Background: DDX3X syndrome accounts for 1-3% of unexplained intellectual disability (ID) in females, presenting also behavioral problems and motor impairments. This syndrome is mostly caused by de novo mutations in DDX3X, an X-linked gene that regulates mRNA translation and has emerging functions in corticogenesis and synaptogenesis. Even though the genetic cause of the syndrome is known, the cellular and molecular mechanisms driving it remain elusive.

The objective of this study is to understand the cellular and molecular mechanisms driving DDX3X syndrome during development, particularly during corticogenesis, and link them to the symptoms observed in DDX3X patients.

Methods: We generated the first Ddx3x haploinsufficient mouse (Ddx3x+/-) model with construct validity for loss-of-function mutations found in females with DDX3X syndrome. To study the impact of Ddx3x haploinsufficiency on development and behavior we followed a standardized battery for assessing developmental milestones during early postnatal life and cognition, social and motor functions in adults. To study the impact of Ddx3x haploinsufficiency on corticogenesis, we performed MRI studies and assessed cortical lamination using layer-specific markers and retrograde tracing to reconstruct sub-cortical connectivity.

Results: Ddx3x+/- mice show physical, sensory, and motor delays that evolve into behavioral anomalies in adulthood, including hyperactivity, anxiety-like behaviors, cognitive impairments, and motor deficits. These behavioral changes are preceded by reduction in brain volume postnatally, with some regions (e.g., cortex and amygdala) disproportionally affected. Cortical thinning is accompanied by defective cortical lamination, indicating that Ddx3x regulates the balance of glutamatergic neurons in the developing cortex.

Conclusions: Our data supports face validity for a novel pre-clinical mouse model and shed new light on the developmental mechanisms driving DDX3X syndrome.
T19. Neural Mechanisms Driving Comorbid Parkinson's and Melanoma

Pamela Del Valle*, Julie Di Martino, George Huntley, Javier Bravo-Cordero, Deanna Benson

Category: Brain Disease and Disorders

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: To investigate this, we are characterizing melanoma progression and its neural microenvironment in WT and LRRK2-G2019S-knock in (GSKI) mice.

Results: 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.

T20. Hippocampal-Entorhinal Desynchronization in Chronically Epileptic Mice

Yu Feng*, Lucia Page-Harley, Keziah Diego, Sophia Lamsifer, Tristan Shuman

Category: Brain Disease and Disorders

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 the 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 simultaneously 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 dentate gyrus regions of the hippocampus. 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.

T21. Characterization of Induced Neurons From Monogenic Forms of Autism Spectrum Disorder for Drug Discovery and Development

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Category: Brain Disease and Disorders

Background: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by impaired social and communication skills along with repetitive and restrictive behavior. ASD affects 1–1.5% of individuals and is highly heritable with both common and rare variants contributing to its etiology. Gene discovery approaches, followed by functional analysis in model systems, have elucidated the neurobiology of several
monogenic subtypes of ASD, including ADNP, FOXP1, SHANK3 and DDX3X, which are amongst the top high-risk autism genes. Genetic network analyses and genetic functional studies of these genes have led to identification of the affected processes including synaptic cell adhesion, neurotransmission, scaffolding protein assembly at the synapse, synaptic gene transcription, chromatin remodeling, calcium signaling and others. For instance, SHANK3 is a key scaffolding protein component of the glutamatergic postsynaptic density (PSD), playing a critical role in synaptic plasticity; ADNP is involved in gene regulation and microtubule integrity via its interaction with chromatin remodeling complexes and microtubule binding proteins; FOXP1 is a pivotal transcription factor during embryonic development, having an important role in regulation of gene transcription and neurogenesis; and DDX3X is an RNA helicase involved in gene expression regulating transcription, mRNA maturation, mRNA export and translation. Moreover, pathway analysis elucidated that many ASD implicated genes, including ADNP, FOXP1, SHANK3 and DDX3X, are involved in pathways critical for neuronal development and/or synaptic formation and function. In-depth characterization of cellular phenotypes in human neurons generated from iPSC obtained from a subset of ASD individuals in which the genetic cause and pathobiology are better understood offer a unique opportunity to constrain ASD heterogeneity and identify pathways that can more readily be targeted for treatment, offering the opportunity to identify pharmaceutical compounds affecting core symptoms of ASD.

Methods: Reprogramming iPSC into induced glutamatergic neurons

To evaluate phenotypic differences between ASD-iPSCs and control cell lines, induced neurons (iN) co-cultured with glial cells are generated by the NGN2-mediated cell fate conversion method. This method directly converts human iPSCs into glutamatergic neurons and is a straightforward way to generate human neurons mature enough to robustly study neuronal, morphological and synaptic biology. Phenotypic characterization of iPSC-derived human glutamatergic neurons from individuals with ASD Automated and simultaneous measurement of presynaptic vesicles, postsynaptic structures, and neurites are achieved by identifying primary neuronal cells by neuron specific marker and detecting synapses on the spines of neurites with pre- and postsynaptic markers. Our approach measures neuronal shape and neurite extension using MAP-2 as a cell body and neurite marker. Analysis of four different neuritic network parameters will be prioritized: soma size, neurite count per neuron, neurite length per neuron and neurite branching point number per neuron. Sholl analysis will also be assessed to reveal the number of branches, branch geometry, and overall branching patterns of neurons. Synaptic density are measured using PSD95 or Homer1 as postsynaptic markers and synaptophysin as a presynaptic marker. Three synaptogenesis parameters will be assessed: pre- and postsynaptic structures, and synapse number quantified as puncta densities of co-localized PSD95 or Homer1 and synaptophysin per MAP2 length. The multiplexed targets, including a nuclear marker, will be simultaneously detected with four fluorescent colors. Fluorescent images of the labeled neurons and synapses are acquired by automated High-Content Screening (HCS) Platform. Integrated data collection and analysis are performed with the in-built HCS Studio software and ImageJ, using the co-localization of presynaptic and postsynaptic markers to identify synapses and correlate them with neuronal and neurite morphology.

Results: In order to enable discovery and validation of drug candidates targeting functional deficits in ASD, the aim of this project is to perform an in-depth characterization of the cellular phenotypes in human neurons generated from iPSC lines derived from individuals with mutations in high risk autism genes. We focus on ADNP, FOXP1, SHANK3 and DDX3X. Focusing on these genes will enable us to assess biological effects of drug candidates in human neurons bearing mutations/deletions in genes associated with monogenic ASDs. Two different types of assays are being implemented for the phenotype characterization: CRISP/Cas9 engineered cell lines which allow comparison to the genotype-matched control cell lines and phenotype validation in patient-derived haploinsufficient cell lines compared to control lines derived from unaffected siblings. Three different cell lines per gene are being analyzed, with two clones per cell line to control for clonal variation. Preliminary tests using iPSCs derived from patients with SHANK3 haploinsufficiency indicated successful iN generation from probands and siblings. Moreover, optimization of immunofluorescence assays resulted in the detection of pre and post-synaptic markers HOMER1 and synaptophysin, as well as neuronal shape and neurite detection using MAP2 as a cell body and neurite marker. This indicates that the NGN2-mediated protocol and immuno-fluorescence assays can be applied for the remaining genes for the generation of glutamatergic neurons for large-scale studies and phenotypic characterization. Once the phenotypes are validated, development of in vitro
assays suitable for screening of existing compound libraries and discovery of novel drug candidates will be conducted.

**Conclusions:** There have been intense research efforts to develop pharmacological treatments for ASD without notable success. Characterization of cellular phenotypes have been proved to be useful for drug screening and discovery. Therefore, morphological changes in neuronal cultures caused by mutations associated with monogenic ASD represent a powerful tool to describe a common disrupted phenotype in a human model for ASD that can be used as a platform for drug screening and evaluation. Importantly, molecules effective in monogenic ASD could also have a therapeutic potential in a subset of patients with idiopathic autism, offering an opportunity to identify pharmaceutical compounds targeting core symptoms of autism.

**T22. A Stress-Responsive Circular RNA Regulates Depression-Like Behavioral Abnormalities in Mice**


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**Background:** Circular RNAs (circRNAs) are formed by back-spllicing 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.

**Methods:** Depression-related behavioral deficits were induced using social defeat (SDS) or restraint stress (RS). circRIMS2 was overexpressed using an AAVD1-sEF1a-ZKSCAN1-circRIMS2-sYFP vector. Single-cell RNA sequencing (scRNAseq) was performed using 10X Chromium.

**Results:** We found that expression of circRIMS2, derived from exons 20-22 of the RIMS2 gene, was increased in postmortem NAc from male, but not female, patients who suffered from major depressive disorder. SDS increased, whereas RS decreased, circRIMS2 levels in the NAc of male mice. 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.

**T23. Impaired Social Control in Misophonia**

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**Background:** Misophonia is a syndrome in which specific sounds lead to strong 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, with little understanding of its causes, mechanisms, or comorbidities, posing major challenges for patients seeking diagnosis and treatment. To fill this knowledge gap, the current study aimed to use large-scale online assessment to characterize misophonia by identifying the relationship between misophonia symptoms and existing psychiatric symptom dimensions.

**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 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: In sum, this study utilized digital phenotyping to investigate the relationship between misophonia and other psychiatric diagnoses and characterize the role of social control in the pathophysiology of the disorder. In taking a transdiagnostic approach, this study provides novel insight into the underlying constructs of misophonia. The results suggest that misophonia and OCD symptoms may represent a latent psychiatric dimension characterized by maladaptive exertion of control.

T24. The Long Noncoding RNA Fedora is a Cell-Type and Sex-Specific Regulator of Mood

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Category: Brain Disease and Disorders

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. Epigenetic processes, that mediate interactions between genetic predispositions and stressful life experiences, are known to play a key role in depression risk. We recently reported that long non-coding RNAs (lncRNAs), a class of epigenetic regulators, are robustly regulated in depression in a sex-specific manner. Identification of novel epigenetic targets will aid in developing diagnostics and therapeutics for depression for both sexes.

Methods: We integrated cutting-edge molecular, bioinformatics, behavioral, and physiological approaches spanning both humans and mice. We bioinformatically analyzed our RNA-sequencing (RNA-seq) dataset from postmortem brain tissue from depressed humans compared to healthy controls and identified a sex-specific lncRNA regulated in depression. We developed cell-type-specific viral tools to express this lncRNA in mouse prefrontal cortex (PFC) either in oligodendrocytes or neurons where its normal expression in humans predominates. Such mice of both sexes were phenotyped using novelty-suppressed feeding, marble burying, forced swim test and operant learning, slice electrophysiological recordings of excitatory postsynaptic potentials and excitability, transcriptome profiling using RNA-seq and electron microscopy analysis of myelin thickness. Additionally, we tested blood levels of the lncRNA in depressed and control subjects of both sexes using qPCR.

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 InCRA). FEDORA is enriched in the brain and is expressed in oligodendrocytes as well as in neurons. We found that expressing FEDORA exclusively in neurons promoted anxiety- and depression-like behaviors in females only, which mirrored the human sex-specific phenotype. These behavioral changes were associated with transcriptional changes that resemble the sex-specific transcriptional signature of chronic stress and were associated with changes in neuronal electrophysiological properties. Expression of FEDORA in oligodendrocytes again had a female-specific effect on motivational behavior, which was associated with changes in myelin thickness and gene expression. Finally, we found that circulating FEDORA levels are elevated in depressed women only compared to healthy 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 findings provide a new view of molecular adaptations that contribute to depression risk and point to promising new targets that may serve as foundations for novel depression diagnosis and treatment.

T25. The COVID-19 Effects on the Brain: Chronic or Transient Neuropathology?

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T27. Behavioral Traits Impact Heroin and Food Reward Sensitivity following Adolescent delta-9-Tetrahydrocannabinol Exposure

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1Addiction Institute of Mount Sinai

Category: Cognitive and Systems

Background: Cannabis is one of the most commonly used substances in the United States, particularly among adolescents which has increased concerns given the shift towards cannabis legalization. Prior studies have shown
that exposure to delta-9-Tetrahydrocannabinol (THC), the main psychoactive cannabinoid in cannabis, during adolescence increases substance use disorder (SUD) risk in the future. However, not all cannabis users develop SUDs with factors such as genetics and behavioral trait potentially contributing to the sensitivity of THC use. For instance, cannabis users frequently report using cannabis to self-medicate impulsivity and depression. Here, we leverage rodent models of impulsivity and depression to investigate individual differences to adolescent THC exposure in relation to behavior and neurobiological processes.

**Methods:** We utilized two strains of rats—Spontaneously Hypertensive (SHR) and Wistar Kyoto rats (WKY). SHRs display impulsivity and hyperactivity phenotypes, while WKYs model depression-like behavior. SHRs and WKYs were administered (i.p) vehicle or 1.5 mg/kg of THC during adolescence (post-natal day 28-49) and heroin and palatable food (chocolate) self-administration (SA) were studied in adulthood. Additional behavioral tests were conducted to assess anhedonia, impulsivity, depression-like behavior, and social anxiety.

**Results:** Adolescent THC exposure reduced heroin SA and there was a trending reduction in chocolate SA in WKYs. WKY-THC animals also showed reduced sucrose preference (anhedonia) and a trend for reduced immobility time in the forced-swim test (depression-like), compared to the WKY-Vehicle group. No differences in natural and drug reward sensitivity were observed between the SHR-Vehicle and SHR-THC groups. Instead, SHR-THC animals displayed increased inactive lever pressing (indicative of enhanced impulsivity) during heroin SA, but decreased inactive lever pressing during chocolate SA. No significant differences in impulsivity during the intolerance to delay task, or social anxiety during the social interaction task were observed among any groups.

**Conclusions:** The results suggest that behavioral traits contribute to the individual variability seen with adolescent THC exposure. Molecular studies and in-vivo fiber photometry are currently underway to understand underlying neural signatures in the ventral tegmental area (VTA), a key sub-cortical brain region that mediates reward relevant to the behavioral traits.

**T28. Open Board**

**T29. The Neural Basis of Cuttlefish Camouflage**

*| Isabelle Rieth, Daniella Garcia-Rosales, Larry Abbott, Richard Axel*  
*1 Columbia University*

**Category:** Cognitive and Systems

**Background:** To navigate the visual world, animals create an internal representation of the environment and extract salient features, permitting the generation of appropriate behaviors. Cuttlefish present a unique system for studying the internal representation of visual stimuli. Cuttlefish dynamically change their skin pigmentation and texture to camouflage to their surroundings, creating a physical readout of what they see. This is achieved by expanding and contracting pigment-filled saccules called chromatophores using motor neurons projecting from the brain. Thus, the skin of cuttlefish can be likened to a digital display in which the chromatophores (“pixels”) create a physical manifestation of neural activity. We are using this system to understand how the physical properties of the visual world are represented by patterns of neural activity in the brain, and how this representation is transformed into an approximation of the physical world on the skin.

**Methods:** Cuttlefish provide an ideal system to study this transformation because the brain utilizes just 3 hierarchical lobes during camouflage and the motor output is measurable. We are generating transgenic cuttlefish that express genetically encoded calcium indicators and light-activated channels, permitting the live imaging and manipulation of neural activity.

**Results:** TBD

**Conclusions:** By establishing a behavioral paradigm in which changes in the visual environment evoke simple changes in skin patterning, we will simultaneously record neural activity and measure behavior to uncover how visual information is deconstructed in the brain, and then reconstructed into an image of the physical world on the skin.

**T30. The Hippocampus Represents Place in Abstract Social Space: Encoding and Decoding Evidence in Independent Samples**
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1Department of Psychiatry, Mount Sinai School of Medicine, 2Stony Brook University

Category: Cognitive and Systems

Background: 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: 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 changes in social relationships as movement in an abstract two-dimensional social space.

Results: 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: 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.

T31. Real-Time Functional MRI Neurofeedback Targeting the Amygdala in a Healthy Adult Shows Rapid Gain of Control

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1Department of Psychiatry, Mount Sinai School of Medicine, 2Icahn School of Medicine at Mount Sinai

Category: Cognitive and Systems

Background: The impaired response inhibition and salience attribution (iRISA) model proposes that impaired response inhibition and salience attribution underlie drug seeking and taking. In particular, this model implicates deficits in emotion processing and regulation associated with abnormalities in the circuit linking rostral anterior cingulate cortex (rACC) and amygdala. Importantly, abnormalities of this circuit have been linked to craving, which in turn can be modulated via noninvasive functional manipulation of this circuit. One such technique is real-time functional MRI neurofeedback (rt-fMRI NF), a form of noninvasive brain stimulation that allows subjects to gain volitional control over activity in precisely defined regions of their brains, and has previously been associated with beneficial outcomes in nicotine addiction, as well as in mood and anxiety disorders.

Methods: Our group aims to use noninvasive functional manipulation of the amygdala through rt-fMRI NF to test the potential to rehabilitate the amygdala-rACC circuit in opioid use disorder (OUD), particularly women with OUD, who comprise an especially at-risk group. We hypothesize that such training would translate into improvements in the emotional regulation of craving, a proxy for clinical outcomes such as OUD relapse and treatment adherence.

Results: We present initial feasibility results for our pilot subject, a healthy adult woman who was initially naïve to rt-fMRI NF. In each NF block of our task, her amygdala signal showed a trajectory (from time t to t+Δt, where Δt = 1 TR, repetition time) of moving toward the goal signal level >62% of the time. Treating each time interval as a “coin flip” where the signal can move either toward-goal or away-from-goal, the cumulative probability of this toward-goal rate or better is p<0.026. We had similar results for an expanded range of Δt intervals spanning the hemodynamic response (3-8 seconds). Signal in the non-NF condition moved toward goal approximately 50% of the time, i.e., at chance level.

Conclusions: Our initial feasibility run of our rt-fMRI NF task shows evidence supporting that a healthy NF-naïve female subject was able to gain volitional control rapidly upon NF exposure. This paves the way for testing the same protocol in our clinical group of interest: women with OUD, with the goal of reducing craving as potentially relevant to ultimately improving outcomes in this vulnerable population.

T32. Entorhinal-Hippocampal Synchronization in a Mouse Model of Alzheimer’s Disease Pathology

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1Icahn School of Medicine at Mount Sinai
Abstract Not Included

T33. Hippocampal Somatostatin Interneurons Implicated in Fear Extinction Memory Retrieval

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Category: Cognitive and Systems

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.

T34. Sex Differences in the Developmental Trajectory of Attentional Behavior in Mice Revealed by Accelerated Protocol

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Category: Cognitive and Systems

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 both male and female wild-type mice.

Methods: Male and female mice are trained to perform a freely moving attentional task using an accelerated protocol. Changes in the protocol include increasing the number of sessions run per day, creating dynamic criterion to pass each training stage, and reducing the number of total days spent training to ten days on average to start testing. The 5-choice serial reaction time task (5CSRTT) measures attention by randomly illuminating one out of five possible screens in a chamber using a translational automated touchscreen system at specific inter-trial intervals and stimulus durations. The mouse is rewarded with milk after correctly touching the illuminated screen or punished with a houselight after an incorrect or omitted response. An LED light distractor was briefly introduced prior to the appearance of the stimulus 20% of the time to measure selective attention to relevant stimuli in mice at adolescence (~p35) and adulthood (~p74).

Results: Male mice show an improvement in attentional behavior from adolescence (n=18) to adulthood (n=17), (p=0.0005), whereas the behavior of female mice (n=25) remains stable. As a result, adult male mice show better attentional performance compared to adult female mice (n=16). However, the developmental difference in male mice is no longer visible when a light distractor is introduced during an anticipatory attention period. Notably, female mice show better attentional performance than male mice in the presence of a distractor, suggesting that female mice can more effectively filter out the irrelevant stimulus (p=0.006).
Conclusions: An accelerated 5CSRTT protocol revealed sex differences in the developmental trajectory of attentional behavior in mice. Future studies will examine mouse models of neuropsychiatric disorders across development in attentional behavior.

T35. Patient’s Response in Trust Game Predicts Psychotherapeutic Relationship

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Category: Cognitive and Systems

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.

T36. Resilience Versus Susceptibility to Stress Differentially Alters Two Distinct Forms of Regret in Mice

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Category: Cognitive and Systems

Background: Regret describes the phenomena in which individuals recognize 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, Restaurant Row, translated for use across species. 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 animal model of depression, we separated 32 C57BL/6J mice into non-defeated, defeated-susceptible, and defeated-resilient phenotypes defined by a post-stress social interaction assay and then tested them on the Restaurant Row task. Mice were trained to forage for food rewards (sole source of food) of 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 fundamentally unique ways in how mice react to distinct economically disadvantageous scenarios only when in a reward-scarce environment. 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.
T37. Neural Correlates of Trajectory Encoding in Olfactory Perceptual Space

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Category: Cognitive and Systems

Background: During spatial navigation, neural activity in the hippocampus and entorhinal cortex is correlated to navigational variables like location, speed, and boundaries, providing a map-like representation of physical space. This observation, however, is not limited to spatial navigation. Mounting evidence support roles for the same substrates in encoding and representation of multiple cognitive maps, ranging from abstract knowledge to social status. Notably, the same mechanisms were shown to map sensory input such as visual fields or acoustic spaces. In human olfaction, grid-like representations were reported in a mental navigation task within an olfactory landscape. These signals were observed following intensive training in discrimination between binary mixtures of two constituents. Given the innate and hardwired nature of the axes guiding olfactory perception, we hypothesized the same circuitry will represent trajectories traversed in a task-free subset of odors embedded in a larger, innate and naturally derived olfactory perceptual space. We further posited this will occur in the absence of training or navigation-related instruction.

Methods: Two participants underwent multiple fMRI scans while rating 4 odors (3s on, 26-30s ISI) amassing to 200 trials. We determined each odor’s location along the 2 main axes of a computationally derived perceptual space and modelled trajectories between them according to their sequence of presentation in scan. Rated pleasantness served as a regressor to dampen pleasantness-driven signal.

