

BRAIN & BEHAVIOR RESEARCH FOUNDATION

2026 Young Investigators



BRAIN &
BEHAVIOR
RESEARCH FOUNDATION

Awarding **NARSAD** Grants



“BBRF Young Investigators represent a new generation of researchers who will pioneer breakthroughs in mental health research. We are excited to be able to support the work of these young scientists, who will apply powerful new technologies and insights to understanding, treating, and curing mental illness.”

October 2026

We are pleased to present the 2026 Young Investigator grantees of the Brain & Behavior Research Foundation. Initiated in 1987, the BBRF Young Investigator Grant program provides support for the most promising young scientists conducting neurobiological and psychiatric research. Their project proposals are carefully selected by members of our Scientific Council, composed of 192 world-renowned scientists and clinicians with expertise in every area of brain research.

I am gratified to report that for the current year, BBRF is funding 180 Young Investigator grants, an increase of 15 grants from 2025 and an increase of 30 from the level in 2024. We are able to enhance our funding of young scientists because of the generous support of our donors.

The latest cohort of BBRF Young Investigators are focused on a broad range of psychiatric illnesses. While many of their projects have relevance in multiple disorders, this year, as in past years, more than half (52%) are relevant to depression or schizophrenia. Significant numbers also have relevance for anxiety disorders, addiction/substance-use disorders, autism spectrum disorders (ASDs), PTSD, bipolar disorder, ADHD, OCD, as well as suicide prevention.

Over 30 grant projects for 2026 (about 1 in 6) are pertinent to the early years of life—“Prenatal Brain Development” and “Childhood & Adolescence.” These categories reflect the fact that many psychiatric illnesses begin to manifest symptomatically in the years before adulthood, and that in many cases, biological factors that give rise to symptoms have their roots early in life, before birth and/or in the childhood and adolescent years.

This is true not only for conditions now widely regarded as “neurodevelopmental,” such as ASDs and schizophrenia, but others not usually thought of in this way. One emerging developmental risk factor for psychiatric disorders is early-life stress. “ELS” is the focus of a number of projects, including one studying the impacts of early-life unpredictability (ELU), which can increase risk for depression and anxiety. Accumulating evidence indicates ELU precedes and predicts the severity of anhedonia, the inability to experience pleasure. The neural mechanisms underlying the relation of ELU and anhedonia in depression and anxiety remain unclear, and are an intriguing target for new research.

Other factors involved in the origins of mental illness cut across diagnostic categories and are being explored by our grantees. A number of projects focus on decision-making

and the updating of beliefs, central issues in many disorders. Some, including OCD and addiction, involve a breakdown in everyday decision making. People may lock into a choice too quickly, struggle to revise when circumstances change, or keep repeating actions even when the outcomes are harmful. Difficulty in revising one’s course of actions, a function of cognitive rigidity, is a core feature of rumination, which is seen in depression, anxiety, PTSD, OCD, and eating disorders.

Many of our grantees are engaged in efforts to improve existing therapies and test new ones. A few examples include grantees who are setting out to: quantify the impact of vagus nerve stimulation (VNS) in depression, anxiety, and panic disorder; test the efficacy of rTMS non-invasive brain stimulation when combined with a ketogenic diet in depressed people with metabolic disorder; and extend the effects of rapid-acting zuranolone in postpartum depression. Several Young Investigators will be testing the psychedelic compounds psilocybin and 5-MeO-DMT in new clinical trials or basic research paving the way to new trials.

What happens in the brain when mood suddenly shifts in bipolar disorder? How are atypical patterns of circadian rhythms, and the biology underlying them, related to suicidal thoughts and behaviors? How are disruptions in the brain’s processing of social signals implicated in autism and other disorders? The 2026 Young Investigators seek answers.

We thank our generous donors for supporting scientists in brain and behavior research so that more people can live full, happy, and productive lives. **With your support we can continue to empower researchers to explore promising ideas, deepen our understanding of the brain, and accelerate the search for better treatments, cures, and methods of prevention.**

As always, 100% of every dollar donated for research is invested in our research grants. Our operating expenses are covered by separate foundation grants. Together we can continue to fund innovative scientists across the field of neuropsychiatry.

Sincerely,

Jeffrey Borenstein, M.D.
President & CEO

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SUMMARY OF 2026 YOUNG INVESTIGATOR GRANTS BY CATEGORY*

26

**ADDICTION / SUBSTANCE-
USE DISORDERS**
(pp. 7–12)

9

ADHD
(pp. 12–14)

31

ANXIETY
(pp. 14–21)

7

**AUTISM
SPECTRUM DISORDERS**
(pp. 21–23)

9

**BIOLOGY OF
THE BRAIN**
(pp. 23–25)

9

**BIPOLAR
DISORDER**
(pp. 25–27)

2

**BORDERLINE
PERSONALITY
DISORDER**
(p. 27)

29

**CHILDHOOD &
ADOLESCENCE**
(pp. 27–33)

57

DEPRESSION
(pp. 33–45)

6

**EATING
DISORDERS**
(pp. 45–46)

11

**OBSESSIVE-COMPULSIVE
DISORDER (OCD)**
(pp. 46–48)

10

OTHER PROJECTS
(pp. 48–51)

21

PTSD
(pp. 51–55)

11

**PRENATAL BRAIN
DEVELOPMENT**
(pp. 56–58)

8

PSYCHOSIS
(pp. 58–60)

37

SCHIZOPHRENIA
(pp. 60–67)

7

SUICIDE PREVENTION
(pp. 68–69)

* Many projects are relevant in more than one category; in the pages that follow, grantee project descriptions appear under each relevant category

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“BBRF Young Investigator grants fund groundbreaking research aimed at reducing suffering in people with mental illness. These early-career scientists are pushing the boundaries in basic and clinical research to establish new approaches to early prediction, prevention, and intervention and to develop next-generation therapies that offer hope for those with brain and behavior illnesses.”

Judith M. Ford, Ph.D.

SINCE 1987



THE 2026 YOUNG INVESTIGATOR GRANTEES

The Foundation is pleased to announce over \$12.5 million in 180 new two-year grant awards to support the work of promising young scientists with innovative ideas in mental health research.



RESEARCH CATEGORIES

-  **Basic Research** (158 Grants)
To understand what happens in the brain to cause mental illness
-  **Next-Generation Therapies** (43 Grants)
To reduce symptoms of mental illness and ultimately cure and prevent brain and behavior disorders
-  **Diagnostic Tools/Early Intervention** (30 Grants)
To recognize early signs of mental illness and treat as early as possible
-  **New Technologies** (5 Grants)
To advance or create new ways of studying and understanding the brain

About 88 percent of the projects funded are **basic research**, the wellspring of innovation in brain research, as in all sciences.

About 24 percent of the projects funded specifically aim to develop **next-generation therapies**.

About 17 percent of the projects funded are **diagnostic tools/early intervention** that aim to prevent brain and behavior disorders.

About 3 percent of projects fund the development of **new technologies** that will power both basic research and new developments in the clinic.

Many projects have multiple classifications.

Seventy-nine percent of grantees are from the United States (143 grantees). Twenty-one percent of grantees come from 15 other countries (37 grantees): Australia, Belgium, Canada, Denmark, France, Germany, Israel, Italy, Japan, The Netherlands, People's Republic of China, Portugal, Spain, Switzerland, United Kingdom.

THE 2026 BBRF YOUNG INVESTIGATOR GRANTEES

ADDICTION / SUBSTANCE-USE DISORDERS

Joseph Aloï, M.D., Ph.D., Indiana University School of Medicine, is interested in the potential of contingency management (CM), a behavioral intervention that reinforces abstinence via rewards in the context of treating substance-use disorders. This project will investigate how instrumental learning response and frontostriatal white matter connectivity shape cannabis-using youths' treatment response to CM. At the heart of CM is an instrumental learning process: youths must update the values they assign to cannabis reinforcers relative to non-drug reinforcers. Emerging evidence indicates that altered reward prediction error (RPE) signals and cannabis-specific reinforcement biases may interfere with this process. This project pilots a cannabis-related instrumental learning task in 30 cannabis-using youths to confirm it elicits expected behavioral and neural responses, specifically preferential choice of cannabis-associated stimuli and RPE-related activity in ventromedial frontal cortex and ventral striatum. It will also test whether white matter integrity in frontostriatal tracts predict CM treatment outcomes, operationalized as reductions in 30-day cannabis use frequency.

 *Next-Generation Therapies*

 *Basic Research*

Samantha Ayoub, Ph.D., University of California, San Diego, notes that while physical symptoms of opioid withdrawal (OW) resolve in days, cognitive disturbances can persist into protracted abstinence and predict relapse vulnerability. One cognitive deficit is impaired decision-making under risk, observed in drug-abstinent individuals with opioid use disorder (OUD) and strongly predictive of relapse. The neural mechanisms through which OW disrupts adaptive risk-based decision-making are poorly understood. Dr Ayoub hypothesizes that OW increases relapse vulnerability by weakening neural encoding of negative outcomes in the nucleus accumbens (NAc), reducing the ability to adjust behavior following losses and increasing risk-taking behavior. To test this, the team will use a rat model of opioid exposure and withdrawal, combined with a cross-species decision-making task. Predicting that OW will weaken neural responses to losses and disrupt the relationship between loss-related neural signals and subsequent decision-making, they will test whether restoring normal activity of certain NAc dopamine neurons improves risk-based decision-making during OW.

 *Basic Research*

David Baranger, Ph.D., Medical College of Wisconsin, will test the idea that heavy drinking temporarily disrupts two brain systems linked to mood: reward processing (responding to positive outcomes) and cognitive control (staying focused and regulating impulses). Mood may worsen when these systems are dampened, leading to increased likelihood of additional heavy drinking, creating a self-reinforcing cycle. The team will collect data on 6 college students reporting intermittent heavy drinking along with moderate to severe depressive symptoms. They will be added to an ongoing study of college students, yielding 36 participants in total. Each will complete 8–10 sessions across several months. At each session, participants will also complete brief questionnaires about recent mood and alcohol use, perform simple decision making and attention tasks, and undergo a 1 hour MRI scan. In the scanner, participants will complete tasks that engage reward and attention networks. This will make possible testing whether higher depressed mood is associated with weaker engagement of reward and control systems, especially after recent heavy drinking; if short-term reductions in these brain systems predict worse mood days later; and if neural measures help explain the short-term link between heavy drinking and subsequent mood.

 *Diagnostic Tools/Early Intervention*

 *Basic Research*

David Carroll, M.D., Wayne State University, is tackling the question of why medications for opioid use disorder, particularly buprenorphine (BUP), after non-fatal opioid overdose are so rarely used despite strong evidence of benefit. A major barrier to progress is that the acute biological and neurocognitive sequelae of non-fatal overdoses are largely uncharacterized, leaving clinicians without mechanism-informed targets to improve recovery during the high-risk post-overdose window. Dr. Carroll proposes that opioid-related hypoxemia during non-fatal overdose triggers a rapid inflammatory response contributing to acute neurocognitive dysfunction and predicting lower short-term BUP uptake/retention and higher near-term recurrent overdose risk. The objective is to define the ultra-early post-non-fatal opioid overdose inflammatory response and test its clinical relevance using objective, patient-oriented outcomes.

 *Basic Research*

Ari Cuperfain, M.D., University of Toronto/Centre for Addiction and Mental Health, Canada, notes older adults with alcohol use disorder (AUD) are at elevated risk for cognitive impairment and dementia. Abstinence may help, but the extent of improvement varies widely and mechanisms underlying this variability remain poorly understood. Evidence suggests chronic alcohol exposure disrupts the brain's balance between

excitatory and inhibitory signaling (E/I balance), perhaps dysregulating brain circuits and increasing vulnerability to cognitive dysfunction and neuronal injury. The team has demonstrated in older adult drinkers increased “interference intrusions,” i.e., errors in which previously learned information intrudes during new learning tasks, which may reflect impaired inhibitory control within the prefrontal cortex (PFC). They will now use TMS and EEG to measure E/I inhibitory imbalance in the PFC. By quantifying these responses in older adults with AUD they hope to determine if signaling balance is disrupted following alcohol withdrawal and whether this predicts cognitive outcomes during abstinence.

 **Diagnostic Tools/Early Intervention**

 **Basic Research**

Elizabeth Doncheck, Ph.D., University of Alabama at Birmingham, seeks to uncover the moment-to-moment brain activity patterns that make addiction relapse more or less likely. Imaging individual brain cells in real time while an animal is seeking drugs, the team can identify small groups of neurons, called neural ensembles, that “light up” when drug-seeking behavior occurs. Previous work has shown that relapse is caused by specific clusters of cells whose activity predicts when relapse will happen. This work focuses on biological sex and hormone states. Men and women often show different relapse patterns. Hormones estradiol and allopregnanolone play opposing roles in shaping the brain’s vulnerability to relapse. Estradiol can increase the activity of relapse-driving neurons, while allopregnanolone appears to quiet these circuits and reduce the likelihood of returning to drug use. These hormonal effects can shift across the menstrual cycle, which may help explain why relapse risk is not constant but fluctuates over time for many women. This project will investigate how these hormones influence neural circuits at both the cellular and network levels, and how this changes the brain’s response to drug-related cues.

 **Basic Research**

Carlos Dostal, M.D., Ph.D., University of Texas Medical Branch at Galveston, notes kratom (*Mitragyna speciosa*) is marketed as a safer alternative to opioids, yet more than half of regular kratom users develop symptoms typical of opioid use disorder (OUD). The kratom alkaloid 7-hydroxymitragynine (7-OHM) is a partial agonist at mu-opioid receptors (MOR). This project seeks to characterize the clinical phenotype of 7-OHM withdrawal and affective dysregulation during cessation in a prospective observational cohort study of adults diagnosed with 7-OHM-use disorder initiated on either cessation or buprenorphine (BUP) or naloxone (NX) treatment. They will also evaluate BUP/NX induction outcomes in 7-OHM UD participants. They hope to perform the first systematic clinical phenotyping of 7-OHM use disorder vs. OUD, integrating affective markers within a focus on concentrated 7-OHM products. This could establish 7-OHM-UD as a clinically

definable disorder with quantifiable affective dimensions and inform evidence-based BUP/NX protocols for 7-OHM-UD.

 **Next-Generation Therapies,**

 **Basic Research**

Joaquin Douton, Ph.D., University of North Carolina at Chapel Hill, is interested in how negative affective states associated with substance-use disorders alter brain activity. To study the effects of negative affective states elicited by drugs of abuse, the project will use taste reactivity, local field potentials, and transcranial alternating current stimulation (tACS) to determine how cocaine-conditioned taste aversion alters affective valuation in the Infralimbic Cortex (IL)→Nucleus Accumbens shell (NAcSh) and salience coding in Prelimbic Cortex (PrL)→NAc Core across sexes, and test whether beta-frequency tACS can restore circuit activity and reduce aversive responding. This may provide insight into how negative emotional states associated with substance use disorders alter brain activity in both males and females. By identifying specific brain wave patterns linked to relapse vulnerability and testing a non-invasive approach to directly target them, this research aims to advance new treatment strategies and lay the groundwork for future development of targeted interventions for substance use disorders and related mood disorders.

 **Basic Research**

Mingzhou Fu, Ph.D., New York Genome Center, observes that rare genetic coding variants indicating shared biological mechanisms across addictive disorders likely account for a substantial portion of “missing heritability” in substance-use disorders, yet remain incompletely characterized. This project explores the genetic architecture of alcohol use disorder (AUD) using two large biobanks: All of Us (AoU) and UK Biobank (UKBB). The team will identify rare and common genetic risk factors for AUD and develop a machine learning-derived “continuous risk score” to represent the AUD phenotype spectrum by integrating electronic health records, survey data, psychiatric prescriptions and social determinants of health. They will investigate shared genetic liability across substance use disorder traits, then explore specific enriched common biological pathways underlying addiction vulnerability. The project thus offers an advanced analytical framework for addiction genetics that could deepen understanding of the genetic architecture of AUD risk, better define AUD phenotypes, and inform shared genetic risk factors and associated neurobiological pathways for addictive disorders.

 **Basic Research**

Atsushi Fujimoto, M.D., Ph.D., University of Minnesota Medical Center – Fairview, notes the salience network plays a central role in integrating reward signals, autonomic state, and behavioral adaptation. Neuroimaging shows the anterior insula (aINS) and dorsal anterior cingulate cortex (dACC) are activated

during risky decisions and mediate switching between large-scale brain networks as key salience network hubs. Clinical evidence further links dysregulated or excess salience network activity to addictive disorders and major depression. This project will define how neuronal populations within the salience network integrate autonomic and decision variables and determine whether this network causally governs affective choice. The team hopes to establish a mechanistic framework linking salience network dynamics to maladaptive risk behavior. This could provide insight into how autonomic and reward signals are integrated at the network level and lay the groundwork for circuit-based therapeutic strategies for addiction and related psychiatric disorders.

Basic Research

Carolyn Gaiser, Ph.D., University Medical Center Rotterdam/Erasmus Medical Center, The Netherlands, observes that young people with ADHD are at increased risk for early substance use and are often treated with stimulant medications such as methylphenidate. These medications act on brain systems involved in reward and motivation. It remains unclear whether early treatment, or stopping treatment too soon, influences later risk of substance use. This project will use data from the Generation R Study in the Netherlands, a large long-term study that has followed children from before birth into adulthood. A combination of brain imaging and real-world treatment data provides an opportunity to understand how brain development and medication exposure together influence substance-use risk. By identifying early biological and treatment-related factors that predict substance use initiation, this research aims to improve early identification of vulnerable youth and support more personalized prevention and care strategies.

Basic Research

Diagnostic Tools/Early Intervention

Malte Gueth, Ph.D., University of Minnesota, will investigate whether TMS brain stimulation can strengthen brain circuits that support cognitive flexibility in psychostimulant use disorder (PSUD), which includes methamphetamine and cocaine addiction. The team will use personalized targeting of the dorsolateral prefrontal cortex (DLPFC) for each participant. Targets are selected based on their connectivity with the amygdala, measured via fMRI. They will also employ a novel closed-loop TMS system, which synchronizes stimulation pulses to each participant's natural theta rhythms, measured via EEG. Theta rhythms in the prefrontal cortex are closely linked to cognitive flexibility and behavioral adjustment. Timing stimulation to these rhythms may enhance circuit engagement and produce stronger, longer-lasting effects. Each participant will receive conventional open-loop TMS and two closed-loop TMS protocols synchronized to different phases of theta oscillations. By comparing open-loop and closed-loop protocols, the team will evaluate whether synchronizing TMS to individual patients' brain rhythms improves neural engagement and adaptive behavior.

Next-Generation Therapies

Alexander Hatoum, Ph.D., Washington University, St. Louis, is studying fatal opioid overdose (OOD), which presents difficulties since most research happens after death, when assessment of relevant traits is no longer possible. Genetic tools provide a way to overcome this limitation to infer associated traits. By defining individualized genetic liability to OOD, characterizing its molecular underpinnings, and examining how it operates across behavioral and environmental contexts, this work aims to advance early prediction and prevention strategies for high-risk individuals. Dr. Hatoum seeks to develop a "Behavioral Genetic Autopsy" framework to generate individualized OOD risk profiles by integrating OOD decedent-derived polygenic risk scores (PRS), functional genomic annotation, and environmental and healthcare data, using statistics derived from the team's GWAS of fatal OOD cases. They will generate a decedent-derived PRS for OOD using genome-wide summary statistics from 13,555 cases and 30,874 controls. A conditional PRS accounting for shared liability with OUD will be constructed and tested in the All of Us Research Program cohort (N > 400,000) to identify behavioral phenotypes associated with elevated individualized risk.

Basic Research

Diagnostic Tools/Early Intervention

Leanne Holt, Ph.D., Temple University, notes histone posttranslational modifications are epigenetic gene regulatory mechanisms that drive lasting gene expression changes implicated in addiction. Recently it was determined that the Warburg phenomenon observed in cancer biology results from the addition of the metabolic molecule lactate to histone lysine residues to drive the conversion to pro-inflammatory immune cell phenotypes. Disruptions to lactate metabolism and signaling are also implicated in several neuropsychiatric disorders, including addiction and cocaine use disorder, but the role of histone lactylation has yet to be addressed. This project investigates the hypothesis that histone lactylation is a mechanistic factor in cocaine-induced transcriptional plasticity. Spatial and cell type specific changes in histone lactylation will be determined in key brain regions associated with addiction, and sequencing will elucidate histone lactylation's direct gene targets and downstream biological pathways induced by cocaine self-administration in male and female mice.

Basic Research

Mi-Seon Kong, Ph.D., University of Washington, focuses on a defined population of neurons in the central amygdala, a brain region that regulates emotional state and motivated behavior. These neurons express the glucagon-like peptide-1 receptor (GLP-1R), the target of FDA approved medications for the treatment of metabolic disorders. Emerging evidence suggests that GLP-1R signaling influences brain circuits involved in addiction, yet how this pathway regulates neural activity during opioid withdrawal remains unknown. This project in mice seeks

to determine how central amygdala GLP-1R-expressing neurons encode opioid withdrawal and whether modulating this pathway alters withdrawal-associated brain states and behavior.

Basic Research

Will Lawn, Ph.D., King's College London, UK, studies tobacco-use disorder (TUD). Although evidence implicates the nucleus accumbens (NAc) and right inferior frontal gyrus (rIFG) as key regions underpinning compulsive drug-seeking and inhibitory control, their causal contributions to human addiction have not been established. This project will use causal circuit perturbation with low-intensity, focused transcranial ultrasound stimulation (TUS) to transform our mechanistic understanding of how reward and control systems underpin addiction. The results will provide data for larger translational studies and future clinical trials. The team will employ TUS to non-invasively modulate cortical and deep brain regions. Twenty dependent daily smokers (≥ 10 cigarettes/day) will attend one baseline MRI session and three stimulation sessions: (i) NAcc-TUS, (ii) rIFG-TUS, and (iii) sham-TUS (mimicking auditory and sensory sensations). Following stimulation, participants will complete two well-validated behavioral assays. The hypothesis is that NAcc-TUS will selectively modulate compulsive drug-seeking and that rIFG-TUS will selectively modulate inhibitory control.

Next-Generation Therapies

Alessandro Livi, Ph.D., Washington University, St. Louis, notes many psychiatric illnesses, including OCD and addiction, involve a breakdown in everyday decision making. People may lock into a choice too quickly, struggle to revise when circumstances change, or keep repeating actions even when the outcomes are harmful. These patterns suggest a problem not only with valuing options, but also with when a decision becomes stable enough to drive action. The orbitofrontal cortex (OFC) is central for value-based decision making, yet we still do not understand how OFC activity is converted into a firm, “winner-take-all” decision state that becomes resistant to change. This project will use an all-optical approach to explore whether a layered circuit in the OFC transforms distributed value signals into a stable choice outcome. Mice will perform a value-based decision-making task in which odor cues indicate different reward options. While they deliberate and choose, the team will measure neural activity and deliver time-specific perturbations to targeted neural populations. Seeking to pinpoint how value representations are converted into a committed decision, this work may reveal a circuit-level mechanism that can fail in disorders marked by impulsive commitment, perseveration, and reduced cognitive flexibility.

