MPA Molecular Psychiatry Association

MPA 2026

Molecular Psychiatry Meeting

ROYAL SONESTA KAUA'I RESORT

MARCH 29 - APRIL 01, 2026

POSTER ABSTRACTS

Monday, March 30, 2026

M1. Calcium Transients in Microglia Drive Repetitive and Anxiety Behaviors

Naveen Nagarajan, University of Louisville, School of Medicine

Disruption of the mouse Hoxb8 gene causes chronic anxiety and pathological over-grooming. The cause for this pathology is defective Hoxb8 microglia. Furthermore, optogenetic stimulation of Hoxb8 microglia in specific brain regions induces elevated anxiety and/or grooming. Herein we show that the signals for inducing anxiety and/or grooming in response to optogenetic activation are calcium ions. Conversely, induction of grooming and anxiety in mice produces calcium transients within microglia. Significantly, the calcium transients are not produced in Hoxb8 mutant mice in response to induction of these behaviors, the likely cause being retention of high constitutive levels of free calcium ions within Hoxb8 mutant microglia. This calcium, in turn, serve as relentless signals to increase anxiety and grooming leading to production of chronic anxiety and pathological overgrooming in Hoxb8 mutant mice. In summary calcium signaling is used by microglia: 1) to induce anxiety and/or grooming by optogenetics in WT mice, 2) to respond to the induction of these behaviors in WT mice and 3) as the causative agent for producing chronic anxiety and pathological overgrooming in Hoxb8 mutant mice.

M2. Dorsal and Ventral Mossy Cell Dynamics in Fear Learning

Yi-Chen Liou, National Yang Ming Chiao Tung University

Background: The hippocampus is essential for regulating anxiety and fear, but exhibits functional specialization along its dorsal-ventral axis. How these two regions coordinate during fear learning remains unclear. Mossy cells (MCs) in the dentate gyrus form longitudinal projections linking distant hippocampal domains and are implicated in emotional processing and memory.

Methods: We combined in vivo calcium imaging with chemogenetic and optogenetic approaches to investigate how dorsal and ventral MCs contribute to associative fear learning in mice subjected to auditory fear conditioning. Neural responses were recorded during both conditioning and recall phases, followed by functional perturbation experiments to test causal roles.

Results: During conditioning, dorsal MCs preferentially responded to the conditioned stimulus (CS; tone), whereas ventral MCs showed stronger responses to the unconditioned stimulus (US; footshock). During recall, dorsal MCs remained responsive to the CS, and ventral MCs exhibited temporally coordinated activation despite the absence of the US. Chemogenetic silencing of either dorsal or ventral MCs impaired fear expression, while optogenetic inhibition reduced freezing behavior, indicating diminished fear responses.

Conclusion: Our findings reveal distinct yet complementary roles of dorsal and ventral MCs in associative fear learning. Dorsal MCs encode predictive (CS) signals, ventral MCs convey aversive (US) information, and coordinated activity between these populations is required for the expression of learned fear.

M6. Context-Dependent Estradiol Modulation of Autism Spectrum Disorder Risk Genes

April Pruitt, Yale Child Study Center

Background: The biological basis for the significant, four-fold male to female sex bias in autism spectrum disorder (ASD) is poorly understood. Differential exposure to estrogens during neurodevelopment has been proposed as a potential modulator of risk, yet how estrogens interact with the growing number of large-effect ASD genes to influence risk has yet to be investigated. In this study,

we test the hypothesis that early exposure to the principal biologically active estrogen, 17β-estradiol, confers a protective effect against ASD and neurodevelopmental disorder (NDD) genetic mutants.

Methods: Leveraging hiPSCs and larval zebrafish, we conduct a large-scale, multi-modal screen of 36 highly penetrant, functionally diverse, large-effect ASD genes following exposure to 17β-estradiol across sensorimotor and arousal behavioral assays, in vitro calcium imaging of neuronal network activity, and in vitro pooled CRISPR single-cell RNAseq.

Results: Our screen uncovers highly context-dependent effects of estradiol across ASD genes and modalities, revealing convergent and divergent gene-by-estrogen interactions at the behavioral, circuit, and transcriptomic levels. Particularly, we define a subset of ASD genes with convergent baseline phenotypes and shared estradiol response, two of which, ASH1L and SCN2A, are particularly amenable to estradiol rescue across three modalities. We find that estradiol rescues cell-autonomous and network bursting activity in ASH1L and SCN2A mutant glutamatergic neurons as well as sleep-wake phenotypes in larval zebrafish mutants.

Conclusions: Together, our functional screen reveals a novel role of estrogens in modulating network hyperexcitability in the context of select ASD gene loss of function.

M8. Investigating the Role of Early Postnatal Neuromodulation in Cerebellar Development

Meghan Carlton, Albert Einstein College of Medicine

Background: The cerebellum shapes motor behavior, cognition, and emotion, and in consequence, its functional disruption during early development is one of the highest risk factors for neurodevelopmental disorders. Due to its protracted development and anatomical location, the cerebellum is highly susceptible to perinatal disruptions. For example, during parturition, the infant cerebellum is not only prone to injury, but it also experiences surges of neurohormones like oxytocin. Previous studies suggest that neonatal oxytocin exposure contributes to functional maturation of cortical and hippocampal circuits, but the impact of those hormone surges on cerebellar development remains unknown. Recent transcriptomic profiling of the developing mouse cerebellar cortex revealed that GABAergic progenitors transiently express oxytocin receptor mRNA, peaking during early development. Our study elucidates the role of early postnatal oxytocin signaling in the development of GABAergic neurons.

Methods/Results: Gene expression analysis and labeling across early postnatal development revealed that Oxtr mRNA expression is confined to molecularly identified cell types that correspond to developing GABAergic neurons, including interneurons and Purkinje cells. Patch clamp electrophysiology shows that oxytocin excites these neurons from P4 to P10, after which the receptor is sharply downregulated. This time window coincides with the GABA functional switch from excitatory to inhibitory, anatomical maturation, and widespread synaptogenesis. Preliminary findings also suggest that developmental disruption of oxytocin signaling leads to lasting changes in calcium-binding protein expression and neuronal activity.

Conclusion: Our findings provide insight into how oxytocin, a hormone associated with childbirth, nursing, and mother-infant bonding, may support cerebellar circuit maturation.

M9. Maternal Immune Activation Significantly Affects Neuronal Gene Expression Along the Medial Prefrontal Cortex-Amygdala Circuit in Rhesus Macaque Offspring

Erin Carlson, MIND Institute, Cell Biology and Human Anatomy, University of California Davis School of Medicine

Background: Activation of the maternal immune system while pregnant can shape the trajectory of offspring brain development with effects on social behavior and cognitive function. Previous research

using our nonhuman primate model of maternal immune activation (MIA) shows that immune stimulation via the viral mimic Poly:IC/LC results in significant changes in species-typical social behavior that implicates functional changes in the medial prefrontal cortex (mPFC)-amygdala circuit.

Methods: We used single nucleus RNA sequencing (snRNA-seq) to investigate gene expression in 26 rhesus macaque offspring (14 controls, 12 first trimester Poly:IC/LC MIA-exposed). Independent samples from the amygdala (lateral, accessory basal, and central) and mPFC (subgenual anterior cingulate cortex) were collected, processed into fixed suspensions, and sequenced. We evaluated differential gene expression and used Reactome to identify the ongoing biological processes resulting from prenatal MIA exposure. Additionally, we ran multiplexed smFISH (RNAscope HiPlex) to gain insight in the spatial distribution of key differentially expressed genes and cell types.

Results: We observed that excitatory neurons across the circuit demonstrate the highest levels of differential expression, and these transcriptional changes consistently reflect pathways involving axon guidance, synaptic structure, ion regulation, and neurotransmission.

Conclusions: MIA exposure results in gene expression changes along the mPFC-amygdala circuit that are evident through late adolescence. These transcription changes suggest alterations exist in synaptic architecture and neurotransmission and are reminiscent of those observed in some neurodevelopmental and psychiatric disorders.

M11. Single-Nucleus Multi-Omics and Spatial Transcriptomics Reveal Region-Specific Molecular Alterations in Cortical and Thalamic Circuits in Autism Spectrum Disorder

Lucy Bicks, David Geffen School of Medicine at UCLA

Autism Spectrum Disorder (ASD) presents with high phenotypic heterogeneity, yet studies over the past decade have consistently identified a shared molecular endophenotype in post mortem brain in the majority of cases. This molecular signature is characterized by decreased synaptic and interneuron marker genes and neuroinflammatory changes in microglia, astrocytes and oligodendrocytes. Emerging evidence also points to a dampening of regional cortical identity and a shift in the balance of local versus long range connectivity across brain in ASD. To date findings demonstrate that molecular alterations in ASD are relatively similar across the cortex, but with a posterior-anterior severity gradient. The nature of this gradient and the origin of the significant involvement of primary sensory cortex are not well understood. In this study, we performed single-nucleus multi-omics (snMulti) profiling across all four cortical lobes from 60 ASD and CTRL brains. For the first time, we extended this analysis to three thalamic nuclei: Medial Dorsal (MD), Lateral Geniculate (LGN) and Medial Geniculate (MGN) to test alterations in thalamocortical pathways and to compare sensory and association thalamic nuclei. To further investigate the topology of molecular differences in the ASD brain, we performed single-cell spatial transcriptomics by MERFISH to examine molecular changes in a spatial context within the frontal cortex and occipital lobe. We investigate region-specific and cross regional differential regulatory programs to elucidate the molecular basis of altered regional signatures across the cortex and thalamus in ASD.

M12. Prenatal Exposure to Polyethylene Nanoplastics: Preliminary Evidence of Accumulation and Potential Neurodevelopmental Effects in Human Brain Organoids

Luca Trovò, University of California, San Diego

Background: Nanoplastics are emerging environmental contaminants that are increasingly detected in human tissues and biological fluids. Their nanoscale size raises the possibility of placental transfer and fetal exposure during critical windows of development. However, their potential impact on human brain development remains poorly understood.

This study aims to investigate whether polyethylene (PE) nanoplastics accumulate in developing neural tissues and whether such accumulation could perturb early neurodevelopmental processes. Specifically, we examined the distribution of PE nanoparticles within human brain organoids as a model for fetal brain development.

Methods: Human pluripotent stem cell–derived cortical organoids were exposed to fluorescently labeled PE nanoparticles (50–65 nm). Nanoparticle localization was assessed using confocal microscopy on both optically cleared whole organoids and cryosections. Accumulation was quantified within neural rosette regions, representing early neuroepithelial structures. Organoid diameter and growth dynamics will be monitored to detect morphological changes following exposure. To confirm nanoplastic identity and aggregation, transmission electron microscopy (TEM) and dynamic light scattering (DLS) analyses are being conducted. Cytotoxicity and apoptosis markers will be analyzed to evaluate potential neurotoxic effects of PE exposure.

Results and Conclusions: Preliminary imaging data indicate that PE nanoplastics are internalized by brain organoids and appear to accumulate within neural rosette-like structures. These findings suggest that developing neural tissues can uptake and possibly retain nanoplastics during early differentiation. Ongoing analyses will determine nanoparticle aggregation state and the degree of cellular stress and apoptosis. In future studies, both fluorescently labeled and non-tagged environmentally relevant plastics - collected from ocean samples and subsequently prepared - will be tested to better mimic real-world exposure scenarios. Together, these results provide early evidence that prenatal exposure to environmental nanoplastics may pose risks to human neurodevelopment.

M13. A Brain-Enriched Circular RNA Blood Biomarker Can Predict SSRI Antidepressant Response

Eleni Tzavara, INSERM CNRS UPC

Background: Non-coding circular RNAs (circRNAs) generate from non-canonical backsplicing and covalent RNA joining. They are highly enriched in the brain, cross the BBB and due to their inherent stability are readily-detectable in blood. As such they could provide a “window to the brain” for better understanding and monitoring of mental health pathologies. Here we investigate CDR1as (a circRNA that regulates activity-dependent gene expression and synaptic plasticity) in antidepressant response.