Results: A model accounting for inter-odor Euclidean distance and angle change revealed that odor-induced activity in the left hippocampus tracked passive trajectories traversed in perceptual space, (x=−32; y=−25; z=−15 SVC FWE P<0.05). Activity in this region of interest was sequence-specific, ranking higher than either sequence or odorant shuffles. Finally, a representational dissimilarity analysis revealed that recurring similar trajectories in olfactory space shared higher pattern similarity extracted from bilateral hippocampus.

Conclusions: These preliminary findings suggest that olfactory sensory information may be stored according to a coordinate-based map of perceptual space, whose axes are derived from basic sensory properties. Notably, this organization is not the product of persistent training and was observed in the absence of a high-level task.

T38. Pathway-Specific Chemogenetic Neuromodulation Enhances Working Memory in Rhesus Macaques

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Category: Cognitive and Systems

Background: Acetylcholine plays a critical role in promoting neuronal plasticity and shaping synaptic connections throughout the brain, largely by projections from the basal forebrain cholinergic system. 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, we transduced hM3D-Gq-coupled DREADDs (designer receptors exclusively activated by designer drugs) into the basal forebrain, to reversibly activate projections from the nucleus basalis of Meynert 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 (SCOP) or by presentation of a distractor in two young male rhesus monkeys. In the spatial-delayed response task, working memory performance was assessed after combined intramuscular injections of either SCOP and vehicle, the DREADD actuator deschloroclozapine (DCZ) and vehicle, or a combination of SCOP and DCZ. In the distractor task, working memory was assessed following injection of vehicle or DCZ.
Results: In the spatial-delayed response task, monkeys showed significant working memory deficits following scopolamine injection. Notably, monkeys showed significant working memory improvement after SCOP plus DCZ injection compared to SCOP alone, indicating that the activation of the nucleus basalis to dorsolateral prefrontal circuit could offset working memory impairment caused by the cholinergic antagonist. In the distractor task after vehicle, monkeys showed significant memory impairment after the distractor compared to no distractor. Monkeys showed significant improvement in the distractor condition following DCZ injection compared to performance after vehicle.

Conclusions: Activation of this neuromodulatory system from the basal forebrain ameliorated memory deficits caused by scopolamine and improved task performance in a distractor paradigm, demonstrating the importance of this circuitry in working memory and attentional processing functions. 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.

T39. Characterizing the Role of Dopamine D3 Receptors on Dopaminergic Neurons on Anxiety-Like Behavior

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Category: Cognitive and Systems
Background: Dopamine transmission in the striatum plays an important role in alcohol reward and reinforcement and is mediated by a family of G protein-coupled dopamine receptors, D1 – D5. The D1 and D2 receptors are often the focus of addiction research, and while the dopamine D3 receptor has been indicated in alcohol-seeking and relapse, very little is known about the specific role of this receptor. The purpose of this project is to behaviorally characterize the role of the dopamine D3 receptor (D3R) on midbrain dopaminergic neurons in alcohol intake.

Methods: We utilized a novel transgenic mouse with a selective knockdown of D3Rs (DATD3 KO) on the midbrain dopamine neurons. We used qPCR to determine a successful and selective knockdown. Because we are using a new transgenic model, we explored potential behavioral phenotypes including locomotion and anxiety-like behavior. Using elevated zemoraze, light/dark box, open-field and novelty suppressed feeding, the anxiety-like behavior of these mice was evaluated. Finally, we looked at alcohol intake using an ethanol preference test and intermittent ethanol intake paradigm.

Results: We saw no differences between DATD3 KO mice and littermate controls in basal locomotion or anxiety-like behavior. Furthermore, we saw no differences in ethanol intake on either drinking paradigm.

Conclusions: Together, these data indicate that D3Rs on dopaminergic neurons do not seem to be mediating increased preference for or consumption of ethanol.

T40. Local Overlap but Distal Specificity: Distal Connectivity Dissociates Hand and Tool Processing Networks

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Category: Cognitive and Systems
Background: How object information is represented in the brain? Several studies have been contributed to answer this question and these research efforts led to the understanding that local computations and feedforward/feedback connections are essential to our representations and their organization. However, recent data has showed that distal computations also play a role in how information is locally processed.

Methods: Here we focus on how distal connectivity and local functional organization are related, by exploring two regions that show overlapping category-preferences for tools and hands (the inferior parietal lobule (IPL) and the posterior middle temporal gyrus (pMTG)). We tested how connectivity from these overlap regions relate to category-preferences in two ventral temporal areas dedicated to the processing of tools and hands separately – the left medial fusiform gyrus (mFUG) and the fusiform body area (FBA) respectively – as well as across the brain. To do this, we used two approaches: an ROI analysis and a searchlight analysis. In the first one, we computed the multivoxel linear correlation between the distribution of functional connectivity (with each overlap region) and the category-preferences for each voxel in the target ROIs (mFUG and FBA). Finally, we conducted a whole-brain
searchlight analysis in order to perform the same correlation as before (relating functional connectivity to category-preferences).

**Results:** In the ROI analysis (N = 15), the results showed that correlation between tool-preferences and functional connectivity (irrespective of the overlap region) was higher than the correlation between hand-preferences and functional connectivity in mFUG (t(14) = 4.73, adjusted p = .0006). The reverse was true for FBA – the correlation between hand-preferences and functional connectivity was higher than the correlation between tool-preferences and functional connectivity (t(14) = 2.26, adjusted p = .040).

In our searchlight analysis (N = 15), we showed that left IPL and left pMTG correlated with local category preferences in different areas across the brain for the two categories. Specifically, connectivity from pMTG was correlated with tool-preferences in a large part of left dorsal occipital cortex, including the superior parietal lobule, and in the mFUG bilaterally, whereas connectivity from IPL was correlated with tool-preferences in left mFUG. Regarding the hand preferences, connectivity from pMTG was correlated with hand-preferences in the right superior temporal sulcus (STS), whereas connectivity from IPL was correlated with hand-preferences in the left somatosensory cortex and the left STS.

**Conclusions:** In conclusion, our results show how areas that have a local overlap response to two categories (tools and hands) manifest different patterns of connections for their preferred categories. This suggests that distal connections from an overlap area are dependent on the category being processed and connectivity has a crucial role in determining object representation.

**T41. Genetic Mapping Links a Thalamic GPCR to Working Memory**

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**Category:** Cognitive and Systems

**Background:** The ultimate goal of this study is the eventual identification of causal and novel biological substrates underlying variation in cognitive performance. Working memory posits the center of the cognitive system for reasoning and the guidance of behavior. Working memory requires coordinated function between the brain regions of perceptual encoding, maintenance of its representation, and subsequent execution of behavioral responses.

**Methods:** In this study we aimed to 1) Generate predictive genetic models of working memory performance, 2) Delineate the roles of multiple brain regions during working memory, and 3) Identify causal genetic factors driving variability in working memory performance. To carry out unbiased, genome-wide screening of cognitive traits, we used a state-of-the-art diverse outbred (DO) mouse resource and Quantitative Trait Locus (QTL) mapping to detect genomic loci associated with the performance of working memory.

**Results:** The single significant QTL locus (WMqtl1) further guided the identification of highly specific genetic models that re-capsulated the performance variations of working memory phenotype. Behavioral phase-specific bulk neural activity recordings from brain regions interacting with PFC were evaluated using multi-region fiber photometry (MFP) in freely moving animals during the working memory task. Thalamocortical contribution to cognitive performance was systematically explored at the molecular level and circuit level, using genome-wide sequencing and MFP, respectively. Causal genetic factors were assessed by adenovirus-mediated circuit-specific delivery of the gene and RNA interference as a tool for manipulating gene expression in vivo, and subsequent behavior validation.

**Conclusions:** To this end, we presented a workflow for investigating molecular mechanisms that support complex cognitions. Our results demonstrated that the dissimilarities of mediodorsal thalamic nuclei molecular (i.e., differential expression in WMqtl1 genes) and circuit (i.e., phase-specific mdTh-PFC activity coordination) characteristics in high and low performing genetic models significantly affect cognitive performance. In addition, we discovered an orphan GPCR-mediated thalamocortical signaling that is likely to be driving variability in working memory performance. Together, we demonstrated an unbiased forward genetic approach, spanning molecules to circuits, to bridge the gap between genes and cognitive behavior. The combination of new tools (i.e., DO mice) and in vivo recordings (MFP), used at the appropriate behavior task, may enable the identification of genetic modifiers of cognitive performance that can be targeted as new therapeutic opportunities.
T42. Formerly Known as Latent: Characterization of a Decision Variable on Single Trials Using Neuropixel Recordings From Macaque Area Lip

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Category: Cognitive and Systems

Background: The concept of a dynamic firing rate, r(t), is elemental to principles of computational systems neuroscience. Yet it is elusive, or latent, because single neurons produce spikes separated by silent interspike intervals. r(t) is thus estimated by averaging across repetitions on the assumption that the brain has many neurons that also approximate the expectation, <r(t)> - what we term the neurophysiologist's assumption of ergodicity. With few exceptions, the “many neurons” in the preceding sentence have been inaccessible to electrophysiology, either because they lie deep in sulci or because they are intermingled among a heterogeneous population. This is especially problematic for the study of stochastic dynamic processes, such as decision making, where a decision variable, V(t) is itself stochastic. On single trials, V_i(t) is thought to represent the cumulative sum of iid random values, x_t, as in discrete drift-diffusion. Averaging across repetitions renders only a ramp - a line with slope <x>, termed the drift rate. The diffusion component of V_i(t) is latent.

Methods: Two monkeys indicated the net direction of dynamic random dots by making a saccadic eye movement to a left or right choice target when ready (choice-response time). We recorded simultaneously from ~200 neurons in the lateral intraparietal area (LIP) using high density, multichannel, primate neuropixel probes (IMEC/HHMI-Janelia). We focused on groups of 7-18 neurons (sample-populations) with response fields that overlap a common choice target.

Results: The mean firing rates from such sample-populations, S_i(t), approximate drift-diffusion processes on single trials. (1) The variance of S(t), across trials, increases linearly over time. (2) Samples of S_i(t) obtained at the beginning of the decision are predictive of the choice and response time, consistent with temporal integration. (3) The predictive power of such early samples is nullified (i.e., blocked) by samples at later time points, consistent with the Markovian nature of a diffusion process. (4) When the decision ends with an eye movement to the choice-target in the common response field, S_i(t) achieved a stereotyped level 50-100 ms before saccade initiation, consistent with the hypothesis that decision termination is accomplished via a threshold applied to S_i(t).

Conclusions: Small populations of simultaneously recorded neurons with a common response field render estimates of firing rates, as a function of time, on single trials. The sample-population firing-rate S_i(t) approximates the latent decision variable, V_i(t), inferred from behavioral analyses of choice-response time experiments - the accumulation of noisy samples of evidence. It confirms conclusions inferred indirectly from single neuron recordings. Access to V(t) on single trials is likely to prove useful in future experiments, for example, those that examine interactions between circuits.

T43. Intergenerational Inheritance of Taste Aversion

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Category: Epigenetics

Background: Following the Dutch Hunger Winter famine of 1944-1945, the children and grandchildren of famine survivors — who themselves had not experienced this period of stress — exhibited elevated rates of both metabolic illness (e.g. obesity, diabetes, and cardiovascular disease) as well as adverse psychological outcomes (e.g. schizophrenia, anxiety, and depression). This phenomenon of physical or emotional trauma being transmitted to offspring via epigenetic modifications, called transgenerational epigenetic inheritance, is an intriguing mechanism by which a learned behavior in a parent can become an innate behavior in their offspring.

In 2014, Dias and Ressler demonstrated that the pairing of an odor with a light foot shock leads to a significant increase in the number of olfactory sensory neurons that express the receptor for the conditioned odor, in both the conditioned male mice and in their naive, untrained offspring. Studies performed by John Garcia in the 1960s demonstrated that a taste aversion can be reliably produced through pairing a tastant with nausea. This study examines whether a learned taste aversion can also be inherited.
Methods: We utilize behavioral assays and transgenics to manipulate flavor preferences in male wild-type mice and their offspring. To produce conditioned taste aversion, we pair consumption of 5.5mM saccharin (sweet) water with injection of lithium chloride (LiCl), which makes the mice nauseous, or PBS. We then test saccharin preferences by letting the mice choose between water and saccharin solution and measuring how much time the mouse spends drinking from each bottle. The treated males are then mated with female wild-type mice and removed from the cage before the litter is born such that there is no contact between the father and offspring. The naive offspring are exposed to saccharin water for 5 hours to eliminate any neophobia, and later given the same saccharin vs. water preference test.

Results: Our preliminary results demonstrate a highly significant difference (p < 0.0001) between the saccharin preferences of F0 (first generation) PBS-injected and LiCl-injected male mice, with the PBS-paired mice exhibiting a preference for saccharin and the LiCl-paired mice showing a strong aversion (F0 PBS n = 12, F0 LiCl n = 11). We have also found a very significant difference (p = 0.0002) between the saccharin preferences among the offspring (F1) of the PBS-paired fathers and LiCl-paired fathers, with the F1 of LiCl-conditioned males demonstrating an innate aversion to what is innately appetitive in controls (F1 PBS n = 12, F1 LiCl n = 23).

Conclusions: The brain’s memory of trauma is much more complex than the memory of a single sense during a traumatic event. While instances of transgenerational epigenetic inheritance have been demonstrated in the olfactory system in mice, there is limited evidence of this phenomenon in other sensory systems. This project will elucidate whether this mechanism of epigenetic inheritance is also inherent in the gustatory system. The gustatory system is highly entwined with olfaction, and we also hope to examine how these two systems interact and individually contribute to taste aversion and its inheritance. Furthermore, achieving an understanding of how to intervene when these epigenetic adaptations no longer benefit the offspring would be of immense translational value.

T44. Molecular Mechanisms Underlying Chromatin Regulation of Cerebellar Development

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Category: Epigenetics

Background: Terminally differentiated cells including neurons dynamically regulate their genome despite leaving the cell-cycle early in life in order to assimilate new information throughout adulthood. The molecular basis of this dynamic gene-regulation remains poorly understood yet underlies defects in synaptic plasticity and cognition. Work from our lab has shown the dynamic, post-mitotic redistribution of the repressive histone modification H3K27me3 in a locus-specific fashion across the genome of the maturing cerebellar granule neuron (CGN). We are interested in asking how a fully fate committed neuron marks particular loci for differential histone methylation, what is the molecular consequence of this process, and ultimately what is its role in synaptic plasticity and cognition.

Methods: We are using the maturation of CGNs in the murine cerebellum as a model system to study post-mitotic chromatin regulation. The cerebellum has a protracted developmental timeline and is involved in a variety of cognitive and neurodevelopmental disorders. CGN-precursors terminally differentiate postnatally and undergo several timed gene expression events in order to migrate, populate the innermost layer of the cerebellar folium, and undergo dendrite outgrowth and synaptogenesis. We are utilizing a method of low-input native Chromatin Immunoprecipitation (ChIP) to ask how CGNs in culture and in vivo redistribute H3K27me3 in response to genetic, pharmacological and physiological perturbations.

Results: We find that H3K27me3 regulators EZH2 and KDM6B are both involved in the regulation of genes essential for cerebellar maturation in culture. We show that we can measure changes in H3K27me3 with high-throughput and resolution, despite having a limiting number of cells. Finally, we also show that we can fluorescently label a homogenous and homochronic population of CGNs in vivo, to study H3K27me3 dynamics in real time, and in response to physiological stimuli.

Conclusions: Chromatin regulators, including the readers, writers and erasers of H3K27me3, are implicated in the onset and pathophysiology of a multitude of human neurodevelopmental disorders, but their exact role in mediating brain development remains poorly understood. We seek to bridge this gap in knowledge through our expertise in chromatin immunoprecipitation and epigenome editing methods.
T45. Circadian Control of DNA Hydroxymethylation Drives Axon Growth in Neuroregeneration

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**Category:** Epigenetics

**Background:** Circadian rhythm impacts cell renewal in regenerating tissues such as liver, pancreas, and skin, yet its contribution to regeneration of post-mitotic neurons is currently unknown. We discovered an enrichment of circadian clock binding motifs in neuroregeneration associated differential hydroxymethylated regions. Here, we investigate the interaction between the circadian clock and DNA hydroxymethylation in axon growth and neuroregeneration.

**Methods:** Axon growth capacity of mouse sensory neurons was compared in early active phase (7PM to 10PM) and early resting phase (7AM to 10AM), in vivo using mouse sciatic nerve injury or in vitro using primary mouse DRG neuron culture. Global DNA hydroxymethylation was compared before and after injury using 5hmC immunostaining. Gene expression and immunofluorescence analyses were used to analyze circadian clock rhythmicity in DRGs and identify putative clock-controlled regeneration associated genes.

**Results:** We show that adult 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, and reduction of Gadd45g. Active phase injury enhanced ATF3 expression, an important regeneration associated gene and a known target of Tet3-mediated hydroxymethylation. Pathway enrichment analysis of circadian regulated DhMRs implicated cAMP and CREB1 signaling in the diurnal regulation of neuroregeneration. Analysis of CREB1 phosphorylation at serine 133 revealed injury independent circadian regulation, peaking in the active phase and troughing in the resting phase. Knockdown of BMAL1, the central regulator of the circadian clock, impaired axon growth capacity of hESC-induced sensory neurons after replating injury.

**Conclusions:** Our data uncover an epigenetic mechanism that allows neurons to anticipate injury in the time of high activity to initiate a fast repair response. Circadian regulation of DNA demethylation in neuroregeneration may represents an important pathway in mediating chronological responses in emerging neurotherapeutics.

T46. Histone Serotonylation: A Novel Regulator of Stress-Induced Neuroplasticity

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**Category:** Epigenetics

**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 serotoneic 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 24h 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 greater SI than control groups.

**Conclusions:** 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.

T47. Cell-Type Specific Profiling of Chromatin Accessibility in Human Orbitofrontal Cortex Identifies Epigenetic Regulator of Astrocytic Plasticity in MDD
Background: Major Depressive Disorder (MDD) is a chronic debilitating disease that arises from a complex interaction of genetics and environmental influences, such as stress, leading to persistent alterations in frontolimbic gene expression and cellular function. However, the epigenetic mechanisms that transduce stress into coordinated gene expression changes are not well understood. A major goal of our current project is to profile cell-type specific accessibility patterns of genome-wide chromatin structure in human clinical Depression and to utilize rodent models to investigate the mechanistic function of novel chromatin regulators identified through those profiles for the study of MDD. Although MDD has been predominantly studied in the context of neuronal function, emerging evidence indicates that dysregulation of glia may be equally important – particularly during chronic neuroinflammation in response to stress, which is known to contribute to the pathophysiology of MDD.

Methods: Our laboratory has implemented FANS (Fluorescence-Activated Nuclear Sorting)-coupled ATAC-seq (Assay for Transposase-Accessible Chromatin- Sequencing) to profile the cell type-specific regulatory landscape in human MDD orbitofrontal cortex (OFC), a brain region that processes reward-based decision-making and may mediate anhedonic symptoms in MDD.

Results: Using this approach, we identified a key pioneer factor, ZBTB7A, which regulates chromatin structure specifically in astrocytes to facilitate feed-forward pro-inflammatory transcriptional cycles driven by NF-Kb (with which ZBTB7A also directly interacts). Astrocyte-specific overexpression (OE) of ZBTB7A in rodent OFC is sufficient to induce NF-Kb inflammatory transcription and to produce deficits in reward-processing and stress-related behaviors, as well as alterations in OFC neurotransmission, which mirror the deficits observed in human MDD.

Conclusions: These experiments offer mechanistic insights into disease pathology in the context of a relatively understudied cell-type, astrocytes, in neuroinflammation and stress. Overall this project underlines the utility of chromatin accessibility profiles in the identification of common regulators of chromatin structure and gene targets observed between rodent and human studies, which are of especially high priority for functional validation in order to facilitate identification of pharmacologically relevant factors that may contribute to depression-associated behavioral syndromes.
acquire ipsilateral RGC identity. Our results also show that albino and CyclinD2-deficient mice have reduced depth perception, indicated by their compromised performance in the visual cliff task.

**Conclusions:** Using the albino visual system as a comparative model, our study elucidates how RGC neurogenesis is controlled during the formation of the binocular circuit and provides a route by which to interrogate factors related to melanin in the RPE that control these processes.

**T49. Apolipoprotein E Isoforms Differentially Control Transcriptome and Development of Hippocampal Neurons in Vitro**

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**Background:** Apolipoprotein (apo) E is expressed in the brain mainly by astrocytes and secreted as high-density lipoprotein (HDL) particles. The APOE gene has three polymorphic allele ε2, ε3 and ε4, encoding apoE isoforms E2, E3, and E4. The ε4 allele is associated with a higher risk of developing late-onset Alzheimer's disease (AD), while the ε2 allele endows a protective effect in ε4 allele non-carriers. Previous studies have evidenced reduced neuronal complexity in apoE4 transgenic mice compared to age-matched apoE2 and apoE3 lines. However, differential effects of apoE isoforms on neuronal development and modus operandi underlying these effects have not been elucidated.

**Methods:** Conditioned medium from immortalized astrocytic lines expressing apoE2, apoE3, apoE4 isoforms or those with apoE knockout (control medium) was recollected and 10-fold concentrated. Primary cultures of hippocampal neurons established from CD1 mouse pups were treated with equal amounts of each apoEHDL-isofrom or control medium between 10 and 17 day in vitro (DIV). At 17 DIV, the experiment was concluded, and neurons were subjected to morphological, biochemical, and transcriptomic analysis. Deep RNA sequencing was performed and differentially expressed genes between each apoEHDL treatments were classified using KEGG pathway analysis and literature revision.

**Results:** Astrocyte expressed apoEHDL-like particles induced an isoform-dependent gene expression pattern in neurons. ApoE2HDL and apoE3HDL upregulated genes related to enhancement of neuronal maturation and synaptic signaling compared to control medium, while apoE4HDL showed no such effect. These transcriptomic changes correlates with morphological differences in hippocampal neurons. Neurons, which matured in the environment enriched with apoE2HDL and apoE3HDL particles show significantly higher degree of dendritic complexity and dendritic spine maturation, while apoE4HDL treated neurons showed modest a reduction in the morphological metrics compared to neurons cultured in control medium. In addition, neurons treated with apoE2HDL and apoE3HDL activated genes related to chaperone proteins as a survival mechanism while neurons treated with apoE4HDL failed to activate such genes.