Basic Research

Ana Manea, Ph.D., University of Minnesota Medical Center-Fairview, will assess a new pharmacological intervention for substance-use disorders (SUDs) and whether it is sensitive to the particular substance of abuse. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), beyond their established metabolic effects, may have a broader impact on brain function. While their therapeutic potential appears broad, their neuronal mechanism of action, in particular on reward processing and executive function, remains largely unexplored. This project employs a translational nonhuman primate model of chronic drug use to examine the efficacy and long-term effects of GLP-1 RAs as a pharmacological intervention for SUDs, and assesses neurobehavioral changes associated with GLP-1 RA administration. The team will address how and where these agents act on the brain, and how drug history and substance-specific effects modulate their efficacy. They will assess efficacy in the context of two substances of abuse, cocaine and heroin, seeking to distinguish acute pharmacological effects from lasting brain changes, critically assessing whether an intervention promotes sustained recovery or risks inducing relapse upon cessation, thereby informing strategies conducive to long-term abstinence.

Next-Generation Therapies

Basic Research

Juan Morici, Ph.D., Sorbonne University, France, notes that in addiction, small or incomplete reminders of past drug use can trigger intense cravings and relapse, even when the full context is not present. In other words, the brain may treat partial cues as if they strongly predict a reward. We still do not understand how communication between the dorsal and ventral parts of the hippocampus and prefrontal cortex determines whether a situation truly signals reward, especially when information is limited. This project will investigate how these brain regions work together to evaluate whether a context predicts reward. The team will examine how the dorsal and ventral hippocampus are connected to the dorsal and ventral prefrontal cortex, how their communication changes when contextual information is reduced, and how these circuits contribute to inappropriate reward-seeking in a model of cocaine addiction. Using advanced techniques to measure and influence brain activity in animals performing memory-guided tasks, they will study how the brain interprets contextual cues to guide reward-seeking based on prior experience.

Basic Research

Arghya Mukherjee, Ph.D., University of Pennsylvania/Children's Hospital of Philadelphia, notes dysfunctional GABAergic inhibitory signaling is a key cellular deficit thought to underlie cognitive symptoms and impairments in schizophrenia and substance-use disorders. Beyond inhibitory neurons, the postsynaptic molecular machinery that makes inhibition possible is dysfunctional in mouse models of psychosis

and substance use disorders, Dr. Mukherjee's work has shown. GABA signaling depends on neurons maintaining low levels of intracellular chloride. A protein called KCC2 performs this essential function. Using RNA expression data from patients with schizophrenia, the team discovered that KCC2 is selectively depleted in prefrontal excitatory neurons. Remarkably, OV350, a small molecule activator of KCC2, rescued deficits in working memory and attentional flexibility in animals. This project focuses on the mechanistic specificity needed to translate this discovery into a genuine clinical strategy. It seeks to identify precisely which prefrontal neuron populations are most vulnerable to chloride dysregulation, establish causal proof that KCC2 loss drives cognitive failure, and determine which cell types respond most powerfully to OV350.

Basic Research

Next-Generation Therapies

Nathan Nakatsuka, M.D., Ph.D., New York University, notes the majority of heroin and fentanyl users first mis-used prescription opioids. Understanding the molecular changes in opioid use is critical to developing new therapeutics. The team is exploring an alternative approach to current treatments, targeting the molecular adaptations in long term opioid use. This requires understanding the neurobiological changes involved in long term opioid use and how they might be reversed. The team will study this in its mouse model of oral oxycodone use in which some mice demonstrate high escalation (HE) and others lower escalation (LE), similar to humans. They are developing algorithms analyzing RNA changes to determine how biological pathways are changed in a coordinated manner across different cell types and brain regions. Results may provide improved understanding not only of opioid biology but more generally of the mechanisms of reward and addiction.

Basic Research

Marta Pratelli, Ph.D., Research Foundation for the State University of New York/Stony Brook University, is interested in transmitter plasticity, a process in which neurons gain and/or lose one or more of the neurotransmitters and/or neuropeptides they use to communicate. When a neuron changes the transmitter or peptide it releases, connected cells adapt accordingly, altering circuit function and often influencing behavior. Experimental evidence shows that artificially preventing or reversing transmitter plasticity can mitigate maladaptive behaviors. This project tests the hypothesis that social stress and voluntary alcohol drinking recruit transmitter plasticity in hypothalamic orexin neurons. These neurons co-express glutamate and dynorphin, are activated by stress and alcohol-related cues, regulate alcohol-seeking behavior, and undergo transmitter plasticity in response to opioids and cocaine, making them strong candidates for mediating stress–alcohol interaction effects. To test this, the team will use a mouse model of adult social defeat stress followed by voluntary ethanol drinking, which reliably produces stress-induced escalation of alcohol intake. They will determine

if social stress alone, alcohol alone, or their combination induces transmitter plasticity in hypothalamic orexin neurons.

Basic Research

Kathia Ramirez Armenta, Ph.D., University of California, Los Angeles, is interested in how we learn that environmental cues can predict particular forthcoming events. Such memories form the basis of the internal model of environmental relationships (e.g., cue-reward associations) that support the prospective considerations, predictions, and inferences needed for adaptive decision making. Deficits in this process characterize several psychiatric conditions, including substance use and OCD. Studies have established the basolateral amygdala and orbitofrontal cortex as crucial for associative learning and adaptive decision making. This project aims to reveal how the regulation of local brain circuits contributes to adaptive decision making. Evidence suggests dopamine regulation of basolateral amygdala circuitry is likely involved. Basolateral amygdala (BLA) projection neurons to the lateral orbitofrontal cortex (LOFC) not only mediate cue-reward learning but also adaptive decision making. Yet little is known about how this works. One potential mechanism involves dopaminergic modulation, which this research will explore. It aims to reveal how dopamine modulates amygdala microcircuitry to support adaptive decision making.

Basic Research

Ghazaleh Soleimani, Ph.D., University of Minnesota, cites neuroimaging evidence indicating disrupted large-scale brain connectivity, particularly reduced synchrony within the frontoparietal control network, contributes to cognitive impairments associated with opioid use disorder (OUD). Restoring coordinated network activity via transcranial alternating current stimulation (tACS) is a potential therapy; it can modulate brain oscillations that support large-scale network communication. Most prior stimulation approaches in OUD have relied on standardized, one-size-fits-all protocols. This project will test a personalized traveling-wave tACS (twACS) approach designed to modulate individualized alpha-frequency activity within the frontoparietal network directionally. In a double-blind, sham-controlled, randomized crossover study, 30 individuals with OUD will receive three different stimulation conditions: frontal-to-parietal, parietal-to-frontal, and sham stimulation, while completing inhibitory control and memory tasks. Individualized MRI-based modeling will optimize electrode placement, intensity, and phase configuration, and resting-state EEG will guide personalized frequency selection.

Next-Generation Therapies

Hayley Thorpe, Ph.D., Western University, Canada, notes that in the context of comorbid schizophrenia and cannabis use, disruption of shared neural pathways and networks may partially explain comorbidity. Most neuroimaging research on cannabis'

role in schizophrenia occurs after its emergence and does not consider genetic sharedness. It is thus unclear if brain divergences existed before or because of the disorder and substance use, or how much genetics contributes to developmental trajectories. Dr. Thorpe will analyze neuroimaging phenotypes in genetically at-risk adolescents (N=11,632; ages 9-17) without schizophrenia or cannabis use. Using youth genetic data and trait-partitioned GWAS, the team will develop cannabis-only, schizophrenia-only, and shared schizophrenia-cannabis biomarkers (i.e., polygenic scores) and analyze their associations with brain structure and function before and after cannabis use and psychosis onset. The hypothesis is that neurodevelopmental variance in cannabis use and schizophrenia-related brain regions of interest is a function of genetic biomarkers, and variance will be more pronounced in those who also use cannabis and/or report psychotic-like experiences.

Basic Research

Benjamin Weekley, Ph.D., Icahn School of Medicine at Mount Sinai, cites prior work showing that cocaine reshapes the epigenome through changes in histone acetylation and methylation. His team is focused on how dopamine is involved in persistent changes in gene expression that sustain relapse vulnerability. Recent discoveries reveal that dopamine can be covalently incorporated into chromatin as histone H3 glutamine 5 dopaminylation (H3Q5dop), a modification enriched at transcription start sites of active genes. Accumulation of H3Q5dop during abstinence drives enduring transcriptional programs associated with cocaine seeking. This project concerns the nuclear machinery which interprets this chromatin-embedded dopamine signal. The lab has identified a set of nuclear proteins that preferentially bind H3Q5dop relative to unmodified histone H3; they are enriched for regulators of RNA Polymerase II elongation. Among them, the polymerase-associated factor 1 complex (PAF1c) emerged as the strongest candidate. They now seek to determine the structural and functional basis of the H3Q5dop–PAF1 interaction and its role in regulating transcriptional elongation; and assess how this chromatin signaling axis in vivo is changed during cocaine re-exposure genome-wide, and how this affects transcriptional programs in the nucleus accumbens and relapse-related behaviors.

Basic Research

ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

Scott Bolkan, Ph.D., University of Iowa, seeks to better understand how internal states regulate brain activity. He has developed a novel statistical framework that reliably identifies internal states during decision-making behavior in humans and mice. It has shed light on how in periods of engagement, decisions are guided by reward-predicting sensory evidence, and in periods of disengagement, they are driven by past choices or habit. Despite transitioning between states in single sessions of behavior, this work also revealed that inactivation of the dorsomedial striatum in mice disrupted decisions selectively during the engaged state. This demonstrates that internal state can gate the causal involvement of brain regions in behavior and raises the question of whether this is a localized or globalized phenomenon. Expanding beyond the striatum, this project seeks to uncover the brain-wide neural mechanisms of internal decision-making states and their relevance to ADHD. The goal is to establish a mechanistic framework for understanding how internal states are generated and controlled.

Basic Research

Carolyn Gaiser, Ph.D., University Medical Center Rotterdam/Erasmus Medical Center, The Netherlands, observes that young people with ADHD are at increased risk for early substance use and are often treated with stimulant medications such as methylphenidate. These medications act on brain systems involved in reward and motivation. It remains unclear whether early treatment, or stopping treatment too soon, influences later risk of substance use. This project will use data from the Generation R Study in the Netherlands, a large long-term study that has followed children from before birth into adulthood. A combination of brain imaging and real-world treatment data provides an opportunity to understand how brain development and medication exposure together influence substance-use risk. By identifying early biological and treatment-related factors that predict substance use initiation, this research aims to improve early identification of vulnerable youth and support more personalized prevention and care strategies.

Basic Research

Diagnostic Tools/Early Intervention

Kenta Hagihara, M.D., Ph.D., Allen Institute for Brain Science, observes that receptors for different neuromodulators are often co-expressed within the same neurons, and that chemical systems likely operate in a concerted, combinatorial fashion. To understand how they do, Dr. Hagihara developed a method to monitor dopamine, serotonin, acetylcholine, and norepinephrine simultaneously in living rodents. He can observe this activity while mice engage in a decision-making game. The goal of this

research is to improve how we understand and treat disorders like ADHD. He will use specific genetic mouse models to see exactly how this delicate chemical balance is tuned differently in ADHD-like states. He will first characterize how these models differ from healthy subjects at the behavioral level, focusing on their choice efficiency and reaction times. By repeating the simultaneous measurements, he seeks to identify how these chemical dynamics are altered in disease models. Finally, he will test the effects of a common ADHD medication, modafinil, to measure how it changes the interplay between all four chemicals at once.

Basic Research

Shiori Honda, Ph.D., Research Foundation for the State University of New York, Stony Brook University, notes that studies investigating the substantia nigra (SN) and locus coeruleus (LC), the principal dopaminergic and noradrenergic brain nuclei, remain limited. Thus it is not known whether age-related differences in the SN and LC diminish with age, remain stable, or follow altered developmental trajectories during late childhood, a period when symptoms of ADHD often consolidate and treatment is commonly initiated. Clarifying these possibilities may help determine if developmental change in ADHD reflects delayed neural maturation or enduring neurobiological alteration. This study will enroll 60 children ages 7–14, including children with ADHD and typically developing participants, and use neuromelanin-sensitive magnetic resonance imaging (NM-MRI) to quantify neuromelanin (NM) accumulation in the SN and LC. The team seeks to determine whether neural patterns are more consistent with delayed maturation or stable neurobiological differences. They will also examine associations with dimensional symptom measures and executive function.

Basic Research

Aaron Kucyi, Ph.D., Drexel University, observes that neurofeedback interventions in ADHD have not shown reliable benefits for sustained attention. Problems may include selection of suboptimal neural targets, reliance on effortful cognitive strategies that are difficult for patients to follow, and data quality issues. The team recently developed a real-time fMRI (rt-fMRI) approach, termed network-based closed-loop neuromodulation, designed to overcome these limitations. This project will target competitive interactions between the default mode (DMN) and dorsal attention (DAN) networks, which are activated, respectively, during internally- and externally-oriented modes of attention. The team will leverage a covert neurofeedback strategy where target levels of DMN and DAN activation are reinforced through an implicit reward mechanism that requires minimal cognitive effort and thereby promotes patient compliance. They will apply rt-fMRI computational methods to acquire high-quality estimates of activity from individual-specific DMN and DAN regions, testing the effects of network-based closed-loop neuromodulation in adults with ADHD.

Next-Generation Therapies

Ellen McGinnis, Ph.D., Wake Forest University, notes office-based screening often fails to identify childhood mental health diagnoses, in part due to caregiver reporting challenges. Of children with a diagnosis, 62% are perceived as not having mental health problems by their parents. Of children without diagnoses, 21% are perceived as having problems if the parent exhibits psychological impairment. Dr. McGinnis works toward an objective tool for pediatricians to improve screening for child mental health. The team has developed a digital screening app that is secured on a child's waist and captures movement and vocal biomarkers while the child completes a short (<7 minute) battery of behavioral tasks. In two samples, the team has demonstrated that movement and vocal biomarkers paired with machine learning approaches can accurately identify child anxiety, depression, and ADHD. They now aim, across 2 years, to collect data from 50 children 5–10 years old to optimize digital phenotypes of mental health conditions, with the help of AI.

Diagnostic Tools/Early Intervention

Jorge Miranda-Barrientos, Ph.D., Johns Hopkins University/Lieber Institute for Brain Development, is interested in sustained attention, the ability to focus on an activity or stimulus over time. Attention is impaired across multiple neuropsychiatric disorders, including ADHD and schizophrenia. The team seeks to better understand the cellular mechanisms of sustained attention to support development of targeted, mechanism-based interventions to ameliorate attentional deficits and improve functional outcomes. This project focuses on the cellular and molecular mechanisms by which projection-defined medical prefrontal cortex (mPFC) circuits to catecholaminergic nuclei regulate sustained attention. To enhance translational impact, they hope to molecularly characterize mPFC-LC (locus coeruleus) projectors using single-nucleus RNA sequencing, which can facilitate identification of potential pharmacological targets for this cellular population. Overall, the aim is to link cellular mechanisms underlying circuit dynamics to molecular identity, providing a framework for the development of novel, targeted therapies for attentional impairments.

Basic Research

Mary Patton, Ph.D., University of Tennessee Health Science Center, will investigate a circuit underlying attentional deficits in a mouse model of 22q11 deletion syndrome (22q11DS), a genetic disorder that significantly predisposes individuals to psychiatric disorders characterized by attentional deficits, notably schizophrenia and ADHD. Results stand to further understanding of the neural circuits underlying attention deficits across psychiatric disorders and may help generate novel treatment options for this symptom. Thalamic signaling onto dorsal striatal cholinergic interneurons (CHIs) is necessary for identifying and filtering out relevant information from background noise. Following a salient environmental cue, excitatory synaptic transmission from the thalamus drives

CHIs to fire in a characteristic “burst-pause” manner, in which CHIs increase their firing rate before entering a prolonged silent period. In a mouse model of 22q11DS, the team finds increased thalamic-CHI synaptic transmission and an increase in CHI firing activity, suggesting altered burst-pause firing in these mice. They will test the hypothesis that enhanced thalamic-CHI synaptic transmission alters burst-pause activity in CHIs of 22q11DS mice and causes attentional deficits.

 *Basic Research*

Deepa Ramamurthy, Ph.D., University of California, Riverside, notes that impairments in both attention and reward processing are widespread across psychiatric conditions, yet the specific cellular mechanisms that regulate how the brain balances past and present influences remain poorly understood. This project investigates two populations of inhibitory neurons in sensory cortex, VIP neurons and NDNF neurons, that may serve as cellular gatekeepers of attention. Both cell types influence cortical processing through disinhibition, releasing nearby excitatory neurons from suppression and amplifying sensory signals. This “double negative” wiring enables selected sensory signals to become more prominent. Both cell types are influenced by acetylcholine and serotonin, but VIP and NDNF neurons occupy distinct positions within the cortex and are embedded in different local circuits, suggesting they may regulate separate components of attentional control. The goal of this research, conducted in mouse experiments tracking attentional shifts, is to determine how these two gatekeeper systems differ in function, how they interact to balance flexibility and stability in attention, and how they may be differentially disrupted in neuropsychiatric disorders.

 *Basic Research*

ANXIETY DISORDERS

Dario Aspesi, Ph.D., Georgia State University, studies biological mechanisms by which environmental stress alters the maternal brain. Much research focuses on circulating hormones, but hormones are also produced and regulated in the brain, where they can act locally to shape behavior. Pregnancy is marked by sustained high levels of 17 β -estradiol (E2), a primary form of estrogen, followed by a rapid decline after childbirth. Individual sensitivity to these hormonal shifts may contribute to psychiatric risk. The brain contains enzymes that convert testosterone into estradiol (E2) and dihydrotestosterone (DHT). This hormone-conversion system allows brain regions involved in caregiving to dynamically regulate emotional and social behavior. Disruption of this finely tuned balance may impair how mothers interpret and respond to infant cues. This project tests the hypothesis that chronic stress during late pregnancy and early postpartum disrupts this local steroid hormone balance within maternal brain circuits. It will explore in animal models whether stress alters how testosterone is converted into E2

and DHT in the brain, leading to changes in neural activity that impair infant-cue processing and result in fragmented or disorganized caregiving behaviors resembling features of postpartum anxiety.

 *Basic Research*

Sarah Banker, Ph.D., New York University, will explore biological pathways through which symptoms of depression and anxiety in pregnancy might alter fetal brain development. Using a combination of tools, the team will test whether changes in the mother’s physiology help explain how her mood and anxiety symptoms might impact the fetal brain. For example, disruptions to normal changes in sleep and nervous system regulation during pregnancy could influence how the fetal brain develops before birth. This study will draw on two independent cohorts of pregnant women, examining how self-reported depression and anxiety symptoms relate to patterns of fetal brain development, particularly in brain areas involved in emotions and mental health, such as the hippocampus and the amygdala. It will also investigate whether poor sleep or altered nervous system regulation (as indexed by heart-rate variability) in the mother help explain these patterns. Finally, the study will explore whether there are specific weeks of pregnancy when these associations are strongest.

 *Basic Research*

Veronica Begni, Ph.D., IRCCS Centro San Giovanni di Dio Fatebenefratelli, Italy, notes that mast cells, present throughout the brain, respond to stress hormones and when activated release a variety of signaling molecules, including histamine, cytokines, and proteases, which can influence neuronal activity, brain inflammation, and the integrity of the blood-brain barrier. Their role in determining vulnerability versus resilience to stress-induced depression remains largely unexplored. This project will investigate whether brain mast cells contribute to individual differences in vulnerability and resilience following chronic stress. Using a validated chronic mild stress model, the team will identify animals that develop depressive-like behaviors, specifically anhedonia, and those that remain resilient, and examine how mast cells differ between these groups at both the molecular and cellular levels, defining their transcriptional and epigenetic signatures. They will also test whether pharmacologically stabilizing mast cells after the emergence of depressive-like behavior can reverse these deficits, thereby establishing a causal role.

 *Basic Research*

Jennifer Bussell, Ph.D., Columbia University, is developing a novel approach to uncover circuit mechanisms regulating animals' desire to resolve punishment uncertainty, a state linked by computational psychiatry to OCD, anxiety, and depression. Building on prior work demonstrating that the orbitofrontal cortex (OFC) encodes the intrinsic value of uncertainty reduction in a reward-based information-seeking task for mice, Dr. Bussell designed an aversive information-seeking task in which mice choose whether to receive cues predicting unavoidable shock without altering shock probability. Preliminary evidence shows that mice exhibit stable individual preferences for such aversive information, and that OFC neurons predict reduction of threat-related uncertainty. She seeks to show that the OFC encodes a generalized value signal for reducing uncertainty and that in compulsive states this signal becomes selectively amplified and inflexible for aversive outcomes, leading to compulsive information seeking (i.e., an insatiable desire to reduce uncertainty).

 *Basic Research*

Flurin Cathomas, M.D., University of Zurich, Switzerland, notes that adipose tissue, beyond fat storage, is an active endocrine and immune organ that releases inflammatory signals, hormones, and metabolites into the bloodstream. He proposes that, in the context of obesity, chronic psychosocial stress shifts visceral adipose tissue toward an inflammatory state and alters what it secretes, and that these adipose-derived signals contribute to brain changes in reward circuitry that promote social withdrawal and reduced reward. Using a mouse model of chronic social stress in male and female mice maintained on a high-fat diet, the team seeks to quantify three depression-relevant behavioral outcomes to define how chronic stress changes visceral adipose biology and test whether adipose-derived signatures predict neurobiological changes at a key brain-body interface. They will also test if the GLP-1 drug semaglutide and an adipocyte-targeted genetic reduction of a top candidate mediator can normalize an adipose inflammatory state and prevent stress-induced behavioral and brain changes—counterpart to an ongoing human project examining semaglutide effects on brain health and reward processing in obesity.

 *Basic Research*

 *Next-Generation Therapies*

Boushra Dalile, Ph.D., KU Leuven, Belgium, notes gut bacteria produce molecules that can enter the bloodstream and reach the brain, where they can affect gene expression, inflammation, and emotional learning. One such molecule, butyrate, can influence gene expression to promote synaptic plasticity. It is produced when gut bacteria ferment dietary fiber found in complex carbohydrate-rich foods and in animals, and has been shown to enhance the brain's capacity to “unlearn” fear and strengthen extinction memories. This project seeks to learn more about how butyrate affects fear related processes in humans.

Dr. Dalile will investigate how butyrate shapes communication between key brain regions involved in fear and safety including the amygdala, hippocampus, and prefrontal cortex, and how it alters HDAC activity and histone acetylation in the blood, molecular switches that regulate memory formation. These mechanisms mirror those disrupted in PTSD and anxiety disorders. By identifying how a naturally occurring microbial metabolite can boost the brain's ability to regulate fear, this research has the potential to guide the development of novel treatment-enhancing strategies.