Methods: Preclinically, we used mouse cortical cultures in vitro or adult C57BL/6J mice in vivo. In humans, we measured CDR1as at baseline (before treatment) blood PAXgene samples from the EMBARC (NCT01407094; n=91) and ANTARES (NCT05568823; n=35) cohorts, both designed for prediction of response to antidepressants including sertraline (SERT).

Results: In vitro inhibition of the BDNF, CREB and ERK pathway caused a significant reduction of CDR1as expression. In vivo inhibition of 5-HT2A receptors resulted in a 40% reduction of CDR1as expression in cortical/subcortical regions. In data from both clinical cohorts (N = 126 patients in total) blood levels of CDR1as measured before treatment clearly distinguished between future SERT responders and non-responders ($p = 0.0003$). A receiver operating characteristic (ROC) curve analysis showed an area-under-the-curve (AUC; index of potential use as a predictive biomarker) of 0.8 ($p<0.0001$), with positive-predictive-value of 79.7 (71.5-86; 95%CI), and negative-predictive-value of 75.65 (62.9-85; 95%CI).

Conclusions: Neuronal/brain CDR1as is regulated by antidepressant-related 5-HT2A and BDNF/TrkB-ERK/CREB pathways. Blood expression levels of CDR1as circRNA at baseline provided reliable prediction of response to the SSRI sertraline in two independent cohorts.

M14. Towards Reliable Brain Connectivity Biomarkers for Psychiatric Disorders: Defining the "Trait Connectome"

Andrey Anokhin, Washington University School of Medicine

Background: fMRI-based resting-state functional brain connectivity (FC) metrics have been increasingly used as potential biomarkers of risk for psychiatric disorders, albeit with mixed findings and limited reproducibility. One possible source of this problem is that FC reflects both stable, reliable individual differences (traits) and transient functional states. Since reliability is a key prerequisite for a biomarker, it is important to identify reliable FC features constituting a "trait connectome" representing stable individual differences in functional brain organization.

Methods: fMRI data including 15 min of resting-state and 30 min of cognitive tasks were collected from a sample of n = 264 adolescents at ages 14, 16, and 18. Connectivity computed using the Gordon, 2016 parcellation and subcortical volumes yielding a total of 61,600 edges (connections). Longitudinal test-retest reliability was assessed for each edge.

Results. Mean edge-level reliability was poor (r=.37), while reliability of average FC within the "canonical" functional networks was fair (average: r=.48). Across the connectome, only 16.2% and 3.4% of edges showed good (>.6) and excellent (>.75) reliability, respectively. These reliable edges included both within- and between-network connections, forming "trait connectome". Pooling resting and task data boosted reliability, with 15.6% of edges showing excellent reliability. Using these reliable FC traits improved associations with dimensional psychopathology and cognitive performance.

Conclusion: Focusing on the "trait" part of the connectome can increase the power of FC studies concerned with individual and group differences. In contrast, inclusion of unreliable FC measures introduces noise, leading to dilution of effects and reduced power.

M15. Rare Coding Variation in 256,147 Individuals Identifies 13 Genes and Transcriptional Convergent Synaptic Mechanisms Underlying Bipolar Disorder

Cal Liao, Broad Institute of MIT and Harvard

Background: Bipolar disorder (BD) is a highly heritable psychiatric condition, yet its genetic basis remains incompletely resolved. We present the latest Bipolar Exome (BipEx) analysis leveraging whole-exome sequencing from 65,437 BD cases and 190,710 controls to define gene-level associations and identify convergent molecular mechanisms.

Methods: We performed ultra-rare variant burden analyses (minor allele frequency <0.0001) for protein-truncating and damaging missense variants across ancestrally diverse cohorts. Gene-based signals were integrated with human brain transcriptomic coexpression networks and mapped to three-dimensional protein structures derived from AlphaFold to identify convergent transcriptional and structural signatures.

Results: Thirteen genes reached exome-wide significance, including AKAP11, SHANK1, GRIN2A, ATP2B2, and DOP1A. Convergent coexpression analysis revealed strong transcriptional convergence across brain tissue from GTEx, highlighting enrichment for anterograde trans-synaptic signaling ($P = 8.1 \times 10^{-17}$), glutamatergic synapse ($P = 1.4 \times 10^{-23}$), and abnormal synaptic transmission and physiology in mice ($P < 3 \times 10^{-14}$). The convergent gene set was further enriched for schizophrenia ($P = 2.7 \times 10^{-5}$), neurodevelopmental disorder ($P = 5.0 \times 10^{-5}$), and intellectual disability gene lists ($P = 4.6 \times 10^{-2}$). Structural analyses identified spatially clustered damaging missense variants in KDM5B and DOP1A suggesting focal disruption of neuronal calcium and signaling domains.

Conclusion: BipEx reveals 13 BD risk genes and convergent synaptic and neurodevelopmental pathways across variant classes, implicating shared glutamatergic and calcium-signaling mechanisms that bridge rare variant architecture in BD and related psychiatric disorders.

M16. Reward Expectancy-Related Left Ventrolateral and Right Dorsolateral Prefrontal Cortical Functional Connectivity is Differentially Associated With Depression and Mania Risk, Replication in Two Samples

Manan Arora, Western Psychiatric Hospital

Background: Mania/hypomania is the pathognomonic feature of bipolar-disorder(BD), and is characterized by elevated reward-sensitivity, goal-overvaluation, impulsivity and sensation-seeking. Unfortunately, BD is often misdiagnosed as major-depressive-disorder(MDD). Replicable neural markers of mania-risk are needed for earlier BD diagnosis and pathophysiologically based treatment development. We previously showed that reward-expectancy(RE) related left-ventrolateral-prefrontal-cortex(L-vlPFC) activity is associated with higher mania-risk, with this relationship being specific to mania, and not common to depression-risk, but it is unknown whether this pattern of elevated-activity is accompanied by elevated functional-connectivity(FC) with regions in the reward, executive and other neural-networks.

Methods: In a discovery-sample of 171 non-BD individuals(mean-age=23.7±3.4years), 2 whole-brain regressions identified regions where RE-related FC with the L-vlPFC seed was associated with lifetime depression or mania-risk(MOODS-SR -Lifetime-Total-Manic or Depressive-Domain-Scores), controlling for the alternate risk-domain. Age, sex, education, and mean-framewise-displacement were covariates. Significant clusters were used to extract FC-parameters for replication in an independent Test-sample(n=231;mean-age=21.7±2.1years) using Poisson-loglinear regression models with the same covariates.

Results: In the discovery-sample, greater RE-related L-vlPFC–right dorsolateral prefrontal cortex(R-dlPFC) FC was associated with higher depression-risk(cluster-level Pfwe<0.05;peakT=4.09,kE=133,MNI=34,50,30). No significant clusters were associated with mania-risk. However, extracted FC-parameters showed a negative association with mania-risk(β=–0.12,qFDR< 0.001). In the test-sample, this pattern replicated: L-vlPFC–R-dlPFC FC positively predicted depression-risk(β=0.03,qFDR=0.012) and negatively predicted mania-risk(β=–0.04,qFDR=0.012).

Conclusion: RE-related L-vlPFC–R-dlPFC FC differentially predicts mania and depression-risk across independent-samples, showing positive associations with depression-risk and negative with mania-risk. The R-dlPFC, a central-executive-network-hub involved in cognitive-control and affect-regulation, exerts greater top-down regulation of reward-related L-vlPFC processes in individuals at higher depression-risk, while reduced integration may characterize mania-risk

M17. Adolescent Circadian Rhythm Disruption Leads to Increased Risk-Taking and Transcriptional Changes in Adulthood

Kaitlyn Petersen, University of Pittsburgh School of Medicine

Background: Circadian rhythm disturbances have long been associated with the development of psychiatric disorders, including mood and substance use disorders. Adolescence is a particularly vulnerable time for the onset of psychiatric disorders and for circadian rhythm disruptions (CRD). The goal of this study was to determine the long-term effects of adolescent CRD.

Methods: We exposed mice to four 12 h shifts in the light/dark cycle over the course of adolescence (P28-P37). 4 weeks following the last shift, mice either underwent behavioral testing or were sacrificed across 4 times of day for RNA sequencing. To identify possible mechanisms by which CRD during adolescence affects behavior later in life, we measured gene expression in the SCN, PFC and NAc, respectively.

Results: We first identified that adolescent CRD alters behavior later in life, namely increasing reward and risk-taking. We measured differential expression (DE) between control and adolescent CRD mice across time of day in male and female mice and found that the transcripts affected by CRD were largely distinct across time, sex, and brain region. The SCN was particularly affected, with the most DE transcripts identified at $q<0.05$. These transcripts were largely involved in circadian rhythms, adipogenesis, and intracellular signaling. Downstream of the SCN we also observed significant changes in the PFC of males at ZT0. Transcripts with altered gene expression were associated with neuronal activity, translation, and the extracellular matrix.

Conclusion: Overall, these studies suggested that adolescent CRD in mice is sufficient to persistently increase risk-taking behavior and alter gene expression long-term.

M18. Age of Onset and Co-morbidity of Binge Eating With Alcohol Use Disorder and Suicide in American Indian and Mexican American Young Adults: Genetic Correlation With GLP-1 and NBEA

Cindy Ehlers, The Scripps Research Institute

Background: Binge eating and binge drinking may have common neuro-substrates that are both impacted by GLP-1 therapies. This study documented the age of onset and comorbidity of binge eating in young adult Mexican and American Indians (age 18-30 yrs). Methods: The AI participants resided on reservations, MA participants resided in San Diego County. Each participant completed an interview with the Semi- Structured Assessment for the Genetics of Alcoholism and a blood sample was collected. They were also queried as to: How old were you when you first went on an eating binge? And to whether they: went on eating binges as often as twice a week for at least 3 months (DSM-4 binge eating disorder). Out of 1280 participants 286 reported binge eating. Results: Those with binge eating were significantly more likely to have: alcohol use disorder, anxiety disorder, affective disorder and suicidal thoughts and acts (all $p<0.0001$, Odds Ratios: 2.7-3.0). Those who began binging under the age of 15 were more likely to develop binge eating disorder ($p<0.009$). A genome scan of the GLP1A and NBEA genes phenotype was significant in the American Indians (GLP1R: 1.27 kb downstream $p<0.02$; NBEA 21.3 kbp downstream $p<0.004$) and Mexican Americans (GLP1R: intron $p<0.003$; NBEA intron $p<0.05$). Conclusions: These data suggest that binge eating has a genetic component ,early age of onset can lead to eating disorders, is comorbid with substance abuse and affective/anxiety disorders in Mexican and American Indian young adults, suggesting screening for this phenotype in these racial groups (AA027316; AA026248).

M19. Altered Functional Connectivity and Expression of Neuroimmune Proteins in the Amygdala and Prefrontal Cortex in a Nonhuman Primate Model of Maternal Immune Activation

Kari Hanson, University of California-Davis

Background: Preclinical models highlight pathways by which exposure to maternal immune activation (MIA) in gestation may alter offspring neurodevelopment and behavior. Previous research in our Poly-IC-based rhesus macaque model has demonstrated reduced prefrontal cortex (PFC) volumes, altered neuronal morphology, and dysregulated synaptic gene expression in MIA-exposed offspring.

Methods: Male offspring of rhesus macaque dams that received either Poly-IC or saline during the first trimester were scanned using a Siemens Skyra 3T MRI scanner. Data were processed using HCP minimal preprocessing pipelines. Functional connectivity matrices were computed using 82 brain regions and analyzed using Pearson correlations. Multiplexed bead assays were used to measure 48 brain cytokines, chemokines, and growth factors in these animals in 3 subregions of the amygdala, caudate, entorhinal cortex, and prefrontal cortex.

Results: Functional connectivity results suggest reduced age-related increases in amygdala connectivity in MIA-exposed NHPs compared to controls. We found increased TGF-α in the entorhinal cortex and accessory basal nucleus of the amygdala, as well as trend-level increases in TGF-α in basal amygdala, increased IL-21 in white matter, and decreased IL-5 in the lateral nucleus of the amygdala in MIA-exposed NHPs. In the PFC, mixed profiles of cytokine expression were observed, with significant increases in FGF-2 and trend-level increases in TGF-α observed in DLPFC. Significant heterogeneity in brain cytokine levels were observed across regions.