**Conclusions:** The apoE isoform-dependent change in neuronal transcriptome and neuronal maturation unravel possible mechanisms that regulate neuronal connectivity and potential susceptibility to neurodegeneration.

**T50. The Significance of Dance During Pregnancy in Pre- and Postnatal Neurodevelopment**

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**Category:** Molecular, Cellular and Development

**Background:** Some studies have already shown the positive impact of physical activity on fetal brain development, but the effect of dance has not yet been examined in this area. Other research has examined the
effects of dance on the brain, but not prenatally. The aim of our research was to investigate the efficacy of this physical-artistic activity on pre- and postnatal neurodevelopment using a unique prenatal dance method.

**Methods:** Clinically uncomplicated expectant individuals with singleton pregnancies were allocated into an activity and a control group. The activity group participated in a supervised, 60-minute, twice-weekly, moderate-intensity prenatal dance course at the University of Pécs, Hungary for 20 weeks. The control group did not take part in the intervention. Using the Bayley Scales of Infant and Toddler Development, we examined children’s neurodevelopment in both groups. Follow-up research was conducted in the activity group to assess children’s behavior and neurodevelopment as toddlers, using parental in-depth interviews, video analysis, and the Bayley Scales of Infant and Toddler Development.

**Results:** Of the 35 volunteers, 16 activity and 10 control group infant results were analyzed at 37.88±2.78 and 39.40±1.51 days of age, respectively. We found the following mean developmental ages (in days, from highest to lowest value, p<0.05): fine motor: 96.25±10.25 and 42.00±28.50, receptive communication: 92.50±13.42 and 29.50±21.40, cognitive skills: 71.25±5.00 and 27.00±14.76, gross motor: 62.500±16.13 and 43.00±11.60, expressive communication: 60.00±25.30 and 32.00±24.63. In the follow-up research, 14 participants of the activity group participated in the interviews when the children were 31.29±5.76 months old and 10 of them in the developmental tests when the mean calendar age of the children was 33.10±2.13 months. Music, dancing, singing, and storytelling or rhymes were found to play an essential role in the daily routine of the toddlers, and they were at a higher level than their peers. Their vocabulary and sense of rhythm was outstanding. Most of them used eclectic wordings and put together puzzles corresponding to a higher age. In the tests, the following mean developmental ages were found (in months, from highest to lowest value): expressive communication: 42.40±0.97, gross motor: 42.20±1.03, receptive communication: 41.30±3.59, fine motor: 41.10±3.67, cognitive skills: 40.70±3.68.

**Conclusions:** Significantly higher developmental ages were found in the activity group for all subscales of the infant test compared to the control group. As toddlers, they excelled in speaking, singing, and dancing. Developmental ages of the toddlers were higher on all subscales compared to their calendar age. These results highlight the significance of dance during pregnancy and reveal its long-term beneficial effects on neurodevelopment. Our findings may contribute to a novel approach to dance in neuroscience and prenatal care.

**T51. A Unique Lower Urinary Tract Phenotype is Associated With Markers for Metabolic Syndrome in Aging Rhesus Macaques**

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**Category:** Molecular, Cellular and Development

**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 increased 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.

**T52. The Role of ΔFosB in the Development of Drug Addiction: Identifying ΔFosB Transcriptional Targets in Nucleus Accumbens**
Background: Drug addiction exacts a devastating impact on drug users, their family members, and the nation’s public health. Although different in chemical structures and initial mechanisms affecting the brain, all classes of drugs of abuse induce the expression of the transcription factor ΔFosB in nucleus accumbens (NAc), the central node of the reward circuitry. Studies with ΔFosB genetic manipulation in mouse suggest that ΔFosB in NAc neurons is involved in the development of addiction. However, the molecular mechanisms of ΔFosB remain incompletely understood.

Methods: We extend earlier work on revealing ΔFosB’s transcriptional targets, which interrogated promoter regions only, by leveraging the CUT&RUN (cleavage under targets and release using nuclease) method to pinpoint ΔFosB coverage genome-wide upon chronic cocaine exposure.

Results: Thousands of ΔFosB peaks were revealed; interestingly, one third of the loci are positioned at distal intergenic enhancers while only ~15 percent of the peaks occur within known promoter areas, suggesting that a primary function of ΔFosB is coordinating distal regulatory elements with the transcription machinery. In addition, we identified ΔFosB peaks specific to medium spiny neurons (MSNs) expressing either dopamine receptor D1 or D2 – the two major neuronal types in NAc, which adds to the early discovery that ΔFosB directs differential molecular and synaptic plasticity in D1- versus D2-type MSNs.

Conclusions: Further extension of this CUT&RUN approach to other chromatin regulatory mechanisms in D1- and D2-type MSNs within NAc will set the groundwork for understanding distinct roles of these MSN subtypes, and their adaptations to chronic drug exposure, in drug addiction.

T53. Spatiotemporal Organization of a Central Vestibular Brainstem Nucleus in the Larval Zebrafish

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Category: Molecular, Cellular and Development

Background: Neural circuits must achieve precise wiring between distinct cell subtypes to produce appropriate behaviors. Identity specification and wiring precision in the circuit that stabilizes gaze is a particular case of this general developmental problem. Vertebrates stabilize gaze using excitatory vestibular interneurons that relay head and body destabilization to motoneurons that counter-rotate the eyes. Precise connectivity between directionally sensitive interneuron subtypes and particular sensory afferents and motoneurons is therefore crucial for behavior. The developmental mechanisms that specify excitatory vestibular interneuron identity and connectivity are unresolved, though previous work has suggested a role for spatiotemporal cues and/or motoneuron-derived factors. We tested these hypotheses in the tangential nucleus (TAN) of the larval zebrafish, which contains the excitatory vestibular interneurons necessary for vertical gaze stabilization.

Methods: First, we developed a calcium imaging assay that rapidly and reliably identifies functional nose-up and nose-down interneuron subtypes. We used this assay to map the spatial organization of functional subtypes born at particular times. Second, to investigate the requirement of motoneuron-derived signals, we used our functional assay to measure changes in TAN identity following constitutive motoneuron knockouts.

Results: Our functional assay revealed highly stereotyped, micro-columnar organization complementary to spatiotemporal development. Our results are the first demonstration of subtype organization within the brainstem and reflect a putative role for spatiotemporal identity programs. Additionally, we found that TAN identity and organization is preserved in the absence of motoneurons, arguing against a role for motoneuron-derived cues.

Conclusions: Taken together, we predict that spatiotemporally linked factors organize TAN subtypes into alternating micro-columns. We propose that functional identity acquisition and organization occurs in a motoneuron-independent manner.

T54. High-Precision Noninvasive Gene Delivery to the Brain

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**Category:** Molecular, Cellular and Development

**Background:** Recently, we developed a paradigm that allows such neuromodulation to be performed noninvasively by combining focused ultrasound, viral vectors, and chemogenetics. In our approach, called Acoustically Targeted Chemogenetics, or ATAC, focused ultrasound (FUS) is used to briefly open tight junctions in the blood-brain barrier (FUS-BBBO) in spatially specific brain region(s), allowing localized delivery of adeno-associated viral vectors (AAVs) encoding chemogenetic receptors to neurons and enabling their subsequent excitation or inhibition with bio-orthogonal, orally bioavailable drugs. FUS targets both deep and cortical brain regions with millimeter precision; AAVs allow us to choose a neuronal population using cell-specific promoters; and chemogenetic receptors enable temporally specific neuromodulation. To our knowledge, ATAC is the only neuromodulation technique that achieves temporal, spatial, cell-type, and molecular specificity noninvasively. However, its spatial precision is limited by the precision of FUS itself. While FUS allows for millimeter precision, many brain regions, such as a single layer of cortex or specific hypothalamic nuclei, are significantly smaller than the focus of FUS both in mice and larger animals. Such precision cannot be feasibly achieved in vivo with current FUS devices. To solve this limitation, we propose a novel strategy that decouples the precision of FUS from noninvasive chemogenetic neuromodulation.

**Methods:** We combine established tools for gene editing with FUS delivery to achieve transduction precision comparable to an invasive intracranial injection. To achieve this, we use two independent sessions of FUS-BBBO and allow for a spatial overlap of expression between the fields expressing the gene-editing target and the gene-editing enzyme. We will evaluate the gene-editing efficiency and the targeting precision of the overlapping region.

**Results:** We show that expressing both of these components is safe in mice (n=6) after systemic delivery with sufficient gene-editing efficiency and show ~10-fold improvement in targeting precision.

**Conclusions:** Being able to noninvasively control any neural circuit with a combination of spatial, temporal, cellular, and molecular pathway precision will allow for more precise treatment of neuropsychiatric disorders with fewer side effects.

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**T55. Effects of Neuronal Activation and Psychiatric Treatment on CircHomer1 Biogenesis**

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**Category:** Molecular, Cellular and Development

**Background:** This study is an attempt to characterize a psychiatric disease-associated neuronal-enriched circRNA and examine the mechanisms that control its biogenesis and its interactions with downstream targets. The goal is to significantly advance the current understanding of the molecular mechanisms that may underlie psychiatric disease (SCZ and BD).

**Methods:**
1. circRNA microarray platform to screen for circRNA expression in OFC RNA samples from SCZ, BD, and unaffected controls
2. sequence-verified circRNA-specific qRT-PCR primers aimed at the unique circRNA splice junction
3. Pharmacological inhibition of eif4a3 RBP (control vs inhibitor at concentration 0-5-10-20uM) and timepoints 0-6-24-48 hrs
4. Pharmacological intervention of antipsychotic and mood stabilizers: mice treated for 16 days with vehicle and drugs (Haloperidol-Olanzapine-Lithium-VPA and Risperidone), brain regions studied (frontal cortex, cerebellum, striatum, hippocampus), and methods used RNA extraction, RT-qPCR

**Results:**
1. robust reductions in circHomer1 in BD OFC and SCZ DLPFC (34 SCZ 32 BD and 34 unaffected SMRI) and also validated in a 2nd cohort (reduction in OFC of BD subjects in McLean/Harvard Medical School biobank and DLPFC SCZ subjects of Mt Sinai cohort)
2. Pharmacological inhibition of eif4a3 reduced circHomer1 levels in HEK293 and Neuro2a cell lines. Different concentration and time points tested. Eif4a3 is predicted to bind to circHomer1 and proved by RIP. Both eif4a3 and circHomer1 are conserved between humans and animals. Both experiments on HEK293 and Neuro2a provided similar outcomes.
3. Olanzapine differentially alters mouse circHomer1 levels in brain regions associated with SCZ, such as the prefrontal cortex (decreased) and striatum (increased). Doubling the dose of olanzapine led to similar results. In
addition, lithium and VPA decreased circHomer1 levels in the frontal cortex, a brain region implicated in BD biogenesis.

* the experiments with pharmacological agents and mice were done twice. Initially, we injected 8 males and females with haloperidol-olanzapine-risperidone and then a second experiment had 26 males and 27 females injected with lithium-VPA- and olanzapine was conducted.

**Conclusions:** Altered circHomer1 expression in the frontal cortex of subjects with psychiatric disorders (decreased in OFC of BD subjects and DLPFC of SCZ, validated in 2 different cohorts) eIF4A3 pharmacological inhibition decreases circHomer1 biogenesis in human and mice, whereas does not affect Homer1b biogenesis (both Homer1b and circHomer1 originate from the same pre-mRNA) circHomer1 but not linear Homer1 isoforms profile is differentially expressed after treatment of pharmacological agents of SCZ/BD treatment. Olanzapine alters circHomer1 levels in the frontal cortex and striatum in a contrary way.

**T56. Thalamic Control of Cortical Dynamics in a Model of Flexible Motor Sequencing**

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**Category:** Cognitive and Systems

**Abstract:** The neural mechanisms that generate an extensible library of motor motifs and flexibly string them into arbitrary sequences are unclear. We developed a model in which inhibitory basal ganglia output neurons project to thalamic units that are themselves bidirectionally connected to a recurrent cortical network. We model the basal ganglia inhibitory patterns as silencing some thalamic neurons while leaving others disinhibited and free to interact with cortex during specific motifs. We show that a small number of disinhibited thalamic neurons can control cortical dynamics to generate specific motor output in a noise robust way. Additionally, a single 'preparatory' thalamocortical network can produce fast cortical dynamics that support rapid transitions between any pair of learned motifs. If the thalamic units associated with each sequence component are segregated, many motor outputs can be learned without interference and then combined in arbitrary orders for the flexible production of long and complex motor sequences.

**T57. Open Board**

**T58. Brain by Environment Interactions: Predicting Externalizing Behavior in Youth via the Adolescent Brain and Cognitive Development (ABCD) Study**

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**Category:** Brain Disease and Disorders

**Abstract:** Externalizing behaviors are a constellation of behavioral problems, which include aggression and rule-breaking behaviors. Externalizing behaviors are considered a precursor to later violence and criminal behavior in adulthood. Although literature illustrated that externalizing behavior can be explained by brain correlates (especially the whole-brain wise global changes, such as whole-brain volume) and environmental adversity independently, much less is known about their joint impact. In this study, we examined the combination of altered whole brain brain morphology in conjunction with environmental factors to see its association with externalizing behaviors. Capitalizing on the Adolescent Brain and Cognitive Development (ABCD) study, we examined the available brain morphology data, externalizing behavior and environmental adversity in children aged 9 to 10 years old. Baseline-year data of 9717 participants from the ABCD release 2.0 were included in this study, including 5046 boys and 4671 girls. Externalizing behaviors were defined by t-scores from the Child Behavior Checklist (Achenbach, 1999). Environmental adversity was calculated from neighborhood factors, school environment, parent support, familial conflict, parental monitoring, trauma exposure, and familial history of psychiatric illness (based on Modabbernia et al., 2021). Whole-brain wise morphology data included cortical thickness, cortical area, cortical volume, sulcus depth, cortical ratio, and sub-cortical volume. Using stepwise regression, we found that those with
the combination of higher environmental adversity and greater whole-brain cortical ratio or less whole-brain cortical volume showed higher levels of externalizing behavior. In contrast, those with low environmental adversity exhibited less externalizing behavior than their high adversity counterparts. We found significant brain by environment interactions in predicting adolescent externalizing behaviors. High adversity coupled with brain correlates exacerbated externalizing behavior, whereas low adversity seemed to have a “protective” effect. These results are significant because they illustrate the importance of utilizing biosocial approaches to identifying the etiological basis of externalizing behavior.

**T59. Neurotoxic Astrocytes Secreted Glypican-4 Drives Alzheimer’s Tau Pathology**

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**Category:** Brain Disease and Disorders

**Abstract:** Apolipoprotein E4 (APOE4) is the most crucial genetic risk factor of late-onset Alzheimer’s disease (AD). However, the mechanism through which APOE4 induces AD risk remains unknown. Here, we report the astrocyte-secreted protein glypican-4 (GPC-4), as a novel binding partner of APOE4, drives tau pathology. APOE4-carrying AD patients display more tau accumulation compared to APOE4-noncarring AD patients. GPC-4 is highly expressed in APOE4 AD patients and regulated by microglial factors via NF-κB signaling pathway. The astrocyte-secreted GPC-4 induced both tau accumulation and spreading in vitro and in vivo. Further, GPC-4 is required for APOE4-mediated surface trafficking of low-density lipoprotein receptor-related protein 1 (LRP1) and tau propagation. GPC-4 activates unfolded protein response (UPR) pathway IRE1α, and pharmacological inhibition of IRE1α with KIRA6 blocks GPC-4 induced tau propagation. Together, our data comprehensively demonstrate that the APOE4-induced AD risk is directly mediated by GPC-4, and that perturbing GPC-4 induced IRE1α pathway has therapeutic opportunities.

**T60. Low Electrodermal Activity Predicts High Externalizing Behavior in Children Exposed to Acute Stress In-Utero**

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**Category:** Molecular, Cellular and Development

**Abstract:** Externalizing behavior in children is one of the leading risk factors for violence, juvenile delinquency, and adult crime. Previous studies have established a link between externalizing behavior and decreased autonomic nervous system activation. Prenatal maternal stress and parenting stress have also been implicated as predictors of externalizing behavior. This experiment examined associations between low electrodermal activity (EDA) and externalizing behavior through EDA amplitude and skin conductance responses (SCR). We also investigated whether acute in-utero stress (exposure to Hurricane Sandy) and parenting stress moderates the relationship between the aforementioned psychophysiological measures. The sample was drawn from a longitudinal study, the Stress in Pregnancy Study, that follows offspring from in-utero to 6 years of age. The study used a subsample (n=206) of which the mean age of the participants was 3.89 years old. Approximately 52% was female and the majority was Hispanic (50.5%). Hurricane Sandy exposure significantly moderated the relationship between amplitude and externalizing behavior symptoms (b=3.0344, p=.044); Hurricane Sandy exposure marginally significantly moderated the relationship between externalizing behavior and SCR (b=1.5629, p=.056) such that children who were exposed to Hurricane Sandy had low EDA measures that predicted high externalizing behavior symptoms. Parental stress did not moderate the relationship between externalizing behavior and EDA. The results of the study suggest that EDA is susceptible to environmental influence. These results also stress the importance of biological markers and environmental risk factors when studying externalizing behavior in children and can guide biologically informed treatments and screeners.

**T61. Investigating Cell-Type Vulnerability in Parkinson’s Disease Using an in Vitro Genetic Model**
T62. Adolescent THC Has Dose-Dependent Effects on Reward, Stress Reactivity, and Decision Making in Adulthood via Perturbations in Astrocytes

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Category: Cognitive and Systems

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

Methods: To provide causal mechanistic insight into the protracted effects of adolescent THC exposure on behavior, I leveraged an animal model of recreational cannabis exposure to administer low (1.5 mg/kg) and high (5 mg/kg) dose THC to rats during their adolescent period and assessed effects of the drug on reward processing, anxiety, stress reactivity, and decision making in adulthood. I then used RNA sequencing (RNAseq) on the basolateral amygdala, a region linked to reward processing, stress, and cognition to determine effects of THC on the transcriptome.

Results: Adolescent THC influenced behavior in a dose-dependent manner; while low dose THC influenced reward value and susceptibility to self-administer heroin, the high dose led to greater sensitivity to stressful conditions and re-exposure to THC later in life. RNAseq revealed that rat’s prior history of high dose THC exposure had significant downregulation in genes specific to astrocytes, a subset of glia that maintain homeostasis of the synapse, 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: The long-term effects of adolescent THC exposure are dose-dependent, and ex vivo data indicate that astrocytes, and the so-called “tripartite synapse,” likely play a central role in THC-induced behavioral deficits after stress and drug re-exposure in adulthood.

T63. Serial Time-Multiplexed Incorporation of Evidence to Make Two Decisions About One Object
T64. Neural Representation: Bridging Neuroscience and Philosophy

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Abstract: We understand the brain in representational terms. A paradigmatic example is in the hippocampus, where spatial navigation is understood by appealing to the kinds of spatial properties that hippocampal cells represent, and the operations hippocampal circuits perform on those representations (Moser et al., 2008). Philosophers, and recently neuroscientists, have become concerned with the nature of representation (Baker & Lansdell, n.d.; Egan, 2019; Piccinini & Shagrir, 2014; Poldrack, 2020; Shagrir, 2001). We want to know what representations are, how to discover them in the brain, and why they matter for explaining the brain.

These questions are framed in a traditional philosophical way: we start with explanations that use representational terms, and to more deeply understand those explanations we ask, what are representations? But I argue that this is only one approach among many. We might, rather than asking what representations are, ask what the use of representational notions allows us to do in neuroscience. I argue that this framing makes the problem of representation stand out more starkly and offers more fruitful ground for interdisciplinary collaboration by distinguishing the philosophical concerns that have a place in neuroscience from those that don’t. And I argue for a particular answer to the new question: representational notions allow us to impose (in our imagination and in our models) the structure of one domain (e.g., the spatial structure of the environment) onto another (the dynamics of the hippocampus), so that we can see how the structure of the brain allows it to track and get around in that environment. I put this view to work, intervening in debates over the nature of the hippocampus’ representations, and illuminating the difference between representational and non-representational approaches in neuroscience.

T65. Lower VEGFR2 and TrkB Expression in Untreated Depressed Subjects is at Control Levels in SSRI-Treated Subjects and Correlates With Measures of Neurogenesis and Angiogenesis in the Human Dentate Gyrus

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Category: Brain Disease and Disorders
**Abstract:** Adult neurogenesis is hypothesized to be impaired in major depressive disorder (MDD). Growth factors, including vascular endothelial growth factor (VEGF; receptor VEGFR2) and brain-derived neurotrophic factor (BDNF, receptor TrkB), co-regulate angiogenesis and neurogenesis in the neurogenic niche of the hippocampal dentate gyrus (DG). In rodents, VEGF and BDNF mediate increased neurogenesis induced by selective serotonin reuptake inhibitors (SSRI), yet a role for growth factors in MDD pathogenesis and treatment remains unclear.

In human postmortem DG, we quantified VEGF-2-immunoreactive (IR), TrkB-IR, nestin-IR neural progenitor cells (NPCs) and capillaries, Ki-67-IR proliferating cells, NeuN-IR mature granule neurons, and serotonin 1A receptor (HTR1A) mRNA using immunohistochemistry, in situ hybridization, and Stereoinvestigator and Densitavec software (mBF Biosciences). We compared untreated MDD subjects (MDD*U; N=12), MDDs treated with SSRIs (MDD*SSRI; N=11), and psychiatrically healthy controls (N=14).

We found that MDD*U subjects had a deficit of DG VEGFR2-IR and TrkB-IR cells vs. control (p=.013 and p=.006, respectively), while MDD*SSRI subjects had more VEGFR2-IR cells vs. MDD*U (p<0.001). In anterior DG, VEGFR2-IR cell number correlated with number of NPCs (r²=.427, p=.009), proliferating cells (r²=.414, p=.028), granule neurons (r²=.433, p = .015), and with capillary length (r²=.787, p<.001), anterior DG volume (r²=.454, p=.008), and HTR1A mRNA expression (r²=.363, p=.047). TrkB-IR cell number correlated with NPC number (r²=.329, p=.046), granule neuron number (r²=.348, p=.047), anterior DG volume (r²=.483, p=.002), and VEGFR2-IR cells (r²=.484, p=.012).