 *Basic Research*

 *Next-Generation Therapies*

Caitlyn Edwards, Ph.D., University of Massachusetts Medical School, notes evidence suggesting a potential role for norepinephrine (NE) neurons in the nucleus of the solitary tract (NTS), particularly those co-expressing prolactin-releasing peptide (PrRP), in stress behaviors and control of stress hormones. PrRP neuropeptide may also be important for stress-related behaviors. Guided by the finely tuned anatomy of this system and its likely communication to corticotropin-releasing factor (CRF)-expressing neurons in the ventral bed nucleus of the stria terminalis (vBNSTCRF) as well as in the paraventricular nucleus of the hypothalamus (PVHCRF), the hypothesis tested in this work is that PrRP/NE co-transmission from PrRP+ neurons modulates stress circuitry to coordinate behavioral and hormonal responses to stress. Through various experiments, the team hopes to gain insight into how PrRP+ neurons regulate responses in these key stress-related brain regions and drive stress behaviors and stress hormones. By pinpointing how this brainstem pathway amplifies stress behaviors and hormone release, this project could identify the PrRP pathway as a new entry point for future treatments for people with stress-related mental health disorders.

 *Basic Research*

Lief Fenno, M.D., Ph.D., Dell Medical School, University of Texas at Austin, notes that those who experience early life stress are significantly more likely to develop depression as adults. Does early stress leave a lasting imprint on the brain's reward circuitry—particularly on systems that use dopamine to regulate motivation and pleasure? The team seeks to confirm its hypothesis centered on astrocytes, now understood to actively shape how chemical signals move through the brain. Their work centers on OCT3, a protein found in astrocytes that acts as a molecular sponge to absorb excess dopamine and keep brain circuits in balance. OCT3 is directly suppressed by the stress hormone cortisol, so when stress hormones are chronically elevated, as they are following early life adversity, OCT3 may be persistently silenced, leaving dopamine dysregulated and reward circuits vulnerable. They will conduct experiments seeking to show that OCT3 is a key mediator of the lasting brain changes that follow early life stress, and a therapeutic target that has not yet been exploited in this context.

 *Basic Research*

Sasha Leilani Fulton, Ph.D., Columbia University, notes physical contact during stress can lower cortisol and calm the sympathetic nervous system, reducing anxiety and depression, yet we do not know which somatosensory neurons in the skin detect therapeutic touch, how those signals modulate the brain's stress regulation centers, or how to pharmacologically reproduce these effects for patients suffering from stress-related affective disorders. The team seeks to determine how a protective touch signal modulates the brain's stress response system with focus on the paraventricular nucleus (PVN) of the hypothalamus, which coordinates the hormonal stress response through CRH neurons, which drive cortisol release and amplify physiological stress, and oxytocin neurons, which promote social bonding and suppress CRH activity. They will also generate a high-resolution gene expression atlas of Mrgprb4Lin neurons and two related touch-neuron subtypes specialized to detect deep pressure and soft stroking. This mechanistic investigation into how peripheral social touch neurons protect the brain against stress may generate a molecular foundation for a new class of peripherally targeted antidepressant and anxiolytic therapies.

Basic Research

Andrew Gerlach, Ph.D., University of Pittsburgh, is studying cognitive and neural mechanisms sustaining worry and rumination, core symptoms of anxiety and depression. The goal is to test the hypothesis that dysfunctional belief-updating, a cognitive process in which individuals revise beliefs in response to new information, represents a key mechanism underlying repetitive negative thinking (RNT). Given the striking overlap in brain regions associated with both belief-updating and RNT, the team proposes that the competition for common neural resources plays a key role in the maintenance of RNT. This study will experimentally induce RNT to assess acute impact on belief-updating and investigate how neural signatures modulate that relationship. Eighty adults will complete a task under neutral and RNT-induced states, and a subset of 30 will complete the task during functional MRI imaging. Behavioral results will inform a larger program of research aimed at more thoroughly characterizing belief-updating deficits associated with RNT and informing psychotherapeutic targets.

Basic Research

Ling-Yu Huang, Ph.D., University of Rochester, suggests cognitive rigidity—a core feature of rumination, which is seen in depression, anxiety, PTSD, OCD, and eating disorders—may arise from distinct mechanisms. One is a failure to appropriately adjust the learning rate in response to informative feedback, resulting in insufficient updating of action–outcome mappings (the “blunted adjustment” account). Another is experience-reinforced negative belief priors, causing negative interpretations to dominate decision processes (the “reinforced negative prior” account). This study seeks to dissociate these candidate mechanisms using complementary behavioral paradigms and

multimodal neurophysiological measurements. High-density EEG and concurrent pupillometry will be used to quantify neuromodulatory responses during rule-switching tasks that probe cognitive flexibility under abstract and verbal-emotional contexts. By dissociating candidate mechanisms of cognitive rigidity within the same individuals, the hope is to identify the point(s) of failure underlying rumination-related rigidity.

Basic Research

Anthony Jang, M.D., University of California, Los Angeles, proposes that pathological anxiety may reflect a disruption in the ability to flexibly balance pursuit of goals with avoidance of potential threats, known as approach–avoidance decision-making. This project seeks to uncover the fear-related brain activity involved in approach–avoidance decisions by studying behavior in naturalistic environments. The team will use virtual reality (VR) technology to mimic real-life situations. Participants will wear a VR headset and freely walk through virtual environments containing desirable goals and locations associated with potential threat, requiring them to continuously balance reward-seeking with avoidance. The team will directly record brain activity during these tasks in participants already implanted with a clinically approved neural device for epilepsy or PTSD. Readings will be made from the amygdala and hippocampus. By identifying the neural circuits that govern fear-guided decisions, this work seeks to inform the development of targeted neuromodulation strategies for treatment-resistant anxiety disorders.

Basic Research

Jineun Kim, Ph.D., California Institute of Technology, seeks better understanding of how the brain integrates energy needs with environmental information to guide appropriate behavior. This project investigates how the brain normally balances these competing signals and why this balance can break down in eating and mood disorders. Dr. Kim focuses on the hypothalamus, which receives information from the body about energy status while also processing social and emotional cues from the environment. By integrating these signals, it helps animals prioritize behaviors that support survival. This project aims to understand how hypothalamic neural circuits compute behavioral priorities when animals face competing needs, such as feeding versus responding to social stress. The team will record the activity of individual neurons in freely moving mice while they navigate such competing situations. They hope to reveal whether distinct groups of neurons represent competing drives and how interactions between these groups shape behavioral choices. They will also examine how signals related to metabolic imbalance or chronic stress alter these neural circuits.

Basic Research

Thomas Kraynak, Ph.D., University of Pittsburgh, notes that interoception, the processing of internal bodily signals, plays an

important role in anxiety and related psychopathology. Cardiac interoceptive signals may contribute to the generation and maintenance of worry by serving as internal cues that increase perceived threat and sustain repetitive negative thinking. The dorsal anterior cingulate cortex (dACC) is well positioned to link these processes. This project will test the causal role of the dACC in severe worry and cardiac interoception using transcranial magnetic stimulation (TMS) combined with fMRI. It leverages an ongoing NIMH-funded study examining neural circuitry underlying acute psychological stress reactivity in 25 individuals. The study may provide causal evidence for a neural mechanism hypothesized to integrate bodily signaling with perseverative negative thinking. Findings could advance mechanistic models of anxiety and inform future neuromodulation approaches targeting excessive worry and interoceptive dysfunction in anxiety and related mood disorders.

Basic Research

Lauren Kreeger, Ph.D., University of Pennsylvania School of Medicine, notes that with high stress, neurons in the brain may become overly excitable at the sacrifice of precise computations about our sensory world. Precise computations are critical for understanding speech in noise and a loss of precision during anxiety could contribute to difficulties listening and understanding a conversation. The team uses stress in mouse models to study cellular mechanisms in the auditory brainstem and investigate how anxiety and depression can impact the first stages of auditory processing in the brain. This project focuses on neurons called octopus cells, which compete for the title of “fastest neuron in the brain,” their electrical properties allowing them to be precise and accurate computational machines. The team uses electrophysiological techniques to directly measure electrical activity in octopus cells in stressful and normal conditions. They aim to understand if this specialized neuron that is very good at processing speech in quiet, calm conditions can support listening in stressful, noisy environments. Deficits in octopus cell processing could contribute to deficits in hearing during anxiety.

Basic Research

Zhikai Liu, Ph.D., Harvard Medical School, will study how the heart communicates with the brain through neural pathways and how this communication influences anxiety-like behavior. The focus is on the vagus nerve. Preliminary work identified genetically defined subtypes of vagal neurons in the murine heart that detect the mechanical activity of the heart during each heartbeat. The team will test how heart-derived signals affect emotional state. The hypothesis is that a specific population of heart sensory neurons transmits heartbeat-related information to the brain and contributes to anxiety-like state changes. To test this, they will use mouse genetic tools to selectively silence, remove, or activate defined sensory neuron types and measure their effects on anxiety-related behaviors; and use established

anxiety essays and optogenetics to test whether induced anxiety-like behaviors depend on these sensory pathways. An effort will be made to identify the brain circuits that receive and process these heart-derived signals. This work moves beyond correlational measures in heart-brain communication to test a causal, cell-type-specific mechanism linking cardiovascular signals to anxiety-related brain states.

Basic Research

Xiaotang Lu, Ph.D., University of Illinois at Urbana-Champaign, wants to know, at synaptic resolution, how extinction learning suppresses fear expression. The basolateral amygdala (BLA) contains neuronal ensembles engaged during fear retrieval and during extinction. What is still missing is the wiring logic: how these ensembles are coupled, and which inhibitory microcircuits impose control at the point where behavior is expressed. The team seeks to generate an ensemble-resolved, cell-type-annotated synaptic map of BLA microcircuits that links fear and extinction ensembles within the same tissue volume. The hypothesis is that local inhibitory circuits implement the critical control between extinction and fear ensembles through a set of definable motifs. The wiring diagram obtained could help distinguish between competing models by reading out the synaptic architecture directly. By identifying specific inhibitory motifs and their cellular constituents, this work will nominate concrete circuit elements for subsequent causal tests. More broadly, it establishes a general strategy for translating clinically relevant brain states into mechanistic, synapse-level circuit hypotheses that can guide targeted intervention development.

Basic Research

Ellen McGinnis, Ph.D., Wake Forest University, notes office-based screening often fails to identify childhood mental health diagnoses, in part due to caregiver reporting challenges. Of children with a diagnosis, 62% are perceived as not having mental health problems by their parents. Of children without diagnoses, 21% are perceived as having problems if the parent exhibits psychological impairment. Dr. McGinnis works toward an objective tool for pediatricians to improve screening for child mental health. The team has developed a digital screening app that is secured on a child's waist and captures movement and vocal biomarkers while the child completes a short (<7 minute) battery of behavioral tasks. In two samples, the team has demonstrated that movement and vocal biomarkers paired with machine learning approaches can accurately identify child anxiety, depression, and ADHD. They now aim, across 2 years, to collect data from 50 children 5-10 years old to optimize digital phenotypes of mental health conditions, with the help of AI.

Diagnostic Tools/Early Intervention

Maria Medina Flores, Ph.D., Emory University, notes disruptions to the internal body clock can worsen anxiety by affecting how the brain uses and receives energy. Such changes in brain metabolism may contribute to feeling more on edge, restless, or emotionally overwhelmed. The team's research indicates mice with disrupted endothelial circadian clocks show loss of the typical daily rhythms of brain glucose entry and elevated anxiety-like behavior. They hypothesize that disruption of the circadian rhythm of glucose transport alters daily energy rhythms in the brain and contributes to persistent anxiety-like behavior. To test this, they will measure changes in glucose metabolism in key brain regions and anxiety-like behavior at multiple points across the daily cycle, and investigate whether restoring brain energy supply through increasing glucose uptake can normalize anxiety in mice lacking endothelial clocks. By integrating vascular clock biology, brain energy metabolism, and behavioral neuroscience, this study may uncover a previously unrecognized mechanism linking circadian regulation of brain energy to anxiety.

Basic Research

Farzaneh Najafi, Ph.D., Georgia Institute of Technology, notes that disorders including schizophrenia may involve problems in how the brain updates beliefs in response to unexpected events. This project will investigate how the cerebellum and posterior parietal cortex work together to support belief updating. Imaging studies in patients with psychiatric disorders suggest that communication between the cerebellum and cortex may be disrupted, but we do not yet understand how this affects learning at the level of brain circuits. The team has developed a behavioral task in mice that requires animals to learn patterns in the timing of events and to adjust when those patterns change. This provides a controlled way to measure how quickly and accurately beliefs are updated. Using advanced optical imaging techniques, they will record the activity of specific types of neurons in the cortex while animals perform this task, and selectively manipulate signals coming from the cerebellum to determine whether they influence how strongly the cortex responds to unexpected events. The hypothesis is that cerebellar output regulates how much weight the cortex gives to surprising events, which might shed light on disorders characterized by disrupted perception and belief formation.

Basic Research

Zachary Pennington, Ph.D., University of British Columbia, Canada, notes that only a small proportion of individuals who experience a traumatic event go on to develop PTSD. How variability in the brain's stress circuits confers susceptibility to stress-related illnesses is poorly understood. The team has identified a brain region that regulates stress vulnerability in mice, the anterior hypothalamic nucleus, or AHN. AHN neuron activity was found to reflect stress severity, and stress-vulnerable animals possessed a larger number of stress-responsive

AHN neurons. Dampening AHN activity led to a blunting of stress responses. The specific cell types within the AHN that regulate stress remain unknown. The team seeks to identify these neurons. They will permanently tag the specific subset of neurons in the AHN that respond to stress. They will then bi-directionally manipulate these neurons' activity to test their behavioral function. The overarching hypothesis is that this specific subset of neurons within the AHN titrates the magnitude of the stress response.

Basic Research

Rachel Romeo, Ph.D., University of Maryland, studies parent-child neural synchrony—the alignment of functional brain activity during live interaction—which is a promising candidate mechanism through which caregiver stress may become biologically embedded in children's developing emotion regulation systems. It remains unknown whether caregiver stress alters the stability of dyadic neural coordination and whether such alterations represent an early neurobiological pathway to internalizing risk. This project builds on Dr. Romeo's existing fNIRS hyperscanning study of 60 socioeconomically diverse parent-child dyads assessed at ages 3–5 years, including measures of caregiver stress and family context, neural synchrony during a mildly frustrating task, and children's internalizing symptoms and emotion regulation skills. Half of families qualified as low or extremely low income, enabling examination of how socioeconomic stress becomes biologically embedded. This study will extend this work by following up when children are 7–10 years old to obtain longitudinal measures of anxiety and depression outcomes. Ultimately, this project seeks to move the field beyond documenting socioeconomic disparities toward identifying modifiable neurodevelopmental mechanisms and strengths-based family processes that can inform targeted prevention of mood and anxiety disorders.

Basic Research

Next-Generation Therapies

Michael Schappe, Ph.D., University of Illinois at Urbana-Champaign, notes that anxiety and panic attacks can be accompanied by debilitating and powerful internal sensations including sudden shortness of breath, chest tightness, or a frightening sense of gasping for air. Scientists have proposed panic disorders may begin due to heightened sensitivity of the body's "suffocation alarm system," but we still do not know exactly which cells in the body detect breathing problems, how they send signals to the brain, or how those signals are transformed into feelings of fear and anxiety. Breathing is monitored by sensory nerves that directly connect airways to the brain through the vagus nerve. The team has identified mechanisms of an airway-sensing circuit that reflexively triggers a gasping reflex, distressed breathing, and panic-like behaviors resembling respiratory crisis. It senses airway closure in the lungs through a rare group of sensory cells and the vagus nerve, which can be turned on and

BBRF Grants Are Making a Difference

Research supported by BBRF grants is playing a vital role on some of the most important fronts in the fight against mental illness

The First Rapid-Acting Antidepressants

In 2019, the FDA approved esketamine, the first-ever rapid-acting antidepressant for patients with treatment-resistant depression, and brexanolone, which can lift postpartum depression within 48 hours. 90 BBRF grants over 20 years helped build the foundation for these long-sought advances.

Non-Invasive Brain Stimulation to Treat Depression, OCD, PTSD

BBRF grants seeded research which led to FDA approval in 2008 of rTMS (repetitive transcranial magnetic stimulation) for treatment-resistant major depression. BBRF grantees are now testing more powerful and faster-acting brain-stimulation technologies with a wide range of potential applications.

Computer-Guided Cognitive Remediation for Enhanced Recovery in Schizophrenia

Recovery may be possible for more people with schizophrenia and other disorders in which cognitive function is impaired, including bipolar disorder and depression. Recently, BBRF-funded scientists clinically validated computer-guided methods of enhancing verbal and auditory learning capacity, processing speed, working memory, and recall ability in chronic schizophrenia patients.

Lowering the Child's Mental Illness Risk via Maternal Choline Supplements

BBRF grantees have pioneered choline supplementation in the diet of pregnant women to reduce the risk of mental illness in children. Today, the American Medical Association recommends including choline in prenatal vitamin supplements.

Harnessing Stem Cell Technology to Study Autism, Schizophrenia

BBRF grantees have pioneered the use of stem-cell technologies to create functioning brain “organoids”—living test-beds that can be used to assess new drug candidates as well as reveal how genetic variations cause pathologies in the fetal brain as it develops. This research is especially pertinent in autism, schizophrenia and other disorders with developmental roots.

Computer-Guided Early Diagnosis of Mental Illness

BBRF-funded investigators are training machines that, in turn, train themselves—ultimately, to a level of precision not possible in humans—to recognize potentially diagnostic patterns of clinical data or biological markers in schizophrenia, first-episode psychosis, major depression, and bipolar disorder.

off with neurobiological tools. The team will investigate how this specific internal sense contributes to and influences panic-related symptoms and behaviors in real-time, focusing on discovering how these “airway alarms” are represented in the brain and relate to other panic-inducing signals. Moving beyond broad theories about interoception, they hope to indicate concrete biological mechanisms that will establish whether a specific breathing-sensing circuit can directly drive anxiety.

Basic Research

Stefanie Sequeira, Ph.D., University of Virginia, is interested in experience that might increase risk for anxiety and depression in teens is engaging in negative social comparison (NSC) when using social media. NSC refers to teens’ tendency to compare themselves negatively to others who appear to be better off. High levels of NSC may lead to greater anxiety and depression, especially for teens at risk for anxiety and depression. The team is working with teens to design a brief digital intervention that targets their tendency to engage in NSC on social media; teens will be leading the design and development. The intervention will be tested in a small clinical trial with adolescents (ages 15-18) who report a tendency to engage in NSC on social media and elevated symptoms of anxiety or depression. This project involves adding an fMRI imaging component to the trial. Teens will complete scans before and after the intervention. At each scan, the team will examine activity in brain regions involved in processing social threat, thinking about oneself, and cognitive control. They will test whether activity in these regions might be linked to youths’ tendency to engage in NSC while using social media before and after the intervention.

Next-Generation Therapies

Basic Research

Shana Silverstein, Ph.D., Johns Hopkins University/Moser Research Institute at Kennedy Krieger, focuses on developmental mechanisms through which early experience reshapes social learning circuits. This project will study normative basolateral amygdala (BLA) recruitment during social learning and test whether early adversity accelerates this process. Testing the hypothesis that early caregiving adversity shifts the developmental timing of amygdala engagement, prematurely incorporating the BLA into social learning circuits during juvenility, the project will define normative developmental recruitment of the BLA during social learning in rats. They expect to find increased BLA Fos expression, enhanced calcium activity during entries into the socially conditioned context, and stronger neural-behavioral coupling in adolescents. They will test whether early caregiving adversity accelerates this developmental transition. Together, these studies could determine if early adversity alters the developmental timing of amygdala inclusion in social learning circuits, providing a mechanistic framework for the environmental origins of psychiatric vulnerability.

Basic Research

Melanie Stearns, Ph.D., University of South Florida, is exploring how circadian rhythm and brain circuits that govern stress reactivity interact to shape daily functioning in adolescents with PTSD. This PTSD-CLOCKS study will recruit 50 adolescents ages 13–17, comparing those with PTSD to a group without PTSD. The team will examine whether “social jetlag,” a mismatch between an individual’s internal circadian clock and their externally imposed schedule, is a hidden driver of heightened physiological stress reactivity in adolescents with PTSD. Participants will wear wrist monitors (actigraphy) and complete daily sleep diaries for 10 days. The protocol also includes Dim Light Melatonin Onset (DLMO) testing, which requires collecting saliva samples in low-light conditions to determine when melatonin production begins. The team will also measure physiological stress reactivity using markers of autonomic and neuroendocrine function. The hypothesis is that PTSD not only makes sleep more difficult but also disrupts synchronization of the circadian clock and the body’s stress-regulation systems. Such circadian misalignment is expected to amplify physiological stress reactivity, making adolescents more easily startled, less able to recover from stress, and more vulnerable to daily challenges. Understanding these interlocking biological and neural mechanisms could support moving beyond “one-size-fits-all” approaches to trauma treatment.

Basic Research

Rebecca Suthard, Ph.D., Boston University, notes that difficulties in learning to associate events in the environment with behaviorally-relevant outcomes can lead to exaggerated fear responses, difficulty distinguishing safety from threat, and remaining in a state of anticipation even when danger is absent. Neurons in the hippocampus form coordinated ensembles that encode relationships between internal and external stimuli across time, creating the basis of associative memory. These patterns are especially important when there is a delay between a warning cue and outcome. While neuronal activity has been studied extensively in this context, that of astrocytes has not. This project seeks to learn whether astrocytes directly contribute to forming or stabilizing the associations between stimuli and outcomes during memory, or if they work in parallel with neurons. Simultaneously monitoring astrocytes and neurons in the hippocampus of mice as they learn to associate a tone with a delayed, mildly-aversive stimulus and tracking activity across both cell types at single-cell resolution, they hope to determine how astrocytes coordinate with neuronal ensembles during learning. They will then test if reduction of astrocytic calcium signaling disrupts memory organization and behavioral performance.

Basic Research

Han Tan, Ph.D., University of California, Irvine, is interested in anxiety and social difficulties seen in illnesses like autism spectrum disorders, mood disorders, and anxiety disorders. This

project seeks to uncover how a genetic mutation alters a group of brain cells that regulate emotional and social behavior in a neurodevelopmental disorder called Schaaf-Yang syndrome, caused by mutations in the MAGEL2 gene and associated with anxiety and social difficulties. Using a mouse model, the team aims to understand how precise biological changes in the brain give rise to these behavioral challenges. They will examine how specific neurons in the hypothalamus behave during anxiety-related and social interactions. They hope to determine whether these cells respond abnormally during situations that typically provoke anxiety or require social decision-making. They will also test whether manipulating the activity of these neurons can improve behavioral outcomes. Insights gained may help explain broader mechanisms underlying anxiety and social dysfunction across psychiatric conditions.