Conclusions: Taken together, our results support the hypothesis that prenatal MIA exposure results in lifelong changes in prefrontal and amygdala circuitry that contribute to aberrant social behavior observed in MIA-exposed NHP offspring.

M20. Crossing the Barrier: Decoding Brain–Immune Communication in Living Humans

Nicole Bussola, Icahn School of Medicine At Mount Sinai

Background: The central nervous system (CNS) has long been regarded as segregated from the peripheral immune system, protected by the blood–brain barrier (BBB). Yet, under pathological conditions—where BBB integrity is compromised—peripheral immune cells can infiltrate the brain. Despite emerging evidence of such interactions, key questions remain unresolved: Which circulating immune cells traverse the BBB? How do they reprogram within the brain microenvironment? And what are the molecular mechanisms guiding their communication with brain-resident cells?

Methods: We examined single-cell and bulk RNA sequencing data from 259 matched blood and brain samples obtained through the Living Brain Project at Mount Sinai. Analyses encompassed cell composition, differential gene expression, pathway activity (PROGENy) to characterize the adaptation of brain-infiltrating immune cells. Furthermore, we implemented Tensor-S2R, a data-driven framework that integrates cell–cell communication inference (LIANA), tensor decomposition (Tensor-cell2cell), and downstream ligand–receptor analysis to identify coordinated signaling programs bridging brain and blood cell types.

Results: Our findings reveal that specific blood immune cell types can penetrate the BBB and display unique transcriptional and signaling adaptations within the brain. Moreover, we uncovered a tri-cellular communication module involving monocytes, neurons, and microglia that regulates both the propagation and resolution of inflammation. Selected interactions were validated experimentally in a mouse model.

Conclusions: This work provides direct evidence for coordinated communication between the brain and peripheral immune systems in living humans. Our study delineates the molecular foundations of neuroimmune crosstalk, offering new opportunities for the development of non-invasive biomarkers for neurodegenerative and neuroinflammatory disorders.

M21. Establishment and Characterization of Humanized Mice Expressing DRD4 Variants D4.4 and D4.7

Angela Reiersen, Washington University School of Medicine

Background: The two most common human dopamine receptor D4 gene (DRD4) exon 3 variable number of tandem repeat (VNTR) variants are the 4-repeat (D4.4) and 7-repeat (D4.7) alleles. Genetic studies suggest an association between D4.7 and Attention-Deficit/Hyperactivity Disorder (ADHD), substance use disorders, and other impulse-control-related phenotypes.

Methods: We created mice with human D4.4 or D4.7 alleles, characterized them using molecular methods, and performed behavioral testing to assess ADHD-like mouse behavior phenotypes, with and without pre-exposure to nicotine.

Results: Knock-in D4.4 and D4.7 mRNA brain distribution mirrored wild type (WT) mouse D4 mRNA distribution. Early studies using heterozygous mice suggested WT/D4.7 mice (n=7) exhibited increased rearing (p=0.006) and time in center (p=0.031) behaviors compared to WT/D4.4 (n=6). Compared to 15 WT mice, 15 homozygous D4.4 mice showed increased ambulatory activity overall (overall ANOVA genotype effect p=0.026) and during the light phase when mice are naturally less active (light phase p=0.015), but not significantly during the dark phase (p=0.063). The genotype effect was not significant after exposure to nicotine, suggesting nicotine may at least partially reverse the effect. There were no significant differences in rearing frequency involving genotype or nicotine treatment.

Conclusions: Humanized D4.4 mice show increased activity level compared to wildtype mice, which could be consistent with an ADHD-like phenotype or simply reflect species differences. Future planned studies include comparison of homozygous D4.4 mice to homozygous D4.7 mice to determine whether D4.7 mice have even higher activity level, and to determine whether the effect of nicotine exposure differs depending on genotype.

M22. Integrating Kinase Signaling Networks during Homeostatic Plasticity

Emily Brown, University of Washington

Background: The PI3K/mTOR signaling network regulates neurodevelopment, synaptic plasticity, and local dendritic protein translation. Hyperactive mTOR signaling contributes to several neurodevelopmental and psychiatric disorders, including autism spectrum disorders, but so far clinical trials using mTOR inhibitors to treat patients with PI3K/mTOR-related gene mutations have been unsuccessful. To clarify how neuronal signaling is disrupted by PTEN mutation, we investigated both synaptic and mTOR signaling network dynamics during homeostatic scaling in a mouse model of PTEN haploinsufficiency.

Methods: We prepared primary cortical neurons from neonatal wildtype and PTEN+/- mice. Beginning at 18 days in vitro, we treated neurons with tetrodotoxin or bicuculline for 48 h to induce homeostatic upscaling or downscaling, respectively. We performed quantitative multiplex immunoprecipitation of both glutamate postsynaptic and mTOR-related protein complexes to examine network-level signaling disruption in PTEN+/- mice after scaling.

Results: In PTEN +/- neurons, the response of the postsynaptic signaling network to both up and downscaling was dramatically impaired. Surprisingly, the mTOR signaling network response to scaling appeared largely normal in PTEN +/- neurons despite PTEN's direct opposition to PI3K in the PI3K/mTOR pathway.

Conclusion: These findings suggest that the neurological manifestations of PTEN haploinsufficiency cannot be explained solely by mTOR disinhibition. Instead, PTEN may regulate synaptic signaling through mTOR-independent mechanisms—such as FAK/ERK or AKT/GSK3 pathways—or through direct interactions with postsynaptic scaffolds via its PDZ-binding domain. Alternatively, impaired synaptic scaling in PTEN+/- neurons may represent a compensatory feedback mechanism maintaining mTOR homeostasis despite upstream dysregulation.

M23. Next-Generation Precision Medicine for Pain

Alexander Niculescu, University of Arizona, College of Medicine- Phoenix

Background: Chronic pain remains a massive problem in society in general, and in mental health patients in particular, being strongly bi-directionally connected to mental health. Lack of widespread use of objective information has hampered treatment and prevention efforts. Blood biomarkers that track pain severity can provide a window into the biology of pain, as well as could help with assessment and treatment.

Methods: Here we describe new studies we conducted trans-diagnostically in psychiatric patients, starting with the whole genome, to expand the identification, prioritization, validation and testing of blood gene expression biomarkers for pain. We carried out two separate studies, on two different platforms, microarrays and RNA sequencing, using for each study a multiple independent cohorts design. This ensured biological and technical reproducibility. We then focused at the end on biomarkers that were convergent and reproducible between the two studies.

Results: We found new as well as previously known biomarkers that were predictive of high pain states, and of future emergency department visits related to them. The top biological pathways were related to cellular response to TNF and to neuroinflammation. Drug repurposing bioinformatic analyses identified the potential of carvedilol, sirolimus, budesonide, berbamine, and quetiapine. Additionally, we show how personalized patient reports for doctors would look like based on blood biomarkers testing, to aid with objective assessment, as well with individualized matching to medications and nutraceuticals.

Conclusion: There is an urgent need for insights and tools such as the ones we have developed to be applied to and improve clinical practice.

M25. Effects of D-cycloserine and Accelerated TMS on Resting-State EEG

Hakjoo Kim, Harvard Medical School, McLean Hospital

Background: D-cycloserine (DCS) has been shown to enhance corticospinal excitability when combined with transcranial magnetic stimulation (TMS). However, whether DCS combined with accelerated TMS (aTMS) increases cortical excitability remains unclear. This study investigated the combined effects of DCS and aTMS on cortical excitability and network synchronization using resting-state electroencephalography (rsEEG).

Methods: 10 participants with depression, anxiety, or trauma-related disorders were randomly assigned to one of three groups: DCS (100 mg)+aTMS, Placebo+aTMS, or Placebo+Sham TMS. aTMS was administered at the left dorsolateral prefrontal cortex (DLPFC) at 100% of the resting motor threshold, and the stimulation sessions were repeated hourly, 10 times per day for three days. rsEEG data were collected for 10 minutes (eyes closed/open, 5 min each), prior to the first TMS session and following the last TMS session. Power and coherence analyses were performed.

Results: In the DCS+aTMS group, band power decreased across all frequency bands in the right DLPFC after three days of aTMS. In contrast, the Placebo+aTMS group showed an increase in band power in the left DLPFC, whereas the Placebo+Sham TMS group exhibited an increase in the posterior region. Coherence analysis indicated that, in both the Placebo+aTMS and DCS+aTMS groups, theta-band coherence increased at the left DLPFC, after the first day of aTMS.

Conclusion: These findings suggest that DCS with aTMS may induce region-specific changes in cortical excitability and functional connectivity, particularly in the DLPFC. The changes indicate potential synergistic effects on neuroplastic processes. Further studies with larger samples are needed to confirm these preliminary findings.

M27. TrkB/mGluR5 Crosstalk Underlies a Synaptic Metaplasticity Mechanism of Ketamine

Anisul Arefin, Weill Cornell Medical College

Background: Many forms of synaptic plasticity drive the behavioral state changes associated with antidepressant drug action. These modes of plasticity are mediated by the interplay between an ensemble of membrane receptors; however, understanding of how these receptors functionally interact to drive synaptic plasticity is limited.

Methods: This study utilized techniques ranging from heterologous and primary tissue culture, microscopy, ex-vivo slice electrophysiology, and behavioral pharmacology.

Results: Here, we find that the Brain-Derived Neurotrophic Factor (BDNF)-dependent antidepressant action of ketamine relies on the functional interaction between the receptor tyrosine kinase TrkB, and the metabotropic glutamate receptor 5 (mGluR5), a G Protein-Coupled Receptor. First, mGluR5 amplifies BDNF-driven signaling of TrkB, enabling synaptic potentiation via "signaling crosstalk." At longer timescales, BDNF activation of TrkB drives mGluR5 endocytosis via "trafficking crosstalk" which impairs synaptic depression in a form of metaplasticity. Ketamine enhances these two modes of crosstalk by boosting TrkB surface levels. Finally, we find that an mGluR5 positive allosteric modulator can further enhance both modes of crosstalk and boost antidepressant-like effects of ketamine.

Conclusion: Together, these data unravel the intimate relationship between different classes of neuromodulatory receptors, revealing that intricate receptor-receptor interaction drives therapeutic action.

M28. Pre-Treatment Microstates and Response to Antipsychotic Drugs in First Episode Psychosis

Wadim Vodovozov, Zucker Hillside Hospital

About 40% of individuals with first episode psychosis fail their first antipsychotic trial, which is associated with greater danger to self/others and treatment disengagement. Predictive biomarkers could inform treatment selection and minimize failed trials. Important progress has been made using fMRI, however predictive biomarkers using methods easier to scale are lacking. We acquired EEG in 56 individuals prior to their first treatment for psychosis, consisting in 12 weeks of antipsychotic treatment. A follow-up EEG was recorded at week 12 for 36 participants. We obtained microstates for each EEG acquisition. We examined whether pre-treatment microstate features (coverage, mean duration, explained variance, occurrence) associated with treatment response at week 12, whether these features informed an individual predictive model of treatment response, and whether changes with treatment in the most predictive microstate feature scaled with symptom improvement. A modified k-mean analysis produced six microstates which included four widely reported topographies (A-D). Several pre-treatment microstate features were predictive of treatment response, being mean duration of microstate A of the largest magnitude (OR=2.74, 95% confidence interval: 1.77-4.25). The individual predictive model had a mean area under the curve of 74.9% (p=0.01), being mean duration of microstate A the most predictive feature. Change in the mean duration of microstate A with antipsychotic treatment scaled with symptom improvement (p=0.03). EEG derived microstates are sensitive to treatment response and are a promising tool for personalized medicine in schizophrenia. Mean duration of microstate A, related to sensory processing, may be particularly relevant for antipsychotic effects.