Deficit in TrkB and VEGFR2 cell expression in untreated MDD subjects could contribute to MDD pathology, while greater VEGFR2 expression with SSRI treatment supports a role for VEGF in antidepressant action. Correlations with NPC number, granule neuron number, and capillary length support the hypothesis that growth factors sustain angiogenesis and neurogenesis. Correlation between HTR1A mRNA expression and VEGFR2-IR count suggests that SSRIs may induce neurogenesis and angiogenesis by up-regulating HTR1A-mediated VEGF signaling, as shown in rodents.

**T66. TGF-B Signaling in Motor Neurons in a Mouse Model of ALS**

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**Category:** Brain Disease and Disorders

**Abstract:** Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gherig’s Disease, is a fatal neurodegenerative disease caused by the death of motor neurons in the spinal cord and brain. Diverse mutations can cause ALS by disrupting various interrelated pathways. To date no therapy targeting a single factor can rescue motor neuron loss. Transforming Growth Factor Beta (TGF-B) signaling is a superfamily of signaling pathways that are upstream of many of the pathways changed in disease and have been shown to be dysregulated in ALS. Upregulation of TGF-B signaling has been identified as neuroprotective in many neurodegenerative disease models; however, there is conflicting evidence about the role of TGF-B signaling in ALS.

We found that TGF-B signaling is pre-symptomatically inhibited in a vulnerable population of spinal motor neurons in a mouse model of ALS. In ALS, ablating the Classical arm of the TGF-B signaling pathway in motor neurons does not change disease outcome, however targeting multiple arms of the signaling pathway in motor neurons does increase disease onset in ALS animals. We have completed spatially resolved gene expression profiling to understand how this manipulation changes gene expression in the spinal cord. This sequencing experiment has uncovered potential candidate genes modulated by TGF-B signaling in neurons. We are in the process of designing AAV therapies to modulate the expression of these factors in motor neurons in sick animals with the goal of extending their survival. We hope that these experiments will identify new therapeutic candidates for ALS.

**T67. Effect of Session Time on Mouse Delta9-Tetrahydrocannabinol Intravenous Self-Administration**

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**Category:** Brain Disease and Disorders
Background: Despite the growing legalization of cannabis and THC products in the United States, limited research has examined the biological and behavioral consequences of acute and/or chronic use of cannabinoids particularly in adolescents. Technical hurdles have until recently stymied translationally relevant models of rodent cannabinoid intravenous self-administration (IVSA). Here we investigated sex and circadian effects on mouse THC IVSA.

Methods: Male and female C57Bl/6J mice had 15 daily 2 or 6-hr THC sessions (6.25 – 12.5 µg/kg/inf) with sessions starting 2 to 9 hours into dark light cycle.

Results: The majority of mice started at least four hours into the dark cycle had robust THC IVSA with intakes ~0.2 mg/kg; however, mice with sessions starting 2-3h into dark cycle quickly extinguished SA. Similar session intakes were observed for male and female mice as well as 2 and 6 hr sessions with administration occurring across the duration regardless of session length.

Conclusions: This is the first report of mice stably self-administering THC with unit doses similar to doses administered by human cannabis users. Session start time appears to significantly influence acquisition of THC SA. Further, extending the session length did not potentiation THC intake. No sex difference in session intake was observed. Since females preferentially metabolize THC to 11-hydroxy-THC (an active metabolite) while males produce several mostly inactive metabolites, there may be more robust behavioral and/or neurological consequences in females despite similar session THC intakes.

T68. A CRISPR-Based Screen Identifies Mediators of Motor Neuron Death

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Category: Brain Disease and Disorders

Background: Endoplasmic reticulum (ER) stress is a common feature of neurodegenerative disorders that are characterized by the accumulation of misfolded proteins, including amyotrophic lateral sclerosis (ALS), Alzheimer’s disease, and Parkinson’s disease. If left unchecked, ER stress can ultimately trigger widespread neuronal death. We have previously shown that motor neurons, the primary cell type affected in ALS, are more sensitive to ER stress-inducing agents than other neuronal subtypes in the spinal cord, and that the expression of ALS-causing mutations further heightens their vulnerability.

Methods: To elucidate mechanisms of ER stress-mediated motor neuron degeneration, we performed pharmacological screens in mouse and human stem cell-derived motor neurons. Additionally, we generated individual and combinatorial knockouts of primary candidate kinase inhibitor targets. Finally, we have developed an inducible, CRISPR-based whole-kinome knockout survival screen in post-mitotic motor neurons.

Results: Pharmacological screens found that compounds targeting the mitogen-activated protein kinase kinase (MAP4K) family prevent ER stress-induced neurodegeneration. Combinatorial knockout of MAP4Ks had additive neuroprotective effects but did not fully recapitulate the effects of pharmacological MAP4K inhibitors. The CRISPR-based whole-kinome knockout screen identified additional kinases beyond the MAP signaling pathway that contribute to ER stress-mediated motor neuron degeneration. We then validated the role of these kinases through pharmacological inhibition and single gene knockout screens.

Conclusions: Pharmacological and genetic screening identified components of multimodal kinase signaling that contribute to ER stress-mediated motor neuron degeneration. These findings provide the basis for the advancement of novel, kinase inhibitors for potential therapeutic use.
the ROI_Pons of the healthy subjects experienced a displacement of 0.72± 0.14 pixels (p<0.05). We also observed pons, while the mean of the maximum displacement in the r and the pons were significantly higher in the CMI patients as compared to the healthy subjects (p<0.05). In the

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Results: Modest displacement within the frequency range of 0

Displacement tracking in the amplified data: Having amplified the 3D cine data in 3

3D aMRI algorithm: The 3D aMRI method is based on the extension of the 2D aMRI algorithm to 3D, allowing the visualization and quantification of very subtle voxel displacements in 3 directions. In the first step, a 3D cine MRI data set is used as an input to the algorithm. Then, a 3D steerable pyramid, composed of steerable filters with multi-scale decomposition, is used to decompose the volumetric data, resulting in local phases of each time frame at different scales and orientations. The temporal variations of the decomposed phases are then temporally filtered, amplified, and added back to the original phases. Finally, the modified video is reconstructed by collapsing the pyramid, which allows for visualization of the almost imperceptible motion.

Displacement tracking in the amplified data: Having amplified the 3D cine data in 3-direction, an image registration algorithm based on the Demons algorithm was then applied to the amplified data to quantify the overall 3D brain displacements of the subjects. We then mapped the acquired displacement fields on a brain atlas and selected a circular region (30mm^2) at the bottom of the cerebellum and at the bottom of pons near the medulla. The circular region was further extended to cover 7 adjacent sagittal slices for each subject, and the mean of maximum displacement within this region and across all the slices was then calculated and compared between the healthy and CMI subjects. This region was chosen since previous studies have suggested abnormal motion in the lower parts of the brain in CMI patients.

Results: Having amplified the 3D cine MRI of the healthy and CMI subjects with an amplification factor of 8, and within the frequency range of 0-4 Hz, the displacement fields of each subject were then measured. In both the healthy and CMI subjects, the maximum displacement was observed to be near the pons and the 4th ventricle. When comparing the results between the two groups, we observed that the motion at the bottom of the cerebellum and the pons were significantly higher in the CMI patients as compared to the healthy subjects (p<0.05). When comparing the results between the two groups, we observed that the motion at the bottom of the cerebellum and the pons were significantly higher in the CMI patients as compared to the healthy subjects (p<0.05). In the pons, while the mean of the maximum displacement in the region of interest (ROI_Pons) was 1.00 ± 0.20 pixels, the ROI_Pons of the healthy subjects experienced a displacement of 0.72± 0.14 pixels (p<0.05). We also observed
a significantly higher displacement of 1.25 ± 0.33 pixels in the selected ROI Cerebellum of CMI patients as compared to the displacement of 0.82±0.17 pixels in the healthy subjects (p<0.05).

**Conclusions:** In this work, we used for the first time the 3D aMRI method to measure the brain’s intrinsic motion in CMI patients. We observed that the highest displacement in both the healthy and CMI subjects was near the pons and the 4th ventricles. Additionally, we demonstrated in the CMI patients that the displacement at the bottom of the cerebellum and pons (near the medulla) was significantly higher as compared to the healthy subjects. Our findings are in line with previous observations that reported abnormal brain intrinsic motion in the lower parts of the brain. Using the DENSE method, it was recently shown that the displacement in the lower part of the cerebellum and brainstem was much higher in CMI patients. We hypothesize that this difference is mainly due to the geometrical variances between the cerebellum of the healthy and CMI subjects. CMI related morphological changes could lead to a partial blockage of the subarachnoid space near the foramen magnum, which could result in the obstruction of the CSF circulation and potentially decrease the CSF volume through there. However, since the driving pressure from the blood flow is higher than the intracranial pressure, the same volume of CSF at a higher velocity would potentially pass through the region, which results in a higher displacement of the lower parts of the cerebellum and pons.

Our results show 3D aMRI’s capability as a potential diagnostic tool for CMI. 3D aMRI is a post-processing algorithm which is applied on cine MRI data that is already implemented in the standard clinical routine; therefore, it could be used in the current protocols and potentially have an immediate clinical impact.

**W2. Drugs That Extend Lifespan Also Protect Against Abeta Proteotoxicity in a C. Elegans Model of Alzheimer’s Disease**

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**Background:** Alzheimer’s disease (AD) is one of the top 10 leading causes death in the United States with no current treatments available that effectively prevent disease progression. With the burden projected to increase in the coming decades the need to find new treatments is imperative. Genes that extend lifespan have been shown to delay impairments in animal models of AD. Along that line of thought we screened compounds that have been reported to extend lifespan for their ability to delay impairments in a C. elegans model of AD.

**Methods:** Using day 1 adult age synchronized CL2006 C. elegans, we plated worms into a 96 well plates filled with SMC supplemented with OP50 and the compounds of interest. Using the automated WMicrotracker we recorded movement scores for each well for 30 minutes every day until movement scores hit 0 indicating paralysis.

**Results:** Of the 67 compounds screened, 15 compounds were able to significantly delay the onset of abeta induced impairments (p<0.05 based on 2way ANOVA with Sidak’s test for multiple comparisons, sample size ranged from 4-8 wells per condition).

**Conclusions:** Drugs that increase lifespan also seem to delay impairments due to abeta proteotoxicity. The present screen has identified compounds that may be used in the future as lead compounds for the identification of novel treatments for AD.

**W3. Chronic Social Defeat Stress Increases Intestinal Permeability and Inflammation in Mice**

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**Background:** Major depressive disorder (MDD) represents the leading cause of disability, affecting >300 million people worldwide. Largely characterized behaviorally, it is critical to identify biological changes associated with MDD. Emerging literature recognize a correlation between MDD and inflammation; however, it is not fully known how this inflammation initiates. Recently, several chronic inflammatory conditions have been associated with increased intestinal permeability. We hypothesize that chronic stress compromises the gut barrier, allowing translocation of gut microbial byproducts into circulation, triggering inflammation associated with depression-like behavior.
**Methods:** To model depression-like behavior in mice, a 10-day chronic social defeat stress (CSDS) model was used. 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, IFNγ+ T cells were upregulated, and IL4+ T cells were downregulated in the colon after CSDS. Using ITGβ7-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.

### W4. Traumatic Social Experience Engages Lateral Septum Neurotensin Circuitry to Occlude Social Reward

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**Category:** Brain Disease and Disorders

**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:** Use conditioned place preference (CPP) assay to test the social reward in defeated mice. And iDISCO+ whole brain cFos mapping to identify the differential brain regions. Then using chemogenetics and optogenetics to manipulate lateral septum local and downstream pathways.

**Results:** We find susceptible mice show greater avoidance and spend significantly less time interacting with same-sex juvenile intruders in home-cage intruder test compared to control or resilient mice; we found only susceptible (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:** The social avoidance showed by susceptible in SI test is not only because of conditioned fear, but also a true social reward impairment. LS neurotensin population is important for the regulation of depressive-like behavior.

### W5. Transcriptome Wide Association Study of Individually Imputed Genetically Regulated Gene Expression in the Million Veteran Program

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**Category:** Brain Disease and Disorders

**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). This represents one of the largest GREx experiments to date. Importantly, our novel imputation approach, EpiXcan, integrates epigenetic information as well as genetic, enabling greater imputation precision.

**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 Principal Component Analysis (PCA), GREx based Phenome Wide Association Studies (PheWAS), and Transcriptome Wide Association Studies (TWAS).

**Results:** Results show a significant overlap in top Schizophrenia genes identified by TWAS in over three hundred thousand European individuals and those identified by GWAS of Schizophrenia by the Psychiatric Genetics.
W6. Elucidation of the Astrocyte-Specific Transcriptome Following Exposure to Cocaine

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Category: Brain Disease and Disorders

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 increasingly indicates that astrocytes are also involved in disorders of the nervous system, including addiction. Indeed, candidate genes in astrocytes have been identified and, furthermore, manipulation of astrocyte function has been demonstrated to influence rodent behavioral responses to cocaine administration. However, the astrocyte-specific transcriptome following exposure to drugs of abuse has not been investigated.

Methods: We utilized whole cell sorting of astrocytes and RNA-sequencing to investigate the astrocyte-specific transcriptome in several key brain regions involved in reward-processing, including the nucleus accumbens and prefrontal cortex, following exposure to cocaine.

Results: We observed a robust transcriptional response in astrocytes. Indeed, subsequent gene ontology analysis revealed a variety of pathways, including synaptic regulation, calcium signaling, and GPCR signaling in both brain regions as being prominently regulated by cocaine exposure. 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 subsequently study the role of specific transcripts in contributing to the pathophysiology of addiction.

W7. Phenothiazines to Treat Alzheimer’s Disease

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Category: Brain Disease and Disorders

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

Methods: 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. Congeners to a highly represented class of protective drugs were obtained from the NCI library and further screened in liquid medium for efficacy to reduce Abeta related paralysis in CL2006. 20 of these drugs were assessed for effects on lifespan in wild type C. elegans (N2) in liquid medium. We extended these experiments by assessing markers of aging (pharyngeal pumping rate and body bends) for the 3 most protective drugs. Finally, we tested the 3 most protective drugs in a C. elegans neuronal model of AD, CL2355 with a chemotaxis assay.

Results: The initial screen identified 131 compounds which significantly delayed paralysis as a readout for Abeta proteotoxicity in CL2006. The most significantly protective compound was phenylbutyric acid, now in clinical trials for AD. 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 congeneres were further assessed; 68%
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 phenothiazines protect against Abeta toxicity, and assessment of efficacy to protect against other forms of proteotoxicity are ongoing. 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.

**W8. Role of Hypothalamic Paraventricular Oxytocin Neurons in Social Recognition Memory**

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**Category:** Brain Disease and Disorders

**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.

**W9. Dysregulation of a Hypothalamic Brain Aversion Network Drives Addiction-Like Eating in Obesity**


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**Category:** Brain Disease and Disorders

**Background:** Global obesity rates are on the rise, resulting in a growing threat to public health. Pharmacotherapies that safely reduce body weight in obesity remain elusive, partially due to our incomplete knowledge of the complex neuronal mechanisms that control food choice. Similarly, we know little about the mechanisms by which consumption of palatable food can transition from controlled to compulsive, thereby driving the development of obesity. The lateral hypothalamus (LH) is a brain region considered a critical node in the maintenance of energy homeostasis. We hypothesized that obesity is accompanied by changes to LH function and this in turn impacts a range of downstream brain structures leading to obesity associated behavioral abnormalities.

**Methods:** Single cell sequencing, electrophysiology, chemogenetics, whole brain clearing, optogenetics, photometric recording of neuronal activity in vivo, rodent behavioral feeding assays.

**Results:** Single cell sequencing of LH RNA transcripts from mice revealed excitatory neurons show marked obesity-associated alterations in gene expression. Specifically, transcripts from genes associated with glutamatergic neurotransmission were significantly lower in tissue harvested from obese mice. Using electrophysiology and whole brain clearing with automated quantification of synaptic contacts, we found this transcriptional plasticity accompanied the emergence of LH glutamatergic hypofunction in the LH and a profound restructuring of hypothalamic output to a range of brain loci including the lateral habenula, periaqueductal gray and dorsal raphe nucleus. Finally, using transgenic mice and viral manipulation of neuronal function in vivo we linked this LH glutamatergic hypofunction in individual circuits to the emergence of discrete obesity associated behaviors.
Conclusions: Our research posits rescuing excitatory hypothalamic output as a novel therapeutic strategy to combat the food related motivational deficits that emerge in obesity.

W10. Dorsal Peduncular Prefrontal Cortex Contains Cells Uniquely Sensitive to Opioids: Relevance to Opioid Reward and Addiction.

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Category: Brain Disease and Disorders

Background: The US is in the midst of an opioid abuse and overdose epidemic, with over 115 people dying each day from opioid overdose; this has been declared a public health emergency. The vast majority of research on opioid addiction has focused on a small number of circuits, primarily the mesocorticolimbic circuit.

Methods: We used iDISCO+ tissue clearing and e-Fos staining to create a whole-brain map of transcriptionally responsive neurons following acute oxycodone (5 mg/kg) or saline injection. We then used single-cell RNA sequencing to molecularly characterize the Dorsal Peduncular area (DP), a previously unexplored component of the ventromedial prefrontal cortex (vmPFC). Whole-cell patch clamp electrophysiology was used to characterize Oprm1-expressing neurons in the DP, compared to neighboring Oprm1-negative neurons. To examine contributions of opioid signaling and DP activity to reward and aversive behaviors, we used optogenetic and chemogenetic manipulations in combination with conditioned place preference, self-administration, and naloxone-precipitated withdrawal.

Results: Single-cell RNA-sequencing, qPCR, and RNAscope revealed unique properties of opioid-responsive DP neurons relative to surrounding mPFC. The DP is enriched in Oprm1 (µ opioid receptor) and Slc17a6 (vGlut2) relative to neighboring infralimbic cortex. Surprisingly, Oprm1 and Slc17a6 are co-expressed in DP neurons in layer 5 that show robust transcriptional responses to oxycodone. Patch-clamp recording showed that these neurons are hyperpolarized by µ agonist DAMGO and have decreased intrinsic excitability. Using FosTRAP mice, we tagged opioid-responsive neurons DP, and optogenetic stimulation of this DP ensemble produced aversion-related behaviors that were blocked by oxycodone. Further, optical stimulation of DP in opioid-dependent mice enhanced naloxone-precipitated withdrawal symptoms. Whole-brain projection mapping revealed opioid-responsive DP neurons project to several mid- and hindbrain sites with known involvement in aversive behaviors, including the parabrachial nucleus (PBN). Optical stimulation of DP-PBN circuit recapitulated the aversive phenotype seen during DP somatic stimulation.

Conclusions: The DP is a major prefrontal site that regulates opioid reward and dependence.

W11. Patterns of Disease-Related Cortical and Subcortical Grey Matter Differences in Early Relapsing-Remitting Multiple Sclerosis

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Category: Brain Disease and Disorders

Background: Grey matter atrophy is prevalent, begins early, and is linked to functional decline among persons with multiple sclerosis; however, grey matter changes are not uniform across cortical regions. Recent work highlights posterior cingulate and entorhinal cortices as most vulnerable to disease-related change, whereas medial frontal regions remain relatively preserved. Spatiotemporal patterns of cortical and subcortical atrophy in early relapsing-remitting multiple sclerosis (RRMS) may inform hypotheses about pathophysioligic mechanisms underlying early grey matter changes and functional decline.

Methods: We investigated regional cortical and subcortical grey matter radiographically in a cohort of younger persons with early RRMS (mean age 34.4 years, median 2.0 years since diagnosis). We sought to identify regions of cortical and subcortical grey matter that (a) differ between patients and matched healthy controls, and (b) are most related to inflammatory T2 lesion volume (T2LV; the radiographic hallmark of multiple sclerosis pathology) and microstructural integrity of normal-appearing white matter (NAWM). We also investigated differential atrophy across subcortical grey matter structures, including key thalamic nuclei.

Results: Results showed lower cortical thickness in the posterior cingulate was associated with worse disease burden (i.e., greater T2 lesion volume) in patients. In contrast, increased cortical thickness in the anterior cingulate
cortex was inversely related to disease burden, suggestive of relative preservation. Similarly, white matter microstructural integrity was associated with greater atrophy of temporal and posterior cortices and preservation of anterior regions. Lower entorhinal thickness significantly distinguished patients from healthy controls. Of the deep grey matter structures, lower volume of the pulvinar nucleus of the thalamus robustly differentiated patients and healthy controls and related to disease severity.

**Conclusions:** Our findings support a pattern of vulnerability to aspects of subcortical and posterior cortical regions with relative preservation of anterior cortical regions in patients in the earliest stages of RRMS.

**W12. Integrative Metabolomics-Genomics Approach Reveals Key Metabolic Pathways and Regulators of Alzheimer's Disease**

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**Category:** Brain Disease and Disorders

**Background:** The metabolic basis of Alzheimer’s Disease (AD) is poorly understood, and the relationships between systemic abnormalities in metabolism and AD pathogenesis remain elusive. In this study, we systematically interrogated metabolomics, genetics, proteomics, and clinical data from the matched subjects in the Alzheimer’s Disease Neuroimaging Initiative (ADNI) to identify key drivers and metabolic pathways associated with changes in metabolites with disease severity.