Basic Research

Gregory Telian, Ph.D., University of California, San Francisco/Gladstone Institutes, will investigate behavioral and neural mechanisms by which stress induces anhedonia and alters effort-based reward seeking. He has developed a task that incorporates simultaneous high-density neural recordings across multiple brain regions, cell-type specific manipulations, and high-speed videography of fine-grained behavioral motifs. The team will use these tools to define how stress reshapes behavioral output and neural dynamics across an amygdala–prefrontal cortical–accumbens network. These experiments may help determine how activity across this network supports effort-based choice; the behavioral motifs that accompany escalating effort demands; and how stress perturbs both network dynamics and effort-related behavior. This approach could identify potential biomarkers of perceived effort and susceptibility to stress.

Basic Research

Emilio Valadez, Ph.D., University of Southern California, has performed research suggesting that relying less on plan-ahead control (“proactive control”) and more on in-the-moment control (“reactive control”) may heighten anxiety risk for youths with behavioral inhibition (BI). Most research has tested these processes in emotionally neutral settings. Because social anxiety is triggered by social threat, such as being watched or judged by peers, traditional lab tasks can miss brain processes that matter in real life. This project brings realistic social stress into a well-validated attention and memory task by adding brief blocks where children believe a peer is observing their performance and providing feedback, as EEG is recorded. The team will pilot the social version of the task with young adults to confirm the expected brain markers, then study a larger sample of children with and without BI ages 10–12 years, the years in which social anxiety typically emerges. The team hopes to isolate social context-specific changes in control and test how they relate to social anxiety. By revealing how peer-related social threat derails control processes in at-risk children, the project aims to

uncover actionable brain-based targets for earlier detection and for mechanism-guided prevention – such as training proactive control under social stress.

Basic Research

Diagnostic Tools/Early Intervention

Dale Zhou, Ph.D., University of California, Irvine, notes early life adversity, including early life unpredictability (ELU), can increase risk for depression. While accumulating evidence indicates ELU precedes and predicts the severity of anhedonia, the neural mechanisms underlying this relationship are unclear. One possibility is that ELU alters how brain regions integrate reward signals over time, according to memory adaptations to reward in the highly variable early-life environment. This project will use reinforcement learning models fit to behavior during reward-based decision tasks. These cognitive models isolate how reward and memory signals contribute to decisions. The team expects to find longer time windows of integration in the neural activity associated with memory and reward signals for individuals with high ELU and anhedonia. The team will leverage a cross-sectional cohort (n = 276) of children and youths. Data includes rich multimodal neuroimaging and clinical phenotyping, which will enable study of how neural timescales are linked to ELU and anhedonia. Longitudinal data from the Adolescent Brain Cognitive Development (ABCD) study will be used to test neurodevelopmental within-subjects changes in neural timescale and anhedonia (N = 5,798).

Basic Research

AUTISM SPECTRUM DISORDERS (ASD)

Alan Gerber, Ph.D., Children’s National Hospital, notes that autistic youth are about 4 times more likely to experience depression, which is strongly linked to increased risk for suicidality. This project explores reward sensitivity as a possible neural mechanism of depression in such young people, examining this in 60 autistic adolescents ages 12–17. Participants and caregivers will complete questionnaires assessing reward sensitivity and depressive symptoms. While undergoing electroencephalography (EEG), the youths will complete two reward-processing tasks designed to measure monetary and social reward response; the team will measure their Reward Positivity (RewP), a neural signal of reward response reflecting the brain’s sensitivity to positive and negative feedback. By directly comparing brain responses to monetary and social feedback, this study seeks to determine if depression is associated with reduced responsiveness to monetary reward, heightened sensitivity to social feedback, or a combination of both.

Basic Research

Lindsay Hayes, Ph.D., The University of Oklahoma Health Sciences Center, is interested mechanisms by which developmental immune activation programs long-term alterations in brain development and contributes to risk for neurodevelopmental disorders like schizophrenia and ASD. This project focuses on disruption of microglial maturation, which can profoundly alter neuronal connectivity and behavioral outcomes. The team will use a maternal immune activation (MIA) mouse model in which pregnant dams are delivered an immune stimulus during pregnancy and the offspring are then evaluated. The team hypothesizes that DNA methylation serves as an epigenetic imprint of prenatal immune stress in microglia, driving altered maturation and developmental functions. Among other objectives, they seek to determine the necessity and sufficiency of DNA methylation in regulating microglial maturation and phagocytosis in MIA and control offspring. This may demonstrate that disrupted epigenetic imprinting underlies aberrant microglial developmental functions and which DNA methylation machinery may underlie the imprinting.

 *Basic Research*

Mohsen Jamali, M.D., Ph.D., Harvard University/Massachusetts General Hospital, is interested in how understanding other people's thoughts, intentions, and emotions ("theory of mind") is fundamental to everyday social life. Differences in theory of mind are a core feature of autism spectrum disorder (ASD), particularly in more spontaneous or emotion-related aspects of social understanding. This research seeks to understand how the human brain coordinates activity across multiple regions in real time to support these abilities, specifically, how networks of brain regions work together to support theory of mind and how these network dynamics may differ along the continuum of autism-related traits. To do this, the team will study hospitalized adult patients temporarily implanted with intracranial depth electrodes for clinical seizure monitoring. They hope to provide a detailed account of how distributed brain networks dynamically coordinate to generate social inferences. This could help determine if different components of social understanding, such as explicit reasoning, spontaneous mentalizing, and emotion recognition, rely on shared or distinct neural circuitry, and how these network dynamics vary with autism-related characteristics.

 *Basic Research*

Hyopil Kim, Ph.D., Johns Hopkins University, notes that impaired social interaction is a hallmark feature of multiple primary neuropsychiatric diseases, including autism spectrum disorder (ASD) and schizophrenia, and is strongly associated with reduced long-range functional connectivity (FC) between frontal and posterior cortical regions. Although convergent reductions in FC have been observed across genetically distinct forms of these diseases, the interregional wiring patterns and single neuron projection architectures that support long-

range connectivity and social information flow remain poorly characterized. Dr. Kim aims to generate a brain-wide, high-resolution wiring diagram reflecting reduced long-range FC and disrupted social information flow, as gleaned in two ASD mouse models. Both exhibit reduced long-range FC between frontal and posterior cortical regions but differ in their structural organization. The hope is to identify diverse alterations in wiring underlying disrupted social signal processing, providing insight into structural connectopathies associated with social deficits and suggesting a novel class of connectivity-based therapeutic strategies for ASD.

 *Basic Research*

 *New Technologies*

George Mountoufaris, Ph.D., University of Texas Southwestern Medical Center at Dallas, notes that anxiety disorders occur in up to 40% of individuals with autism spectrum disorder (ASD); aggression is reported in up to 68%, and the lifetime risk of depression is elevated fourfold. Although hundreds of genes have been linked to ASD, individuals carrying different mutations often exhibit similar patterns of emotional dysregulation. This convergence suggests that diverse genetic alterations disrupt shared brain regions that regulate internal emotional states. The team will examine interconnected hypothalamic-limbic circuits that control social interactions, aggression, and responses to social stress—processes frequently disrupted in ASD. Using mouse models, they seek to determine whether and how distinct genetic risks converge on shared network dysfunction. They will also examine the transcriptional programs and cell type of behaviorally engaged neurons to identify molecular pathways linked to ASD-associated emotional dysregulation. By connecting genetic variation to cell types, transcriptional changes, circuit dynamics, and behavioral outcomes, this research aims to clarify how diverse ASD mutations produce common emotional symptoms.

 *Basic Research*

Han Tan, Ph.D., University of California, Irvine, is interested in anxiety and social difficulties seen in illnesses like autism spectrum disorders, mood disorders, and anxiety disorders. This project seeks to uncover how a genetic mutation alters a group of brain cells that regulate emotional and social behavior in a neurodevelopmental disorder called Schaaf-Yang syndrome, caused by mutations in the *MAGEL2* gene and associated with anxiety and social difficulties. Using a mouse model, the team aims to understand how precise biological changes in the brain give rise to these behavioral challenges. They will examine how specific neurons in the hypothalamus behave during anxiety-related and social interactions. They hope to determine whether these cells respond abnormally during situations that typically provoke anxiety or require social decision-making. They will also test whether manipulating the activity of these neurons can improve behavioral outcomes. Insights gained may help explain

broader mechanisms underlying anxiety and social dysfunction across psychiatric conditions.

 *Basic Research*

Shaoyuan Zhu, Ph.D., Stanford University, studies neuronal wiring processes that go awry in neurodevelopmental conditions including ADHD, autism (ASD), and intellectual disability, specifically, molecular instructions that tell specific neurons which partners to connect to. This project investigates a family of proteins called Latrophilins and their binding partners, the Teneurins, which together act as a molecular “address code” guiding the formation of hippocampal circuits. Genetic studies have identified LPHN3 (ADGRL3)—the gene encoding Latrophilin-3—as an ADHD risk gene; related TENEURIN genes have been linked to ASD and intellectual disability. It remains unknown how disruption of Latrophilin–Teneurin signaling damages hippocampal circuits and produces cognitive symptoms. To address this, the team has generated mice lacking all three Latrophilin proteins in forebrain neurons. They will map when and where hippocampal architecture breaks down during development after Latrophilin loss, characterize resulting synapse defects at nanometer resolution, and perform a behavioral assessment to link circuit disruption to cognitive impairment. They will also test whether the physical binding between Latrophilins and Teneurins is what encodes the wiring specificity of two major hippocampal output pathways.

 *Basic Research*

BIOLOGY OF THE BRAIN

OPIOID-FREE PAIN RELIEF

Jonnathan Alvarado, Ph.D., Harvard University/Beth Israel Deaconess Medical Center, focuses on the parabrachial nucleus (PBN), where ascending pain signals from the spinal cord are transformed into the suffering-related components of pain. Inhibiting PBN activity can reduce or prevent chronic pain. Targeting it is tricky, as the PBN contains dozens of distinct cell types. Research needs to identify which specific neurons drive pain and find a way to target them selectively, while sparing cells that would engage the endogenous opioid system. The team has developed novel optical approaches to assess neuronal excitability and local circuit inhibition across thousands of PBN neurons in brain tissue from mice with and without chronic pain. They seek to determine the molecular identity of pain-sensitized neurons, and reveal the specific receptors and neuropeptides that distinguish pain-driving PBN populations from neurons expressing the mu opioid receptor and other neighboring cell types. They will test whether selectively inhibiting these populations produces analgesia in vivo, and whether relief occurs without the two hallmarks of opioid liability: dopamine release in the brain’s reward circuitry and suppression of breathing.

 *Basic Research*

 *Next-Generation Therapies*

GLuD RECEPTORS AND SYNAPTIC PLASTICITY

Dhanasak Dhanasobhon, Ph.D., Institut du Cerveau / Paris Brain Institute, France, seeks to determine how glutamate-delta (GluD) receptors regulate NMDA receptor activity and adult brain plasticity. By identifying how this system operates in healthy brains, and how it becomes disrupted, the team hopes to uncover mechanisms underlying cognitive dysfunction and reveal new targets for therapies designed to restore healthy brain function in a range of disorders, from mood disorders to schizophrenia. GluD receptors help regulate NMDA receptor function in the adult cortex. Originally believed to function mainly during early brain development, the lab has shown that they remain active in adulthood and continue to shape how NMDA receptors operate. Specifically, GluD receptors regulate how D-serine influences NMDA receptor signaling in adult cortical circuits. This involves a distinct subtype of NMDA receptor that persists into adulthood and helps set the limits of synaptic plasticity.

 *Basic Research*

IMMUNE-DRIVEN MEMORY CHANGES POST-HEART ATTACK

Aaron Douglas, Ph.D., Icahn School of Medicine at Mount Sinai, notes that post-heart attack (MI) inflammation is not restricted to the heart, with recent studies demonstrating a complex neuroimmune interaction in the brain. An unanswered question is whether T cells infiltrate the brain after MI, mediating behavioral and psychiatric outcomes. There is evidence of a pathogenic and protective role for innate-like T cells in MI-mediated cognitive decline. Whether changes occur in the immune landscape in the brain and brain-bordering tissues such as the skull bone-marrow and meninges are among the questions driving this project. The team’s data indicate MI mice exhibit increased anxiety-like behavior and memory impairments compared to sham controls. Notably, the mice display both retrograde (former memories) and anterograde (new memories) amnesia for an object memory task, coinciding with decreased activity in the dentate gyrus. Memory engram reactivation is also impaired post-MI, suggesting disrupted memory recall processes. The hypothesis to be tested is whether changes in T cell proportions in the brain, skull bone marrow, and meninges following experimental MI, lead to subsequent neurological changes and cognitive decline.

 *Basic Research*

FUNCTIONAL BRAIN AGE

Kartik Iyer, Ph.D., QIMR Berghofer Medical Research Institute, Australia, has developed the Functional Brain Age platform, an AI-driven tool that converts EEG signals into a clinically interpretable index of age-typical versus atypical brain function. This project aims to validate and extend Functional Brain Age across childhood and adolescence in transdiagnostic

populations. The work conceptualizes development along a continuum of risk and resilience. Core brain networks supporting attention, executive control, emotional regulation, and social cognition undergo dynamic maturation across development. In some children, these trajectories diverge from age-expected norms, signaling vulnerability; in others, protective influences maintain or restore typical patterns. Dr. Iyer hopes to generate developmental growth charts of brain function, analogous to pediatric height and weight charts, to quantify the degree to which functional brain networks diverge from age-expected trajectories in each individual. The team seeks to identify when developmental divergence first emerges, define age-specific windows of heightened neuroplasticity and risk, and determine how protective factors shift trajectories toward resilience.

 *Diagnostic Tools/Early Intervention*

EARLY SOCIAL ISOLATION AND NEURODEVELOPMENT

Megan Kirchgeßner, Ph.D., New York University, will test how the sensory vs. social aspects of early-life social isolation impact auditory cortical development and plasticity for vocal processing and later-life sensory-driven maternal behavior. She will record from auditory cortical neurons in young, postnatal mice and determine how neuronal tuning for vocalization features changes with acoustic experience and/or social isolation. The team will follow many of these animals into adulthood to determine how different aspects of their early-life experiences impact later acquisition of maternal behavioral responses to vocalizing pups, and whether these behavioral consequences involve persistent changes in auditory vocal processing. The hypothesis is that early social isolation will impair experience-dependent auditory plasticity for vocalization features, with consequences for later-life acquisition of sensory-driven maternal behavior. Determining which aspects of early social isolation are detrimental to neurodevelopment will improve our current understanding of neuropsychiatric risk factors.

 *Basic Research*

LACTATION AND THE STRESS RESPONSE

Briana Nixon, Ph.D., Columbia University, notes that lactation involves a body-brain circuit, where the peripherally-detected suckling stimulus triggers neuroendocrine responses in the brain, including release of oxytocin. Some reports suggest lactation is also associated with blunted stress response. While the mammary gland is highly innervated, how these neurons integrate with central circuits in the brain is poorly understood. This project focuses on the interplay between stress and lactation, investigating how the body-brain circuits activated during lactation impact stress responses and anxiety-like behaviors in mice, and how chronic stress can further impact these circuits. Dr. Nixon has identified a population of neurons that experience mechanosensitive activity during lactation and developed a

genetic mouse line that depletes this population and loses this mechanosensitive activity. These mice have a profound defect in lactation, with dramatically slowed pup weight gain. It appears these mice have a disruption in the lactation-associated body-brain circuit, as these mice have a loss of activity of oxytocin neurons in the paraventricular nucleus of the hypothalamus (PVH) during nursing. This model provides an opportunity to specifically manipulate the neurons that normally gets activated at the start of the body-brain circuit during lactation, thus providing specificity and allowing for precise studies to delineate the consequences of their activation on stress responses during the postpartum period.

 *Basic Research*

COUNTERFACTUAL SIMULATION AND INTERNALIZING PSYCHOPATHOLOGY

Kate Nussenbaum, Ph.D., Boston University, studies neurocomputational mechanisms that confer vulnerability to psychopathology during the developmental period. Engaging in upward counterfactual simulation, in which individuals imagine how alternative choices they could have made would have led to better outcomes, may lead individuals to make better decisions in the future, but, in excess, may increase risk for internalizing psychopathology. It has been proposed that improvements in the capacity for model-based control—the use of internal models to simulate possible states of the world—may support adaptive planning and learning, but persistent biases and inflexibility in how internal world models are used may underlie maladaptive repetitive thought, including anxious worry and rumination. Research has been unable to isolate the specific content of model-based simulation. This project seeks to fill this gap by charting the neurodevelopmental emergence of biases and flexibility in counterfactual simulation, in participants ($n = 90$, ages 8–25 years) who will complete a behavioral task that enables precise computational characterization of counterfactual simulation, while undergoing functional magnetic resonance imaging. Results will contribute to efforts seeking to clarify how adaptive learning processes may confer risk for anxiety and depression.

 *Basic Research*

CELLULAR GATEKEEPERS OF ATTENTION

Deepa Ramamurthy, Ph.D., University of California, Riverside, notes that impairments in both attention and reward processing are widespread across psychiatric conditions, yet the specific cellular mechanisms that regulate how the brain balances past and present influences remain poorly understood. This project investigates two populations of inhibitory neurons in sensory cortex, VIP neurons and NDNF neurons, that may serve as cellular gatekeepers of attention. Both cell types influence cortical processing through disinhibition, releasing nearby excitatory neurons from suppression and amplifying sensory signals. This “double negative” wiring enables selected

sensory signals to become more prominent. Both cell types are influenced by acetylcholine and serotonin, but VIP and NDNF neurons occupy distinct positions within the cortex and are embedded in different local circuits, suggesting they may regulate separate components of attentional control. The goal of this research, conducted in mouse experiments tracking attentional shifts, is to determine how these two gatekeeper systems differ in function, how they interact to balance flexibility and stability in attention, and how they may be differentially disrupted in neuropsychiatric disorders.

 *Basic Research*

NEURONAL IDENTITY ACQUISITION AND FUNCTIONAL CONNECTIVITY

Federico Salas-Lucia, Ph.D., University of Chicago, notes that children with ADHD, schizophrenia, epilepsy, autism, and related disorders commonly present changes in the size and connectivity of specific brain regions. These defects may originate from selective neuronal vulnerability to external challenges during critical developmental periods, when neurons acquire their final identity and establish the connectivity and functionality of neuronal networks. One of these challenges could be inadequate exposure to thyroid hormone (T3). This project explores whether unregulated T3 level is important in the etiology of neurodevelopmental conditions and seeks to discover mechanisms involved in appropriate T3 signaling in neurons and their role in neuronal identity acquisition and functional connectivity. The team will study new iPSCs genetically deficient in DIO3 (neuronal enzyme type 3 deiodinase, which reduces T3 action in neural cells) and genetically normal control cells to define the effect of increased T3 action on real-time gene expression during neuronal identity acquisition and functional maturation. This may capture real-time gene expression changes associated with neuronal differentiation and identify developmental periods in which altered T3 states affect critical molecular and cellular processes in the developing human brain, leading to altered populations of neuronal subtypes, with functional brain consequences of relevance to neurodevelopmental disorders.

 *Basic Research*

BIPOLAR DISORDER

Upasana Bhattacharyya, Ph.D., Feinstein Institute for Medical Research/Northwell Health, is interested in specific biological pathways—such as neuroinflammation or synaptic pruning—in individual cases of schizophrenia and bipolar 1 disorder (BD), which share approximately 70% of genetic risk factors. The team aims to deconstruct shared genetic risk into specific, biologically interpretable components; and map these onto clinically meaningful outcomes. They hypothesize the shared genetic foundation of these disorders is composed of distinct biological axes that influence outcomes such as treatment response, illness severity, and physical health. They seek to integrate data on these biological axes with medical data derived from large-scale electronic health records of over 15,000 genetically characterized patients from Singapore and Finland. They will track how well these genetic risk scores derived from biologically grounded genetic components align with outcomes such as treatment resistance, risk for severe hospitalizations, and cardiometabolic complications. Benchmarking these refined polygenic scores against traditional genome-wide polygenic risk scores will support evaluation of whether a more granular approach provides the accuracy and inclusivity needed to better understand patient trajectories.

 *Basic Research*

Julianne Griffith, Ph.D., University of Pittsburgh, notes alterations in neurobehavioral processes related to motivation and reward, known as the positive valence systems (PVS), in anhedonia. Among children of anhedonic mothers, reduced activation in PVS may emerge in early childhood before the onset of symptoms and interfere with important developmental tasks, such as play, social approach, and exploration, conferring risk for persistent psychopathology. This study will investigate associations between maternal anhedonia, mother PVS function, and child PVS function, as well as the role of maternal positive emotion socialization behaviors in moderating these associations. In 75 mother-child pairs, it will test a model in which maternal invalidating and discouraging responses to children's positive affect ("dampening") strengthen biological risk pathways linking maternal anhedonia and reduced maternal PVS activation to child reduced PVS activation, whereas maternal responsive and encouraging responses to children's positive affect ("enhancing") weaken them. Mother and child PVS activation will be assessed using EEG during a reward task and happy-faces viewing task.

 *Basic Research*

Ben Huang, Ph.D., Weill Cornell Medical College, notes that because transitions between major mood episodes in bipolar disorder unfold over time, understanding them requires measuring brain activity as it changes rather than relying on static snapshots. His goal is to determine what drives the brain to

switch from one mood state to another and how these transitions can be guided or stabilized for therapeutic benefit. The team will use a mouse model to monitor and control neural activity across large areas of the brain, down to individual excitatory and inhibitory neurons. To trigger mood-like changes in the animals, they will manipulate their daily light cycle and track how the balance between excitation and inhibition shifts as the brain transitions between states. This approach enables capture of how instability emerges and spreads as the brain moves between mood states. To determine if these changes directly drive mood transitions, they will use genetic tools to test if reactivating functionally tagged neurons can alter how a transition progresses.

 **Basic Research**

Martin Lan, M.D., Ph.D., Research Foundation for Mental Hygiene, Inc./NKI, notes that despite their importance in treating depression, the mechanism of action of second-generation antipsychotics (SGAs) remains largely unknown. This project aims to elucidate this, so that better medications can be designed. The team will test the role of dopamine release in their antidepressant effect. Participants with bipolar disorder who are currently depressed will be recruited. The hypothesis is that participants with a lower neuromelanin-sensitive MRI signal, reflecting lower dopamine signaling, will have a better response to antidepressant treatment with an SGA. This association would show that the SGA may be working by reversing a lack of dopamine signaling in the brain. Participants will also have another type of MRI scan to measure blood flow in the brain. The hypothesis is increased blood flow caused by an SGA will be associated with its antidepressant effect. Such an association would suggest that the antidepressant effect is being caused by a dopamine-related mechanism.