M31. Neuromelanin Accumulation and Treatment Responsiveness in Patients With Schizophrenia: A Cross-Sectional Study with Neuromelanin-Sensitive MRI

Fumihiko Ueno, University of Ottawa

Background: Neuromelanin (NM), a byproduct of monoaminergic metabolism, accumulates in the substantia nigra/ventral tegmental area (SN-VTA) and locus coeruleus (LC), serving as a proxy of long-term dopaminergic and noradrenergic activity. Neuromelanin-sensitive MRI (NM-MRI) enables in vivo quantification of NM levels in these nuclei. Presynaptic dopamine dysfunction is a hallmark of schizophrenia and may influence responsiveness to antipsychotics. Clozapine remains the only proven treatment for treatment-resistant schizophrenia (TRS), yet many patients remain unresponsive (ultra-

resistant schizophrenia; URS). The relationship between clozapine response and NM-MRI markers, however, remains unclear.

Methods: We conducted a cross-sectional study including patients with URS (n=16), clozapine-responsive TRS (non-URS, n=16), first-line antipsychotics responsive patients (FLR, n=20), and healthy controls (HCs, n=26). NM-MRI was used to quantify NM signals as contrast ratios (CR) in the SN-VTA and LC. Group comparisons controlled for age and sex with corrections for multiple testing, and voxel-wise analyses were conducted to localize significant SN-VTA differences.

Results: Both URS and FLR groups showed significantly elevated SN-VTA CR compared with HCs, with voxel-wise analyses revealing signal increases in the dorsal SN-VTA. In the LC, the URS group showed higher CR than FLR, although differences between URS and HCs were not significant. No associations were found between NM-MRI signals and clinical or cognitive measures.

Conclusions: These findings suggest that dopaminergic hyperactivity may characterize both URS and FLR, while additional noradrenergic alterations may be present in URS. Overall, the results should be regarded as preliminary, but NM-MRI may represent a promising non-invasive tool for investigating heterogeneity in schizophrenia.

M32. Trio Haploinsufficiency Connects Schizophrenia Genetic Risk to Hippocampal Circuit Dysfunction

Ariel Cohen, University of Southern California

Background: Hippocampal dysfunction is one of the most robust findings in schizophrenia (SCZ), yet the molecular and circuit-level mechanisms driving this pathology remain poorly understood. Despite decades of imaging and clinical studies, how genetic risk translates into hippocampal circuit disruption in SCZ is largely unknown. TRIO is one of only ten genes to achieve genome-wide significance for SCZ risk, underscoring its importance for disease biology. Intriguingly, TRIO mutations also confer risk for autism spectrum disorders (ASD), though with distinct molecular consequences: SCZ-associated variants reduce Trio protein expression (haploinsufficiency), whereas ASD-associated variants selectively impact Rac1 activation without affecting expression levels.

Methods: To examine how SCZ-relevant TRIO mutations perturb hippocampal circuits, we used miniature endoscopic calcium imaging (miniscopes) in freely behaving mice. Adeno-associated viruses encoding the calcium indicator GCaMP6f under the CaMKII promoter were injected into the dorsal CA1 (dCA1) region, followed by GRIN lens implantation for chronic imaging. After recovery, neuronal activity was recorded during behavioral tasks. Imaging data were processed using Minian, a CNMF-E–based pipeline, and further analyzed with NeuroActivityToolkit and CEBRA. Behavioral tracking and analysis were performed using DeepLabCut and SimBA.

Results: Preliminary findings reveal that Trio haploinsufficiency disrupts correlated neuronal activity in CA1, providing a mechanistic link between TRIO loss-of-function and SCZ-relevant hippocampal circuit dysfunction.

Conclusion: These findings address a critical gap in our understanding of hippocampal pathophysiology in SCZ and set the stage for future studies examining how distinct TRIO mutations contribute to divergent psychiatric outcomes.

M34. Sex-Specific Associations of Prenatal Superstorm Sandy Exposure on Steroid Hormone Trajectories

Melissa Blum, Queens College, City University of New York

Background: Pregnancy represents a sensitive period during which maternal stress can shape long-term child neurodevelopment through reprogramming of the hypothalamic-pituitary-adrenal (HPA) and -gonadal (HPG) axes, with potential for sex-specific vulnerabilities. We examined sex-specific effects of prenatal psychosocial stress on steroid hormone trajectories from early childhood through adolescence using the paradigm of quasi-experimental exposure to Superstorm Sandy (SS) in utero.

Methods: Data were drawn from the Stress in Pregnancy Study (n = 341), a longitudinal study following mother-child dyads annually from pregnancy through adolescence. SS-exposed children were in utero when SS struck New York City in 2012. Steroid hormones (cortisol, cortisone, testosterone, progesterone, dehydroepiandrosterone [DHEA], and estradiol) were assayed from hair samples collected between ages 1.5 and 14 years. Hierarchical linear models estimated SS effects on hormone trajectories (intercept, linear, and quadratic terms) overall and stratified by sex.

Results: SS-exposed children had lower progesterone ($p=.04$) and DHEA levels ($p<.001$) at age 3, a stable, sex-neutral baseline for HPA and HPG axis activity. SS exposure was associated with an increased quadratic term for cortisone ($p=.01$), reflecting a steeper decline from 1.5 years to a trough around ages 8-9, followed by a sharper rise during puberty. Sex-stratified models revealed stronger reductions in progesterone and DHEA at age 3 among SS-exposed males, while associations with cortisone were similar across sexes.

Conclusions: SS exposure is linked to altered steroid hormone trajectories, particularly among males, suggesting sex-specific vulnerability. These findings underscore the need to examine steroid hormones as mediators of the neurodevelopmental impacts of climate-related disasters.

M35. Single-Nucleus Multiome Atlas of the Human Medial Amygdala Reveals Cell Type-Specific Molecular Alterations in the PTSD Brain

Jiawei Wang, Yale School of Medicine

Post-traumatic stress disorder (PTSD) is a prevalent and debilitating psychiatric condition, yet the molecular mechanisms by which the amygdala—specifically the medial amygdala—contribute to trauma-related pathology remain a major research gap. Medial amygdala is essential in processing threat and emotional stimuli, especially fear and stress signals, and has been reported to show transcriptomic changes in response to PTSD. Here we present the findings of a large-scale singlenucleus multiomic study profiling over 1 million nuclei from the medial amygdala (MeA) of 105 human postmortem brains, including individuals with and without PTSD, with major depressive disorder (MDD) as a psychiatric control group. By analyzing the single cell transcriptomic data, we defined distinct neuronal and non-neuronal cell clusters and generated a high-resolution cell type atlas with marker genes for the human medial amygdala. We further identified cell type-specific gene expression changes associated with PTSD. Notably, we uncovered PTSD-associated differentially expressed genes in subtypes of excitatory neurons, as well as astrocytes, implicating pathways related to synaptic signaling and gliogenesis. We identify alterations in cell-to-cell communication in the subtypes of excitatory neurons. Overall, this study provides a comprehensive cell type-resolved map of molecular alteration in the MeA, offering new insights into the transcriptomic architecture of PTSD on the single-cell level within fear-related neural circuits.

M37. Stress Reactivity in Emerging Adults: Age-Related Differences in Trajectories of Neutrophils and Lymphocytes After Acute Social Stress

Jill Åhs, Karolinska Institutet

Background: Exposure to stress impacts risk for anxiety and depressive disorders. These disorders commonly emerge during early adulthood which could be related to immune function. We explored differences in responses of neutrophils and lymphocytes to acute social stress across early adulthood.

Methods: This study examined how participants 18–29 years of age (n=260) respond to acute social stress. Responses to the Trier Social Stress Test were assessed by participant age for markers including neutrophil and lymphocyte counts before, as well as 5, 30, 60 and 90 minutes following stress. Cortisol levels were assessed before, 5 and 30 minutes after stress.

Results: There is a significant interaction of age and time on neutrophils. Base line numbers of neutrophils were similar in younger and older ages, but there was a steeper increase younger than older people 30 to 90 minutes after stress. Younger individuals had greater cortisol levels than older participants across measurements and larger stress-induced cortisol response. Younger people also have more lymphocytes in general than older people. No effect of age on change in lymphocytes after stress was noted. There was an interaction between age and time after stress on Neutrophil-to-lymphocyte ratio. Younger have a less steep change from before to directly after stress, but a steeper change between directly after stress and 90 minutes after stress.

Conclusion: Stress reactivity of neutrophils differs across development. Studying changes in stress reactivity may help inform understanding of how immune function is linked with age differences in prevalence of anxiety and depression.

M39. Early Life Programming of Substance Use Risk: From Placental Stress Genes to Infant Temperament

Claire Brabander, Queens College and Graduate Center, CUNY

The placenta plays a critical role in regulating fetal glucocorticoid exposure and ultimately infant neurodevelopment. Understanding the association of HPA-axis gene expression with child temperament is crucial as emotional dysregulation and heightened reward sensitivity have been linked to increased susceptibility for early substance use initiation. This study analyzed HPA-axis gene expression in placental tissues collected at birth from a subsample of 219 mother-child dyads. Factor analysis identified two distinct gene clusters associated with HPA-axis functioning. The first factor (reliability=0.72) comprised 11β-HSD2, NR3C1, and DYRK1A, while the second factor (reliability=0.87) included CFL1, NCOR1, and NR3C1. The associations between these HPA-axis-related placenta gene clusters and infant temperament were assessed longitudinally at five timepoints between 6 and 36 months of age, with analyses stratified by child sex. We hypothesized that both factors would be associated with emotional difficulties and that boys would be more vulnerable to in-utero HPA-axis dysregulation. Lower expression of HPA factor 1 genes significantly reduced high intensity pleasure (p=.044) in both sexes and effortful control (p=.014) in males only. Lower expression of the HPA factor 2 genes was associated with decreased effortful control (p=.024) and increased sadness (p=.034) in both sexes, while decreased effortful control (p=.010) and increased negative affectivity (p=.014) was observed in males only. Results demonstrated the relationship between HPA-axis regulation and sensation-seeking temperaments, underscoring the importance of placental HPA-axis functioning as a potential early life marker for later substance use vulnerability. Males with lower HPA-axis gene expression may have temperaments more susceptible to early substance use.

M40. Ethanol Regulation of D1 Striatonigral Presynaptic Ca^{2+} Signaling and SNr Activity

Lee Peyton, NIH/NIAAA

Background: Ethanol alters basal ganglia processing, yet its specific effects on direct pathway striatonigral communication remain poorly understood. The mechanisms by which ethanol modulates

presynaptic Ca^{2+} dynamics in D1-expressing striatal projection neuron (SPN) terminals; and how these changes translate to downstream substantia nigra pars reticulata (SNr) output are largely unknown. Identifying these circuit-level actions is essential for understanding how ethanol impacts action selection and motivated behavior.

Methods: To monitor presynaptic Ca^{2+} activity, D1-Cre mice received a synaptophysin-tagged GCaMP viral construct targeting striatonigral terminals. Acute midbrain slices were loaded with Calbryte-520 AM to record Ca^{2+} activity from SNr output neurons. Slice photometry was performed while locally applying electrical stimulation to evoke D1 terminal signaling and SNr responses. Ethanol was dose-dependently bath-applied to assess its effects on presynaptic Ca^{2+} entry and downstream circuit output.

Results: Ethanol produced robust modulation of D1 presynaptic Ca^{2+} signals, altering the amplitude and kinetics of stimulation-evoked synaptophysin-GCaMP responses. Parallel measurements showed corresponding changes in SNr Calbryte signals, indicating ethanol-dependent shifts in direct-pathway output. The relationship between altered presynaptic Ca^{2+} entry and SNr activity suggests that ethanol acts at a presynaptic locus to reshape striatonigral communication.

Conclusions: These findings demonstrate that ethanol alters D1 striatonigral presynaptic Ca^{2+} signaling with measurable consequences for SNr output. This work suggests a potential mechanistic point of ethanol action within basal ganglia circuitry and provides a framework for understanding ethanol-induced alterations in motor and motivational processes.