**Methods:** 140 Metabolites in fasting serum samples from the ADNI (362 controls, 94 significant memory concerns, 764 mild cognitive impairment, and 298 AD) were analyzed using the AbsoluteIDQ-p180 kit. Values adjusted for age, gender, body mass index (BMI), education, cohort, and medication. A metabolite co-expression network was constructed using Multiscale Embedded Gene co-Expression Network Analysis (MEGENA). Co-expressed metabolite modules were then prioritized for the strength of association with clinical/cognitive and pathology biomarker variables. Correlation analysis of the co-metabolite modules and the matched gene/protein expression data was performed. The ROS/MAP cohort was used as a replication study of the co-expression network. Six brain transcriptomic datasets from the Mount Sinai Brain Bank, ROS/MAP, and MAYO clinic cohorts were utilized to build up gene-centered correlation networks to elucidate functions of upstream regulators of candidate metabolites.

**Results:** Modules comprised of short-chain acylcarnitines/amino acids (M8, M3), and medium/long-chain acylcarnitines (M6) were most associated with worse AD clinical outcomes, including episodic memory scores and disease severity (CDR score). CPT1A gene expression was highly correlated with an increased level of the medium/long-chain acylcarnitines (corrected p-value = 1.87x10^-6). Increased ABCA1 gene expression and adiponectin protein (a regulator of ABCA1) corresponded to decreased short-chain acylcarnitines and amines in AD (corrected p-value < 0.02). In addition, CPT1A and ABCA1 were differently expressed in the brains of AD patients compared to controls, and their subnetworks were enriched for AD, aging, and neuronal system-related gene signatures/pathways. Eight out of eleven modules were highly preserved between the ADNI and ROS/MAP cohorts (Z summary preservation score > 5; corrected-value < 0.05).

**Conclusions:** Identification of acylcarnitines enriched modules and their potential upstream genetic and transcriptional regulators paves the way for developing novel biomarkers and targets for AD.

**W13. Exacerbated Worsening of Positive and Negative Mood Among Underage Drinkers During the COVID-19 Pandemic, but Less so in Those With Greater Resilience**

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**Category:** Brain Disease and Disorders
**Background:** Increased stress associated with the COVID-19 pandemic has had harmful effects on adolescents, who are more vulnerable to mood deteriorations. Alcohol use may further exacerbate harmful mood outcomes. However, resilience may lend protection to this type of emotional dysregulation among underage drinkers. The present study sought to evaluate the impact of the pandemic on mood for drinkers versus non-drinkers ages 21 and under and the association between resilience (as well as other traits such as anxiety, anhedonia, and alexithymia) and mood deterioration.

**Methods:** An online survey including the CoRonavIruS health and Impact Survey (CRISIS) and questions regarding anxiety, alexithymia (Toronto Alexithymia Scale, TAS-20), anhedonia (Temporal Experience of Please Scale, TEPS) and resilience (Connor-Davidson Resilience Scale, CD-RISC2) was conducted in individuals ages 21 and younger (N=220; 73.51% female). Of them, 162 reported no or rare use (i.e., non-drinkers) and 58 reported drinking at least once a month (i.e., drinkers). The effect of the pandemic on negative (sadness, anxiety, etc.) and positive mood (happiness, relaxation, etc.) was assessed using mixed ANOVAs, and its association with anxiety, alexithymia, anhedonia, and resilience were assessed using mediation and correlation analyses.

**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. However, drinkers with higher resilience showed lower increase in negative mood. Anxiety regarding the pandemic significantly mediated the relationship between alcohol use and changes in both positive and negative mood while the difference in time spent outdoors mediated the relationship with changes in positive mood. Expectedly, across both groups, lower increase in negative mood was associated with greater alexithymia, and greater decrease in positive mood was associated with greater anhedonia.

**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). Though mood changes were also associated with alexithymia (negative mood) and anhedonia (positive mood), and greater resilience in underage drinkers was remarkably associated with less worsening of negative mood over time.


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**Category:** Brain Disease and Disorders

**Background:** The cerebellum is historically known for its roles in motor learning and coordination, but emerging evidence suggests that the cerebellum also regulates more complex behaviors related to cognition, affect, and reward. Furthermore, cerebellar dysfunction is increasingly linked to the pathogenesis of schizophrenia, autism, and other neurodevelopmental disorders. The cerebellum shares extensive reciprocal connectivity with the neocortex, basal ganglia, and hindbrain nuclei, and is thought to convey sensory experiences that shape cortical development and function. Nevertheless, the genes, cells, and circuits that govern cerebellar interactions with higher-order brain systems are poorly understood. We aimed to determine whether a schizophrenia-associated microRNA might have important functions in the cerebellum.

**Methods:** Detection of miR-206 by RNAscope in situ hybridization and quantitative RT-PCR was performed in developing and adult mouse brain and cerebellum. The miR-206 stemloop was targeted with flanking loxP sites using homologous recombination in mouse embryonic stem cells, and mice were then bred to germline Cre to generate a miR-206 null allele or to other Cre driver lines for conditional deletion. Multiple cohorts of male and female mice were tested across a range of behavioral paradigms. Purkinje cell firing of miR-206 WT and KO males was determined by whole-cell patch clamp or extracellular recordings in acute cerebellar slices. High-throughput sequencing of RNA isolated by crosslinking immunoprecipitation was carried out in cerebellum of WT and miR-206 floxed mice with Parvalbumin-Cre or Pcp2-Cre driving conditional expression of FLAG-tagged Argonaute and deletion of miR-206 if on the floxed background.

**Results:** We find that a schizophrenia-associated microRNA, miR-206, is specifically enriched in cerebellar Purkinje cells. Mice with a targeted deletion of miR-206 exhibit impaired pre-pulse inhibition, an endophenotype of schizophrenia in humans, stress-induced hypolocomotion, and sex-dependent cognitive deficits. Pre-pulse inhibition impairments were recapitulated by conditional deletion of miR-206 in Purkinje cells, suggesting that altered cerebellar output may contribute to these behavioral abnormalities. Consistent with this possibility, the spontaneous firing frequency of Purkinje cells was increased in miR-206 null mice. High-throughput sequencing...
of RNA isolated by crosslinking immunoprecipitation after miR-206 deletion in Purkinje cells revealed potential target mRNAs in pathways related to neuronal excitability, glutamate signaling, and dendritic morphology and development.

Conclusions: Together, these findings indicate that the regulation of cerebellar Purkinje cell function by miR-206 plays a critical role in sensorimotor, cognitive, and affective behaviors that are relevant to schizophrenia.

W15. Atlas of Genetic Effects in Human Microglia Transcriptome Across Brain Regions, Aging and Disease Pathologies

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Category: Brain Disease and Disorders

Background: Microglia are tissue-resident macrophages of the central nervous system that are essential for homeostasis, immune response, neurogenesis, and neuronal plasticity. Genetic studies have strongly implicated microglial dysfunction in multiple neurodegenerative diseases. However, investigating genetically driven changes in gene expression in microglia has been limited by lack of access to these cells from the number of subjects required to perform well-powered genomic analysis.

Methods: Here we describe the transcriptome analysis of 255 primary human CD11b+ microglia samples isolated at autopsy from multiple brain regions of 100 human subjects with neurodegenerative and neuropsychiatric disorders. Using this dataset, we performed systematic analyses to investigate various aspects of microglial heterogeneities including brain region, age, sex, and disease. By intersecting transcriptomics and genetics, we performed expression and splicing QTL analyses and by combining microglia from four different brain regions using a multivariate meta-analysis method (mashR).

Results: We observed widespread transcriptome variation associated with microglia from different regions, suggesting that these genes may play important role in diversified responses to pathological stimuli of microglia at different locations. We also observed 1,693 genes (FDR < 0.05) whose expression is associated with chronological age of subjects including many genes in Alzheimer’s (AD) (MSA6A, FCER1G, and CR1) or Parkinson’s disease (PD) (BST1 and FCGR2A) GWAS loci. We identified 3,611 eQTLs (mashR local false sign rate < 0.05), of which 50% (1,791) show region-specific effects. We find that ~25-30% of AD and PD disease heritability is mediated by the cis-genetic component of microglial gene expression. We identified over 300 eQTLs that colocalize with a known risk locus for a neurodegenerative or neuropsychiatric disease, nearly half of which are not found in prefrontal cortex or in peripheral monocytes. We prioritized 7 and 13 putative causal genes for AD and PD, respectively, many of which are novel genes (ITGAX, USP6NL, TSPOAP1, P2RY12, FCGR2C, and FGF20). Fine-mapping of these colocalized loci with CNS chromatin accessibility (ATAC-seq) and histone modification (H3K27ac) data nominates candidate causal variants that are within microglia-specific enhancers and are likely to modify disease susceptibility by regulating gene expression and/or splicing in microglia.

Conclusions: In summary, we have built the most comprehensive catalog to date of genetic effects on the microglia transcriptome and propose molecular mechanisms of action of candidate functional variants in several neurological and neuropsychiatric diseases.

W16. Electrophysiological Responses to Socially Generated Auditory Stimuli in Misophonia

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Category: Brain Disease and Disorders

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 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 and social condition (p=0.021) as well as the active and passive condition (p=0.012). P2 latency to self-generated tones also showed a strong, positive, linear relationship with the misophonia symptoms (p=0.009).

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.

W17. Prefrontal-Habenular Track Abnormalities Associated With Drug-Seeking and Recent Use in Cocaine Addiction

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Category: Brain Disease and Disorders

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.

Conclusions: 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.

W18. The Bitter Taste Receptors Regulate the Addictive Properties of Nicotine

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Category: Brain Disease and Disorders

Background: 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.

Methods: 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.
Results: 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.

Conclusions: These data suggest that the bitter taste receptor complex may guide nicotine taking behavior, and moreover that the gustatory system may not only guide ingestive behavior, but consumption of substances via different routes.

W19. Nicotine Addiction – the Role of IL-18 in the Medial Habenula

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Category: Brain Disease and Disorders

Background: 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. A major action of IL-18 in the brain is to control microglia activity. Given the unique expression of IL-18 in mHb neurons, we hypothesize that this cytokine regulates excitotoxic effects of nicotine.

Methods: Using intravenous self-administration (IVSA), immunohistochemistry (IHC) and ELISA we collected preliminary data to assess the role of IL-18 in nicotine addiction.

Results: The following preliminary results were collected:-

- IL18-/− mice are more sensitive than wild-type mice to excitotoxic effects of self-administered nicotine, measured by cupric staining.
- Baseline and nicotine-induced increases in Fos were markedly higher in the IPn of IL18-/− mice compared with wild-type mice.
- IL18-/− mice show lower numbers of activated microglia in hippocampus in response to excitotoxic damage.
- Microglia numbers are lower in mHb of IL18-/− mice than wild-type mice, as measured by ionized calcium binding adaptor molecule 1 (IBA1) expression.
- IL18-/− mice have decreased levels of the microglia-derived cytokines TNFa, IL-12 and interferon-g (IFNg) in their mHb.

Conclusions: The findings described above show that IL-18 deficiency enhances excitotoxic effects of nicotine on the mHb-IPn circuit. IL-18 deficiency also decreases the number/function of microglia in habenula. These data suggest the relationship between IL-18 and microglia may play a role in the development of nicotine addiction.

W20. Whole-Brain White Matter Microstructure Abnormalities in Human Cocaine-Use Disorder

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1Icahn School of Medicine at Mount Sinai

Category: Brain Disease and Disorders

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.

**W21. Establishing Reproducibility of Cluster Analysis Across Parkinson’s Disease Cohorts**

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**Category:** Brain Disease and Disorders

**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.

**W22. G-Protein-Independent Activator of GIRK Channels for Treating Alcohol Use Disorders**

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**Category:** Brain Disease and Disorders

**Background:** Activation of G-protein-gated inwardly rectifying K+ (GIRK) channels hyperpolarizes neurons and produces a slow inhibitory postsynaptic current (sIPSC). GIRK channels are composed of four subunits forming either homotetramers (e.g., GIRK2/GIRK2) or heterotetramers (e.g., GIRK1/GIRK2). Many labs have reported a role of GIRK channels in alcohol-mediated behaviors and addiction. In addition to G proteins, alcohol activates GIRK channels by binding to a hydrophobic pocket located in the cytoplasmic domain of the channel. Only a few compounds target GIRK channels.

**Methods:** Fiber photometry and Behavior (Conditioned Place preference)

**Results:** Thus, we virtually screened more than 750,000 compounds to the alcohol binding pocket of GIRK channels, and discovered a selective GIRK1 activator, GIGA1. GIGA1 activates GIRK1/GIRK2 both in vitro and in vivo. Here, we show that GIGA1 blocks ethanol conditioned place preference (EtOH-CPP) and reduces EtOH voluntary drinking in mice. To explore the mechanism, we used an innovative approach of dual fiber photometry (FP) to simultaneously measure DA (or Glu) release and D1 MSN activity (GCaMP) in the NAc core during EtOH-CPP. First, we found EtOH disrupts DA-D1 synchrony and reduces DA reuptake, inducing an increase in DA levels. Second, DA transients become more frequent, higher and faster after EtOH conditioning encoding for
seeking behavior. Third, D1 activity is increased to drive motivation to enter the EtOH-paired compartment. Finally, preliminary FP results showed GiGA1 reduces glutamate release and D1 MSN activity without altering DA transmission which could be key in mediating EtOH-CPP disruption.

Conclusions: GiGA1 could provide potential treatments for alcohol use disorder.

W23. Depression Impacts Brain Functional Connectivity in Neuroinfectious Diseases: Lessons Learned from Research in Individuals Living With HIV

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Category: Brain Disease and Disorders

Background: Depression is a common neuropsychiatric comorbidity in people living with neuroinfectious diseases including HIV and currently also COVID-19. Both depression and neuroinfection can lead to brain functional impairment. This study aimed at exploring interactive vs. additive effects of depressive symptoms and HIV infection on intrinsic brain activity.

Methods: Data obtained from 63 males (age M=38, SD=11; years of education M=16, SD=2.5) included: demographic variables, depressive symptoms measured with the CES-D screening tool, and ReHo (Regional Homogeneity) index illustrating local functional connectivity based on the brain signal recorded using the RS-fMRI technique. Analysis using 2x2 design (i.e., depressive symptoms x HIV status) and controlling for age examined interactive and additive effects of significant depressive symptoms (i.e., CES-D score≥16) and HIV infection (i.e., laboratory test result).

Results: Data revealed that significant depressive symptoms and HIV infection cause interactive effects in increased ReHo in the left medial frontal gyrus. Depression was further linked to increased ReHo in the left superior frontal gyrus while HIV infection to decreased ReHo in the superior temporal gyrus, cingulate gyrus and precuneus.

Conclusions: Depressive symptoms amplify as well as contribute additional disturbances to brain functional connectivity changes in individuals living with HIV. Our data allow to speculate about the adverse impact of depressive symptoms on brain function in individuals struggling with SARS-CoV-2 neuroinfection. These lessons are critical considering the global rise of depression prevalence amid the COVID-19 pandemic. We expect psychological/neuropsychiatric care services to play a pivotal role in brain health outcomes in individuals with neuroinfectious diseases.

W24. Mapping Resting fMRI Connectivity Markers of TMS-Related Inhibition Reduction in Schizophrenia

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Category: Brain Disease and Disorders

Background: The short interval intracortical inhibition (SICI) is a biomarker for altered motor inhibition in schizophrenia, obtained using non-invasive transcranial magnetic stimulation (TMS). We currently lack an understanding of how different brain regions may influence the inhibitory cortical-effector response.

Methods: Our study used fMRI to investigate local and long-distance resting state functional connectivity (rsFC) markers of SICI in a sample of N=23 patients with schizophrenia and N=29 controls. Local functional connectivity was quantified using regional homogeneity (ReHo) analysis and long-range connectivity was estimated using seed-based rsFC analysis. Direct and indirect effects of connectivity measures on SICI were modeled using mediation analysis.

Results: Higher SICI ratios (indicating reduced inhibition) in patients were associated with lower ReHo in the right insula. Moreover, higher SICI scores (indicating reduced inhibition) were associated with reduced connectivity between right insula and hubs of the corticospinal pathway: sensorimotor cortex and basal ganglia.
Mediation analysis supported a model in which the direct effect of local insular connectivity strength on SICI is mediated by the interhemispheric connectivity between insula and left sensorimotor cortex.

**Conclusions:** The broader clinical implications of these findings are discussed with emphasis on how these preliminary findings might inform novel interventions designed to restore or improve SICI in schizophrenia and deepen our understanding of motor inhibitory control and impact of abnormal signaling in motor-inhibitory pathways in schizophrenia.

**W25. Examining the Role of Touch Neurons in Reward and Stress Resilience**

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**Category:** Brain Disease and Disorders

**Background:** Social touch is rewarding, motivating social interactions and relationships, and can act as a stress buffer, regulating physiological and behavioral responses to short-term challenges. However, the skin-to-brain neuronal circuits by which touch is rewarding and promotes stress resilience remain unknown. Discovery of specific peripheral neurons that play a role in the rewarding and/or anxiolytic nature of touch would be the first step in elucidating such a circuit. A subset of cutaneous mechanoreceptors (neurons in the skin that respond to mechanical stimuli) called C-tactile (CT afferents) in humans are implicated in soothing, comforting touch.

**Methods:** Here, we target a molecular population of mechanoreceptors in mice that is anatomically and functionally similar to human CT afferents and investigate its role in reward and stress resilience. We assessed the effects of constitutive ablation, optogenetic activation, and DREADD-mediated activation of these neurons on stress- and reward-related behavioral assays in mice.

**Results:** Our results indicate that activation of a specific molecular population of C-fibers is rewarding, and ablation of the same population increases stress susceptibility, as evidenced by behavioral assays in mice. We are currently testing the therapeutic potential of activation of these neurons.

**Conclusions:** These results further our understanding of the relationship between the peripheral nervous system and reward and stress and could provide new therapeutic targets for treatment of mood disorders.

**W26. Machine Learning Identifies SHISA7 as a Translational Target of Heroin Abuse Directly Relevant to Drug-Seeking and Reversal Learning**

*Randy Ellis*, *Jacqueline-Marie Ferland*, *Joseph Landry*, *James Callens*, *Teddy Uzamere*, *Gaurav Pandey*, *Yasmin Hurd*

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**Category:** Cognitive and Systems

**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.

**W27. Olfactory Landmarks and Path Integration Converge to Form a Cognitive Spatial Map**


**Category:** Cognitive and Systems

**Background:** Olfactory navigation in mammals has been described by the landmark hypothesis, which posits that a mouse forms a spatial map based on the olfactory cues in its environment. The second hypothesis is the path integration hypothesis, which suggests that a mouse utilizes odors and proprioceptive information to form a cognitive spatial map. So far, there is no clear evidence of convergence of these two hypotheses in the mouse.

**Hypothesis:** Olfactory landmarks and path integration are both necessary to form a cognitive spatial map.

**Methods:** We infused mice with synthetic blackberry, adrenalin, and, as a control, menthol into the orbitofrontal cortex (OFC). We trained the mice to follow the synthetic odors to the sucrose reward. We then tested the mice in a novel environment and observed their behavior. We recorded the mice’s head direction and sniffing behavior and analyzed the data using machine learning algorithms.

**Results:** Our results indicate that activation of a specific molecular population of C-fibers is rewarding, and ablation of the same population increases stress susceptibility, as evidenced by behavioral assays in mice. We are currently testing the therapeutic potential of activation of these neurons.

**Conclusions:** These results further our understanding of the relationship between the peripheral nervous system and reward and stress and could provide new therapeutic targets for treatment of mood disorders.

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**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.
Background: In order to navigate accurately over long distances an animal must keep track at all times of where it is in relation to its desired destination. Cognitive spatial maps that can be stored and recalled from memory are thought to play an essential role in spatial awareness and many navigational behaviors. The importance of landmarks for cognitive spatial maps and path integration makes the neural systems that underlie landmark recognition a fundamental component of spatial awareness and navigational behaviors. Spatial representations within the hippocampus are thought to support such cognitive spatial maps and thus provide an animal with knowledge of its exact location within a world-centric reference frame. This study seeks understand how the convergence of internal path integration and external sensory landmarks generates a cognitive spatial map in the hippocampus.

Methods: To study how the activity of a cognitive spatial map might support path integration and landmark recognition we examined the activity of hippocampal neurons in mice performing navigational behaviors that rely solely on path integration and sparse olfactory sensory cues. We designed a novel virtual reality navigation task that required mice to combine internal path integration signals with the recognition of odor landmarks, which were the only spatially informative sensory features, while navigating in the dark. While mice performed this odor landmark-guided virtual navigation task, we monitored large-scale neural ensemble activity in the CA1 region of the hippocampus using a head-mounted miniature fluorescence microscope in combination with expression of the genetically encoded calcium sensor G-CaMP6f.

Results: Our ability to record the activity of ~2,500 neurons across 5 mice in CA1 during a novel olfactory landmark guided virtual navigation paradigm allowed us to observe a process by which internal path integration signals can impose a spatial meaning, that of a landmark, onto an odor cue. Initially, we observe that internal path integration signals alone cannot support stable place fields or accurate navigational behaviors over distances longer than ~2 m from the starting point of the virtual track. The rapid decline in place field densities as the distance from the last encountered landmark increases is consistent with an accumulation of errors in the internal path integration signals. We observe that the presentation of an odor cue at 1m, a distance at which path integration alone can support stable place fields, leads to the formation of a new peak in place fields at the location of the cue thus reflecting the establishment and recognition of a new spatial landmark at 1m. This is followed by an increase in the density of place fields over distances beyond the 1m odor cue reflecting an extension of the distance over which path integration alone can support stable place fields presumably due to the ability of an odor landmark to correct for any errors that accumulated using path integration. The new place fields formed at and beyond the site of the odor cue are specific to the identity of the odor and thus reflect a recognition that the 1m landmark does not simply represent an abstract measure of geometric distance but instead has a spatial meaning that is unique to the sensory context provided by the identity of the odor. The “remapping” of place fields at and beyond the location of cues with different odor identity is present at the initial day of exposure, maintained throughout all 4 days of exposure, and is also reflected in a decorrelation of the population vector that represents the activity of all recorded neurons. Taken together these observations provide strong evidence for a Ouroboros-like circular process by which internal path integration signals can impose spatial landmark status onto a sensory feature with no inherent spatial meaning after which the recognition of this spatial landmark can improve the accuracy of the very same internally generated path integration signals used for the establishment of the spatial landmark.