 **Basic Research**

Syed Muhammad Ahsan Mehdi, M.D., University of Texas Health Science Center at Houston, notes the possibility that lithium exposure in late-life bipolar disorder may not determine cognitive trajectory and that biological heterogeneity among treated individuals may govern whether lithium engages neuroprotective mechanisms. This project proposes that lithium modulates a coordinated biological resilience network spanning synaptic plasticity, axonal integrity, and systemic aging regulation. The team will quantify 3 complementary peripheral biomarkers and construct a standardized composite Resilience Index integrating these domains to capture the balance between adaptive and degenerative processes. In a cohort of older adults with bipolar disorder, they will examine whether lithium exposure is associated with a higher Resilience Index and whether this biologically defined profile predicts baseline cognition and cognitive trajectory over time.

 **Diagnostic Tools/Early Intervention**

 **Basic Research**

Jochen Michely, M.D., Ph.D., Freie Universität Berlin/Charité-University Medicine Berlin, Germany, aims to better understand mechanisms that drive mood instability in bipolar disorder (BD), specifically, how brain-based processes drive the transition from normal mood fluctuations into pathological mood spirals. The team will explore the hypothesis that BD reflects a disturbance in how mood and reward processing influence each other. In everyday life, rewarding events lift our mood, and our mood, in turn, shapes how strongly we experience future rewards. When well-balanced, this two-way feedback loop supports flexible adaptation to our environment. But when excessively amplified, small emotional shifts can trigger runaway cycles in which mood and reward perception reinforce one another, pushing mood toward extremes. This project applies tools from cognitive computational neuroscience to measure these dynamics in BD with mathematical precision. Using a reward-based learning and decision-making task combined with real-time mood tracking and computational modeling, the team will estimate how strongly a person's current mood amplifies, or dampens, their sensitivity to rewards. This yields a quantitative computational measure of how tightly mood and reward processing are linked in an individual. They will assess whether these computational measures predict short-term symptom changes in patients.

 **Diagnostic Tools/Early Intervention**

 **Basic Research**

Francisco Diego Rabelo da Ponte, Ph.D., King's College London, UK, notes research indicating that bipolar disorder usually develops gradually. Early warning signs may include emotional instability, sleep disturbances, stress sensitivity, and changes in behavior. But these early signs vary widely from person to person, making it difficult for clinicians to recognize who is at risk. Genetics also plays an important role, but genetic risk alone cannot fully explain why some individuals develop the illness while others do not. This project aims to better understand how bipolar disorder develops over time. Using data from two large long-term studies that have followed more than 34,000 people from birth into adulthood, it will examine patterns of emotional and behavioral changes across the life course. Advanced computational methods will be used to identify common developmental pathways that occur before bipolar disorder is diagnosed. The project will also examine how genetic risk interacts with life experiences to influence these pathways.

 **Diagnostic Tools/Early Intervention**

Gayatri Saraf, M.D., Ottawa Hospital Research Institute, Canada, will recruit participants from a randomized controlled trial of psilocybin assisted therapy (PAT) in depression associated with bipolar II disorder that has not responded to treatment. Participants will either receive a 25mg dose of psilocybin or 1mg dose of psilocybin and will receive a PET/MRI scan. Scans will be made before and 1 week after a single dose of psilocybin. The

team will compare changes in the brain before and after the dose of psilocybin. The main goal is to see whether there are changes in synaptic density in specific brain areas that are involved in BD and if any changes in synaptic density are associated with changes in memory, thinking, or mood. Results from this study may shed light on how psilocybin acts as an antidepressant.

 *Next-Generation Therapies*

 *Basic Research*

Marlene Tahedi, M.D., Ph.D., University of Zurich, Switzerland, hypothesizes that common polygenic risk for bipolar disorder (BD) partly manifests through structural and functional variations in central circadian circuits, contributing to the characteristic circadian rhythm disruptions in BD. The suprachiasmatic nucleus (SCN) functions as the main circadian clock, receiving input primarily through the retinohypothalamic tract within the optic nerve. Recent evidence links structural alterations in the hypothalamic SCN region to evening chronotype in BD, independent of comorbid psychiatric conditions. This project focuses on the genetic basis of these neuroanatomical circadian features and their specificity to BD compared to affective or psychotic disorders. The team will examine whether BD polygenic risk scores correlate with key circadian neuroanatomical measures in healthy individuals and clinical cohorts, and whether these associations are pronounced in BD patients exhibiting circadian-predominant symptoms. The team will make use of multimodal neuroimaging and genetic data from the UK Biobank (>9,000 healthy controls) and clinical cohorts: BD (N=113, including 23 on lithium), major depressive disorder (N=205), and psychotic disorders (N=91).

 *Basic Research*

BORDERLINE PERSONALITY DISORDER

Songjun Li, M.D., Ph.D., Yale University, notes that in individuals with cluster B personality disorder and trauma-related conditions, socio-affective flexibility is severely impaired, leading to rigid, maladaptive interpersonal patterns and poor decision making. A major developmental risk factor for these disorders is early life stress (ELS). This project utilizes a naturalistic behavioral paradigm in pairs of rats that requires them to engage in a series of complex decisions to either compete or cooperate for reward. Preliminary data suggest ELS behaviorally disrupts prosocial-specific decision-making, leading to the hypothesis that this is driven by perturbation of the neuronal balance between the normally coordinated activity of prefrontal brain networks connecting the anterior cingulate cortex to basolateral amygdala and anterior cingulate cortex to anterior insula, which together promote prosocial behavior. One part of this project will test whether ELS chronically restricts the network to a self-focused state and therefore prevents the

acquisition of cooperative strategies in susceptible animals. Another part seeks proof-of-principle data exploring how this dysregulation is sustained at the molecular level and whether it can be therapeutically reversed.

 *Basic Research*

Nicole Rigney, Ph.D., University of California, Los Angeles, notes that in PTSD the failure to appropriately modulate behavior in social contexts manifests as irritable behavior and reactive aggression. Emotional dysregulation also drives impulsive aggression in borderline personality disorder, and irritability is increasingly recognized as a prominent feature of treatment-resistant depression. Despite the transdiagnostic significance of impaired social sensitivity, the neural circuits that detect distress in others and modulate behavior accordingly remain poorly understood. A significant barrier has been a lack of behavioral paradigms that capture this socially modulated behavioral response. Dr. Rigney's team has discovered a clear example of social sensitivity in mice: when a male mouse encounters an acutely stressed intruder, it robustly suppresses its own aggression and increases affiliative allogrooming toward the stressed individual. This behavioral shift is driven by olfactory stress cues. They identified a neuronal population in the lateral septum that is both necessary and sufficient for this response. They now seek to determine the molecular identity and projection targets of stress-responsive lateral septum neurons, and to test whether chronic corticosterone exposure impairs both the behavioral response to stressed conspecifics and the activation of the underlying circuit.

 *Basic Research*

CHILDHOOD & ADOLESCENCE

Joseph Aloï, M.D., Ph.D., Indiana University School of Medicine, is interested in the potential of contingency management (CM), a behavioral intervention that reinforces abstinence via rewards in the context of treating substance-use disorders. This project will investigate how instrumental learning response and frontostriatal white matter connectivity shape cannabis-using youths' treatment response to CM. At the heart of CM is an instrumental learning process: youths must update the values they assign to cannabis reinforcers relative to non-drug reinforcers. Emerging evidence indicates that altered reward prediction error (RPE) signals and cannabis-specific reinforcement biases may interfere with this process. This project pilots a cannabis-related instrumental learning task in 30 cannabis-using youths to confirm it elicits expected behavioral and neural responses, specifically preferential choice of cannabis-associated stimuli and RPE-related activity in ventromedial frontal cortex and ventral striatum. It will also test whether white matter integrity in frontostriatal tracts predict CM treatment

outcomes, operationalized as reductions in 30-day cannabis use frequency.

Next-Generation Therapies

Basic Research

Rachel Bandler, M.D., Ph.D., Yale University, reports research from her lab showing that during development humans have a unique way of using the Cbln2 gene to assemble extra connections in the prefrontal cortex. Cbln2 appears to be linked to OCD, helping to organize how brain cells connect. When the gene is missing, mice show compulsive behaviors like excessive nest building. These mice improve when they are given standard OCD medication or a boost of the protein produced by the Cbln2 gene in the dorsal raphe. Dr. Bandler hypothesizes that OCD might start very early in life if Cbln2 is not functioning properly, causing the dorsal raphe and prefrontal cortex to misconnect. To test this, the team will use a modified “barcoded” virus to track how individual brain cells connect to each other in a strain of mice genetically modified to mimic human brain circuits. The goal is to better understand how these early brain connections form and potentially miswire in the hope of better understanding OCD pathology.

Basic Research

Natasha Chaku, Ph.D., Indiana University, is investigating links between puberty timing, the menstrual cycle, and internalizing problems. She notes 12%-14% of adolescent users of oral contraceptives (OCs) report serious mood-related side effects such as depression. These may occur because of how synthetic estrogens and progestins act on developing neurobiological systems including the fronto-limbic circuitry that supports cognitive control and emotion regulation. It remains unclear how risk for depression unfolds in the first months of use and whether it is associated with changes in neurocognitive processes. This project seeks to estimate trajectories of depression in first-time adolescent OC users and matched non-users across the first 90-days of use and the first year of use; and to examine patterns of cognitive control and emotion regulation among first-time adolescent OC users vs. controls to understand how changes in cognitive control and emotion regulation may contribute to depression risk. In assessing how adolescent OC users experience depression and cognitive/emotional dysregulation over the first months of use, the team may provide insights on how to improve clinical decision-making regarding OC initiation and continuation in relation to psychiatric vulnerabilities.

Diagnostic Tools/Early Intervention

Basic Research

Rebecca Cooper, Ph.D., Harvard University/Boston Children’s Hospital, studies psychotic-like experiences (PLEs), a transdiagnostic risk factor for adverse psychiatric, educational and functional outcomes. Emotion dysregulation is considered a predisposing factor for PLEs, but current assessments rely

on retrospective self-report or lab-based paradigms that lack scalability and ecological validity. Linguistic distancing—use of language that creates psychological distance from an emotive event—is an emotion regulation strategy that can be expressed through smartphone communication, providing an opportunity to measure emotion regulation at scale in a real-world setting. Dr. Cooper aims to validate language expressed in real-world smartphone communication as a digital marker for emotion regulation, using data from 500 early adolescents, quantifying its potential predictive value for emerging PLEs, over and above self-report measures of emotion regulation.

Diagnostic Tools/Early Intervention

Marc Dos Santos, Ph.D., Northwestern University, notes that while schizophrenia is often described as a disorder with fewer synapses in adulthood, several genetic risk factors show the opposite pattern in youth. Some high-risk genetic variants are linked to excessive connectivity during adolescence. This indicates a transient phase of hyperconnectivity during peri-adolescence which could lay the basis for altered brain function and cognitive problems in adulthood. To find molecules that might guide new synaptic treatments, the team found people with schizophrenia have lower CSF levels of synaptic protein PTPRD, a cell-adhesion and signaling protein at synapses that can be cleaved at the cell surface, releasing its outer portion into the extracellular fluid. The team believes the soluble extracellular portion of PTPRD may act as a normalizing signal for brain connectivity. In genetic mouse models of schizophrenia that show excessive connectivity during adolescence, a precisely timed dose during early adolescence could restore brain activity to healthy levels, a theory that will be tested in this project. It will also test if giving soluble PTPRD during adolescence improves brain activity and behavior in rodents. This could open a path to novel circuit-normalizing therapies based on endogenous brain-fluid proteins for schizophrenia.

Basic Research

Next-Generation Therapies

Travis Faust, Ph.D., University of Massachusetts Medical School, cites evidence that in schizophrenia, synaptic pruning is disrupted during adolescence in the prefrontal cortex, leading to excessive synapse loss. This research is driven by the question of how certain synapses are selected for removal and why particular brain regions and developmental periods are vulnerable. Dr. Faust has identified a mechanism that helps explain this selective vulnerability, involving communication and contacts between microglia and astrocytes. This project will test if genetic and environmental risk factors for schizophrenia disrupt astrocyte-based control of synapse vulnerability during adolescence in the prefrontal cortex, using mouse models linked to schizophrenia risk. The team will measure whether certain risk factors increase synapse vulnerability by altering astrocyte contact and whether restoring astrocyte contact can prevent abnormal synapse loss; they also seek

to identify differences in the proteins present at synapses closely contacted by astrocytes compared to those that are not.

Basic Research

Lief Fenno, M.D., Ph.D., Dell Medical School, University of Texas at Austin, notes that those who experience early life stress are significantly more likely to develop depression as adults. Does early stress leave a lasting imprint on the brain's reward circuitry—particularly on systems that use dopamine to regulate motivation and pleasure? The team seeks to confirm its hypothesis centered on astrocytes, now understood to actively shape how chemical signals move through the brain. Their work centers on OCT3, a protein found in astrocytes that acts as a molecular sponge to absorb excess dopamine and keep brain circuits in balance. OCT3 is directly suppressed by the stress hormone cortisol, so when stress hormones are chronically elevated, as they are following early life adversity, OCT3 may be persistently silenced, leaving dopamine dysregulated and reward circuits vulnerable. They will conduct experiments seeking to show that OCT3 is a key mediator of the lasting brain changes that follow early life stress, and a therapeutic target that has not yet been exploited in this context.

Basic Research

Carolyn Gaiser, Ph.D., University Medical Center Rotterdam/Erasmus Medical Center, The Netherlands, observes that young people with ADHD are at increased risk for early substance use and are often treated with stimulant medications such as methylphenidate. These medications act on brain systems involved in reward and motivation. It remains unclear whether early treatment, or stopping treatment too soon, influences later risk of substance use. This project will use data from the Generation R Study in the Netherlands, a large long-term study that has followed children from before birth into adulthood. A combination of brain imaging and real-world treatment data provides an opportunity to understand how brain development and medication exposure together influence substance-use risk. By identifying early biological and treatment-related factors that predict substance use initiation, this research aims to improve early identification of vulnerable youth and support more personalized prevention and care strategies.

Basic Research

Diagnostic Tools/Early Intervention

Maria Teresa Gallo, Ph.D., University of Milan, Italy, will use an animal model to investigate how early-life disruptions of the serotonin system affect depression-like behaviors and associated molecular changes in the brain and blood. A particular focus is on brain metabolism. Growing evidence indicates that disturbances in energy systems play a crucial role in major depressive disorder (MDD). Dr. Gallo will examine the effects of serotonergic manipulation during pregnancy and early postnatal life, assessing outcomes at multiple developmental stages. The team will also

test whether positive environmental interventions can serve as preventive strategies. Environmental enrichment, providing stimulating surroundings, social interaction, and opportunities for physical activity have been shown to strengthen brain resilience in animal studies. The proposed research will examine whether such interventions can normalize metabolic alterations and reduce specific depression-like behaviors, offering insights into preventive approaches that do not rely on medication.

Basic Research

Alan Gerber, Ph.D., Children's National Hospital, notes that autistic youth are about 4 times more likely to experience depression, which is strongly linked to increased risk for suicidality. This project explores reward sensitivity as a possible neural mechanism of depression in such young people, examining this in 60 autistic adolescents ages 12–17. Participants and caregivers will complete questionnaires assessing reward sensitivity and depressive symptoms. While undergoing electroencephalography (EEG), the youths will complete two reward-processing tasks designed to measure monetary and social reward response; the team will measure their Reward Positivity (RewP), a neural signal of reward response reflecting the brain's sensitivity to positive and negative feedback. By directly comparing brain responses to monetary and social feedback, this study seeks to determine if depression is associated with reduced responsiveness to monetary reward, heightened sensitivity to social feedback, or a combination of both.

Basic Research

Julianne Griffith, Ph.D., University of Pittsburgh, notes alterations in neurobehavioral processes related to motivation and reward, known as the positive valence systems (PVS), in anhedonia. Among children of anhedonic mothers, reduced activation in PVS may emerge in early childhood before the onset of symptoms and interfere with important developmental tasks, such as play, social approach, and exploration, conferring risk for persistent psychopathology. This study will investigate associations between maternal anhedonia, mother PVS function, and child PVS function, as well as the role of maternal positive emotion socialization behaviors in moderating these associations. In 75 mother-child pairs, it will test a model in which maternal invalidating and discouraging responses to children's positive affect ("dampening") strengthen biological risk pathways linking maternal anhedonia and reduced maternal PVS activation to child reduced PVS activation, whereas maternal responsive and encouraging responses to children's positive affect ("enhancing") weaken them. Mother and child PVS activation will be assessed using EEG during a reward task and happy-faces viewing task.

Basic Research

Tina Gupta, Ph.D., University of Oregon, notes anhedonia symptoms tend to coincide with pubertal maturation. Prior to puberty, internalizing symptoms like depression are

approximately equal between boys and girls. The onset of puberty is where the differences start to emerge; girls tend to show higher rates of depressive symptoms than boys. Influences of puberty on neurodevelopment extend beyond just onset, which underscores the importance of investigating pubertal hormones throughout adolescence. This study will test the nature of associations between pubertal hormone levels and brain structure of reward-specific regions, and how they predict anhedonia development two-years later. The team leverages data from an ongoing longitudinal study of adolescent girls (N=170) that will provide 1) pubertal hormone levels, 2) structural brain properties of reward-related regions, and 3) anhedonia severity 2 years later. The hypothesis is that lower pubertal hormone levels will be associated with anhedonia development 2 years later for youth with lower volumes and less cortical thickness of reward-related regions.

 *Basic Research*

 *Diagnostic Tools/Early Intervention*

Shiori Honda, Ph.D., Research Foundation for the State University of New York, Stony Brook University, notes that studies investigating the substantia nigra (SN) and locus coeruleus (LC), the principal dopaminergic and noradrenergic brain nuclei, remain limited. Thus it is not known whether age-related differences in the SN and LC diminish with age, remain stable, or follow altered developmental trajectories during late childhood, a period when symptoms of ADHD often consolidate and treatment is commonly initiated. Clarifying these possibilities may help determine if developmental change in ADHD reflects delayed neural maturation or enduring neurobiological alteration. This study will enroll 60 children ages 7-14, including children with ADHD and typically developing participants, and use neuromelanin-sensitive magnetic resonance imaging (NM-MRI) to quantify neuromelanin (NM) accumulation in the SN and LC. The team seeks to determine whether neural patterns are more consistent with delayed maturation or stable neurobiological differences. They will also examine associations with dimensional symptom measures and executive function.

 *Basic Research*

Ka Ip, Ph.D., University of Minnesota, studies social disconnection in the context of teens with depressive symptoms. Such youths often struggle to sustain engagement during peer interaction and report diminished feelings of belonging. This project will examine whether patterns of “peer neural coupling” differentiate adolescents whose depressive symptoms persist from those who show clinically meaningful improvement over time. Peer neural coupling refers to the degree to which two individuals’ brain activity becomes aligned during shared interaction. Adolescents ages 12-17 with elevated depressive symptoms will participate in Imagination Studio, a 12-week creative arts after-school program providing structured

opportunities for peer engagement. The team will test whether trajectories of peer neural coupling track depressive symptom trajectories across the 12 weeks. This project, a longitudinal functional near-infrared spectroscopy (fNIRS) hyperscanning study to examine peer interaction in adolescents with depressive symptoms, seeks to shift focus from individual brain markers to interpersonal neural dynamics, distinguishing phenomena associated with symptom persistence versus improvement.

 *Next-Generation Therapies*

Kartik Iyer, Ph.D., QIMR Berghofer Medical Research Institute, Australia, has developed the Functional Brain Age platform, an AI-driven tool that converts EEG signals into a clinically interpretable index of age-typical versus atypical brain function. This project aims to validate and extend Functional Brain Age across childhood and adolescence in transdiagnostic populations. The work conceptualizes development along a continuum of risk and resilience. Core brain networks supporting attention, executive control, emotional regulation, and social cognition undergo dynamic maturation across development. In some children, these trajectories diverge from age-expected norms, signaling vulnerability; in others, protective influences maintain or restore typical patterns. Dr. Iyer hopes to generate developmental growth charts of brain function, analogous to pediatric height and weight charts, to quantify the degree to which functional brain networks diverge from age-expected trajectories in each individual. The team seeks to identify when developmental divergence first emerges, define age-specific windows of heightened neuroplasticity and risk, and determine how protective factors shift trajectories toward resilience.

 *Diagnostic Tools/Early Intervention*

Ellen Jopling, Ph.D., Dalhousie University, Canada, notes a key pathway through which neglect is thought to impact vulnerability to depression is alterations of the hypothalamic-pituitary-adrenal (HPA) axis. Dr. Jopling has demonstrated that stress responsivity does not simply “normalize” during puberty. Instead, patterns of recalibration across puberty differ by early caregiving history and are linked to later depressive symptoms. This project extends this work by following Bucharest Early Intervention Project (BEIP) participants into adulthood to determine whether puberty-driven changes in cortisol reactivity are associated with adult stress biology and risk for depression. The team hopes to elucidate how trajectories of HPA-axis reactivity from puberty through to adulthood predict vulnerability to depression, and whether clinical risk differs based on characteristics of the adult environment. By leveraging randomized assignment to early caregiving environments, this project could provide the causal evidence of whether adolescent recalibration of adversity-altered stress systems buffers or amplifies depression risk during adulthood, when stress physiology meets real-world demands.

 *Basic Research,*

 *Diagnostic Tools/Early Intervention*

Janne Tidselbak Larsen, Ph.D., Aarhus University, Denmark, focuses on children born to mothers who have eating disorders including anorexia nervosa, bulimia nervosa, or other unspecified eating disorders. This project will systematically examine key areas of development that together reflect the general physical, mental, and social well-being of children whose mothers have eating disorders. Using Danish nationwide registry data and longitudinal surveys, the team will study patterns in children's physical development throughout childhood (height, weight, and body mass index); their school performance (including national tests in primary school and grades from final exams in lower and upper secondary school); and self-reported well-being in school. They will compare children of mothers with different types of eating disorders to children whose mothers have no diagnosis of an eating disorder.

Basic Research

Ellen McGinnis, Ph.D., Wake Forest University, notes office-based screening often fails to identify childhood mental health diagnoses, in part due to caregiver reporting challenges. Of children with a diagnosis, 62% are perceived as not having mental health problems by their parents. Of children without diagnoses, 21% are perceived as having problems if the parent exhibits psychological impairment. Dr. McGinnis works toward an objective tool for pediatricians to improve screening for child mental health. The team has developed a digital screening app that is secured on a child's waist and captures movement and vocal biomarkers while the child completes a short (<7 minute) battery of behavioral tasks. In two samples, the team has demonstrated that movement and vocal biomarkers paired with machine learning approaches can accurately identify child anxiety, depression, and ADHD. They now aim, across 2 years, to collect data from 50 children 5–10 years old to optimize digital phenotypes of mental health conditions, with the help of AI.