M43. Behavioral Phenotypes and Brain-Wide Functional Network Changes in a Mouse Model of Passive Electronic Cigarette Inhalation

Selene Bonnet-Zahedi, Aix-Marseille University, France

Although several circuits mediating nicotine addiction-like behaviors are well characterized, the brain-wide impact of nicotine vaping remains unresolved. These unanswered questions persist due to the lack of high-resolution, whole-brain mapping of neuronal activity across distinct stages of nicotine use, including single intoxication, dependence, and withdrawal

Transgenic mice expressing tdTomato in cholinergic neurons were exposed to passive nicotine vapor (15 mg/mL in 1:1 propylene glycol/vegetable glycerin, PG/VG), PG/VG vehicle, or air under three paradigms: a single 1-hour exposure, chronic exposure (3 × 1h/day, 5 days/week for 3 weeks), or acute withdrawal (24h after the final exposure). We quantified locomotion, anxiety-like behavior, nociception, temperature and body weight. Brains were collected, PFA-fixed, cleared with iDISCO+, and immunolabeled for Fos and RFP.

Both PG/VG and nicotine increased locomotion after a single exposure, with a stronger nicotine effect. Chronic exposure reduced locomotion and body temperature, increased anxiety-like behavior, and decreased analgesia and weight gain. During withdrawal, locomotion and temperature normalized, whereas anxiety and hyperalgesia intensified, accompanied by partial rebound in body weight. Pulse oximetry revealed acute nicotine-induced decreases in oxygen saturation and heart rate, with partial physiological tolerance after chronic exposure but persistent respiratory suppression.

These results validate the model by demonstrating stage-specific, addiction-relevant behavioral alterations and the effect of PG/VG vapor alone. Whole-brain Fos mapping with light-sheet microscopy and cholinergic neuron labeling, has yielded single-cell resolution datasets. Ongoing network analyses aim to correlate functional connectivity with behavioral phenotypes to identify novel biomarkers and therapeutic targets for nicotine use disorder.

Tuesday, March 31, 2026

T1. Autistic Individuals Display Altered Neuroimmune Protein and Gene Expression Within Entorhinal Cortex

Evan Haley, U.C. Davis, MIND Institute; Cell Biology and Human Anatomy, University of California, Davis, Sacramento, CA

Background: Autism spectrum disorder (ASD) is a behaviorally defined neurodevelopmental disorder characterized by restricted interests, repetitive behaviors, and socioemotional difficulties. The pathophysiology of ASD is still unknown, but evidence suggests neuroinflammation as a central component. There is a gap in knowledge concerning how the molecular pathways involved in ASD change across the lifespan. This study identifies changes in neuroimmune pathways in autistic adults in the entorhinal cortex (ERC), a region principally involved in aging.

Methods: Fresh-frozen postmortem samples from 40 controls (CTRL) and 28 ASD cases were collected utilizing the expansive biorepository available through Autism BrainNet. For protein analyses, samples were lysed and entered a 48-plex bead immunoassay to detect cytokines, chemokines, and growth factors. Values were normalized to total protein concentration via BCA assay. For gene expression analyses, additional samples were homogenized and evaluated using a QuantiGene Plex Assay. This assay probed 70 different neuroimmune-related genes. Gene expression was normalized to the geometric mean of housekeeper genes.

Results: ASD cases exhibited altered levels of several proteins, including elevated cytokines IL-12(p40), IL-1RA, and fractalkine. FGF-2, a growth factor, was also increased in ASD. IL-18, a pro-inflammatory cytokine, showed a significant age-related trend between ASD and CTRL cases, indicating significantly different aging trajectories. Gene expression analyses also showcase altered neuroimmune pathways including NF-kB, JAK/STAT, and AP-1 mediated neuroinflammation.

Conclusion: Together, these data support the role of neuroinflammation within the ASD entorhinal cortex, and that these changes persist throughout adulthood underscoring the need for identifying immune-related targets that could inform therapeutic targets.

T2. Clinical and Neurobiological Significance of Comorbid ASD in Early Psychosis

Cameron Carter, University of California, Irvine School of Medicine

Despite advances in understanding the mechanisms and causes of psychotic disorders, they have increased in prevalence and remain a major cause of suffering and disability. Early intervention improves outcomes but up to 40% of early psychosis (EP) individuals have a poor treatment response. A potentially important source of heterogeneity in EP is the presence of comorbid autism spectrum disorders (ASD), yet the clinical impact and underlying neurobiology have received relatively little attention. An initial, study by our group showed that more than 20% of EP referrals have ASD. The present study is a systematic analysis of subjects entering EP care. In addition to clinical assessments we investigated neurobiological differences between EP subjects with and without ASD, using the neuromelanin (NM) contrast, a proxy measure of dopamine activity in the midbrain. Compared to EP, ASDEP had higher BPRS scores at baseline ($p < 0.05$) and follow up ($p < 0.05$), higher negative symptoms ($p < 0.05$), and lower GAF scores ($p < 0.05$) at follow-up . There were no differences in positive symptoms. Initial analysis revealed that ASDEP had lower NM in the SN (p=.03)) than EP. These findings add an important new dimension to understanding heterogeneity in EP by identifying unique clinical and neurobiological differences in EP patients with and without comorbid ASD. They

help shed new light on a common but neglected aspect of the heterogeneity of EP and may inform the development of more targeted assessments and treatments.

T3. Contributions of mTORC2 and AKT to Neuronal Hypertrophy in PTEN-Driven Neurodevelopmental Disorders

Mackenzi Prina, The University of Alabama At Birmingham

Mutations to phosphatase and tensin homolog (PTEN) are a known contributor to Autism Spectrum Disorder (ASD), macrocephaly, and epilepsy. PTEN negatively regulates the mTOR signaling pathway. Pten knockout (KO) mouse models exhibit neuronal hypertrophy, hyperexcitability, seizures, and ASD-like behaviors. Using transgenic mouse lines and retroviral-mediated genetic alterations, we can analyze pathway outputs in response to the manipulation of various genes. In doing so, we have characterized the interplay between mTORC2 and AKT as the specific downstream signaling intermediates driving Pten-loss- induced neuronal hypertrophy through mTORC1 activation. We are investigating AKT isoform-specific roles and their contributions to this phenotype. Understanding the interactions of the downstream effectors within the mTOR pathway and how these differ in patients with ASD, macrocephaly, hydrocephalus, and epilepsy will broaden the knowledge of these disease pathologies and identifies potential therapeutic targets.

T5. Identification of Stimulus-Dependent Mechanisms in 16p11.2 Deletion Syndrome Using Cell Villages

Rachel Fox, David Geffen School of Medicine, Los Angeles, CA

Background: Heterozygous proximal deletion of chromosome 16p11.2 (16pdel) accounts for ~0.5% of autism spectrum disorder (ASD) cases and often co-occurs with macrocephaly, language delay, and obesity. Though 16pdel is a strong genetic risk factor for ASD, the molecular mechanisms driving clinical phenotypes remain unknown and no clear therapeutic targets have been identified. Macrocephaly and region-specific brain overgrowth implicate neural progenitor cell (NPC) hyperproliferation and neurogenesis defects. To properly establish regional identity and cell type proportions, NPCs must respond to tightly-regulated signaling pathways, including SHH and WNT. The extent to which disrupted signaling response drives downstream dysfunction in 16pdel has not been interrogated.

Methods: To interrogate baseline and stimulus-dependent gene expression, we generated a multiplexed “cell village” of human NPCs, including 16pdel (n=11), 16pdup (n = 6), and unaffected controls (n = 21). Replicate village wells were treated with vehicle, the SHH-pathway agonist SAG, or WNT-pathway agonist CHIR99021, followed by single-cell RNA sequencing. Differentially expressed genes were identified using Dreamlet and gene expression modules were identified with weighted gene co-expression network analysis (WGCNA).

Results: Baseline conditions revealed modest transcriptional differences between 16pdel and controls. Meanwhile, SAG treatment revealed strong context-specific differences in 16pdels, including hypersensitivity to the SHH pathway itself. Both differentially expressed genes and expression modules presented a signature of SHH hyperactivation in 16pdel cells.

Conclusion: The cell village platform allows a scalable method to observe 16pdel-associated molecular dysfunction. Dysregulated SHH response in 16pdel may disrupt proliferation, differentiation, and dorsal-ventral patterning, presenting a link to clinical phenotypes like macrocephaly.

T6. Investigating the Role of Iron Deficiency on Neural Development in 3q29 Deletion Syndrome

Allyson Herriges, Fralin Biomedical Research Institute at Virginia Tech

Background: 3q29 Deletion Syndrome (3q29Del) is a rare copy number variant (~10,000 individuals in the U.S.) that increases risk for schizophrenia (40x), autism spectrum disorder (20x), ADHD, and anxiety. Registry data show individuals with 3q29Del are 10x more likely to report anemia, commonly caused by iron deficiency (FeD). The deletion includes TFRC, encoding the primary cellular iron import receptor, suggesting a mechanistic link between TFRC hemizygosity and FeD.

Methods: We analyzed frontal cortex and cerebellum from 3q29Del mice fed iron-replete chow and performed proteomic profiling. In vitro, HEK and iPSC-derived neural progenitor cells were exposed to the iron chelator deferoxamine (DFO) to assess TFRC regulation. Mitochondrial Complex I (CI) activity was measured under mild iron chelation.

Results: 3q29Del mice exhibited reduced brain iron and proteomic signatures of FeD compared to wild-type controls. In cell models, 3q29Del cells showed minimal TFRC upregulation under DFO, while controls responded robustly. CI activity was significantly impaired in 3q29Del cells under mild iron chelation, whereas controls were unaffected.

Conclusion: 3q29Del increases vulnerability to FeD, likely through TFRC hemizygosity, impairing iron homeostasis and mitochondrial function. Ongoing studies aim to define mechanisms and test whether iron supplementation can rescue these deficits.

T7. Microglial-Neuronal Dysregulation and Communication in Human Stem Cell Models of CHD8 Haploinsufficiency

Natalie Hawken, David Geffen School of Medicine, University of California, Los Angeles

De novo mutations in chromodomain-helicase-DNA-binding-protein 8 (CHD8) are a significant risk factor for autism spectrum disorder (ASD). Most autism research has centered around CHD8's function on neurons, however post-mortem brain signatures in individuals with ASD have consistently shown microglial alterations. Whether microglial disruptions in ASD occur due to cell-autonomous or non-cell-autonomous impacts of mutations is still unknown. Here we examine how CHD8 haploinsufficiency alters neuronal and microglial function.

Control human stem cell (SC) lines (1F, 1M) with doxycycline-inducible NGN2 overexpression cassettes were CRISPR edited for heterozygous mutations in CHD8. SC were differentiated into microglia (MG) through growth factors and into excitatory neurons (iN) through NGN2 overexpression. Bulk RNA sequencing was performed on microglia in monoculture. Then, we co-cultured all combinations of CTL and CHD8+/- iN and MG to assess cellular responses to the mutation on both cell types via single nucleus RNA sequencing.

CHD8+/- MG had a small set of differentially expressed genes (48 genes, FDR<0.1); GO analysis enriched GO pathways in mutation-associated modules related to p53/apoptosis (down) and cell projection (up). CHD8+/- iN had altered expression of genes related to axonogenesis and apoptosis. We identified differentially expressed ligand-receptor sets between iN and MG that suggest altered cell-cell communication.

CHD8 haploinsufficiency alters human stem cell-derived microglia activation both due to cell-autonomous mechanisms and non-cell-autonomous processes with CHD8 neurons. These results suggest that it will be valuable to study multiple mutations to interrogate how microglial activation occurs in ASD brain and to investigate shared mechanisms across mutations.

T10. 5-HTTLPR Methylation and Left Ilf Microstructural Alterations in Major Depressive Disorder

Daun Shin, Korea University of ANAM Hospital

Background: Serotonergic epigenetic regulation and white-matter microstructure have both been implicated in drug-naïve major depressive disorder (DNM). However, the extent to which positional 5-HTTLPR methylation relates to tract-specific alterations and clinical symptom severity remains unclear. We examined positional methylation levels of 5-HTTLPR alongside TRACULA-derived fractional anisotropy (FA) to identify mechanistic links in DNM.