Our experiments were designed in way that allowed us to also address whether internal path integration signals provide a means by which spatial landmarks with the same ego-centric sensory features can be recognized as distinct locations in allocentric space. By presenting the same brief odor cue at two different locations on the virtual track, 1m and 3m, a recognition of the odor cue alone does suffice in establishing whether it represents a 1 m or 3 m landmark and therefore the animal’s spatial location. We observe that on the initial days of exposure to the odor cues unique place fields only form at the location of the odor cue at 1 m and not at 3 m. After 4 days of exposure to odor cues at both 1 m and 3m, a large peak in the density of unique place fields eventually forms at the location of the 3 m odor cue that is roughly equivalent to the density at the 1 m odor cue. Interestingly, we observe that on the initial days of exposure to the odor cues a relatively large number of neurons have firing fields at both the 1m and 3 m odor cue locations and this is reflected by a high correlation in population level activity when the animal is at both locations. Over 4 days of exposure to odor cues at 1 m and 3m we observe a decrease in the numbers of neurons with firing fields at both locations and a decrease to a near-zero correlation in the population level activity when the animal is at both locations. Based on two key observations with regards to the
evolution of the cognitive spatial map in CA1 over several days we were able to gain insights into both how path integration allows the same odor cue presented at multiple locations to acquire distinct allocentric spatial meanings and why the initial presence of firing fields at both odor cue locations is consistent with an animal’s internal misrepresentation of the 3 m odor cue as a return to the 1 m location. One, we observed that over several days the increase in place field densities along the virtual track was a sequential process that began at the start of the virtual track and extended outwards to incorporate the nearest odor cue at 1 m first and later the odor cue at 3 m only after the 2 m long gap was bridged by stable place fields and presumably accurate path integration. The gradual and sequential extension of place fields over the entire virtual track was mirrored by the gradual improvement in navigational behavior and therefore the disambiguation of the two odor cues as distinct spatial landmarks. Consistent with these observations, on the initial days of exposure only the odor cue at 1 m would have acquired a spatial meaning and thus encounters with the odor cue at virtual distances of either 1 m or 3 m from the start would likely be recognized by the animal and represented in CA1 as the same a “1 m” landmark. Two, the evolution over days of population level activity in CA1 provides further evidence that does not depend on the firing properties of select groups of individual neurons. We observe that initially the population level activity in CA1 shows a high degree of similarity when animal’s encounter the same odor cue at multiple locations and gradually over days the activity evolves into orthogonal patterns of activity. Furthermore, using principal component analysis (PCA) we are able map trajectories in high-dimensional state-space taken by large populations of neurons in CA1 onto a low-dimensional manifold aligned to positions along the virtual track. The evolution over days of the state-space trajectories observed in CA1 are consistent with the odor cue at 1 m being initially recognized as a unique landmark and a misrecognition of the odor cue at 3 m as a return to the “1 m” location. This is reflected in the trajectories taken after the 3 m odor cue that closely align with and appear to retrace trajectories taken after 1 m odor cue. After several days, the trajectories taken after the 1 m odor cue and the 3 m odor gradually disentangle to form well separated arcs of a larger circular manifold that better reflects the spatial structure of the virtual track.

Our understanding of how path integration and odor cues interact to form a cognitive spatial map in CA1 motivated us to create a theoretical model of how plasticity within a simple network architecture might explain such a fundamental process. This model is consistent with our experimental observations. First, in the model and in our experimental data following odor training, equivalent sensory inputs presented at different locations activate distinct subpopulations of place cells. In the model, this occurs because only the place cells active when an odor cue is encountered are involved in resetting the path integrators and this, in turn, strongly drives a location-specific set of place cells in the vicinity of the cue. This is consistent with the role of the hippocampus in the transformation of egocentric sensory information into an allocentric cognitive spatial map of the external world. Second, the model predicts that place cell density and reliability will decrease as a function of distance from odor cues, with local peaks in density and reliability at the site of each cue. This is a consequence of model place cells being driven by a population of path integrators with independently accumulating errors. If path integration is implemented by grid cells, as has been widely suggested, these independent path integrators could correspond to distinct grid modules. In addition, the model predicts that the reliability of place cells along the entire track will improve over several days of training in the presence of odor cues. Both of these model predictions are in agreement with our experimental data.

Finally, the iterative mechanism of spatial map extension posited by the model is consistent with our experimental findings regarding the evolution of place cell representations over the course of training. The model predicts that the same sensory cue presented at two different locations will lead to the formation of local peaks in place cell density in an iterative and sequential manner. In both the model and our data, a peak in place cell density initially emerges at the sensory cue nearest the start (1 m), and over several training sessions, the place cell map tiles the gap between 1 m and 3 m, eventually forming a second peak at 3 m. Interestingly, our model predicts that an odor cue cannot be recognized as a landmark if its distance from a proximal cue is much greater than the decay length scale of the place cell representation.

**Conclusions:** In summary, we combined CA1 population recordings with theoretical modeling to provide evidence for a process in which odor cues serve as landmarks that reset noisy path integrators, enabling the iterative expansion of a cognitive spatial map in the hippocampus. The convergence of path integration and olfactory landmarks in the hippocampus allows mice to construct spatial maps that support navigation over distances far greater than would be possible with path integration alone. This work establishes that odors can serve as landmarks to guide navigation and provides a novel theoretical model that shows how path integration and
odor landmarks might interact in a sequential, iterative process to generate cognitive spatial maps in the hippocampus that can support navigation over long distances.

W28. Top-Down Control of Sweet and Bitter Taste in the Mammalian Brain

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Category: Cognitive and Systems

Background: This study examines how the brain modulate its hardwired circuit to control taste behavior.

Methods: fiber photometry, optogenetics, slice recording, circuit mapping, mouse behavior

Results: we first identified and characterized the neurons in the brainstem that transmit sweet and bitter signals from the tongue to the cortex. We next dissected the basis for bitter-evoked suppression of sweet taste and show that the taste cortex and amygdala exert strong positive and negative feedback onto incoming bitter and sweet signals in the brainstem. Finally, we demonstrated that blocking the feedback markedly alters responses to ethologically relevant taste stimuli.

Conclusions: These results illustrate how hardwired circuits can be finely regulated by top-down control and reveal the neural basis of an indispensable behavioral response for all animals.


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Category: Cognitive and Systems

Background: Numerical cognition is essential to most animals for various survival tasks such as foraging or defending from predators. Many species can qualitatively discriminate between large and small amounts, some species are thought to have a form of exact numerical cognition, and a few species can be trained to learn symbolic representations of integers. However, it is not clear whether nonhuman animals which have numerical cognition, such as honeybees, could grasp the more complex concept of simple arithmetic operations. In a recent study, Howard et al. 2019 have tested whether honeybees can learn simple operations. They found that trained honeybees can add or subtract 1 element from small sets containing 1-5 elements through appetitive-aversive reinforcement learning. However, the limited experimental design and the far from perfect performance of the honeybees challenges the claim that they learn the abstract concepts of addition or subtraction.

Methods: We investigate whether numerical cognition and reinforcement learning are sufficient to develop arithmetic ability. We built a computational model to replicate the Howard et al. 2019 experiment and extend it by adding or subtracting numbers other than 1. Our model is based on a reinforcement learning agent powered by an artificial neural network. We study the behavior of our model before, during, and after training and dissect it to quantify the operations it performs.

Results: We find that our trained model does not learn addition or subtraction; it doesn’t generalize well on examples that it hasn’t been trained on and it performs poorly on hard examples in which the presented numbers are close together. Rather, our model learns other solutions to accurately solve the problem on training examples, as well as testing examples which are similar to the training ones. There was a significant difference between the accuracies of the models (n = 30) in tests similar to those of training and more difficult tests after performing ANOVA (p < 0.05) and post-hoc Bonferroni t-tests (p < 0.002).

Conclusions: We argue that complex arithmetic concepts require more neural specialization and more advanced cognition than basic and memory-based numerical cognition.

W30. The Impact of Social Stress on Approach-Avoidance Behaviors

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Category: Cognitive and Systems

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.

### W31. Characterizing Glutamatergic Inputs to Oxytocin Neurons in the Hypothalamus

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**Category:** Cognitive and Systems

**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.

### W32. Chemogenetic Silencing of Amygdala Alters Resting State Functional Connectivity in Macaques

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**Category:** Cognitive and Systems

**Background:** 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.

**Methods:** 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).

**Results:** 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).

**Conclusions:** 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.

**W33. Interpretable Connectivity-Based Decoding Models for Chronic Marijuana Use**

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**Category:** Cognitive and Systems

**Background:** Psychiatric neuroimaging typically proceeds with one of two approaches: encoding models which aim to model neural mechanisms and decoding models which aim to predict clinical features from brain data. In this study, we seek to 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 healthy controls (n=128) completed a cue-elicited craving task, consisting of repeated presentations of marijuana and control cues during functional magnetic resonance imaging. Linear machine learning algorithms were used to classify group status based on task-evoked, whole-brain functional connectivity. Novel interpretation methods, including graph theoretical measures to explore ‘predictive functional connectivity’, were used to elucidate whole-brain regional and network involvement implicated in chronic marijuana use.

**Results:** We obtained high accuracy (~80% out-of-sample) across four different linear models, demonstrating that task-evoked, whole-brain functional connectivity can successfully differentiate chronic marijuana users from non-users. Subsequent network analysis revealed key predictive regions that are often found in neuroimaging studies of substance use disorders, with some exceptions - including sensorimotor and visual areas. 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, as well as suggested other neural processes. This novel approach may complement other approaches for a more complete understanding of neural mechanisms in drug use disorders.

**W34. Distributed Representations in Primate DLPFC With Strategy Use in a Self-Ordered Working Memory Task**

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**Category:** Cognitive and Systems

**Background:** The limited capacity of working memory (WM) does not always inconvenience our daily life, because we can use cognitive strategies to overcome the constraints. We previously showed that self-generated sequencing strategies reduced incorrect responses when monkeys performed a spatial target selection task. At the same time, the spatial tuning observed in dorsolateral prefrontal cortex (DLPFC) neurons decreased with more stereotyped sequencing. In the present study, we examined how neuron populations in primate DLPFC represent task-relevant information under these different self-generated behaviors.

**Methods:** We re-analyzed data simultaneously recorded from multiple electrodes in two monkeys performing a self-ordered WM task with six identical visual targets (Chiang and Wallis, 2018). Subjects were trained to make a saccade to each target, one at a time in any order, returning their eyes to the screen center after each selection. Reward was delivered only after the first visit to each target within a trial. When all targets had been visited, the reward contingency was reset and a new trial began. Therefore, monkeys had to use WM to track which targets
had been visited and prepare for the next target selection. Blocks of 40 trials with the same target configuration enabled us to quantify selection patterns as more or less sequenced. Within this block-wise design, we used linear discriminant analysis (LDA) to categorically decode information about target location or saccade order from ensembles of simultaneously recorded DLPFC neurons.

Results: We found that target location and saccade number could be decoded from ensembles of DLPFC neurons. Interestingly, decoding performance was similar or better when monkeys used more stereotyped selection strategies, seemingly contradicting single unit results that found less spatial tuning. To investigate this further, we used multiple approaches to demonstrate that the informative contribution of single units to the ensemble decreased, and the optimal ensemble sizes for decoding increased under the self-generated sequencing strategies, suggestive of a more distributed but less efficient neural code. Lastly, we found that the informative dimensionality of neural ensembles was positively correlated with WM loads, and negatively correlated with stereotyped strategy.

Conclusions: Together, these data indicate that sequencing strategies change the local distribution of WM representations in DLPFC. As behavior becomes more stereotyped, task information is represented by a larger number of neurons that each makes smaller informative contributions, consistent with a more distributed neural code. Because these strategies improve performance, it suggests that distributed codes may increase representational capacity in cognitive tasks and optimize performance of a limited capacity processing system.

W35. A Map for Goals in the Human Brain

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Category: Cognitive and Systems

Background: Often in different psychiatric disorders there is an impairment in goal setting. For example, in addition, 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.

Methods: 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.

Results: 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.

Conclusions: Multi-voxel pattern analyses are ongoing to more resolutely examine how the brain maintains an updated representation of a goal’s temporal proximity.

W36. Closed-Loop Control of Spike Timing

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Category: Cognitive and Systems

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.

**W37. In Vivo Functional Connectivity of Ventral Hippocampal Inputs to Medial Prefrontal Cortex Interneurons in a Mouse Model of 22q11.2 Deletion Syndrome**

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**Background:** Neural communication between rodent ventral hippocampus (vHPC) and medial prefrontal cortex (mPFC) supports cognitive functions such as spatial working memory. Impaired vHPC-mPFC communication underlies cognitive deficits in rodent models relevant to schizophrenia. Neural activity in vHPC-mPFC projections and mPFC somatostatin-positive (SST+) interneurons are critical for normal vHPC-mPFC communication and spatial working memory. Whether and how these neural substrates interact to support vHPC-mPFC communication is unclear. Thus, we assessed in vivo cell-type-specific connectivity between vHPC projections and mPFC inhibitory microcircuits.

**Methods:** We optogenetically stimulated vHPC-mPFC projections while monitoring activity of discrete mPFC neuronal populations using fiber photometry in mice modelling the schizophrenia-predisposing 22q11.2 deletion syndrome (Df16A+/-) and their wildtype counterparts. We expressed excitatory opsin ChrimsonR in vHPC and calcium indicator GCaMP6f in SST+ (n=34 mice) or parvalbumin-positive (PV+, n=5 mice) interneurons in mPFC. We delivered red light pulses to vHPC terminals in mPFC and characterized evoked photometric responses in both interneuron populations. We further assessed how daily high-frequency stimulation influenced these evoked responses over time.

**Results:** Stimulation-evoked photometric responses in SST+ interneurons varied systematically with pulse number (1-40) and frequency (1-40Hz). SST+ interneurons were preferentially engaged by 40-pulse stimulation delivered at 40Hz. Matched stimulation elicited weak biphasic photometric responses in PV+ interneurons. Stimulation-evoked responses in SST+ interneurons appear to be attenuated in Df(16)A+/- mice. Interestingly, minimal stimulation once a week progressively increased evoked SST+ responses over time in Df(16)A+/- and wildtype mice, which may be further potentiated by daily high-frequency stimulation.

**Conclusions:** These findings suggest that repeated stimulation induced in vivo target-dependent changes in vHPC-mPFC connectivity. Moreover, we reveal properties of cell-type-specific functional connectivity within intact vHPC-mPFC circuits that inform how discrete circuit elements may interact to mediate normal and disordered cognitive function.

**W38. Development and Validation of Photo-Caged Oxytocin Analogs**


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**Category:** Cognitive and Systems

**Background:** Oxytocin is an evolutionarily conserved neuropeptide associated with social behavior by modulating cognitive functions such as processing of sensory stimuli, social recognition, and social memory. Deficiencies in oxytocin signaling has been linked with a number of neurodevelopmental disorders such as autism spectrum disorder. At the molecular level, oxytocin activates its respective G protein-coupled receptor (OXTR) which is expressed in many regions of the brain. Specifically, oxytocin modulates neuron excitability and synaptic transmission. However, methods to precisely deliver and activate neuropeptides like oxytocin within a specific region of the brain with spatiotemporal specificity is lacking. To achieve spatiotemporal activation of oxytocin in mammalian brain tissue, we synthesized photocaged analogs of oxytocin. These caged-oxytocin peptides are functionally inactive prior to photolysis and irradiation with ultraviolet light causes the release of native oxytocin.
Methods: We validated the caged compounds in vitro via cell culture using a fluorescent calcium flux assay and calcium imaging. We further demonstrated its utility in brain tissue by performing whole-cell electrophysiological recordings in acute brain slices of the mouse auditory cortex.

Results: We demonstrated that both pharmacological applications of oxytocin peptide and photorelease of oxytocin cause significant membrane depolarization of OXTR+ neurons but not OXTR- neurons.

Conclusions: These results demonstrate that photocaged-peptides are useful tools for spatiotemporal control of neuropeptide release in the mammalian brain.

W39. Comparing Denoising Approaches in Ultra-High Field Resting State fMRI

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Category: Cognitive and Systems

Background: One of the biggest challenges in functional Magnetic Resonance Imaging (fMRI) research has been parsing brain activation (BOLD signal) from artifact noise. Multi-echo (ME) acquisition of fMRI data facilitates BOLD separation by capturing every slice at multiple echo times. The use of ultra-high field 7-Tesla ME fMRI additionally allows increased spatial resolution. There are several mathematical approaches to combining and denoising ME data to obtain BOLD signal but the optimal method for high-resolution data is unknown.

Methods: In this project, we aim to compare the predominant ME preprocessing pipelines and compare them to single echo data. 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.

Results: Our preliminary data suggest that with minimal processing, smoothing and normalization, there was a significant effect of the combining and denoising method on the whole-brain tSNR [F(4, 35) = 61.15, p <0.01] and functional connectivity of key nodes of the default mode network (DMN) [F(4, 35) = 6.66, p <0.01] and motor network [F(4, 35) = 29.48, p <0.01].

Conclusions: Our preliminary results suggest that denoising and multi-echo combining approaches significantly impact the pre-processed BOLD signal. Comprehensive results of various pipelines will be presented and discussed in terms of finding the optimal preprocessing pipeline.

W40. The Development of Joint Attention in Bilingual and Monolingual Infants

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Category: Cognitive and Systems

Background: A key aspect of communication involves an awareness of sharing attention towards an object or event within a dyad, also referred to as joint attention (Van Hecke et al., 2007). This shared awareness influences the development of language in infancy as children interact with their caregivers. Past literature suggests that joint attention in infancy predicts later receptive language ability (Salo et al., 2018). However, few have established the role that the home language environment has on the relationship between joint attention and language development. In the United States, about 1 in 3 children reside in a household where the primary language is not English (Child Trends, 2014). In regard to the bilingual experience, past research has found that the bilingual experience can potentially change the functional organization of the frontal cortex for attentional control at 6 months of age (Arredondo et al., 2019). With the growing number of children being raised in multilingual households, bilingualism could potentially be associated with the development of joint attention early on. In the present study, we aim to answer two main questions. Firstly, are there differences seen in the development of joint attention between monolingual and multilingual infants? Secondly, are there associations between exposure or no exposure to multiple languages by 3 months of age and joint attention at 9 months of age? This study is based on the hypothesis that early exposure to multiple languages accelerates development of the frontal cortex, which is associated with attentional control. In turn, other cognitive functions that rely on attentional control, such as joint attention, are also facilitated by early exposure to bilingualism.

Methods: The present study used data from a sample of socio-economically and ethnically diverse mothers and infants from the New York City area participating in the Stress, Home Environment, Language, and Learning study (N= 79). Infants were followed longitudinally from when infants were 3 months to 9 months of age. To measure bilingualism, caregivers completed a language exposure survey at both time points. A bilingualism score
was calculated to reflect the infant’s language exposure. To measure joint attention at 9 months, the experimenter conducted a looking task with the infants (Elison et al., 2013). During the looking task, the experimenter used cues to engage the infants in episodes of joint attention.

**Results:** Analyses are currently in progress and results are pending.

**Conclusions:** The current study will provide further insight into the cognitive development of bilingual children. With the growing number of children growing up in bilingual homes and the significance of joint attention for language development, it is important to understand the relationship between bilingualism and joint attention to better support children growing up as bilingual learners. In addition to providing a basis for language development (Tomasello and Farrar, 1986), joint attention has been associated with autism spectrum disorder (ASD). Past research has shown that children with ASD experience difficulties in interactions of joint attention (Beauchamp and MacLeod, 2017). Therefore, the current study can provide evidence to support future research on bilingualism and joint attention in children with ASD to support families, educators, and providers.

**W41. Mechanisms of Histone Serotonylation in Neurodevelopment**

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**Category:** Epigenetics

**Background:** Emerging evidence suggests chromatin mechanisms contribute to brain development, including organization of H3 lysine 4 tri-methylation (H3K4me3) domains. In particular, 'broad' H3K4me3 peaks, which correspond to enhanced patterns of transcriptional activation, associate with cell-specific processes such as synaptic signaling in neurons. Across multiple species including humans and mice, the top 5% broadest H3K4me3 domains enrich for biological pathways associated with nervous system development, and aberrant broadening of H3K4me3 domains has been observed in postmortem brains from ASD patients, suggesting the importance of appropriate broad H3K4me3 domain organization in neurodevelopment, though how this regulation occurs is unclear. Serotonin (5-HT) is an essential monoamine that regulates neuronal maturation, and dysregulation of 5-HT signaling has been implicated in several neurodevelopmental disorders, including ASD. In 2019, our lab identified a novel epigenetic role for 5-HT, whereby this biogenic monoamine can be transamidated to glutamine 5 of histone H3. Deposition of 5-HT at this site stabilizes neighboring H3K4me3, resulting in the combinatorial H3K4me3Q5ser modification that recruits specific regulatory machinery to increase permissive transcription. Together, we hypothesize that histone serotonylation impacts organization of H3K4me3 broad domains to regulate important gene expression programs during brain development.

**Methods:** Bulk forebrain tissue from C57BL/6J embryos/fetuses were subjected to ChIP-sequencing and RNA-sequencing. Immunoprecipitation and protein array technology were used to examine H3K4me3Q5ser interaction with putative chromatin reader domains in vitro.

**Results:** Genomic enrichment of H3K4me3Q5ser and associated gene expression showed sex-dependent patterns across embryogenesis, where H3K4me3Q5ser exhibited broad domains that occupy 4- to 35-kilobases across the genome. Broad H3K4me3Q5ser domains showed specific enrichment for nervous system development-related biological processes. To determine potential upstream regulators of histone serotonylation broad domains, we identified Lysine methyltransferase 2e (Kmt2e) whose binding to H3K4me3 by its PHD finger is potentiated by the presence of H3Q5ser. Furthermore, Kmt2e expression is greater in male vs. female fetal forebrains, that may correspond to male biased Kmt2e mutations in children with symptoms related to developmental delay, intellectual disability, and ASD.