Diagnostic Tools/Early Intervention

Kate Nussenbaum, Ph.D., Boston University, studies neurocomputational mechanisms that confer vulnerability to psychopathology during the developmental period. Engaging in upward counterfactual simulation, in which individuals imagine how alternative choices they could have made would have led to better outcomes, may lead individuals to make better decisions in the future, but, in excess, may increase risk for internalizing psychopathology. It has been proposed that improvements in the capacity for model-based control—the use of internal models to simulate possible states of the world—may support adaptive planning and learning, but persistent biases and inflexibility in how internal world models are used may underlie maladaptive repetitive thought, including anxious worry and rumination. Research has been unable to isolate the specific content of model-based simulation. This project seeks to fill this gap by charting the neurodevelopmental emergence of biases and flexibility in counterfactual simulation, in participants (n = 90, ages 8–25

years) who will complete a behavioral task that enables precise computational characterization of counterfactual simulation, while undergoing functional magnetic resonance imaging. Results will contribute to efforts seeking to clarify how adaptive learning processes may confer risk for anxiety and depression.

Basic Research

Jagadeesh Puvvula, Ph.D., University of Pennsylvania, notes flame retardants and plasticizers (phthalates) are synthetic compounds that are widely used in food packaging and consumer products. These compounds structurally and functionally mimic the role of natural hormones essential for neurodevelopment. Exposure to these chemicals during a susceptible period, such as pregnancy, can interfere with the endocrine system and may affect how an offspring's brain develops and how they behave. In addition, some newborns inherit genetic traits that increase their vulnerability to behavioral problems, and complex interactions between these genetic risks and environmental exposures may heighten the risk of adverse neurobehavioral outcomes. This study aims to examine the joint effects of genetic and environmental risks on the offspring's brain structure and behavior. The team also will evaluate gene-environment interactions using genetic markers that influence neurotransmission pathways in the offspring's brain and their effects on brain structure and behavior. Using data collected from 256 mother-child dyads, this prospective study seeks to elucidate the contributions of genetic and environmental risk factors towards offspring neurobehavior.

Basic Research

Manivel Rengasamy, M.D., University of Pittsburgh School of Medicine, is interested in mechanisms behind ketamine's effects on suicidality in adolescents. One theory is that ketamine's prophylactic effects on stress reactivity lead to downstream reductions in suicidal thoughts and behaviors. Ketamine, administered before a stressor, protects against maladaptive reactions to the stressor. The drug may reduce stress-induced inflammation, seen in the increase in peripheral inflammatory markers such as IL-6 and TNF α that follows a stress response. This study will examine effects of a single dose of IV ketamine over 1 week while measuring stress reactivity at different timepoints in a cohort of adolescents with recent suicidal thoughts and behaviors (STBs). Among the objects is to determine if baseline stress reactivity predicts ketamine's treatment effects on STBs. Findings may provide a foundation for a future randomized controlled trial in adolescents that can rigorously probe whether changes in stress reactivity, across a range of biological mediators, act as a mediator between ketamine treatment and STBs.

Basic Research

Next-Generation Therapies

Rachel Romeo, Ph.D., University of Maryland, studies parent-child neural synchrony—the alignment of functional brain activity during live interaction—which is a promising candidate mechanism through which caregiver stress may become biologically embedded in children’s developing emotion regulation systems. It remains unknown whether caregiver stress alters the stability of dyadic neural coordination and whether such alterations represent an early neurobiological pathway to internalizing risk. This project builds on Dr. Romeo’s existing fNIRS hyperscanning study of 60 socioeconomically diverse parent-child dyads assessed at ages 3–5 years, including measures of caregiver stress and family context, neural synchrony during a mildly frustrating task, and children’s internalizing symptoms and emotion regulation skills. Half of families qualified as low or extremely low income, enabling examination of how socioeconomic stress becomes biologically embedded. This study will extend this work by following up when children are 7-10 years old to obtain longitudinal measures of anxiety and depression outcomes. Ultimately, this project seeks to move the field beyond documenting socioeconomic disparities toward identifying modifiable neurodevelopmental mechanisms and strengths-based family processes that can inform targeted prevention of mood and anxiety disorders.

 **Basic Research**

 **Next-Generation Therapies**

Lauren Shuffrey, Ph.D., New York University, notes experiences early in life, particularly exposure to adversity such as household dysfunction, abuse, or neglect, may shape how the body responds to stress decades later. Childhood trauma may become “biologically embedded,” altering immune system function in ways that increase vulnerability to mental health disorders. The team has shown that pregnant individuals with a history of childhood adversity exhibit heightened activity across multiple inflammatory signaling pathways. This project seeks to determine if inflammatory immune patterns linked to early-life adversity can help identify women at elevated risk for perinatal depression before clinical symptoms arise. The team will examine networks of immune proteins measured during pregnancy and test whether specific inflammatory signatures predict depressive symptoms. For women whose stress-response systems were shaped by early adversity, embedded physiological shifts may unmask underlying vulnerability to mood disorders. By identifying immune markers of risk, this research aims to move the field toward earlier detection and more personalized prevention strategies.

 **Diagnostic Tools/Early Intervention**

 **Basic Research**

Shana Silverstein, Ph.D., Johns Hopkins University/Moser Research Institute at Kennedy Krieger, focuses on developmental mechanisms through which early experience reshapes social learning circuits. This project will study normative basolateral amygdala (BLA) recruitment during social learning and test whether early

adversity accelerates this process. Testing the hypothesis that early caregiving adversity shifts the developmental timing of amygdala engagement, prematurely incorporating the BLA into social learning circuits during juvenility, the project will define normative developmental recruitment of the BLA during social learning in rats. They expect to find increased BLA Fos expression, enhanced calcium activity during entries into the socially conditioned context, and stronger neural–behavioral coupling in adolescents. They will test whether early caregiving adversity accelerates this developmental transition. Together, these studies could determine if early adversity alters the developmental timing of amygdala inclusion in social learning circuits, providing a mechanistic framework for the environmental origins of psychiatric vulnerability.

 **Basic Research**

Huili Sun, Ph.D., University of Pennsylvania School of Medicine, cites evidence suggesting children with prenatal cannabis exposure (PCE) face higher risks of psychiatric conditions, including ADHD, anxiety, and depression. This project hopes to uncover underlying brain mechanisms during development through which PCE shapes these transdiagnostic vulnerabilities. The project seeks to clarify when PCE-related brain alterations emerge, how these changes evolve across early life, and how strongly they affect risks for emerging psychopathology. The team will use the large-scale developmental neuroimaging datasets with the recent release of infant data from the HEALthy Brain and Child Development (HBCD) Study to determine whether PCE-related brain alterations are detectable in infancy, whether they persist across development, and whether early brain deviations predict later psychiatric risks. They will quantify how the brain structural network shapes its dynamic activities. Controllability, measuring the brain’s capacity to support dynamic brain functions, has been implicated in multiple neurodevelopmental psychiatric disorders, offering a sensitive tool for detecting transdiagnostic psychiatric risk following PCE. Demonstrating that brain network deviations are detectable in the first months of life, and that they predict dimensional psychiatric risk years later, would establish infancy as a sensitive window for early intervention.

 **Basic Research**

Han Tan, Ph.D., University of California, Irvine, is interested in anxiety and social difficulties seen in illnesses like autism spectrum disorders, mood disorders, and anxiety disorders. This project seeks to uncover how a genetic mutation alters a group of brain cells that regulate emotional and social behavior in a neurodevelopmental disorder called Schaaf-Yang syndrome, caused by mutations in the MAGEL2 gene and associated with anxiety and social difficulties. Using a mouse model, the team aims to understand how precise biological changes in the brain give rise to these behavioral challenges. They will examine how specific neurons in the hypothalamus behave during anxiety-related and social interactions. They hope to determine whether

these cells respond abnormally during situations that typically provoke anxiety or require social decision-making. They will also test whether manipulating the activity of these neurons can improve behavioral outcomes. Insights gained may help explain broader mechanisms underlying anxiety and social dysfunction across psychiatric conditions.

Basic Research

Emilio Valadez, Ph.D., University of Southern California, has performed research suggesting that relying less on plan-ahead control (“proactive control”) and more on in-the-moment control (“reactive control”) may heighten anxiety risk for youths with behavioral inhibition (BI). Most research has tested these processes in emotionally neutral settings. Because social anxiety is triggered by social threat, such as being watched or judged by peers, traditional lab tasks can miss brain processes that matter in real life. This project brings realistic social stress into a well-validated attention and memory task by adding brief blocks where children believe a peer is observing their performance and providing feedback, as EEG is recorded. The team will pilot the social version of the task with young adults to confirm the expected brain markers, then study a larger sample of children with and without BI ages 10-12 years, the years in which social anxiety typically emerges. The team hopes to isolate social context-specific changes in control and test how they relate to social anxiety. By revealing how peer-related social threat derails control processes in at-risk children, the project aims to uncover actionable brain-based targets for earlier detection and for mechanism-guided prevention – such as training proactive control under social stress.

Basic Research

Diagnostic Tools/Early Intervention

Lisanne van Houtum, Ph.D., University Medical Center Rotterdam/Erasmus Medical Center, The Netherlands, notes that having a parent with severe mental illness (SMI), e.g., bipolar disorder, schizophrenia, or major depressive disorder, is the most important risk factor for developing mental illness. This project is part of a larger study (“PANDA”) exploring the earliest neurodevelopmental and socioemotional consequences related to this risk. The perinatal period, specifically, is a critical developmental window, making it the optimal time for interventions. Perinatal brain characteristics (e.g., intracranial volume [ICV] growth, connectome development) and infant socioemotional development may mediate how genetic and environmental factors ultimately translate into mental illness. The team is investigating if familial risk for SMI influences fetal and neonatal ICV growth and resting-state functional connectivity; and if fetal and neonatal ICV growth and resting-state functional connectivity relates to infant socioemotional development, in children of parents with vs. without SMI. The hope is that such data findings will inform development, implementation, and/or adaptation of early-life, low-threshold

preventive strategies for families at risk.

Diagnostic Tools/Early Intervention

Basic Research

Dale Zhou, Ph.D., University of California, Irvine, notes early life adversity, including early life unpredictability (ELU), can increase risk for depression. While accumulating evidence indicates ELU precedes and predicts the severity of anhedonia, the neural mechanisms underlying this relationship are unclear. One possibility is that ELU alters how brain regions integrate reward signals over time, according to memory adaptations to reward in the highly variable early-life environment. This project will use reinforcement learning models fit to behavior during reward-based decision tasks. These cognitive models isolate how reward and memory signals contribute to decisions. The team expects to find longer time windows of integration in the neural activity associated with memory and reward signals for individuals with high ELU and anhedonia. The team will leverage a cross-sectional cohort (n = 276) of children and youths. Data includes rich multimodal neuroimaging and clinical phenotyping, which will enable study of how neural timescales are linked to ELU and anhedonia. Longitudinal data from the Adolescent Brain Cognitive Development (ABCD) study will be used to test neurodevelopmental within-subjects changes in neural timescale and anhedonia (N = 5,798).

Basic Research

DEPRESSION

Jenna Adams, Ph.D., University of California, Irvine, studies biological mechanisms linking depressive symptoms and subtle memory changes in aging, arguing repetitive negative thinking and memory deficits arise from a shared vulnerability of hippocampal circuit dynamics driven by age-related dysregulation of the noradrenergic system. She notes the locus coeruleus (LC), a brainstem nucleus that provides the major noradrenergic input to the hippocampus, begins to accumulate pathology in mid-life, which may disrupt noradrenergic modulation of hippocampal dynamics. The project will test a model in which age-related disruption of LC-noradrenergic modulation constrains hippocampal circuit dynamics, biasing computations toward persistent, overgeneralized representations that manifest as repetitive negative thinking and reduced memory specificity. The team will leverage a sample of cognitively unimpaired older adults with depressive symptoms who have undergone extensive neuroimaging and behavioral characterization. Establishing a novel hippocampal-noradrenergic circuit signature of depression vulnerability in aging could provide a foundation for studying how LC-driven hippocampal circuit vulnerability interacts with tau accumulation to influence late-life depressive symptom trajectories and Alzheimer’s progression.

Basic Research

Dario Aspesi, Ph.D., Georgia State University, studies biological mechanisms by which environmental stress alters the maternal brain. Much research focuses on circulating hormones, but hormones are also produced and regulated in the brain, where they can act locally to shape behavior. Pregnancy is marked by sustained high levels of 17 β -estradiol (E2), a primary form of estrogen, followed by a rapid decline after childbirth. Individual sensitivity to these hormonal shifts may contribute to psychiatric risk. The brain contains enzymes that convert testosterone into estradiol (E2) and dihydrotestosterone (DHT). This hormone-conversion system allows brain regions involved in caregiving to dynamically regulate emotional and social behavior. Disruption of this finely tuned balance may impair how mothers interpret and respond to infant cues. This project tests the hypothesis that chronic stress during late pregnancy and early postpartum disrupts this local steroid hormone balance within maternal brain circuits. It will explore in animal models whether stress alters how testosterone is converted into E2 and DHT in the brain, leading to changes in neural activity that impair infant-cue processing and result in fragmented or disorganized caregiving behaviors resembling features of postpartum anxiety.

 *Basic Research*

Sarah Banker, Ph.D., New York University, will explore biological pathways through which symptoms of depression and anxiety in pregnancy might alter fetal brain development. Using a combination of tools, the team will test whether changes in the mother's physiology help explain how her mood and anxiety symptoms might impact the fetal brain. For example, disruptions to normal changes in sleep and nervous system regulation during pregnancy could influence how the fetal brain develops before birth. This study will draw on two independent cohorts of pregnant women, examining how self-reported depression and anxiety symptoms relate to patterns of fetal brain development, particularly in brain areas involved in emotions and mental health, such as the hippocampus and the amygdala. It will also investigate whether poor sleep or altered nervous system regulation (as indexed by heart-rate variability) in the mother help explain these patterns. Finally, the study will explore whether there are specific weeks of pregnancy when these associations are strongest.

 *Basic Research*

David Baranger, Ph.D., Medical College of Wisconsin, will test the idea that heavy drinking temporarily disrupts two brain systems linked to mood: reward processing (responding to positive outcomes) and cognitive control (staying focused and regulating impulses). Mood may worsen when these systems are dampened, leading to increased likelihood of additional heavy drinking, creating a self-reinforcing cycle. The team will collect data on 6 college students reporting intermittent heavy drinking along with moderate to severe depressive symptoms.

They will be added to an ongoing study of college students, yielding 36 participants in total. Each will complete 8–10 sessions across several months. At each session, participants will also complete brief questionnaires about recent mood and alcohol use, perform simple decision making and attention tasks, and undergo a 1 hour MRI scan. In the scanner, participants will complete tasks that engage reward and attention networks. This will make possible testing whether higher depressed mood is associated with weaker engagement of reward and control systems, especially after recent heavy drinking; if short-term reductions in these brain systems predict worse mood days later; and if neural measures help explain the short-term link between heavy drinking and subsequent mood.

 *Diagnostic Tools/Early Intervention*

 *Basic Research*

Veronica Begni, Ph.D., IRCCS Centro San Giovanni di Dio Fatebenefratelli, Italy, notes that mast cells, present throughout the brain, respond to stress hormones and when activated release a variety of signaling molecules, including histamine, cytokines, and proteases, which can influence neuronal activity, brain inflammation, and the integrity of the blood-brain barrier. Their role in determining vulnerability versus resilience to stress-induced depression remains largely unexplored. This project will investigate whether brain mast cells contribute to individual differences in vulnerability and resilience following chronic stress. Using a validated chronic mild stress model, the team will identify animals that develop depressive-like behaviors, specifically anhedonia, and those that remain resilient, and examine how mast cells differ between these groups at both the molecular and cellular levels, defining their transcriptional and epigenetic signatures. They will also test whether pharmacologically stabilizing mast cells after the emergence of depressive-like behavior can reverse these deficits, thereby establishing a causal role.

 *Basic Research*

Ellen Bradley, M.D., University of California, San Francisco/Gladstone Institutes, notes standard antidepressants are often ineffective for depression that occurs in Parkinson's disease (PD), potentially because PD involves widespread neurodegenerative changes that disrupt glutamate and other neurotransmitter systems implicated in mood regulation. It is currently unknown if ketamine might help in PD depression. Leveraging an ongoing, clinical trial of ketamine for PD depression, this project will add MRI at baseline and 24 hours post-treatment to identify functional connectivity changes and white-matter microstructural changes that may be markers of ketamine-induced neuroplastic remodeling. The team will evaluate whether greater changes in these neuroimaging metrics correlate with greater improvement in participants' depression symptoms. The project will also generate neuroimaging data for future trials aimed at predicting and optimizing ketamine

response among people with PD and related neurodegenerative conditions.

Next-Generation Therapies

Jennifer Bussell, Ph.D., Columbia University, is developing a novel approach to uncover circuit mechanisms regulating animals' desire to resolve punishment uncertainty, a state linked by computational psychiatry to OCD, anxiety, and depression. Building on prior work demonstrating that the orbitofrontal cortex (OFC) encodes the intrinsic value of uncertainty reduction in a reward-based information-seeking task for mice, Dr. Bussell designed an aversive information-seeking task in which mice choose whether to receive cues predicting unavoidable shock without altering shock probability. Preliminary evidence shows that mice exhibit stable individual preferences for such aversive information, and that OFC neurons predict reduction of threat-related uncertainty. She seeks to show that the OFC encodes a generalized value signal for reducing uncertainty and that in compulsive states this signal becomes selectively amplified and inflexible for aversive outcomes, leading to compulsive information seeking (i.e., an insatiable desire to reduce uncertainty).

Basic Research

Flurin Cathomas, M.D., University of Zurich, Switzerland, notes that adipose tissue, beyond fat storage, is an active endocrine and immune organ that releases inflammatory signals, hormones, and metabolites into the bloodstream. He proposes that, in the context of obesity, chronic psychosocial stress shifts visceral adipose tissue toward an inflammatory state and alters what it secretes, and that these adipose-derived signals contribute to brain changes in reward circuitry that promote social withdrawal and reduced reward. Using a mouse model of chronic social stress in male and female mice maintained on a high-fat diet, the team seeks to quantify three depression-relevant behavioral outcomes to define how chronic stress changes visceral adipose biology and test whether adipose-derived signatures predict neurobiological changes at a key brain-body interface. They will also test if the GLP-1 drug semaglutide and an adipocyte-targeted genetic reduction of a top candidate mediator can normalize an adipose inflammatory state and prevent stress-induced behavioral and brain changes—counterpart to an ongoing human project examining semaglutide effects on brain health and reward processing in obesity.

Basic Research

Marina Celestine, Ph.D., Harvard University/McLean Hospital, notes that invasive neurosurgical interventions like Deep Brain Stimulation (DBS) or precise lesion procedures can provide life-changing relief in various disorders and brain-based illnesses including treatment-resistant depression and OCD. This project is part of an effort to significantly improve procedure outcomes by mapping interindividual variability in brain regions involved

in symptoms, including the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), ventrolateral prefrontal cortex (vlPFC), amygdala, and insula. The team is utilizing data from a large group of epilepsy patients who underwent stereoelectroencephalography (sEEG) coupled with advanced brain imaging. By aggregating varied electrode trajectories, they aim to reconstruct high-resolution, dense maps of the circuits involved in OCD and depression at a level of detail that standard imaging cannot achieve. After identifying local connections between emotional and decision-making centers, they will use these “seed points” to trace global networks across the brain. The findings will be validated using anatomical data from non-human primates. The ultimate aim is to facilitate personalized neurosurgical strategies.

Next-Generation Therapies

Natasha Chaku, Ph.D., Indiana University, is investigating links between puberty timing, the menstrual cycle, and internalizing problems. She notes 12%-14% of adolescent users of oral contraceptives (OCs) report serious mood-related side effects such as depression. These may occur because of how synthetic estrogens and progestins act on developing neurobiological systems including the fronto-limbic circuitry that supports cognitive control and emotion regulation. It remains unclear how risk for depression unfolds in the first months of use and whether it is associated with changes in neurocognitive processes. This project seeks to estimate trajectories of depression in first-time adolescent OC users and matched non-users across the first 90-days of use and the first year of use; and to examine patterns of cognitive control and emotion regulation among first-time adolescent OC users vs. controls to understand how changes in cognitive control and emotion regulation may contribute to depression risk. In assessing how adolescent OC users experience depression and cognitive/emotional dysregulation over the first months of use, the team may provide insights on how to improve clinical decision-making regarding OC initiation and continuation in relation to psychiatric vulnerabilities.

Diagnostic Tools/Early Intervention

Basic Research

Mark Chen, Ph.D., Harvard University, examines how flexibility in the body's stress response system (autonomic nervous system, or ANS) and in brain circuits involved in emotional response (ER) relates to real-time ER flexibility and depression. Dr. Chen will use data from a recently completed study in which participants with depressive symptoms completed tasks involving cognitive control, acute stress, and emotion regulation while ANS activity was recorded using cardiac impedance and electrocardiography. Participants also completed an ecological momentary assessment protocol, reporting their ER strategies and stressor contexts four times daily over 21 days. He will test whether greater autonomic flexibility during the lab tasks is associated with greater real-time ER flexibility and fewer symptoms of depression and related disorders. Neuroimaging data will be used to examine how amygdala-PFC connectivity

changes from rest to an emotion regulation task and test whether greater neural flexibility predicts greater autonomic flexibility, greater real-time ER flexibility, and fewer depression symptoms.

Basic Research

Nick Corriveau-Lecavalier, Ph.D., Mayo Clinic, Jacksonville, notes that in some instances depressive symptoms may represent a prodromal feature, core manifestation, or consequence of neurodegenerative conditions such as Alzheimer's disease or Lewy body dementia. Early and accurate differential diagnosis is critical. Data-driven diagnostic tools powered by machine learning offer an opportunity to assist clinicians with diagnostically complex decisions. This project expands on StateViewer, a tool developed by the team which combines fluorodeoxyglucose positron emission tomography (FDG-PET) imaging with machine learning. The system is optimized for the differential diagnosis of dementia syndromes and achieves over 90% accuracy across 14 neurodegenerative conditions. This project seeks to extend the tool's utility beyond neurodegenerative diseases to primary psychiatric disorders, with an initial focus on major depression. The team will leverage clinical data from MDD patients who have undergone FDG-PET imaging and use machine learning to compare patterns of cerebral glucose metabolism in MDD (n = 150) with those observed in neurodegenerative dementia syndromes including Alzheimer's, Lewy body dementia, and frontotemporal dementia spectra (n = 2,121).

Diagnostic Tools/Early Intervention

Basic Research

Swastik De, Ph.D., Columbia University, studies circular RNAs (circRNAs), a class of covalently closed transcripts highly enriched in the mammalian brain and which have emerged as regulators of gene expression and, in many cases, as templates for protein synthesis through cap-independent internal ribosome entry site (IRES)-driven translation. CircRNAs are robustly dysregulated in schizophrenia and major depressive disorder (MDD). Whether such dysregulation has functional consequences at the protein level is not known. The structural mechanisms by which circRNA IRES elements recruit the ribosomal initiation machinery are undefined, limiting biological understanding and therapeutic exploitation of this RNA class. This project will test whether three circRNAs implicated in MDD and schizophrenia function as authentic IRES-driven translational templates in human neuronal cells and will map their protein interaction networks. It will also determine the first cryo-EM structure of a psychiatrically relevant circRNA IRES bound to human ribosomal initiation complexes. Findings may establish circRNA translation as a previously unrecognized molecular layer in psychiatric disease.