Methods: Forty-four participants with DNM and 100 healthy controls (HC) underwent diffusion MRI, from which FA values of major white-matter tracts were extracted, including the left inferior longitudinal fasciculus (Lt ILF), left uncinate fasciculus (Lt UNC), and right ILF (Rt ILF). Peripheral 5-HTTLPR CpG methylation levels were quantified. Group differences and within–DNM group correlations were evaluated while controlling for age, sex, education, and intracranial volume.

Results: The DNM group showed significantly lower FA in the Lt ILF (DNM: 0.462 ± 0.0476; HC: 0.493 ± 0.031; F=12.69, $p=5.99\times10^{-4}$). The DNM group also exhibited elevated methylation at pos2 (2.3387 ± 1.6336 vs. 1.5605 ± 1.1836; p=0.023) and pos3 (7.3790 ± 1.649 vs. 6.294 ± 1.592; p=0.003). Within the DNM group, pos4 methylation showed negative correlations with FA in the Lt ILF, Lt UNC, and Rt ILF, whereas all FA measures were positively correlated with Hamilton Depression Rating Scale (HDRS) severity. Furthermore, pos5 methylation was negatively associated with suicide risk (r=–0.50, p=0.008).

Conclusion: DNM is characterized by serotonergic epigenetic alterations and reduced ILF microstructural integrity, with positional 5-HTTLPR methylation showing tract-specific associations with FA and symptom severity. These findings suggest a potential epigenetic–white-matter pathway underlying depression pathophysiology.

T11. Divergent and Shared Transcript Splicing Dynamics in Post-Traumatic Stress Disorder and Major Depression

John Lee Soto-Vargas, Yale University School of Medicine

Background: Post-traumatic stress disorder (PTSD) is a trauma-based disorder with a prevalence of 7.5% among civilian populations. It is commonly co-morbid with major depressive disorder (MDD) in (>50% of diagnosed patients). PTSD and MDD share overlapping symptoms, etiology, and gene expression signatures despite being distinct disorders. We therefore posit a role for alternative splicing of transcripts to distinguish PTSD from MDD.

Methods: We performed RNA sequencing in four regions of the human brain: dorsal prefrontal cortex, dorsal anterior cingulate cortex, basolateral amygdala, medial amygdala in postmortem brain across three diagnoses, including neurotypical controls (n=109/region), MDD (n=109/region) and PTSD (n=107/region). We conducted differential gene expression, transcript/isoform expression, transcript/isoform usage, and intron usage analyses.

Results: Our findings reveal a high correlation of gene expression between PTSD and MDD (R2=0.50-0.65) while analysis at the isoform-level was lower (R2=0.32-0.41), capturing isoform-specific regulation unique to each disorder. Splicing events revealed a weak negative correlation between PTSD and MDD (R2=0.13-0.18), and showed low overlap (3-6%) across regions in significant splicing events. We observed divergent splicing between disorders for 1853 events, including for the gene NRXN2 in medial amygdala. NRXN2 shows a splicing event with different use of exon 17 for MDD (FDR=0.04) and PTSD (FDR=0.02). In PTSD, exon 17 is skipped (ΔPSI=-0.06), with exon 17 included in MDD (ΔPSI=+0.04).

Conclusion: These findings suggest that PTSD and MDD exhibit distinct transcriptomic regulation profiles across fear-related human brain regions, with minimal overlap in transcript expression and divergent splicing regulation not captured at the gene-level.

T13. Improvement in Youth Depression and Anhedonia Associated With Reward Circuit Changes Following Continuous Theta Burst Stimulation of the Dorsomedial Prefrontal Cortex

Kalyan Tripathy, University of Pittsburgh Medical Center, Western Psychiatric Hospital

Background: Early-onset depression and anhedonia predict poor treatment outcomes. Neuroimaging studies implicate underlying reward circuit impairment, with dorsomedial prefrontal cortex (dmPFC) hyperactivity suppressing striatal reward responses. Therefore, we tested whether inhibiting dmPFC with continuous theta burst stimulation (cTBS) could alleviate anhedonic depression and examined associations of treatment response with baseline symptoms and neural reward circuit functioning.

Methods: Fifty youth (15–25 years, 78% female) with SCID-5 depressive diagnoses, MADRS ≥12, and at least one failed antidepressant trial received 20 sessions of dmPFC-targeted cTBS over 10 days, individualized using connectivity to the nucleus accumbens (NAc), with 10 integrated sessions of positive affect training. Questionnaires and fMRI monetary reward tasks were completed before and after treatment. Changes and relationships between variables were examined using paired t-tests, Pearson correlation analysis, and linear mixed effects models.

Results: Depression improved following reward circuit stimulation ($d=-0.94$, $p<0.001$). Greater improvement was observed among individuals with weaker initial NAc responses to reward ($r=-0.4$, $p=0.008$). A linear mixed effects model examining how pre-treatment symptoms influenced changes in depression identified greater depression improvement with more severe baseline depression ($B=-1.1$, $\beta=-0.87$, $p<0.001$) and less depression improvement with more severe anhedonia ($B=0.39$, $\beta=0.31$, $p=0.021$) or anxiety ($B=0.75$, $\beta=0.39$, $p=0.001$).

Conclusions: Youth with more severe pre-treatment depression and reward circuit dysfunction showed greater improvements in depression following reward circuit stimulation. Higher levels of anhedonia and anxiety may interfere with reward system modulation conferring treatment resistance or involve additional aberrant circuits requiring additional neuromodulation targets.

T17. Transcriptomic Impact of Polygenicity: Methods to Interrogate Aggregate Trait- And Tissue-Specific Expression Effects

Toni Boltz, Center for Genomic Medicine, Massachusetts General Hospital

Gene regulation is shaped by both linear genomic distance and higher-order 3D genome architecture, leading to context-dependent effects across tissues and cell types. Recent work on chromosomes 22q and 16p has shown that common polygenic risk for neuropsychiatric disorders, including schizophrenia, autism, ADHD, and low IQ, is associated with widespread decreases in gene expression across these chromosome arms, particularly in neuronal cell types. These findings raise the question of whether long-range, polygenicity-linked expression patterns are specific to a few genomic regions or represent a broader feature of the genome, and whether they are unique to neuronal tissues or neuropsychiatric traits.

To address this, we developed an analytic framework that computes local polygenic scores (PRS) across ~30 Mb regions genome-wide and evaluates their association with regional gene expression. Using GTEx, we observed replication of extended cis-effects at 22q and 16p in brain tissue, with markedly weaker or absent effects in non-brain tissues. Associations were trait- and cell type–specific, reinforcing the importance of cellular context. Notably, regions exhibiting significant distal PRS–

expression associations were enriched for chromatin contacts defined by Hi-C, suggesting a potential mechanistic basis involving 3D genome organization.

Our results demonstrate that polygenic influences on gene expression can extend across large genomic domains, with specificity to neuropsychiatric traits and neuronal tissues. This work establishes a framework for genome-wide interrogation of long-range regulatory effects, laying the groundwork for meta-analyses across cohorts, integration with eQTL-based models, and mechanistic studies of the genetic architecture underlying neuropsychiatric disease.

T18. Vagus Nerve-Mediated Gut-Brain Signaling Modulates Memory via Septal Acetylcholine Release: Implications for Diet-Induced Cognitive Dysfunction

Logan Tierno Lauer, University of Southern California

Consumption of a Western diet (WD) elicits both reductions in gut-to-brain vagus afferent nerve (VAN) signaling and hippocampal (HPC)-dependent memory impairment. However, it is unclear whether the former phenomenon is causally related to the latter. The medial septum (MS) is an anatomical relay between the brainstem and the dorsal HPC, and MS acetylcholine (ACh) neurons extensively innervate the HPC. Thus, we hypothesized that WD-induced disrupted VAN signaling contributes to HPC dysfunction via changes in MS-HPC ACh release. Consistent with this hypothesis, our results reveal that male Sprague Dawley rats chronically exposed to a WD during development demonstrate insensitivity to the food-intake reducing effects of peripheral cholecystokinin administration relative to controls raised on standard laboratory chow. Analyses of eating patterns using automated food intake monitoring further reveals that early life WD-exposed rats also consume larger meals than controls when tested in adulthood. Using in vivo fiber photometry and fluorescent ACh sensors (iAChSnFR), we next demonstrate that HPC ACh release is elevated immediately after consumption of a meal in control rats, but not in rats receiving subdiaphragmatic vagotomy (SDV), ablation of MS ACh neurons (1921gG saporin immunotoxin), or in rats exposed chronically to a WD during adolescence. Finally, all three treatments (SDV, MS ACh neuron ablation, and early life WD) lead to analogous impairments in hippocampal-dependent spatial working memory for meal location relative to respective controls. Collectively, our findings identify ACh signaling as a substrate for gut-originating VAN potentiation of HPC function, and impairments in this pathway may underlie WD-induced HPC dysfunction.

T19. Mapping the Genetic Research Disparities and Genetic Architecture of Mood Disorders Among African-ancestry Populations Worldwide: A Scoping Review

Kwabena Kusi-Mensah, Mayo Clinic

Background: Mood disorders are major causes of disability and premature mortality in low- and middle-income countries (LMICs), accounting for up to 45% of youth DALYs. Despite strong genetic underpinnings, psychiatric genomics research remains dominated by populations of European ancestry (EA), limiting relevance to African-ancestry (AA) populations and creating critical knowledge gaps. This scoping review summarises genetic and epigenetic studies on mood and psychotic disorders in AA populations and examines progress in polygenic risk score (PRS) development.

Methods: Following PRISMA-ScR guidelines, we searched seven bibliographic databases and two clinical trial registries (from inception to Nov 13, 2024). From 11,296 citations, 193 studies met the inclusion criteria

Results: Although all studies involved AA participants, only 8.8% were based in sub-Saharan Africa (SSA), and none conducted genetic analyses locally. Just 13% had key authors affiliated with SSA institutions. Genetic findings showed both shared and ancestry-specific associations, with only ~30% replication across populations. Effect sizes for replicated SNPs and pharmacogenomic responses often differed across ancestries, and EA-derived PRS performed poorly in AA populations, likely due to

shorter linkage disequilibrium blocks among AA. Epigenetic studies also revealed ancestry-specific gene–environment effects, such as stronger links between maternal depression and low birth weight among Black women compared to whites

Conclusions: Persistent underrepresentation of AA populations, limited local research capacity, population stratification challenges and poor transferability of EA-based genomic findings highlight an urgent need for larger, better-powered, cross-ancestry studies and capacity building in SSA to ensure equitable advances in psychiatric genomics.

T20. Molecular and Functional Phenotyping of 30 NPD Genes in iPSC-Derived Neurons

Ramin Ali Marandi Ghoddousi, David Geffen School of Medicine

Background: Large-scale genomics studies have identified hundreds of risk genes for neurodevelopmental and neuropsychiatric disorders (NPDs). While single-gene knockout (KO) studies provide important insights, understanding biological points of convergence across genes requires parallel, multi-phenotype investigations in human in vitro models.

Methods: We used CRISPR/Cas9 editing to generate an isogenic repository of ~700 human iPSC KO lines representing 100 NPD-associated genes. Here we highlight 30 gene KOs differentiated into excitatory neurons using a doxycycline-inducible NGN2 system (NGN2-iNeurons), enabling rapid and uniform induction for reproducible high-throughput phenotyping. We performed bulk RNA-sequencing, quantitative proteomics (LC-MS), gene network analysis and high-resolution calcium imaging at day 28 to identify shared molecular and functional changes across KOs.

Results: Transcriptomic and proteomic profiling revealed both unique and shared co-expression patterns across KOs. A neuron arborization co-expression module was selectively upregulated in SP4 KOs, whereas a splicing and synaptic transport module enriched for ASD risk genes (PMID: 35982160; SFARI) was uniquely downregulated in TCF4 KOs. Shared modules included immune reactivity (upregulated in RB1CC1, KMT2C, ASXL3) and dendrite development (downregulated in DNMT3A, ASXL3). Functional profiling revealed multiple groups of KOs with similar changes in firing frequency and burst interval responses compared to controls.