**Conclusions:** These data suggest that histone serotonylation may recruit Kmt2e to regulate H3K4me3 broad domains, which may direct important developmental gene expression programs in brain.

**W42. Sperm Transcriptional State is Associated With the Paternal Transmission of Stress Phenotypes**

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†Icahn School of Medicine at Mount Sinai, ‡Vanderbilt University, §McGill University, ¶Adelphi University, ¶Princeton University
CaMKII as: 1) it is highly
3) it is upregulated in its dopaminylation state following abstinence from heroin SA, an effect that persists to

repr
phosphorylated to direct Calmodulin (CaM) sequestration and subsequent nuclear translocation

[Q]285), a site that exists only two amino acids away from the critical threonine (T) residue 287. T287 is

in the context of normal neural functi

Results:

Transglutaminase 2 (TGM2) enzyme. I sought, then, to unbiasedly identify additional synaptic substrates of dopamine for DA, termed dopaminylation, whereby DA itself acts as a post-translational modification (PTM) on substrate proteins via transamidation by the Transglutaminase 2 (TGM2) enzyme. I sought, then, to unbiasedly identify additional synaptic substrates of dopaminylation in vivo, utilizing a novel chemical tagging approach coupled to mass spectrometry.

Results: I identified 164 novel putative synaptic substrates of dopaminylation in Nucleus Accumbens (NAc), both in the context of normal neural function and in response to abstinence from chronic heroin self-administration. Following validation of a number of putative substrates, I turned my focus to CaMKII as: 1) it is highly abundant 2) it is dopaminylated at a single amino acid residue, located within its autoinhibitory helix (glutamine |Q|285), a site that exists only two amino acids away from the critical threonine (T) residue 287. T287 is phosphorylated to direct Calmodulin (CaM) sequestration and subsequent nuclear translocation – thus, this site, represents an exciting ‘test’ case for establishing the importance of this signaling moiety in post synaptic plasticity 3) it is upregulated in its dopaminylation state following abstinence from heroin SA, an effect that persists to

Category: Epigenetics

Background: The risk for developing mood disorders such as depression and anxiety is highly influenced by both genetic and environmental factors. Recently, it has been proposed that epigenetic mechanisms also contribute. Importantly, studies have found that exposure to adverse experiences such as stress, induce long-lasting, heritable alterations in the epigenome of germ cells, potentially relaying information about the paternal environment to offspring across multiple generations.

Methods: Here by leveraging the segregation of males exposed to chronic social defeat stress (CSDS) into either resilient or susceptible categories, we examine differences in the intergenerational transmission patterns of paternal stress phenotypes between the two categories. Adult male mice exposed to CSDS, or control non-defeated mice, were bred with non-stressed female mice and their offspring were assessed behaviorally to examine anxiety-like measures at baseline and following offspring exposure to a submaximal stressor. Artificial insemination (AI) was used to assess the direct role of male gametes in the transmission of stress phenotype to offspring. Finally, using RNA sequencing in combination with a variety of bioinformatic tools we examine the transcriptomic profiles of sperm genome-wide before and after exposure to CSDS.

Results: We show that both male and female offspring from resilient and susceptible fathers show altered stress-induced anxiety-like phenotypes when produced via natural mating and AI suggesting that sperm mediates some aspects of the paternal transmission of stress in this model. RNA-sequencing revealed distinct changes in the transcriptomic profiles of sperm following CSDS in susceptible vs resilient fathers, with alterations in long noncoding RNAs (lncRNAs) predominating especially in susceptibility. Correlation analysis revealed that these alterations were accompanied by a loss of regulation of protein-coding genes by lncRNAs in sperm of susceptible males. We also identify several co-expression gene modules that are enriched in differentially expressed genes in sperm from either resilient or susceptible fathers.

Conclusions: We were able to identify the phenotypic differences in the paternal transmission of stress phenotypes across generations between the two lineages. Importantly, this work also alludes to the significance of both long noncoding RNAs and protein-coding genes mediating the paternal transmission of stress. The knowledge gained from these data is of particular interest in understanding the risk for the development of psychiatric disorders such as anxiety and depression.

W43. Identification of Camkii as a Novel Substrate of Dopaminylation Following Heroin Self-Administration

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Category: Epigenetics

Background: Heroin use disorder (HUD) represents an enduring public health issue resulting in significant socioeconomic burdens to the United States, with domestic opiate-related deaths quadrupling from 1999 to 2017. Despite this the neurobiological mechanisms underlying HUD remain poorly understood. All drugs of abuse modulate dopaminergic signaling and have long been thought of as disorders of dopamine (DA) signaling. However, pharmacotherapeutic interventions targeting receptor mediated DA-signaling have not resulted in efficacious treatments.

Methods: Our laboratory recently identified a novel signaling moiety for DA, termed dopaminylation, whereby dopamine undergoes a novel post-translational modification (PTM) on substrate proteins via transamidation by the Transglutaminase 2 (TGM2) enzyme. I sought, then, to unbiasedly identify additional synaptic substrates of dopaminylation in vivo, utilizing a novel chemical tagging approach coupled to mass spectrometry.

Results: I identified 164 novel putative synaptic substrates of dopaminylation in Nucleus Accumbens (NAc), both in the context of normal neural function and in response to abstinence from chronic heroin self-administration. Following validation of a number of putative substrates, I turned my focus to CaMKII as: 1) it is highly abundant 2) it is dopaminylated at a single amino acid residue, located within its autoinhibitory helix (glutamine |Q|285), a site that exists only two amino acids away from the critical threonine (T) residue 287. T287 is phosphorylated to direct Calmodulin (CaM) sequestration and subsequent nuclear translocation – thus, this site, represents an exciting ‘test’ case for establishing the importance of this signaling moiety in post synaptic plasticity 3) it is upregulated in its dopaminylation state following abstinence from heroin SA, an effect that persists to
AD14 and 4) represents a critical substrate involved in mediating long range signals from the synapse to the nucleus in brain, ultimately promoting CREB activation. I have additionally demonstrated that monoamine molecules can infiltrate striatal and cortical neurons in vitro, as well as that treatment of these neurons with DA induces CaMKII dopaminylation. I also observed the dynamic regulation of CaMKII/CaM localization and subsequent downstream CREB signaling in response to DA treatment.

**Conclusions:** I therefore hypothesize that CaMKIIQ285dop may represent a novel dopaminergic signaling moiety in brain and may play a direct role in mediating heroin relapse behaviors via aberrant modulation of CREB signaling in NAc.

**W44. Neuronal Nsun2 Deficiency is Associated With Codon-Specific Epitranscriptomic Dysregulation of Gly-Trnas and Corresponding Proteomic Shift Impacting Synaptic Signaling and Behavior**

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**Category:** Epigenetics

**Background:** Targeting the brain's translational machinery bears promise for psychiatric disease treatment, but the role of transfer (t)RNAs-- key players for ribosomal protein synthesis-- remains unexplored. RNA cytosine methylation (m5C) 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. Previous work has shown that loss of m5C produces deficits in protein synthesis in non-neuronal cells, but the role of tRNA methylation in adult neuronal function has not been explored.

**Methods:** We used viral overexpression and Cre-driven conditional knockout of Nsun2 in the postnatal mouse cortex to alter tRNA methylation levels. We used targeted RNA bisulfite sequencing and tRNA sequencing to assess tRNA methylation/expression, LS-MS/MS to measure protein expression, electrophysiological recordings to assess synaptic transmission, and behavioral testing for cognition and depressive-like behaviors.

**Results:** We report that depressive and cognitive behaviors are highly sensitive to bi-directional changes in Nsun2 in prefrontal cortex (PFC) neurons. Nsun2-deficient mutant cortex showed a selective deficit in multiple 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 impacting synaptic signaling and behavior.

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

**W45. Inheritance of learned fear: cell proliferation in response to stress**

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**Category:** Epigenetics

**Background:** The field of transgenerational epigenetic inheritance has gained traction in recent years though its molecular basis has not been well characterised. Specifically, the causal interactions leading to heritable phenotypes are not understood in the context of the transgenerational epigenetic inheritance of learned fear. In our paradigm, we aim to investigate the molecular mechanisms underlying induced fear towards a previously neutral odor in the parental generation in order to uncover the basis on which this phenotype is inherited by future generations.
Methods: We use a classical odor fear conditioning paradigm to condition mice against multiple previously neutral odors. Within this behavioral paradigm there is a paired paradigm in which the odor presentation is coterminated with a shock and an unpaired paradigm in which there is a 60 second gap between the odor and the shock. We placed some of these mice in a trichamber where the time spent in the conditioned odor side was compared to the time spent in an unconditioned odor side to generate an approach avoidance index. Another cohort of the conditioned mice were sacced and processed for tissue analysis in both iDISCO cleared olfactory epithelium and cryosectioned olfactory epithelium to visualize and quantify individual olfactory receptor neurons.

Results: We observed an increase in olfactory receptor neuron number specific to the conditioned odor in both the F0 (N=6) and F1 (N=8) (F0 Unpaired vs. F0 Paired p=0.0088, F0 Unpaired vs. F1 Paired p=0.0375). Furthermore, our preliminary results indicate an increase in cell proliferation in the paired group after fear conditioning compared to the unpaired group (n=8 p=0.0016). These two results demonstrate a morphological change in response to learned fear.

Conclusions: In this study we have shown that inducing fear towards a previously neutral odor in the F0 generation is sufficient to increase olfactory receptor neuron count specific to the conditioned odor. Moreover, this environmentally induced phenotype is transmitted to the F1 mice who also display a specific increase in olfactory receptor neuron count prior to undergoing any conditioning themselves. Furthermore, this increase in olfactory receptor neurons in the F0 generation represents an increase in cell proliferation that is observed only in the paired group.

W46. Early Life Experiences Selectively Mature Learning and Memory Abilities

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Category: Molecular, Cellular and Development

Background: The biological mechanisms underlying the maturation of hippocampus-dependent learning and memory abilities are poorly understood, and important questions remain to be addressed: what types of cellular and molecular mechanisms are recruited for the maturation of memory abilities? Does the experience-dependent maturation develop the functions of the hippocampal memory system as a whole, or does it mature selective abilities, reflective of the specific learning experiences encountered? In this study, we tackled these questions, which have vast implications for education, mental health and diseases.

Methods: We employed contextual aversive and spatial non-aversive types of learning in infant (at postnatal day 17 - PN17) and juvenile (at PN24) rats and mice, along with chemogenetic memory trace reactivation, biochemical and electrophysiological analyses.

Results: Here we show that episodic learning produces unique biological changes in the hippocampus of infant rats and mice compared to juveniles. These changes include slow and persistent inductions of immediate early genes Zif268, c-Fos and Arc, BDNF-dependent increase in the excitatory synapse markers synaptophysin and PSD-95, and significant maturation of AMPA receptor synaptic responses. Inhibition of PSD-95 upregulation following learning impairs both AMPA receptor response maturation and infantile memory formation, indicating that the synapse formation/maturation is necessary for creating infantile memories. Conversely, capturing the learning-induced changes by repetition of the initial learning experience or by chemogenetic reactivation of the neural ensembles tagged by learning in infancy matures memory functional competence. This memory competence maturation is selective for the type of experience encountered, as it transfers within similar hippocampus-dependent learning domains but not to other hippocampus-dependent types of learning. Thus, experiences in early life produce selective maturation of memory abilities.

Conclusions: Our results imply that specific experiences during the infantile developmental period make a major contribution to individual differences in learning and memory abilities. Although all individuals are exposed to general learning of facts, people, things, time, and spaces, and therefore must develop a wide range of abilities and competences processed by the hippocampal memory system, our results suggest that the individual history shapes the maturation of selective learning and memory abilities. These conclusions may explain why early-life experiences influence the development of personality traits and are in agreement with the idea of enduring individual effects of experiences consolidated during early childhood. Therefore, we speculate that limited and/or selected experiences will build selected functional competences, whereas enriched, emotionally balanced, and diversified experiences will provide the greatest capacity for adaptive functional capabilities throughout life.
W47. Kinesins in Brain Development

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Category: Molecular, Cellular and Development

Background: In mammalian brain development, most neurons are produced by a specific stem cell population called Radial Glial Progenitors (RGPs). These cells can divide either symmetrically to proliferate, or asymmetrically to generate neurons. Over the course of development, the proportion of neurogenic divisions increases to boost neural production. If this process is inhibited or dysfunctional, the overall structure of the cortex is affected, and can result in microcephaly and other neurodevelopmental disorders. Whether a division is proliferative or neurogenic is determined by inheritance of the RGP apical membrane, which may be influenced by the mitotic spindle orientation relative to the ventricular surface, centrosomal inheritance, or proliferative signaling pathways. It is unclear just how this behavior is controlled, although several components have been identified, including both plus-end and minus-end microtubule motors.

Kif13B, a plus-end directed microtubule motor, has been shown to affect spindle orientation in Drosophila S2 cells and neuroblasts. RNAi for the Drosophila Kif13B orthologue resulted in S2 cells dividing at random angles, indicating Kif13B is important for proliferative, symmetric divisions. Kif1A has previously been shown to be important for a symmetric division in RGPs. It remains to be shown whether mammals require both kinesins in RGPs, and whether their functions are complementary or distinct. Both Kif1A and Kif13B are members of the kinesin-3 family, and have very similar overall structures, however, the few domain differences between these two motors may indicate different functions during mitosis.

Methods: In utero electroporation is used to introduce plasmids into embryonic rat brains. The brains are dissected and fixed, sliced, and stained for relevant markers. Additionally, brains are sliced live and the tissue is observed via confocal microscopy for several days to observe the behavior of individual cells in real time.

Results: Kif13b depletion results in an increase in early neurogenesis at the expense of the stem cell population. Kif13b depleted brains show 37% of electroporated cells in the cortical plate, compared to 11% in control brains at E19 (N = 8,7, p = 2.45x10^-9). Kif13b depletion also results in an increase in intermediate progenitors, 48% of dividing cells in the ventricular zone compared to 18% in control brains at E19 (N = 6,3, p = 0.004).

Conclusions: This work shows the novel contribution of a kinesin, Kif13B, in mammalian cortical development. Despite being very closely related to Kif1A, a kinesin also critical for neurodevelopment, these two kinesins have very distinct roles in this process. The results indicate that Kif13b is important for inhibiting early neural differentiation to maintain the RGP cell population.


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Category: Molecular, Cellular and Development

Background: Mitochondria are dynamic organelles that grow and degrade, divide and fuse, and move along cytoskeletal filaments within cells. The molecular mechanisms underlying mitochondrial dynamics are well defined. However, it is unclear how these molecular mechanisms are integrated over several orders of magnitude to give rise to stable, cell-scale mitochondrial distributions. Maintaining steady-state mitochondrial distributions is particularly challenging in complex, elaborately branched neurons. In this work, we investigated the relationship between mitochondrial motility and dendritic architecture in vivo using well-characterized horizontal system (HS) neurons in the Drosophila visual system.

Methods: In this study we investigate the mitochondrial dynamics in the horizontal system (HS) neurons. HS function relies on the integration of synaptic inputs across its highly branched dendritic arbor, with individual dendritic branches summing with approximately equal weight. HS dendritic branches should therefore have equivalent energetic demands and thus equally distributed mitochondria. Using EM images from the Full Adult Female Fly Brain (FAFB), we reconstructed mitochondria in HS neurons both in 3D and sparsely across the neuron, allowing us to identify both mitochondrial volumes and distributions across the neuron. In addition, we measured mitochondrial motility throughout HS dendritic arbors in intact flies using in vivo confocal microscopy. By bleaching one region of the dendrite we individually tracked mitochondria moving through the region to capture the flow of mitochondria as well as speed and length measurements. To determine how HS neurons
maintain stable branch-to-branch mitochondrial densities, we compared measurements of dendritic architecture with mitochondrial movement. Dendritic arbors can be decomposed into successive subtrees, and we reasoned that steady-state mitochondrial distributions could be maintained if, at each branch point, the relative amount of mitochondrial movement through each daughter branch scales with the relative size of the subtree supported by that branch.

**Results:** From our EM reconstructions of HS neurons we found mitochondrial densities are roughly uniform from branch-to-branch, yet the total mitochondrial density also varies from cell to cell. Mitochondrial density increases with distance from the cell body such that distal axons and dendrites have a higher density than primary dendrites. In addition, we measured significant mitochondrial motility throughout HS dendritic arbors in intact flies using in vivo confocal microscopy. By measuring dendritic subtree lengths, we found, first, that HS dendritic branch patterns are highly asymmetric: one daughter subtree, is, on average, approximately 2.5 times longer than the other. Second, dendritic subtree length asymmetry is tightly correlated with the dendritic cross section area asymmetry: larger subtrees have proportionally thicker trunks. Finally, we found that mitochondrial transport also scales with dendrite thickness, with proportionally more mitochondria moving into the thicker daughter branch.

**Conclusions:** Using the Drosophila visual system, we were able to identify patterns of mitochondrial movement and distribution using both EM and in vivo measurements. Together, these results show that mitochondrial transport scales with dendritic branch patterns, providing a mechanism for maintaining steady-state mitochondrial distributions within highly branched dendritic arbors.

W49. Temporal Dynamics in Drosophila Taste Coding Influence Synaptic Plasticity

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**Category:** Molecular, Cellular and Development

**Background:** The taste system ensures that animals consume nutritious foods and avoid ingesting toxins. Taste can also modulate responses to other stimuli; for example, animals learn to avoid cues that are associated with bitter taste. The timing of neuronal responses is a key feature of neural encoding in many systems, but few studies have investigated the temporal dynamics of taste sensory responses in any organism.

**Methods:** We used genetically targeted calcium imaging to investigate the temporal dynamics of taste responses in Drosophila. We then used mutant analysis, genetic manipulations, and optogenetics to study the mechanisms and implications of these dynamics.

**Results:** We found that different types of Drosophila taste sensory neurons show striking differences in their response dynamics. Most classes of taste neurons show a sustained response throughout the stimulus presentation that rapidly diminishes upon stimulus removal. However, some bitter-sensing neurons show strong, transient responses at both the onset and offset of the stimulus. Experiments using bitter receptor mutants, optogenetic activation, and synaptic transmission blockade revealed that these dynamics are generated cell-intrinsically via bitter receptors. This bitter encoding is modulated by experience: with repeated bitter presentations, the relative strength of the offset response increases. Interestingly, we observed the same bitter response dynamics in a set of downstream neurons, the PPL1 dopaminergic neurons (DANs). PPL1 DANs innervate the mushroom body, the learning and memory center of the fly brain, and these DANs specifically mediate aversive olfactory learning, in which pairing an odor with an aversive stimulus induces odor avoidance. Previous studies have shown that PPL1 DANs are activated by aversive stimuli and drive learning by inducing synaptic depression at synapses onto mushroom body output neurons. Unexpectedly, we found that pairing odor with bitter taste induced synaptic potentiation, not depression, at these synapses. However, synaptic depression could be induced by pairing odor with the removal of bitter. By using optogenetic activation to mimic PPL1 DAN activation by bitter, we found that these unexpected effects on plasticity could be explained by the timing of the bitter offset response.

**Conclusions:** These studies reveal previously unknown features of taste responses that impact neural circuit function and may be important for behavior. Moreover, these studies show that offset responses can dramatically influence timing-based synaptic plasticity, which is thought to underlie associative learning across many species.

W50. Complexity and Graded Regulation of Neuronal Cell-Type-Specific Alternative Splicing Revealed by Single-Cell RNA Sequencing
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Category: Molecular, Cellular and Development

Background: The structural and functional complexity of the mammalian cortex is determined by the enormous diversity of neuronal cell types and their connections that form intricate neural circuitries. Traditionally, neuronal cell types are defined by their morphological or electrophysiological properties, connectivity, or a small set of molecular markers. Recent advances in single-cell RNA sequencing (scRNA-seq) have enabled the unbiased discovery and characterization of neuronal cell types based on global steady-state transcript level, while mammalian genes undergo alternative splicing (AS) which are essential for diversifying the final protein products in time and space. The use of AS in the nervous system is particularly extensive. Previous studies have compared neuronal cells broadly (brain vs other organs, neurons vs. glia in the cortex, CNS to PNS), but the contribution of AS to molecular diversity across neuronal cell types has not been systematically investigated.

Methods: Here we systematically characterized AS regulation across over 100 transcriptomically defined neuronal types of the adult mouse cortex using deep single-cell RNA-sequencing (scRNA-seq) data. We identified differentially spliced (DS) alternative exons in major neuronal classes and subclasses at different hierarchical levels. By integrating de novo motif analysis, RBP expression profiles, their target networks and position-dependent RNA-maps, we investigated the major regulators of neuronal cell-type-specific splicing.

Results: We found distinct splicing programs between glutamatergic and GABAergic neurons and between subclasses within each neuronal class, consisting of overlapping sets of alternative exons showing differential splicing at multiple hierarchical levels. Using an integrative approach, our analysis suggests that RNA-binding proteins (RBPs) Celf1/2, Mbnl2 and Khdhrs3 are preferentially expressed and more active in glutamatergic neurons, while Elavl2 and Qk are preferentially expressed and more active in GABAergic neurons. Importantly, these and additional RBPs also contribute to differential splicing between neuronal subclasses at multiple hierarchical levels, and some RBPs contribute to splicing dynamics that do not conform to the hierarchical structure defined by the transcriptional profiles.

Conclusions: Alternative splicing (AS) is extensively used in the mammalian brain, but its contribution to the molecular and cellular diversity across neuronal cell types remains poorly understood. Through systematic and integrative analysis of over 100 transcriptomically defined cortical neuronal types, we found neuronal subclass-specific splicing-regulatory programs consist of overlapping alternative exons showing differential splicing at multiple hierarchical levels. Evidence is provided that this graded AS regulation is controlled by unique combinations of RNA-binding proteins (RBPs). Importantly, these RBPs also contribute to splicing dynamics across neuronal cell types that do not conform to the hierarchical taxonomy established based on transcriptional profiles, suggesting that the graded AS regulation may provide a molecular mechanism orthogonal to transcriptional regulation in specifying neuronal identity and function.