Basic Research

Caitlyn Edwards, Ph.D., University of Massachusetts Medical School, notes evidence suggesting a potential role for norepinephrine (NE) neurons in the nucleus of the solitary tract (NTS), particularly those co-expressing prolactin-releasing peptide (PrRP), in stress behaviors and control of stress hormones. PrRP neuropeptide may also be important for stress-related behaviors. Guided by the finely tuned anatomy of this system and its likely communication to corticotropin-releasing factor (CRF)-expressing neurons in the ventral bed nucleus of the stria terminalis (vBNSTCRF) as well as in the paraventricular nucleus of the hypothalamus (PVHCRF), the hypothesis tested in this work is that PrRP/NE co-transmission from PrRP+ neurons modulates stress circuitry to coordinate behavioral and hormonal responses to stress. Through various experiments, the team hopes to gain insight into how PrRP+ neurons regulate responses in these key stress-related brain regions and drive stress behaviors and stress hormones. By pinpointing how this brainstem pathway amplifies stress behaviors and hormone release, this project could identify the PrRP pathway as a new entry point for future treatments for people with stress-related mental health disorders.

Basic Research

Lief Fenno, M.D., Ph.D., Dell Medical School, University of Texas at Austin, notes that those who experience early life stress are significantly more likely to develop depression as adults. Does early stress leave a lasting imprint on the brain's reward circuitry—particularly on systems that use dopamine to regulate motivation and pleasure? The team seeks to confirm its hypothesis centered on astrocytes, now understood to actively shape how chemical signals move through the brain. Their work centers on OCT3, a protein found in astrocytes that acts as a molecular sponge to absorb excess dopamine and keep brain circuits in balance. OCT3 is directly suppressed by the stress hormone cortisol, so when stress hormones are chronically elevated, as they are following early life adversity, OCT3 may be persistently silenced, leaving dopamine dysregulated and reward circuits vulnerable. They will conduct experiments seeking to show that OCT3 is a key mediator of the lasting brain changes that follow early life stress, and a therapeutic target that has not yet been exploited in this context.

Basic Research

Gabriele Floris, Ph.D., Yale University, notes mechanistic understanding of psilocybin's antidepressant impact remains incomplete. Prior work has characterized psilocybin-induced dendritic spine formation but the molecular mechanisms enabling this plasticity remain unclear. Current models focus on neuronal events, leaving a critical gap: the contribution of non-neuronal cells to antidepressant-evoked structural plasticity. This project explores the possible role of microglia, with preliminary data indicating psilocybin rapidly reverses stress-induced microglial morphological changes in the prefrontal

cortex, consistent with reductions in activation and phagocytic markers. Dr. Floris hypothesizes that psilocybin restores a plasticity-permissive microglial state that enables dendritic spine growth. To test this, the team will quantify stress- and treatment-dependent changes in microglial phagocytic activity and dendritic spine engulfment to resolve the temporal dynamics of microglia–neuron interactions following psilocybin treatment, and determine whether these interactions precede and predict subsequent spine formation.

 *Basic Research*

 *Next-Generation Therapies*

Atsushi Fujimoto, M.D., Ph.D., University of Minnesota Medical Center – Fairview, notes the salience network plays a central role in integrating reward signals, autonomic state, and behavioral adaptation. Neuroimaging shows the anterior insula (aINS) and dorsal anterior cingulate cortex (dACC) are activated during risky decisions and mediate switching between large-scale brain networks as key salience network hubs. Clinical evidence further links dysregulated or excess salience network activity to addictive disorders and major depression. This project will define how neuronal populations within the salience network integrate autonomic and decision variables and determine whether this network causally governs affective choice. The team hopes to establish a mechanistic framework linking salience network dynamics to maladaptive risk behavior. This could provide insight into how autonomic and reward signals are integrated at the network level and lay the groundwork for circuit-based therapeutic strategies for addiction and related psychiatric disorders.

 *Basic Research*

Sasha Leilani Fulton, Ph.D., Columbia University, notes physical contact during stress can lower cortisol and calm the sympathetic nervous system, reducing anxiety and depression, yet we do not know which somatosensory neurons in the skin detect therapeutic touch, how those signals modulate the brain's stress regulation centers, or how to pharmacologically reproduce these effects for patients suffering from stress-related affective disorders. The team seeks to determine how a protective touch signal modulates the brain's stress response system with focus on the paraventricular nucleus (PVN) of the hypothalamus, which coordinates the hormonal stress response through CRH neurons, which drive cortisol release and amplify physiological stress, and oxytocin neurons, which promote social bonding and suppress CRH activity. They will also generate a high-resolution gene expression atlas of Mrgprb4Lin neurons and two related touch-neuron subtypes specialized to detect deep pressure and soft stroking. This mechanistic investigation into how peripheral social touch neurons protect the brain against stress may generate a molecular foundation for a new class of peripherally targeted antidepressant and anxiolytic therapies.

 *Basic Research*

Maria Teresa Gallo, Ph.D., University of Milan, Italy, will use an animal model to investigate how early-life disruptions of the serotonin system affect depression-like behaviors and associated molecular changes in the brain and blood. A particular focus is on brain metabolism. Growing evidence indicates that disturbances in energy systems play a crucial role in major depressive disorder (MDD). Dr. Gallo will examine the effects of serotonergic manipulation during pregnancy and early postnatal life, assessing outcomes at multiple developmental stages. The team will also test whether positive environmental interventions can serve as preventive strategies. Environmental enrichment, providing stimulating surroundings, social interaction, and opportunities for physical activity have been shown to strengthen brain resilience in animal studies. The proposed research will examine whether such interventions can normalize metabolic alterations and reduce specific depression-like behaviors, offering insights into preventive approaches that do not rely on medication.

 *Basic Research*

Andrew Gerlach, Ph.D., University of Pittsburgh, is studying cognitive and neural mechanisms sustaining worry and rumination, core symptoms of anxiety and depression. The goal is to test the hypothesis that dysfunctional belief-updating, a cognitive process in which individuals revise beliefs in response to new information, represents a key mechanism underlying repetitive negative thinking (RNT). Given the striking overlap in brain regions associated with both belief-updating and RNT, the team proposes that the competition for common neural resources plays a key role in the maintenance of RNT. This study will experimentally induce RNT to assess acute impact on belief-updating and investigate how neural signatures modulate that relationship. Eighty adults will complete a task under neutral and RNT-induced states, and a subset of 30 will complete the task during functional MRI imaging. Behavioral results will inform a larger program of research aimed at more thoroughly characterizing belief-updating deficits associated with RNT and informing psychotherapeutic targets.

 *Basic Research*

Julianne Griffith, Ph.D., University of Pittsburgh, notes alterations in neurobehavioral processes related to motivation and reward, known as the positive valence systems (PVS), in anhedonia. Among children of anhedonic mothers, reduced activation in PVS may emerge in early childhood before the onset of symptoms and interfere with important developmental tasks, such as play, social approach, and exploration, conferring risk for persistent psychopathology. This study will investigate associations between maternal anhedonia, mother PVS function, and child PVS function, as well as the role of maternal positive emotion socialization behaviors in moderating these associations. In 75 mother-child pairs, it will test a model in which maternal invalidating and discouraging responses to

children's positive affect ("dampening") strengthen biological risk pathways linking maternal anhedonia and reduced maternal PVS activation to child reduced PVS activation, whereas maternal responsive and encouraging responses to children's positive affect ("enhancing") weaken them. Mother and child PVS activation will be assessed using EEG during a reward task and happy-faces viewing task.

 **Basic Research**

Xuanming Guo, Ph.D., Icahn School of Medicine at Mount Sinai, notes research on immune contributions to depression has concentrated on innate inflammatory mediators—cytokines and microglial activation—while the role of the adaptive immune system, particularly antibodies, has received little attention. This project, conducted in mice, tests an "Antibody-Brain Axis" hypothesis: chronic psychosocial stress drives the production of brain-reactive autoantibodies that cross the blood-brain barrier via neonatal Fc receptor (FcRn)-mediated transcytosis, accumulate in the perivascular space, and promote neuroinflammation and depressive-like behavior. If experiments indicate that the Antibody-Brain Axis is causative, it could open several treatment avenues: FcRn antagonists approved for other autoimmune conditions could be repurposed for psychiatry; interventions targeting meningeal lymphatic-mediated antibody production could prevent autoantibody generation at its source; and brain-reactive IgG subclass profiles could serve as biomarkers to identify patients most likely to benefit from immune-targeted therapy.

 **Basic Research**

Tina Gupta, Ph.D., University of Oregon, notes anhedonia symptoms tend to coincide with pubertal maturation. Prior to puberty, internalizing symptoms like depression are approximately equal between boys and girls. The onset of puberty is where the differences start to emerge; girls tend to show higher rates of depressive symptoms than boys. Influences of puberty on neurodevelopment extend beyond just onset, which underscores the importance of investigating pubertal hormones throughout adolescence. This study will test the nature of associations between pubertal hormone levels and brain structure of reward-specific regions, and how they predict anhedonia development two-years later. The team leverages data from an ongoing longitudinal study of adolescent girls (N=170) that will provide 1) pubertal hormone levels, 2) structural brain properties of reward-related regions, and 3) anhedonia severity 2 years later. The hypothesis is that lower pubertal hormone levels will be associated with anhedonia development 2 years later for youth with lower volumes and less cortical thickness of reward-related regions.

 **Basic Research**

 **Diagnostic Tools/Early Intervention**

Umair Hassan, Ph.D., Stanford University, is studying sleep spindles, brief bursts of brain activity that occur during deep sleep. They are generated deep in the brain by the thalamus and travel to the outer brain surface, where they help strengthen memories and maintain healthy brain connections. Sleep spindles are likely altered in people with depression, and this project seeks to learn where in the brain these problems originate and how they unfold. Using recordings made directly from inside the brains of neurosurgical patients., Dr. Hassan will compare sleep spindle activity between patients with and without depression, tracking how they are generated in the thalamus, how they travel to the brain surface, and how individual neurons participate in this process. The team will also build a publicly available atlas mapping deep brain spindle features to patterns visible on standard scalp recordings, so that researchers and clinicians can infer what is happening inside the brain from a simple overnight sleep recording. By tracking how sleep spindles change across treatment, they will test whether spindle patterns can predict who responds to treatment and who does not.

 **Basic Research**

 **Diagnostic Tools/Early Intervention**

Chenfeng He, Ph.D., University of Wisconsin-Madison, notes that in Alzheimer's disease (AD) patients, depression worsens cognitive decline, reduces life quality, and complicates care. Clinically, depression in Alzheimer's (dAD) often looks similar to major depressive disorder (MDD) in people without dementia, yet treatments for MDD show limited benefit in dAD patients. This suggests underlying biological mechanisms may differ. This project seeks to define shared and distinct mechanisms to enable more precise diagnosis and more effective, mechanism-based treatments. Advances in single-cell genomics make it possible to measure gene activity in millions of cells from human postmortem brain tissues. Large single-cell datasets for both dAD and MDD are accumulating. This project will build on Dr. He's recently developed AI framework, PASCode, designed to identify "phenotype-associated cells"—subpopulations most strongly linked to a given clinical phenotype. Using PASCode models trained on each disorder, the team hopes to identify cell populations and gene programs that converge and diverge between the two disorders, providing a map of their shared versus distinct biology.

 **Basic Research**

 **Diagnostic Tools/Early Intervention**

Joseph Heffner, Ph.D., Yale University, investigates how prediction error processing contributes to decision-making problems in major depressive disorder (MDD) and obsessive-compulsive disorder (OCD). The research is rooted in the idea that if a person cannot accurately predict how a choice will make them feel, or learn from that feeling afterward, their ability to make adaptive decisions will suffer. Dr. Heffner will combine computational modeling of behavior, clinical interviews, and

analysis using AI tools of how participants use language to describe their mental health which he has developed. This research follows participants weekly over a three-week period. This longitudinal design allows the team to determine if observed computational deficits are stable traits or if they change as symptoms fluctuate. Dr. Heffner hypothesizes a specific “anxious-depression” dimension, identified through language data and validated with standardized questionnaires, which will explain why individuals across both MDD and OCD populations fail to use emotional signals constructively when making choices.

 *Basic Research*

 *Diagnostic Tools/Early Intervention*

Ling-Yu Huang, Ph.D., University of Rochester, suggests cognitive rigidity—a core feature of rumination, which is seen in depression, anxiety, PTSD, OCD, and eating disorders—may arise from distinct mechanisms. One is a failure to appropriately adjust the learning rate in response to informative feedback, resulting in insufficient updating of action–outcome mappings (the “blunted adjustment” account). Another is experience-reinforced negative belief priors, causing negative interpretations to dominate decision processes (the “reinforced negative prior” account). This study seeks to dissociate these candidate mechanisms using complementary behavioral paradigms and multimodal neurophysiological measurements. High-density EEG and concurrent pupillometry will be used to quantify neuromodulatory responses during rule-switching tasks that probe cognitive flexibility under abstract and verbal-emotional contexts. By dissociating candidate mechanisms of cognitive rigidity within the same individuals, the hope is to identify the point(s) of failure underlying rumination-related rigidity.

 *Basic Research*

Anna Ingebreton, Ph.D., University of Minnesota, notes that despite being used for over 20 years to treat refractory depression, vagus nerve stimulation (VNS) therapy lacks a reliable, objective way to determine whether stimulation settings are effectively engaging the vagus nerve. This project uses heart rate variability (HRV), a measure of the natural variation in the time between heartbeats, as a real-time indicator of whether VNS is effectively activating the vagus nerve. Because the vagus nerve directly influences heart rate through its connections to the heart, measuring changes in HRV during VNS can reveal whether the stimulation is reaching and activating the nerve’s fibers. The team will monitor heart activity continuously during VNS programming sessions to determine which settings produce measurable changes in HRV, seeking to identify settings that show clear evidence that the vagus nerve and related brain-body circuits are being activated. They will follow patients over 12 months to determine whether those who show HRV changes during initial programming go on to have better depression outcomes compared to those who do not.

 *Next-Generation Therapies*

Ka Ip, Ph.D., University of Minnesota, studies social disconnection in the context of teens with depressive symptoms. Such youths often struggle to sustain engagement during peer interaction and report diminished feelings of belonging. This project will examine whether patterns of “peer neural coupling” differentiate adolescents whose depressive symptoms persist from those who show clinically meaningful improvement over time. Peer neural coupling refers to the degree to which two individuals’ brain activity becomes aligned during shared interaction. Adolescents ages 12–17 with elevated depressive symptoms will participate in Imagination Studio, a 12-week creative arts after-school program providing structured opportunities for peer engagement. The team will test whether trajectories of peer neural coupling track depressive symptom trajectories across the 12 weeks. This project, a longitudinal functional near-infrared spectroscopy (fNIRS) hyperscanning study to examine peer interaction in adolescents with depressive symptoms, seeks to shift focus from individual brain markers to interpersonal neural dynamics, distinguishing phenomena associated with symptom persistence versus improvement.

 *Next-Generation Therapies*

Alec Jamieson, Ph.D., University of Melbourne, Australia, notes the precise neurobiological mechanisms underlying antidepressant discontinuation symptoms remain unclear. Animal research suggests that the dorsal raphe nucleus (DRN), the largest source of serotonin neurons in the brain, plays a key role in antidepressant discontinuation. This project will leverage ultra-high field (7 Tesla) imaging of the DRN to gain novel insights into the neurobiology of antidepressant discontinuation. By integrating deep neural and clinical phenotyping, Dr. Jamieson hopes to determine if DRN functioning is associated with relapse and/or withdrawal symptoms following cessation of antidepressants.

 *Basic Research*

 *Next-Generation Therapies*

Quan Jiang, Ph.D., Nanjing University, People’s Republic of China, hypothesizes that psilocybin induces durable antidepressant effects by selectively engaging defined pyramidal neuron subtypes and triggering activity-dependent circuit plasticity that reorganizes cortical network dynamics. Specifically, the team proposes that psilocybin alters the functional activity and connectivity of pyramidal neurons, resulting in persistent changes in neural circuit organization that support recovery of depression-relevant behavioral functions. To test this, they will use neural recording to monitor activity from identified pyramidal neuron populations in animal models before and after psilocybin administration. These experiments may help determine how psilocybin reshapes neuronal activity patterns and establish relationships between cell-type-specific circuit plasticity and behavioral outcomes relevant to depression.

 *Basic Research*

 *Next-Generation Therapies*

Ellen Jopling, Ph.D., Dalhousie University, Canada, notes a key pathway through which neglect is thought to impact vulnerability to depression is alterations of the hypothalamic-pituitary-adrenal (HPA) axis. Dr. Jopling has demonstrated that stress responsivity does not simply “normalize” during puberty. Instead, patterns of recalibration across puberty differ by early caregiving history and are linked to later depressive symptoms. This project extends this work by following Bucharest Early Intervention Project (BEIP) participants into adulthood to determine whether puberty-driven changes in cortisol reactivity are associated with adult stress biology and risk for depression. The team hopes to elucidate how trajectories of HPA-axis reactivity from puberty through to adulthood predict vulnerability to depression, and whether clinical risk differs based on characteristics of the adult environment. By leveraging randomized assignment to early caregiving environments, this project could provide the causal evidence of whether adolescent recalibration of adversity-altered stress systems buffers or amplifies depression risk during adulthood, when stress physiology meets real-world demands.

 *Basic Research*

 *Diagnostic Tools/Early Intervention*

Tomomi Karigo, Ph.D., Johns Hopkins University/Hugo W. Moser Research Institute at Kennedy Krieger, suggests postpartum mood symptoms often emerge when two factors converge: the abrupt drop in reproductive hormones after childbirth and psychosocial stress. Yet only some who are exposed to these changes develop postpartum depression (PPD). Dr. Karigo’s research aims at better understanding how hormonal changes and stress interact in the brain to influence caregiving behavior. This project focuses on hypothalamic brain circuits known to regulate social behavior and emotional state. Using mouse models, the team will test the hypothesis that hormone withdrawal combined with emotional stress biases a pathway connecting two hypothalamic regions toward a maladaptive state, preventing engagement of caregiving pathways. They will combine a hormone-withdrawal paradigm that mimics pregnancy- and parturition-related hormonal changes with an emotional stress model that induces psychological stress without physical injury, and assess how this combination alters behavior toward infant mice and affects underlying brain circuit function.

 *Basic Research*

Jineun Kim, Ph.D., California Institute of Technology, seeks better understanding of how the brain integrates energy needs with environmental information to guide appropriate behavior. This project investigates how the brain normally balances these competing signals and why this balance can break down in eating and mood disorders. Dr. Kim focuses on the hypothalamus, which receives information from the body about energy status while also processing social and emotional cues from the environment. By integrating these signals, it

helps animals prioritize behaviors that support survival. This project aims to understand how hypothalamic neural circuits compute behavioral priorities when animals face competing needs, such as feeding versus responding to social stress. The team will record the activity of individual neurons in freely moving mice while they navigate such competing situations. They hope to reveal whether distinct groups of neurons represent competing drives and how interactions between these groups shape behavioral choices. They will also examine how signals related to metabolic imbalance or chronic stress alter these neural circuits.

 *Basic Research*

Sang Hoon Kim, Ph.D., University of Pennsylvania, will investigate how the psychoactive drug 5-MeO-DMT restores hippocampal function and spatial encoding after chronic stress. Using a chronic restraint stress (CRS) mouse model, the team will evaluate whether a single dose of 5-MeO-DMT can rescue depression-like behaviors and cognitive decline. Central to this study is the use of advanced in vivo extracellular recordings to monitor the activity of granule cells (GCs) and mossy cells (MCs) in the dentate gyrus, the brain’s primary relay for discriminating between similar environments. The hypothesis is that chronic stress disrupts the “place fields” of these neurons, leading to a breakdown in the brain’s ability to distinguish different contexts, often observed in depressed patients. The team will use machine learning classification and spatial firing analysis to quantify how 5-MeO-DMT facilitates remapping, the reorganization of neural activity that supports flexible behavior, and distinct memory formation. The study thus may provide mechanistic insight into how fast-acting psychedelics repair the neural substrates of memory.

 *Next-Generation Therapies*

 *Basic Research*

Cole Korponay, Ph.D., Harvard University/McLean Hospital, notes biotyping studies demonstrating brain connectivity patterns from fMRI scans can improve prediction of treatment-response likelihood in major depression (MDD). Biomarkers based on functional connectivity (FC) may indicate where dysfunction is present, but not how it arises. This project aims to characterize heterogeneity in corticostriatal circuit dysfunction mechanisms in MDD and test the clinical utility of mechanism-based biomarkers for treatment prediction. Mechanistic corticostriatal profiles will be used to derive subtypes and testing whether mechanistic subtypes show stronger polygenic differentiation than conventional FC-based subtypes across a pre-specified panel of polygenic scores spanning affective (MDD, internalizing), circadian (insomnia), cognitive, metabolic (BMI), and immune/inflammatory domains. Clinical utility will be evaluated in two independent longitudinal treatment cohorts. The team will test whether mechanistic subtypes improve prediction of treatment response over clinical-only and FC-based baselines. Exploratory

analyses will examine whether specific biomechanism profiles are differentially predictive across interventions with distinct mechanisms of action.

Diagnostic Tools/Early Intervention

Thomas Kraynak, Ph.D., University of Pittsburgh, notes that interoception, the processing of internal bodily signals, plays an important role in anxiety and related psychopathology. Cardiac interoceptive signals may contribute to the generation and maintenance of worry by serving as internal cues that increase perceived threat and sustain repetitive negative thinking. The dorsal anterior cingulate cortex (dACC) is well positioned to link these processes. This project will test the causal role of the dACC in severe worry and cardiac interoception using transcranial magnetic stimulation (TMS) combined with fMRI. It leverages an ongoing NIMH-funded study examining neural circuitry underlying acute psychological stress reactivity in 25 individuals. The study may provide causal evidence for a neural mechanism hypothesized to integrate bodily signaling with perseverative negative thinking. Findings could advance mechanistic models of anxiety and inform future neuromodulation approaches targeting excessive worry and interoceptive dysfunction in anxiety and related mood disorders.

Basic Research

Lauren Kreeger, Ph.D., University of Pennsylvania School of Medicine, notes that with high stress, neurons in the brain may become overly excitable at the sacrifice of precise computations about our sensory world. Precise computations are critical for understanding speech in noise and a loss of precision during anxiety could contribute to difficulties listening and understanding a conversation. The team uses stress in mouse models to study cellular mechanisms in the auditory brainstem and investigate how anxiety and depression can impact the first stages of auditory processing in the brain. This project focuses on neurons called octopus cells, which compete for the title of “fastest neuron in the brain,” their electrical properties allowing them to be precise and accurate computational machines. The team uses electrophysiological techniques to directly measure electrical activity in octopus cells in stressful and normal conditions. They aim to understand if this specialized neuron that is very good at processing speech in quiet, calm conditions can support listening in stressful, noisy environments. Deficits in octopus cell processing could contribute to deficits in hearing during anxiety.