Conclusions: Parallel profiling of 30 NPD gene KOs in NGN2-iNeurons revealed shared and distinct molecular and functional phenotypes relevant to neuronal development. Findings from this highly parallel approach using constitutive knockouts, combined with additional experiments on cellular and morphological features, can help to identify convergent mechanisms and serve as a starting point for targeted therapeutic development.

T21. Shared Genetic Architecture of Brain Morphology and Psychiatric Disorders: Insights From a Cross-Trait Analyses Across 180 Cortical Regions

Yingzhe Zhang, Massachusetts General Hospital

Background: Brain imaging links regional structures to psychiatric disorders, and genetics reveals polygenic influences on brain morphology and psychopathology. However, the shared genetic architecture between brain structures and psychiatric traits, especially across multiple disorders remains unclear.

Methods: We analyzed GWAS summary statistics for 180 brain regions and six major psychiatric disorders: ADHD, ASD, anxiety, bipolar disorder, depression, and schizophrenia. Bivariate causal mixture models (MiXeR) estimated genetic overlaps between global brain measures and psychiatric disorders. SumRank, a novel cross-trait analysis method, identified shared genetic loci by jointly modeling 180 brain regions with individual psychiatric disorders, disorder categories, or general psychopathology.

Results: MiXeR revealed that causal variants for global brain surface area overlapped with psychiatric disorders, ranging from 38.9% (ASD) to 94.4% (schizophrenia). SumRank analyses showed mood disorders and bipolar disorder/schizophrenia shared independent genomic loci with fewer, localized brain regions, while neurodevelopmental disorders shared loci with widespread regions. We identified 12 and 5 independent SNPs shared by general psychopathology with surface area and cortical thickness across multiple regions, respectively. Most shared SNPs influenced different brain regions in opposite directions. Notably, variant rs2431112 reduced surface area specifically in primary visual cortex and posterior cingulate while associating with all major psychiatric disorders.

Conclusion: Brain morphology and psychiatric disorders share substantial genetic overlap, with broader brain regions associated with neurodevelopmental disorders than mood or psychotic disorders. While most loci showed heterogeneous effects, one variant linked multiple disorders to specific regions, suggesting genetic bridges that may guide psychiatric biomarkers and therapeutic targets.

T24. Population Geometry Reveals Three Dissociable Components of Visual Mismatch Negativity

Lucas Sjulson, Albert Einstein College of Medicine

Background: Mismatch negativity (MMN) describes differences in neural responses to repetitive “standard” versus infrequent “deviant” stimuli and is altered in many psychiatric disorders. MMN is currently conceptualized as having two components: bottom-up stimulus-specific adaptation (SSA), which reduces responses to repeated stimuli, and top-down deviant detection (DD), which increases responses to unexpected stimuli.

Methods: We re-examined this framework using a visual oddball paradigm with drifting gratings in head-fixed mice, recording hundreds of V1 units with high-density silicon probes. We also used ArchT to silence axon terminals in V1 arising from anterior cingulate cortex (ACC).

Results: MMN was a population-level phenomenon not captured by individual neurons. State-space analyses of stimulus orientation coding uncovered a third component: non-stimulus-specific adaptation (NSSA), comprising rotations of representations on the orientation manifold. NSSA is neither bottom-up nor top-down, but rather intracortical within V1. SSA reflected reduced population response amplitudes on the orientation manifold, whereas DD reflected a selective expansion of population responses in an orthogonal off-manifold subspace. Optogenetic inhibition of ACC inputs to V1 selectively modulated off-manifold dimensions aligned with the DD subspace, suggesting ACC feedback plays a key role in DD.

Conclusion: These results recast visual MMN as a multidimensional population phenomenon with three separable components: SSA, NSSA, and DD. Our optogenetic experiments support the notion that SSA is bottom-up, DD is top-down from ACC, and NSSA is intracortical within V1. This framework helps reconcile inconsistencies in prior single-cell reports and provides circuit-level insights for mechanistic studies and translational biomarker development.

T25. Selective Exclusion of Inactive Neurons Regulates Ensemble Plasticity

Soren Emerson, Vanderbilt University

Background: Repeated cocaine exposure produces enduring behavioral changes by engaging small, transcriptionally active neuronal ensembles in the nucleus accumbens (NAc). Although transcriptional plasticity within these ensembles has been well studied, how they are refined and maintained remains unclear. While a large body of work has focused on the processes within ensemble cells that drive their recruitment and re-recruitment, here we show that molecular effectors outside of ensembles play a key role in shaping cellular recruitment.

Methods: Using high-throughput approaches to profile transcriptional signatures at the single-cell level, we identified lysine acetyltransferase 2a (KAT2A) as a negative regulator of neuronal recruitment by cocaine. We causally linked KAT2A function to ensemble refinement and recruitment using loss-of-function studies in D1 medium spiny neurons, single-nucleus RNA sequencing, longitudinal single-cell calcium imaging, and a novel activity-dependent single-nucleus RNA sequencing approach to track neuronal ensembles over repeated cocaine exposure.

Results: Cocaine increased KAT2A activity on chromatin and KAT2A loss of function reduced cocaine self-administration. KAT2A expression was enriched in non-ensemble neurons and inversely correlated with immediate early gene induction. With repeated cocaine exposure, KAT2A activity rose as the number of active neurons declined. Longitudinal tracking showed that repeated exposure re-recruited a stable subset of highly responsive cells defined by low KAT2A expression.

Conclusion: We identified KAT2A as a cocaine-recruited negative feedback mechanism that acts outside active ensemble neurons. Our findings reveal a mechanism by which transcriptional regulators in surrounding inactive populations shape and stabilize neuronal ensembles, uncovering a previously unrecognized principle of circuit plasticity in addiction.

T27. Investigating the Behavioral Consequences of NPD-Associated Gene Haploinsufficiency Through Region and Cell-Type Specific Dysregulation

Emma Jones, Washington University in St. Louis

Background: Variants in transcription factors (TFs) can alter numerous neural gene programs, leading to neurodevelopmental and psychiatric disorders (NPDs) such as autism spectrum disorder (ASD) and schizophrenia. Pathogenic variants in the TF MYT1L cause MYT1L Neurodevelopmental Syndrome, which is marked by ASD, behavioral disorders, motor abnormalities, language delay, and obesity. Prior research has shown that Myt1l haploinsufficient mice exhibit impaired cortical excitatory neuron differentiation, and human patient stem cell-derived cortical interneurons have altered ion channel expression and electrophysiology.

Methods: As part of the SSPsyGene consortium, which aims to characterize 259 NPD-associated genetic mutations, our data center, Washington University Scalable Mouse Assay Center (WU-SMAC), has generated sex-balanced sample-matched behavioral, single-cell (sc) RNA-seq, and spatial transcriptomic datasets for downstream analyses, thereby aiming to generate a comprehensive phenotypic profiling of >100 NPD mouse models over a 5-year period. Here, we highlight results from MYT1L, a TF essential for neuronal maturation. We examine how the cell-specific and spatial expression of Myt1l and its targets change in Myt1l haploinsufficient mice, including the striatum, amygdala, and hypothalamus, and explore how these changes may explain observed behavioral phenotypes.

Results: We elaborate on how these pathways may contribute to MYT1L Syndrome phenotypes and identify putative targets for interventional strategies. We also explore how this computational framework can be applied downstream to other NPD mouse models studied as part of WU-SMAC.

Conclusion: This is the first research to assess transcriptional changes in Myt1l haploinsufficient mice and establish potential mechanistic links to behavioral phenotypes in the striatum and amygdala.

T29. Cell Type-Specific Mechanisms Driving the Rapid Antidepressant Effects of Transcranial Magnetic Stimulation

Scott Wilke, Semel Institute for Neuroscience and Human Behavior at UCLA

Background: Repetitive transcranial magnetic stimulation (rTMS) is an emerging treatment for depression, but its therapeutic circuit mechanism remains unknown. This lack of mechanistic insight is a key bottleneck hindering the rational development of more effective, durable and precisely targeted interventions.

Methods: To overcome this, we developed a novel mouse model of rTMS with superior clinical face validity and investigated the neural mechanism by which accelerated intermittent theta burst stimulation (aiTBS) - the first rapid-acting rTMS antidepressant protocol - reversed chronic stress-induced behavioral deficits.

Results: Using photometry, we show that aiTBS drives distinct patterns of neural activity in

intratelencephalic (IT) and pyramidal tract (PT) projecting neurons in dorsomedial prefrontal

cortex (dmPFC) (n=5-8 mice/condition). However, only IT neurons exhibited persistently increased activity during both aiTBS and subsequent depression-related behaviors (n=5-8 mice/condition). Similarly, aiTBS reversed stress-related loss of dendritic spines on IT, but not PT neurons, further demonstrating cell type-specific effects of stimulation (n=3-4 mice/condition, >8 cells/mouse). Finally, chemogenetic inhibition of dmPFC IT, but not PT neurons during rTMS blocked the antidepressant-like behavioral effects of aiTBS on both effortful coping (n=5-8 mice) and the balance of reward-approach vs. threat avoidance (n=7-10 mice/condition). All statistics are RM 2-way ANOVA with Sidak's multiple comparisons test ($p<0.05$).

Conclusions: Thus, we demonstrate a prefrontal mechanism linking rapid aiTBS-driven therapeutic effects to cell type-specific circuit plasticity. Ours is the first study demonstrating to use focal, suprathreshold rTMS in vivo to demonstrate that a specific prefrontal cell type is required for the antidepressant-like behavioral effects of rTMS.

T30. Circuit-Guided Identification of Novel Antidepressant Targets

Hermany Munguba, University College London

Major depressive disorder is a debilitating condition, but most treatments are slow-acting and not efficacious to all patients. While fast-acting antidepressants, such as ketamine, led to a recent breakthrough with alleviation of symptoms within hours, a deeper understanding of their mechanism of action is needed to guide the development of safer, more effective therapeutics. We utilized a combination of in vitro, ex vivo, and in vivo techniques, including slice electrophysiology, fiber photometry, electrophysiology, and novel photopharmacological tools to show that activation of the Gi/o signaling pathway in a specific population of neurons is necessary and sufficient for driving switches in behavior. Next, we used RNA sequencing to identify receptors enriched in these neurons, which we characterized before and after chronic stress. Synergistic targeting of new receptors enriched in this key neuronal cell type enabled potent antidepressant-like responses with a reduced side effect profile compared to ketamine, across a panel of behavioural tests in mice. Overall, we reveal a fundamentally new approach to discovering and validating new antidepressant targets and engaging them synergistically to amplify therapeutic effects while minimizing side effects.

T31. Norepinephrine Blocks Psychedelic-Like Effects of Entactogens and Psilocybin in Mice

Axel Rosado, Yale University

Background: Entactogens such as 3,4-methylenedioxymethamphetamine (MDMA) are currently under investigation as adjuncts to psychotherapy for post-traumatic stress disorder (PTSD). Their therapeutic effects are hypothesized to involve monoaminergic modulation and facilitation of fear extinction, however, the mechanisms mediating these actions remain poorly defined.

Methods: I systematically compared the behavioral and neurochemical effects of entactogens (MDMA, methylone, MBDB) and serotonergic psychedelics (psilocybin, 2C-B) in mice. Assays included head twitch response (HTR) quantification, in vivo fiber photometry to measure serotonin (5-HT) and norepinephrine (NE) release in the medial prefrontal cortex (mPFC), and pharmacological manipulations targeting the norepinephrine transporter (NET) and α2 adrenergic receptors (α2Rs). Behavioral assays assessed fear extinction learning, anhedonia, and behavioral despair.

Results: Entactogens elicited minimal HTRs, whereas serotonergic psychedelics induced robust HTRs. MDMA, but not psilocybin, elevated both 5-HT and NE levels. NET inhibition revealed MDMA's capacity to induce HTRs, while exogenous NE suppressed psilocybin-induced HTRs. α2R blockade enhanced, and α2R activation suppressed, HTRs from both compounds, indicating a postsynaptic modulatory role. MDMA facilitated fear extinction learning, whereas psilocybin had no effect in this behavioral paradigm. Conversely, psilocybin alleviated stress-induced anhedonia and behavioral despair; α2R activation selectively attenuated psilocybin's anti-anhedonic, but not antidepressant-like, effects.