W51. Impact of KCNJ6 Expression and Ethanol on Function of Human Excitatory Neurons

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Category: Molecular, Cellular and Development

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 donors (N=6). 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: Preliminary patch clamp data (N = 2 donors) revealed that KCNJ6-upregulated neurons had lower resting membrane potentials (P = 0.02; N = 5 cells each for upregulated and endogenous expression) and were less excitable by current injection (P = 0.006; N = 9 & 8, upregulated & endogenous).
Pilot calcium imaging data (N = 2) revealed a higher rate of basal activity in KCNJ6-upregulated neurons (P = 5.8x10^-5) and a decrease in spontaneous activity in neurons treated with alcohol (P=0.017 endogenous; P = 0.006 upregulated). Alcohol-treatment resulted in increased sensitivity to glutamate in endogenous-KCNJ6 neurons (P=1.4x10^-6), but not in upregulated-KCNJ6 neurons. **Conclusions:** KCNJ6 expression level impacts neuronal electrophysiological maturation and excitability. Furthermore, KCNJ6 attenuates ethanol’s effects on glutamate sensitivity, potentially playing a protective role against alcohol-associated excitotoxicity.


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**Category:** Molecular, Cellular and Development

**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 generates 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.

**W53. The Role of Heart Rate Variability in the Relationship Between Maternal Anxiety During Pregnancy and Subsequent Child Anxiety**

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**Category:** Molecular, Cellular and Development

**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 investigates components of heart rate variability (HRV) as a possible mechanism of action.

**Methods:** A longitudinal study of mother-child dyads (N=89) measured maternal anxiety during the second trimester of pregnancy (self-reported via STAI-S) and subsequent child anxiety (maternal-reported via BASC-3) and baseline autonomic physiological measures (high and low frequency band of HRV power spectrum) at 5-years-old. Mediation analysis was conducted to test whether child high and/or low frequency HRV mediates the relationship between prenatal anxiety and child anxiety.

**Results:** Prenatal anxiety predicted child anxiety (β=0.137, p=0.004) and high frequency HRV (β=-0.0093, p<0.001), but not low frequency HRV (β=-0.002, p=0.231). High frequency HRV predicted child anxiety accounting for prenatal anxiety (β=-4.7441, p=0.026). After controlling for high frequency HRV, prenatal anxiety was no longer associated with child anxiety (β=0.0753, p=0.148). Mediation analysis revealed that high frequency HRV mediated the relationship between prenatal anxiety and child anxiety (β=0.444, 95% CI [0.007, 0.085], p<0.05). Alternatively, low frequency HRV did not predict child anxiety when accounting for prenatal anxiety (β=-4.9058, p=0.063). Prenatal anxiety was still a significant predictor of child anxiety, after controlling for low frequency HRV (β=-0.109, p=0.029). Mediation analysis revealed that low frequency HRV does not mediate the relationship between prenatal anxiety and child anxiety (β=0.0117, 95% CI [-0.007, 0.047], p>0.05).
Conclusions: Results indicate that in-utero exposure to maternal anxiety influences the child’s high frequency but not low frequency HRV. Importantly, changes in only high frequency HRV from prenatal anxiety is driving the relationship between prenatal anxiety and child anxiety. The results suggest that the high frequency portion of the HRV power spectrum (an indicator of vagal tone) should be a focus in a multidimensional model of fetal programming and long-term mental health.

W54. Social Odor Coding in Hippocampal Area CA2

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Category: Cognitive and Systems

Abstract: Although the role of the hippocampal CA2 region in social memory has been well established, how CA2 neurons process social sensory cues to enable the encoding and recall of social information remains unknown. As social memory in rodents is known to depend on social olfactory cues, we have examined the coding of both social and non-social odors in CA2 pyramidal neurons using two-photon imaging in head-fixed mice of fluorescence signals from the genetically encoded calcium indicator GCaMP6s. We find that a fraction of CA2 neurons respond to both social odors (urine) and non-social odors. Moreover, the odor-related activity allows significant decoding of two social odors (urines from two age-matched C57Bl/6 male mice), a prerequisite for social recognition memory. Furthermore, we find that CA2 neuron odor discrimination is enhanced following training in a Go/No-Go task, in which mice learn to associate one of two randomly presented social odors with a water reward. Optogenetic silencing of CA2 impairs the learning of odor-reward associations, supporting a causal role of CA2 in social odor discrimination. To further explore the logic by which CA2 encodes odor stimuli, we trained mice in the Go/No-Go task using two novel social odors and two non-social odors, in which one each of the social and non-social odors was rewarded. After learning, we found that CA2 can distinguish all four odors in a manner consistent with it providing abstract representations of social versus non-social odors. Together these results argue strongly that CA2 forms a hub that classifies and distinguishes multiple forms of olfactory stimuli, which both enhances the learning of olfactory-reward associations and is poised to contribute to social memory storage.

W55. Retrieval spikes: A Dendritic Mechanism for Retrieval-Dependent Memory Consolidation

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Category: Molecular, Cellular and Development

Abstract: Retrieval-dependent processing of new memories are crucial for their long-term retention, yet the underlying mechanisms remain unclear. To address this, we adapted the classical fear-conditioning paradigm to comply with two-photon imaging during training and used a protocol in which cueing retrieval shortly after a tone-shock pairing, improved long-term memory retention. Our work focused on neuronal changes in the primary motor cortex (M1), a region that is essential for retrieval-dependent improvement of conditioned freezing. We found that early retrievals elicited massive calcium spikes on apical dendrites of layer 5 pyramidal neurons, the principal output cells of the cortex. We named these retrieval-evoked dendritic calcium spikes, retrieval spikes. These retrieval spikes emerged as a transient response to the tone, apparent only within less than 30 minutes after training. Notably, postsynaptic dendritic spines that were the most active during retrieval spikes underwent persistent depotentiation, becoming smaller, and less active at later recall tests. Optogenetic inhibition of CaMKII, a calcium-dependent master regulator of synaptic plasticity, disrupted spine structural plasticity, spike transience, and conditioned freezing, only when applied shortly after spiking. We further found that the generation of retrieval spikes coincided with reduced activity of dendritic-targeting inhibitory neurons (SST+, NDNF+) during retrieval, suggesting that the local inhibitory circuit is poised for retrieval-dependent spike generation. Collectively, these results reveal a negative feedback mechanism where cued retrieval evokes spikes, which promote the depotentiation of spines responsive to the cue. In turn, these lead to spike transience, and reduced responses to the cue in M1, which help ensure conditioned freezing.
W56. FMRP Regulates mRNAs Encoding Distinct Functions in the Cell Body and Dendrites of CA1 Pyramidal Neurons

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Category: Molecular, Cellular and Development

Abstract: Neurons are believed to rely on dendritic localization and translation of mRNAs in order to generate activity-dependent changes in the synaptic plasticity. Here, we develop a strategy combining compartment-specific CLIP and TRAP in e-Tag mice to precisely define the ribosome-bound dendritic transcriptome of CA1 pyramidal neurons. This revealed many transcripts that have differentially localized alternative 3'UTR and splicing isoforms. FMRP targets are overrepresented among dendritic mRNAs, and compartment-specific FMRP-CLIP defined 383 dendritic FMRP targets. In the absence of FMRP, dendritic FMRP targets show increased ribosome association, consistent with reported roles for FMRP in translational repression. Surprisingly, this also allowed for segregation of whole-cell FMRP targets into functional modules that are locally regulated by FMRP. Together, the data support a model in which distinct patterns of FMRP localization allow it to differentially regulate the expression of nuclear proteins and synaptic proteins within different compartments of a single neuronal cell type.

W57. Single Nuclei Transcriptomics Relates Glioblastoma Heterogeneity to Fetal Neurodevelopment.

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Category: Brain Disease and Disorders

Background: 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.

W58. Do Biological Neural Networks Perform Identifiable and Verifiable Canonical Computations?

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Category: Cognitive and Systems

Abstract: Once you have a good thing, stick with it. Evolution has clearly incorporated this principle into nervous systems. In contrast to the broad diversity of life forms, their structure and function, nervous systems across species and even phyla are remarkably similar. Essentially all nervous systems use evolutionarily conserved small molecules, neurotransmitters, transmitters, proteins, excitatory and inhibitory neurons, and synapses. At higher
levels, vertebrate and mammalian neuroanatomy conserves relative function and connectivity of nuclei, layers, and regions. At still higher levels, the goals and functions of all nervous systems are similar. But at intermediate levels: are neural circuits and the computations they perform evolutionarily conserved? We offer four reductionist, testable questions:
1. What do brains compute?
2. How are computations implemented by neural circuitry?
3. Do these computations form a small canonical set?
4. Which of the many properties of nervous systems are essential for computation?

Advancing these questions, we present a set of mechanisms common to almost all neural circuits, and a complementary set of mechanisms that we exclude because many neural circuits function without them. From machine learning/AI, we examine neurobiological credit assignment and draw analogies to electronic circuitry. We also consider competing views: 1) there are only ad-hoc network designs, with evolutionary conservation of componentry but not of circuit types; 2) computability may be an emergent property of any circuitry that sums and transforms. Answers may empower new analyses of multineuron recording and inform new neuromorphic designs for future AI systems. New approaches may be needed to explore this question, including a projected Neuromorphic Neural Networks (N³, or Encubed) collaborative, and the Next Cool Virtual Meeting.

W59. Replicable Effects of Deep Brain Stimulation for Obsessive-Compulsive Disorder

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Category: Brain Disease and Disorders

Background: Patients with severe obsessive-compulsive disorder (OCD) can be treated by delivering deep brain stimulation (DBS) to the anterior limb of the internal capsule (ALIC). Distinct white matter pathways have been identified within the ALIC, and stimulation of particular tracts is claimed to be associated with better clinical response to DBS for OCD. We asked a fundamental question — can these putative associations with clinical response be replicated?

Methods: We performed DBS on patients (n = 10; 6 male, 4 female) diagnosed with severe and treatment refractory OCD (baseline Yale-Brown Obsessive Compulsive Scale (Y-BOCS) mean 71 standard deviation: 33.9 ± 2.6). For each New York patient, we utilized normative connectomes to calculate a ‘fiber score’: a sum-score weighted by the published t-value of each tract passing through the patient’s volume of activated tissue (VAT). Fiber scores were then evaluated for a relationship with clinical improvement.

Results: DBS led to 70% of patients achieving clinical response, defined in the standard fashion as a ≥35% Y-BOCS decrease. Mean Y-BOCS decrease was 15.1 points, corresponding to a 44% decrease on average (t = 7.52, 95% confidence interval (CI): 10.56 to 19.64, df = 9, P < 0.001). We were able to replicate the association between clinical response and the previously implicated white matter tracts, finding that our responders had a mean fiber score five times greater than non-responders (t = 2.50, mean-difference 95% Clone-tailed lower bound = 27.62, df = 6.94, Pone-tailed = 0.021).

Conclusions: Our findings confirm the clinical efficacy of DBS for OCD, and replicate the association with white matter tracts derived from large-scale population connectomics. Patient-specific tractography will facilitate more individualized targeting of the full array of clinically relevant cortico-subcortical and subcortico-cortical projections.

W60. Sensorimotor Strategies and Neuronal Representations for Shape Discrimination

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Category: Cognitive and Systems

Background: Humans and other animals can identify objects by active touch, requiring the coordination of exploratory motion and tactile sensation. Both the motor strategies and neural representations employed could depend on the subject’s goals.

Methods: We developed a shape discrimination task that challenged head-fixed mice to discriminate concave from convex shapes.
Results: Behavioral decoding revealed that mice did this by comparing contacts across whiskers. In contrast, a separate group of mice performing a shape detection task simply summed up contacts over whiskers. We recorded populations of neurons in the barrel cortex, which processes whisker input, to identify how it encoded the corresponding sensorimotor variables. Neurons across the cortical layers encoded touch, whisker motion, and task-related signals. Sensory representations were task-specific: during shape discrimination, neurons responded most robustly to behaviorally relevant whiskers, overriding somatotopy.

Conclusions: Thus, sensory cortex employs task-specific representations compatible with behaviorally relevant computations.

W61. Functional Genomics Approach to Modeling Antidepressant Response in Treatment-Resistant Depression

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Category: Molecular, Cellular and Development

Background: SSRIs, such as fluoxetine, are effective in only ~ 50% of major depressive disorder (MDD) patients, and the mechanisms of treatment resistance remain poorly understood. We identified gene pathways involved in the response to fluoxetine in a mouse model for depressive-like behavior and mapped them to specific cellular populations in the dentate gyrus (DG).

Methods: We analyzed gene expression in the DG of mice chronically treated with corticosterone and fluoxetine. We identified gene regulatory networks (GRN) using Principal Component Analysis (PCA) and analyzed their expression in relation to treatment responsiveness. We further characterized the networks through ISH and single-cell RNA-Seq (scRNA-Seq).

Results: (i) PCA shows that transcriptional responses to fluoxetine are quantitative, and several features of gene expression patterns are diminished in non-responders. (ii) We identified a GRN governing the composition of specific postsynaptic density components in the glutamatergic neurons whose expression is reduced in non-responders. This network, triggered by Bdnf, includes regulators of synaptic plasticity such as NTRK2, JAZF1, MEF2C, KLF9, PROX1, and SKI. A GWAS study by 23 and Me identified 13 top genes associated with MDD, 10 of which are present in this gene regulatory network. (iii) In addition to the neurotrophic modulation, chronic fluoxetine treatment upregulates expression of proenkephalin (PENK) in the DG, and this upregulation is associated with treatment responsiveness. scRNA-Seq data analysis shows that, unlike the Bdnf-regulated genes, the PENK co-expression network is localized to an anatomically and transcriptionally specialized subgroup of mature granule cells in the dentate gyrus.

Conclusions: Based on our analysis, we proposed two separate gene regulatory network models that control antidepressant effects in the dentate gyrus. One is mediated via neurotrophic signaling, and the other is routed through upregulation of PENK in a specific subpopulation of mature granule cells.

W62. Effects of Postnatal Cannabis Use and Superstorm Sandy Trauma on Child Heart Rate Recovery

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Category: Molecular, Cellular and Development

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.

Methods: 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.

**W63. The Brain Clock's Portal system: Suprachiasmatic Nucleus and Organum Vasculosum of the Lamina Terminalis**

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**Category:** Cognitive and Systems

**Background:** Vascular portal systems are structures necessary for transporting products directly from the capillary bed of one region to the capillary bed of another region in high concentrations, without dilution in the systemic vasculature. The only known portal system in the brain is the hypophyseal-pituitary portal system, a communication system that is necessary for reproduction and survival. Secretions from specialized hypothalamic neurons travel in portal vessels to their targets. Neurons of the hypothalamic suprachiasmatic nucleus (SCN), locus of the brain’s master clock, also produce secretions deeply implicated in health and survival. The grafted SCN, when encapsulated in a polymer material, can restore behavior rhythmicity. Thus diffusible signal from the SCN sustain circadian rhythms. Although the neural network of between the brain clock and has been extensively studied, its pathway to transport diffusible signals to surrounding brain regions, including the vasculature, has not been studied.

**Methods:** In this study, to obtain the whole-mount vasculature image of mouse anterior hypothalamus without slicing the brain, we cleared the tissue with iDISCO, labeled with markers for identifying SCN, arteries and the complete vasculature in the acquired region, and imaged with light sheet microscopy. The blood vessels were traced with Imaris or Vesselucida 360.

**Results:** We identified a portal system connecting the SCN and organum vasculosum of the lamina terminalis (OVLT). The OVLT is a circumventricular organ (CVO) lacking a blood-brain barrier, enabling communication between the blood, brain, and cerebrospinal fluid.

**Conclusions:** This “clock portal system” points to entirely new routes and targets for secreted signals, restructuring our understanding of brain communication pathways. Whether any of the remaining six CVOs in the mammalian brain bear portal systems is yet to be determined.

**W64. Interactions Between Peripheral Monocytes and the Brain in Stress-Impaired Social Behavior**

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**Category:** Brain Disease and Disorders

**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 system activation and neuronal dysfunction in the Nucleus accumbens (NAc) and as a consequence, deficits in social reward processing, are still poorly understood.

**Methods:** In a murine model of chronic social defeat stress (CSDS), we applied mass cytometry, bulk and single-cell RNA-sequencing to characterize immune cells in circulation and the central nervous system. Using pharmacological and genetic strategies, we investigated the causal effects of the identified murine targets on
stress-induced behavioral and electrophysiological changes in the NAc. Lastly, we validated the murine findings in patients with MDD and non-depressed healthy controls (HC).

**Results:** In circulation, CSDS led to a dysregulation of several leukocyte subpopulation frequencies of both the myeloid and lymphoid lineage. In brain, however, we observed an increased accumulation of Ly6chigh monocytes in brain-border regions specifically in susceptible mice. Single-cell RNA-sequencing of brain infiltrating monocytes identified increased expression of the endopeptidase matrix metalloproteinase 8 (Mmp8) in stress-susceptible versus resilient or control mice. Plasma levels of MMP8 correlated positively with social avoidance. Combination of intraperitoneal administration of recombinant MMP8 and a 3-day subthreshold social defeat was sufficient to induce social avoidance and reduced social reward. Mmp8 bone marrow chimeric mice that lack Mmp8 only in peripheral immune cells also showed decreased CSDS-induced social avoidance compared to wildtype chimeras. These behavioral changes went along with blunted stress-induced increased spontaneous excitatory postsynaptic currents (sEPSCs) and neuronal excitability in the NAc. Finally, we showed that plasma levels of MMP8 were increased in patients with MDD compared to HC.

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

**W65. State and Stimulus Dependence Reconcile Motion Computation and the Drosophila Connectome**

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**Category:** Cognitive and Systems

**Abstract:** Sensory systems dynamically optimize their processing properties in order to process a wide range of environmental and behavioral conditions. However, attempts to infer the function of these systems via modeling often treat system components as having static processing properties. This is particularly evident in the Drosophila motion detection circuit, where the core algorithm for motion detection is still debated, and where inputs to motion detecting neurons remain underdescribed. Using whole-cell patch clamp electrophysiology, we measured the state- and stimulus-dependent filtering properties of inputs to the OFF motion-detecting T5 cell in Drosophila. Simply summing these inputs within the framework of a connectomic-constrained model of the circuit demonstrates that changes in the shape of input temporal filters are sufficient to explain conflicting theories of T5 function. Therefore, with our measurements and model, we reconcile motion computation with the anatomy of the circuit.

**W66. Integrins Protect Sensory Neurons in Models of Chemotherapy-Induced Peripheral Neuropathy**

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**Category:** Brain Disease and Disorders

**Abstract:** Chemotherapy-induced peripheral neuropathy (CIPN) is a major side effect from cancer treatment with no known method for prevention or cure in clinics. CIPN often affects unmyelinated nociceptive sensory terminals. Despite the high prevalence, molecular and cellular mechanisms that lead to CIPN are still poorly understood. Here, we used a genetically tractable Drosophila model and primary sensory neurons isolated from adult mouse to examine the mechanisms underlying CIPN and identify protective pathways. We found that chronic treatment of Drosophila larvae with paclitaxel caused degeneration and altered the branching pattern of nociceptive neurons and reduced thermal nociceptive responses. We further found that nociceptive neuron-specific overexpression of integrins, which are known to support neuronal maintenance in several systems, conferred protection from paclitaxel-induced cellular and behavioral phenotypes. Live imaging and super resolution approaches provide evidence that paclitaxel treatment causes cellular changes that are consistent with alterations in endosome-mediated trafficking of integrins. Paclitaxel-induced changes in recycling endosomes precede morphological degeneration of nociceptive neuron arbors, which could be prevented by integrin overexpression. We used primary dorsal root ganglia (DRG) neuron cultures to test conservation of integrin-
mediated protection. We show that transduction of a human integrin β-subunit 1 also prevented degeneration following paclitaxel treatment. Furthermore, endogenous levels of surface integrins were decreased in paclitaxel-treated mouse DRG neurons, suggesting that paclitaxel disrupts recycling in vertebrate sensory neurons. Altogether, our study supports conserved mechanisms of paclitaxel-induced perturbation of integrin trafficking and a therapeutic potential of restoring neuronal interactions with the extracellular environment to antagonize paclitaxel-induced toxicity in sensory neurons.

W67. A Sensitive Period in the Postnatal Development of Prefrontal Cortical Function and Behavior

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Category: Brain Disease and Disorders

Background: The prefrontal cortex (PFC) is a cognitive structure that is implicated in many psychiatric disorders. It receives reciprocal excitatory inputs from the midline thalamus (MD), and this MD-PFC circuitry is crucial in cognition. In patients with schizophrenia, who have impaired cognitive functions, MD-PFC connectivity is disrupted. This finding is also seen in adolescents at high risk for schizophrenia, before diagnosis. Unfortunately, the development of the MD-PFC circuitry is still poorly understood.

We hypothesize that adolescence represents a sensitive period, during which the PFC is susceptible to transient perturbations, resulting in persistent changes in circuitry. We aim to discover the role of MD inputs in the maturation of PFC circuitry and cognitive behaviors.

Methods: We developed an approach in mice whereby we can transiently modulate MD activity. We chose adolescence, a vulnerable period in the progression of schizophrenia. As a comparison, we also manipulated MD excitability during adulthood. Forty days following the manipulation, we tested for persistent effects on PFC circuitry and behavior.

Results: Our data show that transient adolescent MD perturbation results in deficits in two PFC-dependent cognitive tasks in adulthood. Further, this manipulation results in long-term changes to PFC excitatory currents. However, the same manipulation during adulthood did not result in persistent changes. We also demonstrate that transient adolescent MD perturbation results in a decrease in MD-PFC projections and impairments in both MD and PFC oscillatory activity. Finally, we show that these deficits can be rescued with acute optogenetic stimulation of the MD during adulthood.

Conclusions: These data indicate a sensitive period during adolescence when perturbations to excitatory inputs can have persistent effects on PFC physiology, anatomy, oscillatory activity, and behavior. Moreover, our results indicate that an intervention can reverse these effects. This study furthers our understanding of PFC maturation, offering insights into the pathophysiology of psychiatric disorders.