Conclusion: These findings identify a novel interaction between NE and 5-HT2A receptor signaling, with α2Rs emerging as key modulators of serotonergic associated behaviors. This work provides mechanistic insight into the distinct therapeutic potential of entactogens and psychedelics, informing their clinical application in neuropsychiatric disorders.

T33. Predicting Psychoticlike Experience Severity in Youth with Longitudinal Features Using Long-Short Term Memory Neural Networks: An Adolescent Brain and Cognitive Development Study

Jason Smucny, University of California Davis

Background: Previous work suggests that a combination of baseline demographic, clinical, and neuroimaging features can predict persistent psychotic-like experiences (PLEs) in the Adolescent Brain and Cognitive Development (ABCD) study. Here we tested the hypothesis that incorporating both baseline and two-year follow-up data using the same features would predict persistent distressing PLEs with greater success than the previous two-year study.

Methods: Children aged 9-10 years at baseline from ABCD study release 5.1 were classified as having either persistently elevated distressing PLEs or low-level PLEs. Predictors included speech and motor delays, family history, internalizing symptoms, adverse childhood experiences, fluid and crystallized cognition, average prefrontal cortical thickness, average within-network functional connectivity of the cingulo-opercular and default-mode networks, and demographics. Features included both baseline and two-year follow-up data. A long-short term memory (LSTM) model was tuned to minimize focal loss due to class imbalance. The model was trained and tested using leave-one-site-out cross-validation.

Results: 160 children had severely distressing PLEs at four-year follow-up and 3993 did not. The model with demographics showed 96% accuracy (95% CI: 95%-97%), 97% NPV, 53% PPV and an AUC of 82%.

Conclusions: These results suggest that LSTM models based on data collected during childhood can effectively predict persistent distressing PLEs in adolescence. These results build upon prior ABCD results that predicted persistent distressing PLEs with ~70% accuracy and ~75% AUC. The performance enhancement observed here (96% accuracy and 82% AUC) also illustrates the utility of incorporating features from more than one timepoint using an LSTM architecture.

T34. Single-Nucleus Smart-Seq3 Express Enables Isoform-Level Interrogation in Schizophrenia and in Health

Arvid Harder, Karolinska Institutet

Background: Recent single-nuclei RNA-sequencing (snRNA-seq) studies comparing individuals with schizophrenia to healthy controls have revealed that RNA-binding proteins (RBPs) and splicing machinery components are perturbed in schizophrenia. This finding is particularly noteworthy as RNA splicing has emerged as a potential causal mechanism for disease-associated single nucleotide polymorphisms, and common genetic variants affecting splicing are enriched in schizophrenia associated loci. The recently developed Smart-seq3 Express (SS3X) protocol captures both 5' UMI-tagged and internal reads, providing near–full-length transcript coverage suitable for splicing analysis at single-cell resolution.

Methods: We generated SS3X snRNA-seq data from postmortem prefrontal cortex of individuals with schizophrenia and controls. A subset of samples was also profiled using 10x Chromium to benchmark transcript and gene detection across platforms. Standardized quality control and a reference-free approach were used to quantify splice junctions and isoform usage.

Results: Analysis confirm robust but sparse detection of splice junctions using both internal and 5' reads in SS3X libraries. SS3X yielded a higher median number of detected genes per nucleus compared to matched 10x Chromium data, consistent with improved transcript capture. Cell-type–specific differential expression and isoform-usage analyses are ongoing.

Conclusions: Smart-seq3 Express enables transcript- and isoform-level interrogation of splicing regulation in postmortem human brain, with greater sensitivity than droplet-based methods. Ongoing data generation will provide a high-resolution resource to elucidate cell-type-specific splicing alterations in schizophrenia

T35. Thalamocortical Dysconnectivity and Negative Symptoms in Schizophrenia Spectrum Disorder

Keiko Kunitoki, The University of Texas Health Science Center At Houston

Negative symptoms of schizophrenia are among the most clinically debilitating features of the disorder, contributing substantially to long-term disability. Despite their impact, treatment options remain limited. This study aims to identify the underlying neural mechanisms to inform potential therapeutic targets.

We analyzed 394 structural MRI scans (schizophrenia spectrum disorder [SSD], n = 210; healthy controls [HC], n = 184) to identify cortical and subcortical regions with significant group differences. Regions showing structural variation were tested for associations with negative symptoms, measured by the Brief Negative Symptom Scale (BNSS). We then performed seed-based resting-state functional connectivity analyses using BNSS-associated regions as seeds in a subset of 196 participants (SSD, n = 127; HC, n = 69). SSD and HC groups were compared to identify voxels with nominal group differences, followed by testing their associations with BNSS scores. All analyses were adjusted for age and sex; intracranial volume was additionally controlled in structural analyses.

Among fifty-three regions showing significant structural differences between SSD and HC after correction for multiple comparisons, bilateral thalamic volumes were significantly associated with BNSS total scores. We then conducted seed-based functional connectivity analyses using nine thalamic functional subregions. Functional connectivity within the thalamus, as well as between thalamic subregions with prefrontal, parietal and cerebellar locations, was significantly associated with BNSS total scores.

Based on structural and functional studies, we identified thalamocortical dysconnectivity as a potential underlying pathway for negative symptoms in schizophrenia. This understanding may open doors for developing new treatment targeting this pathway to treat negative symptoms.

T37. Atypical Nucleus Accumbens Neurons Locally Regulate Dopamine and Shape Opioid Withdrawal and Relapse Behaviors

Jason Tucciarone, Stanford University

The opioid epidemic has created an urgent need for effective treatments for opioid use disorder (OUD). Withdrawal-induced negative emotional states and environmental cues drive relapse and increase overdose risk. Although dopamine (DA) signaling in the nucleus accumbens (NAc) rises during opioid use and falls during withdrawal, the underlying neural circuits remain unclear. Using male and female wild-type and transgenic mice, we investigated cell-type-specific mechanisms of opioid dependence and withdrawal. Single-cell RNA sequencing of mouse NAc and human striatum identified distinct neuronal populations. Morphine exposure induced dependence and withdrawal, while DA and calcium sensors, opto- and chemogenetic tools, and Cre-mediated receptor deletion were used to monitor and manipulate neural activity. Morphine withdrawal produced strong aversion and markedly reduced DA release in the NAc, accompanied by inhibition of DA axons independent of midbrain GABAergic input. Transcriptomic analysis revealed a unique NAc population co-expressing mu opioid receptor (Oprm1) and dopamine receptor D1 (Drd1) but lacking dynorphin (Pdyn). These neurons were defined by high expression of the transcription factor Tshz1, present in both mouse and human striatum. Tshz1 neurons were suppressed by morphine and rebound-excited during withdrawal, inhibiting DA release via local GABAergic signaling. Targeted inhibition or Oprm1 deletion in Tshz1 neurons prevented withdrawal aversion and DA suppression. Activation of a Tshz1-specific GPCR reduced withdrawal aversion, while chemogenetic excitation accelerated extinction and decreased reinstatement. These findings identify Tshz1 neurons as a critical NAc cell type regulating withdrawal and relapse, offering potential therapeutic targets for OUD.

T38. GraphOUD: Integrated Genetic and Non-Genetic Predictors of Opioid Use Disorder

Qian Peng, The Scripps Research Institute

Background: The U.S. opioid epidemic remains a major public health crisis, with opioids involved in about three-quarters of drug overdose deaths. Yet only one in five individuals with opioid use disorder (OUD) receive medication treatments, and only half remain in therapy after six months. This project aims to identify socioeconomic and genetic factors influencing OUD susceptibility and medication for OUD (MOUD) assisted outcomes, and to leverage genetic insights for MOUD repurposing.

Methods: We developed GraphOUD, a framework integrating (i) time varying, multi-state survival models tracing OUD onset, remission, and relapse; (ii) genome wide association study (GWAS) and epistasis analysis findings; and (iii) a literature anchored gene-to-drug knowledge graph for transparent drug discovery. Using multimodal data from All of Us (N=214,387), we derived person-period features from longitudinal electronic health records, surveys, and prescriptions, and estimated adjusted hazards with regularized Cox models. GWAS on OUD and remission-under-MOUD, followed by epistasis among the top 10,000 SNPs, were integrated with prior OUD GWAS results into a PageRank style drug prioritization algorithms.

Results: Greater recent clinical activity predicted modestly higher risk of onset and relapse, whereas remission accelerated with more intensive and ongoing MOUD exposure. GWAS identified 422 significant SNPs (175 genes) for OUD and 119 SNPs (57 genes) for MOUD-assisted remission; epistasis revealed numerous interacting SNP pairs for both traits. The knowledge graph successfully recovered approved MOUDs and nominated promising repurposing candidates.

Conclusion: GraphOUD provides an interpretable, end-to-end pipeline linking clinical dynamics with genetic mechanisms to advance prevention, treatment, and recovery research in OUD.

T41. Ventral Pallidal Adaptations Underlying Opioid Intake

Lisa Fang, Washington University in St. Louis

Background: Despite its continued prevalence, there are few effective therapies for opioid use disorder (OUD). A hallmark of OUD is drug intake despite negative consequences; while most individuals will self-administer opioids and stop when a punishment is introduced (punishment-sensitive; PS), a subset will persist (punishment-resistant; PR). Elucidating the molecular underpinnings of PS and PR phenotypes is crucial for understanding why some individuals can use opioids safely for pain management, while others transition to OUD. The ventral pallidum (VP) is a central node in the basal ganglia, and its activity is necessary for opioid seeking and intake. Despite this, little is known about how opioids modulate neural activity and plasticity in the VP, and how this may lead to enduring changes in opioid-seeking.

Methods/Results: We transcriptionally profiled the VP and identified 20 distinct neuronal clusters that are highly conserved across mammalian species. Differential gene expression highlighted an inhibitory Drd1+ and an excitatory vGluT2+ subpopulation as maximally affected by oxycodone self-administration (OXY-SA) in mice. Selective ablation and physiological interrogation of these Drd1-expressing and vGluT2-expressing cells in the VP confirm the necessity of these cell types for opioid seeking behavior. Lastly, we classified mice as PS or PR by pairing OXY-SA with an aversive air puff. We are currently investigating transcriptional signatures in the VP that dissociate PS from PR mice.

Conclusion: Together, this work provides critical insight into the cellular heterogeneity of the VP and may identify new druggable targets to reduce maladaptive opioid seeking in the context of OUD.

T42. Suicide Risk Genes Impact Evolutionarily Conserved Survival Strategies

Donard Dwyer, LSU Health Shreveport

Background: Genome-wide association studies (GWAS) and candidate gene analyses have identified possible suicide risk genes that are highly conserved during evolution and enriched in genes essential for life. However, functional roles for these risk genes have not been confirmed and pathways from risk variant to relevant phenotype to suicidality-related behavior remain unknown, highlighting critical gaps in our knowledge. Here, we report findings from the largest behavioral and mechanistic study of suicide risk genes to date.

Methods: Two behavioral assays measured relevant phenotypes in Caenorhabditis elegans: 1) exaggerated threat assessment (social feeding) and 2) diminished motivation to forage. Aggregates on food were counted for the social feeding assay, and the percentage of animals moving was calculated for the immobility assay (foraging response).

Results: Mutations in risk gene counterparts caused exaggerated threat evaluation in 6 of 19 mutants, which was attenuated with antidepressants, antipsychotics and lithium. In some cases, the beneficial effects of the drugs depended on the genetic background, providing initial clues about pharmacogenetics. Social feeding mutants with defects in neuropeptide Y (NPY) and TGF-□ signaling pathways showed diminished motivation to seek food that was corrected with antidepressants. Putative suicide risk genes were highly co-expressed in human tissues including brain regions such as the claustrum pontine nuclei, nucleus accumbens and amygdala, responsible for sensory integration, motivation, reward and threat evaluation.

Conclusion: Nature's symmetry reveals that risk genes predisposing a person to take their life normally promote fundamental strategies to survive.