Basic Research

Victoria Marshe, Ph.D., Columbia University, notes the co-morbidity of neuropsychiatric symptoms presents a significant challenge for Alzheimer’s disease treatment. One of the most common symptoms is depression. Cognitive decline is accelerated in individuals with increasing late-life depressive symptoms and those with comorbid psychiatric disorders. This project seeks to expand understanding of molecular signatures

across different cell types, as well as genetic signatures associated with the presence of depression in late-life and in individuals with Alzheimer’s disease. Using single-cell transcriptomics, the team will create an atlas across different cell types in the brain to understand which genetic signatures are associated with depression in Alzheimer’s independently of neurodegenerative pathology; whether these signatures are affected before or after cognitive decline; and whether these signatures are driven by genetic variation. This may help expand the understanding of the overlapping risk between depression and Alzheimer’s disease and support the identification of novel pathways and targets.

Basic Research

Ellen McGinnis, Ph.D., Wake Forest University, notes office-based screening often fails to identify childhood mental health diagnoses, in part due to caregiver reporting challenges. Of children with a diagnosis, 62% are perceived as not having mental health problems by their parents. Of children without diagnoses, 21% are perceived as having problems if the parent exhibits psychological impairment. Dr. McGinnis works toward an objective tool for pediatricians to improve screening for child mental health. The team has developed a digital screening app that is secured on a child’s waist and captures movement and vocal biomarkers while the child completes a short (<7 minute) battery of behavioral tasks. In two samples, the team has demonstrated that movement and vocal biomarkers paired with machine learning approaches can accurately identify child anxiety, depression, and ADHD. They now aim, across 2 years, to collect data from 50 children 5-10 years old to optimize digital phenotypes of mental health conditions, with the help of AI.

Diagnostic Tools/Early Intervention

Aaron McInnes, Ph.D., University of Minnesota, notes that some failures in TMS depression therapy may be due to inadequate engagement of brain circuits involved in the illness, meaning that patients never receive an adequate “dose.” This might be mitigated if there were a method of reliably increasing TMS’ activation of the brain. Effects of brain stimulation depend not only on the properties of the stimulation, but also on the state of the targeted brain circuits (e.g., their relative susceptibility to activation). This is known as state-dependence. This project explores ways to deliver brain stimulation at moments when targeted circuits are most responsive. It seeks to identify neural activity patterns that indicate when key brain circuits are engaged. TMS for depression typically targets the left dorsolateral prefrontal cortex (DLPFC). Dr. McInnes has previously shown that rTMS is more effective when the brain is actively engaged in cognitive control, suggesting that delivering brain stimulation during these moments can promote circuit engagement. He will use machine learning to identify distinct brain activity signatures associated with cognitive control in both individuals with MDD and healthy volunteers, a potential foundation for future TMS approaches

that can time stimulation to moments when the brain is most responsive.

 *Basic Research*

 *Next-Generation Therapies*

Madaline Mocchi, Ph.D., University of Iowa, notes that while neurostimulation treatments for depression targeting affect-processing hubs (e.g., dorsolateral and subgenual cingulate cortex) can alleviate treatment refractory depression (TRD), the field lacks objective, individualized physiological markers to titrate stimulation and track recovery. Her team recently identified an electrophysiological biomarker of depression severity using intracranial EEG in patients with TRD, which robustly tracks fluctuations in depression severity on the order of minutes to hours. It may covary with mood change in response to non-invasive transcranial magnetic stimulation (TMS) treatment. This project aims to further translate this neural biomarker toward clinical use by validating autonomic (pupil size, heart rate) correlates that track and predict depression severity and treatment response. If successful, this biomarker tool could be a valuable clinical application for the personalized assessment of depression symptoms overtime in response to treatment.

 *Diagnostic Tools/Early Intervention*

 *Next-Generation Therapies*

Farzaneh Najafi, Ph.D., Georgia Institute of Technology, notes that disorders including schizophrenia may involve problems in how the brain updates beliefs in response to unexpected events. This project will investigate how the cerebellum and posterior parietal cortex work together to support belief updating. Imaging studies in patients with psychiatric disorders suggest that communication between the cerebellum and cortex may be disrupted, but we do not yet understand how this affects learning at the level of brain circuits. The team has developed a behavioral task in mice that requires animals to learn patterns in the timing of events and to adjust when those patterns change. This provides a controlled way to measure how quickly and accurately beliefs are updated. Using advanced optical imaging techniques, they will record the activity of specific types of neurons in the cortex while animals perform this task, and selectively manipulate signals coming from the cerebellum to determine whether they influence how strongly the cortex responds to unexpected events. The hypothesis is that cerebellar output regulates how much weight the cortex gives to surprising events, which might shed light on disorders characterized by disrupted perception and belief formation.

 *Basic Research*

Julia Riddle, M.D., University of North Carolina at Chapel Hill, notes that while new treatments for postpartum depression (PPD) have emerged, including zuranolone, a rapid-acting oral neuroactive steroid, many women do not achieve full or sustained relief, and the biological reasons for these variable

outcomes remain unclear. A related medication, brexanolone, a previously approved intravenous drug for PPD that is no longer on the market, sometimes produced more robust and sustained improvements. Research suggests one meaningful difference between the two drugs: brexanolone appears to reduce inflammation by calming specific components of the innate immune system, while zuranolone may not. Pregnenolone is a naturally occurring neuroactive steroid produced by the body. Laboratory studies show it can inhibit inflammatory signaling by preventing the activation of pathways that trigger the production and release of inflammatory cytokines. This project explores if adding pregnenolone to zuranolone treatment may help restore the anti-inflammatory properties observed with brexanolone. This pilot study will examine how pregnenolone affects immune activity in women with PPD who are receiving zuranolone; 14-20 women with PPD will be recruited who are beginning zuranolone treatment as part of routine clinical care.

 *Next-Generation Therapies*

 *Basic Research*

Nicole Rigney, Ph.D., University of California, Los Angeles, notes that in PTSD the failure to appropriately modulate behavior in social contexts manifests as irritable behavior and reactive aggression. Emotional dysregulation also drives impulsive aggression in borderline personality disorder, and irritability is increasingly recognized as a prominent feature of treatment-resistant depression. Despite the transdiagnostic significance of impaired social sensitivity, the neural circuits that detect distress in others and modulate behavior accordingly remain poorly understood. A significant barrier has been a lack of behavioral paradigms that capture this socially modulated behavioral response. Dr. Rigney's team has discovered a clear example of social sensitivity in mice: when a male mouse encounters an acutely stressed intruder, it robustly suppresses its own aggression and increases affiliative allogrooming toward the stressed individual. This behavioral shift is driven by olfactory stress cues. They identified a neuronal population in the lateral septum that is both necessary and sufficient for this response. They now seek to determine the molecular identity and projection targets of stress-responsive lateral septum neurons, and to test whether chronic corticosterone exposure impairs both the behavioral response to stressed conspecifics and the activation of the underlying circuit.

 *Basic Research*

Rachel Romeo, Ph.D., University of Maryland, studies parent-child neural synchrony—the alignment of functional brain activity during live interaction—which is a promising candidate mechanism through which caregiver stress may become biologically embedded in children's developing emotion regulation systems. It remains unknown whether caregiver stress alters the stability of dyadic neural coordination and whether such alterations represent an early neurobiological pathway to

internalizing risk. This project builds on Dr. Romeo's existing fNIRS hyperscanning study of 60 socioeconomically diverse parent-child dyads assessed at ages 3–5 years, including measures of caregiver stress and family context, neural synchrony during a mildly frustrating task, and children's internalizing symptoms and emotion regulation skills. Half of families qualified as low or extremely low income, enabling examination of how socioeconomic stress becomes biologically embedded. This study will extend this work by following up when children are 7–10 years old to obtain longitudinal measures of anxiety and depression outcomes. Ultimately, this project seeks to move the field beyond documenting socioeconomic disparities toward identifying modifiable neurodevelopmental mechanisms and strengths-based family processes that can inform targeted prevention of mood and anxiety disorders.

 *Basic Research*

 *Next-Generation Therapies*

Stefanie Sequeira, Ph.D., University of Virginia, is interested in experience that might increase risk for anxiety and depression in teens is engaging in negative social comparison (NSC) when using social media. NSC refers to teens' tendency to compare themselves negatively to others who appear to be better off. High levels of NSC may lead to greater anxiety and depression, especially for teens at risk for anxiety and depression. The team is working with teens to design a brief digital intervention that targets their tendency to engage in NSC on social media; teens will be leading the design and development. The intervention will be tested in a small clinical trial with adolescents (ages 15–18) who report a tendency to engage in NSC on social media and elevated symptoms of anxiety or depression. This project involves adding an fMRI imaging component to the trial. Teens will complete scans before and after the intervention. At each scan, the team will examine activity in brain regions involved in processing social threat, thinking about oneself, and cognitive control. They will test whether activity in these regions might be linked to youths' tendency to engage in NSC while using social media before and after the intervention.

 *Next-Generation Therapies*

 *Basic Research*

Lauren Shuffrey, Ph.D., New York University, notes experiences early in life, particularly exposure to adversity such as household dysfunction, abuse, or neglect, may shape how the body responds to stress decades later. Childhood trauma may become “biologically embedded,” altering immune system function in ways that increase vulnerability to mental health disorders. The team has shown that pregnant individuals with a history of childhood adversity exhibit heightened activity across multiple inflammatory signaling pathways. This project seeks to determine if inflammatory immune patterns linked to early-life adversity can help identify women at elevated risk for perinatal depression before clinical symptoms arise. The team

will examine networks of immune proteins measured during pregnancy and test whether specific inflammatory signatures predict depressive symptoms. For women whose stress-response systems were shaped by early adversity, embedded physiological shifts may unmask underlying vulnerability to mood disorders. By identifying immune markers of risk, this research aims to move the field toward earlier detection and more personalized prevention strategies.

 *Diagnostic Tools/Early Intervention*

 *Basic Research*

Subha Subramanian, M.D., Beth Israel Deaconess Medical Center, seeks to better understand how rTMS produces antidepressant effects in treatment-resistant depression (TRD). The team has studied how changes in brain activity over time relate to changes in depressive symptoms, finding that antidepressant response is associated with engagement of the right frontal pole (FP). Decreases in frontal pole activity were linked to symptom improvement. This finding was replicated in an independent cohort of individuals with TRD undergoing electroconvulsive therapy (ECT). Positing that decreased activity in the right frontal pole contributes to antidepressant effects, they will conduct a randomized, sham-controlled trial of rTMS targeting the right FP, followed by an open-label extension of right FP-targeted rTMS. The goal is to establish the safety and feasibility of right FP-targeted rTMS while generating preliminary mechanistic data to guide future clinical trials.

 *Next-Generation Therapies*

 *Basic Research*

Akihiro Takamiya, M.D., Ph.D., Icahn School of Medicine at Mount Sinai, cites research on deep brain stimulation (DBS) showing that stimulating specific white matter pathways contributes to improvement in depressive symptoms. Recent advances in computer modeling now allow researchers to estimate how ECT-related electrical stimulation spreads within the brain. Most studies using this approach have focused on gray matter regions, and associations between ECT-induced E-field strength and clinical outcomes have been inconsistent. This project combines individualized E-field modeling with advanced diffusion MRI techniques that measure the brain's white matter microstructure. The team will examine how ECT engages specific white matter pathways, including DBS-related tracts (e.g., cingulum bundle, uncinate fasciculus, forceps minor). They will analyze longitudinal MRI data from 464 individuals treated with ECT. By clarifying how ECT interacts with white matter networks, they hope to move beyond a “one-size-fits-all” approach and toward more personalized treatment strategies. Also, because many DBS candidates have not benefited from ECT, understanding the biological heterogeneity within ECT nonresponders may help identify a subgroup more likely to respond to DBS.

 *Basic Research*

Can Tao, M.D., Ph.D., Virginia Commonwealth University, focuses on the medial preoptic area, which helps regulate motivation, emotional state, and maternal behaviors, and on a defined set of estrogen-sensitive neurons in this region that may act as a biological switch for postpartum mood. The central idea is that gestational stress together with postpartum estrogen withdrawal disrupts the normal activity of these neurons, pushing the brain into a depression-like state after delivery, and that restoring normal activity may improve symptoms. The team will use a mouse model to measure the activity of estrogen-sensitive medial preoptic neurons during natural behaviors to identify whether postpartum depression-like states show a characteristic neural signature. They will test whether estrogen treatment after delivery improves behavior and whether recovery is associated with normalization of this neural activity. They will employ targeted methods to increase or decrease the activity of specific neurons to determine if they directly drive depressive behaviors or are sufficient to promote recovery. This could reveal a circuit-based explanation of postpartum vulnerability and a candidate neural signature that could guide future development of novel therapies for postpartum depression.

 *Basic Research*

Gregory Telian, Ph.D., University of California, San Francisco/Gladstone Institutes, will investigate behavioral and neural mechanisms by which stress induces anhedonia and alters effort-based reward seeking. He has developed a task that incorporates simultaneous high-density neural recordings across multiple brain regions, cell-type specific manipulations, and high-speed videography of fine-grained behavioral motifs. The team will use these tools to define how stress reshapes behavioral output and neural dynamics across an amygdala–prefrontal cortical–accumbens network. These experiments may help determine how activity across this network supports effort-based choice; the behavioral motifs that accompany escalating effort demands; and how stress perturbs both network dynamics and effort-related behavior. This approach could identify potential biomarkers of perceived effort and susceptibility to stress.

 *Basic Research*

Maria Vasileadi, Ph.D., University of Toronto/Sunnybrook Health Sciences Centre, Canada, will test whether a person's metabolic health affects how their brain responds to rTMS at the level of targeted mood circuits. The team will embed a mechanistic sub-study within an ongoing clinical trial in which individuals with TRD receive accelerated intermittent theta burst stimulation (iTBS), combined with either a ketogenic diet or a standard national food-guide diet. A ketogenic diet shifts the body's metabolism toward more efficient energy use and has shown promise for improving mood and metabolic function. The team will measure real-time chemical changes in the brain during stimulation. The technology they use combines MRI, magnetic resonance spectroscopy (which measures brain

metabolites), and rTMS delivered inside the scanner. This allows quantification of stimulation-induced changes in brain chemistry that reflect neural plasticity and energy metabolism. They hope to determine if individuals receiving the metabolic intervention show stronger neurochemical responses to stimulation and whether brain responses predict improvement in depressive symptoms following a full course of iTBS treatment.

 *Next-Generation Therapies*

 *Basic Research*

Andrew Westbrook, Ph.D., Rutgers University, will test a mechanistic account of diverse cognitive deficits in depression—namely, that imbalances in cortical excitation versus inhibition underlie such deficits, and that treatment efficacy depends on normalizing this balance. A precise balance of excitation and inhibition is essential for cognition: too much excitation creates unstable and chaotic dynamics, while too much inhibition creates dynamics that are hyper-stable and non-responsive. Healthy adult brains appear to operate near a critical point, right at the boundary between stable and chaotic regimes. The team will leverage a large existing sample of electroencephalography (EEG) recordings of adults who completed a full course of TMS for depression. They will evaluate spontaneous dynamics to quantify divergence from criticality and functional excitation-inhibition balance at baseline and test predictions that people with more severe depression show greater divergence from criticality at baseline, and that divergence will relate to specific symptomatology. They will also test whether TMS modulates cortical excitability, and if normalizing excitability predicts greater long-term response to treatment.

 *Next-Generation Therapies*

 *Basic Research*

Guoguang Xie, Ph.D., Harvard University/Boston Children's Hospital, notes that despite the high prevalence and clinical impact of comorbid major depressive disorder (MDD) and chronic pain, the neural mechanisms linking persistent nociceptive signaling to affective dysfunction remain poorly understood. This project seeks to identify neural substrates that integrate pain and mood regulation, in order to promote development of targeted therapeutic strategies. The insular cortex (IC) is uniquely positioned at the intersection of sensory and affective processing. As a central hub for interoceptive integration, it transforms ascending nociceptive inputs into subjective emotional experiences by assigning affective valence to bodily states. Dr. Xie seeks to define the cellular and circuitry mechanisms by which the IC mediates chronic pain-comorbid depression. The project aims to systematically link molecular identity and projection patterns at single-cell resolution, and reveal the cell-type-specific functions of IC in pain-comorbid depression.

 *Basic Research*

Andrew Yang, M.D., University of Arizona/Barrow Neurological Institute, seeks to combine computer-based behavioral tasks with artificial intelligence (AI) to make psychiatric assessments more objective. How patients perform on tasks does not always match what they report on questionnaires. Subtle, person-specific patterns can be missed. AI has the potential to capture richer patterns in behavior, but most models are trained on very large datasets pooled across many people. This project tests a new approach that builds a separate AI model for each person. After learning from a person's task behavior, the model can generate behavior that simulates that individual's idiosyncrasies and real-world imperfections. Preliminary results demonstrate feasibility of training person-specific models using data from a 20-minute task. The model's internal dynamics can be visualized in 3D, allowing the team to study the "shape" of an individual's behavior as it unfolds in time. If successful, the project will show the potential of AI tools that can turn brief task behavior into objective signals that track symptoms and identify individuals with at higher risk for developing or worsening psychiatric illness.

 **New Technologies**

 **Basic Research**

Dale Zhou, Ph.D., University of California, Irvine, notes early life adversity, including early life unpredictability (ELU), can increase risk for depression. While accumulating evidence indicates ELU precedes and predicts the severity of anhedonia, the neural mechanisms underlying this relationship are unclear. One possibility is that ELU alters how brain regions integrate reward signals over time, according to memory adaptations to reward in the highly variable early-life environment. This project will use reinforcement learning models fit to behavior during reward-based decision tasks. These cognitive models isolate how reward and memory signals contribute to decisions. The team expects to find longer time windows of integration in the neural activity associated with memory and reward signals for individuals with high ELU and anhedonia. The team will leverage a cross-sectional cohort ($n = 276$) of children and youths. Data includes rich multimodal neuroimaging and clinical phenotyping, which will enable study of how neural timescales are linked to ELU and anhedonia. Longitudinal data from the Adolescent Brain Cognitive Development (ABCD) study will be used to test neurodevelopmental within-subjects changes in neural timescale and anhedonia ($N = 5,798$).

 **Basic Research**

EATING DISORDERS

Cristine Casingal, Ph.D., University of North Carolina at Chapel Hill, studies primary cilia, a signaling hub in neurons that modulate the formation and function of cortical neural circuits. Disruption of primary cilia signaling in human ciliopathies, resulting from genetic mutations or environmental insults, causes disorders including schizophrenia and mood and eating disorders. This project seeks to delineate neurodevelopmental pathways and mechanisms underpinning the emergence of circuit malformations linked to primary cilia dysfunction, using a multimodal approach based on cortical organoids, CRISPR-Cas9-based ciliopathy gene manipulation, genetic barcode-based mapping of brain developmental trajectories, and proteomic mapping of cilia-driven signaling networks.

 **Basic Research**

Ling-Yu Huang, Ph.D., University of Rochester, suggests cognitive rigidity—a core feature of rumination, which is seen in depression, anxiety, PTSD, OCD, and eating disorders—may arise from distinct mechanisms. One is a failure to appropriately adjust the learning rate in response to informative feedback, resulting in insufficient updating of action–outcome mappings (the “blunted adjustment” account). Another is experience-reinforced negative belief priors, causing negative interpretations to dominate decision processes (the “reinforced negative prior” account). This study seeks to dissociate these candidate mechanisms using complementary behavioral paradigms and multimodal neurophysiological measurements. High-density EEG and concurrent pupillometry will be used to quantify neuromodulatory responses during rule-switching tasks that probe cognitive flexibility under abstract and verbal-emotional contexts. By dissociating candidate mechanisms of cognitive rigidity within the same individuals, the hope is to identify the point(s) of failure underlying rumination-related rigidity.

 **Basic Research**

Jineun Kim, Ph.D. California Institute of Technology, seeks better understanding of how the brain integrates energy needs with environmental information to guide appropriate behavior. This project investigates how the brain normally balances these competing signals and why this balance can break down in eating and mood disorders. Dr. Kim focuses on the hypothalamus, which receives information from the body about energy status while also processing social and emotional cues from the environment. By integrating these signals, it helps animals prioritize behaviors that support survival. This project aims to understand how hypothalamic neural circuits compute behavioral priorities when animals face competing needs, such as feeding versus responding to social stress. The team will record the activity of individual neurons in freely moving mice while they navigate such competing situations. They hope to reveal

whether distinct groups of neurons represent competing drives and how interactions between these groups shape behavioral choices. They will also examine how signals related to metabolic imbalance or chronic stress alter these neural circuits.

Basic Research

Elena Koning, Ph.D., Dalhousie University, Canada, notes psilocybin may quickly reduce depression, increase cognitive flexibility, and reduce rigid or negative thoughts and behaviors, especially when paired with therapy. Early studies suggest it may help in eating disorders, but it hasn't been tested in bulimia nervosa (BN). This project will add brain-focused measurements to a planned clinical trial with 70 adults with BN. Participants will receive 10 weeks of CBT plus two rounds of either a high dose of psilocybin or a very low (control) dose. Before and after treatment, the following will be measured: BDNF levels in the blood as a sign of brain plasticity; and cognitive flexibility using a short computer task and a brief questionnaire. Changes in these measures will be compared between the high-dose and low-dose groups, and linked to any improvements in eating disorder symptoms, mood, and whether people are able to complete therapy.

Next-Generation Therapies

Janne Tidselbak Larsen, Ph.D., Aarhus University, Denmark, focuses on children born to mothers who have eating disorders including anorexia nervosa, bulimia nervosa, or other unspecified eating disorders. This project will systematically examine key areas of development that together reflect the general physical, mental, and social well-being of children whose mothers have eating disorders. Using Danish nationwide registry data and longitudinal surveys, the team will study patterns in children's physical development throughout childhood (height, weight, and body mass index); their school performance (including national tests in primary school and grades from final exams in lower and upper secondary school); and self-reported well-being in school. They will compare children of mothers with different types of eating disorders to children whose mothers have no diagnosis of an eating disorder.

Basic Research

Hailan Liu, Ph.D., University of South Florida, cites previous studies suggesting people with anorexia have unusually high activity in the brain's endogenous opioid system, which normally helps regulate pleasure, motivation, and behavior. The team has discovered that a specific group of opioid-producing brain cells in the brainstem becomes overactive in a mouse model of anorexia. When these cells are activated, mice eat less, move more, lose weight, and develop behaviors resembling anorexia. When they are turned off, the mice eat more, move less, and survive longer. Activating these brain cells also appears associated with a positive emotional state that can overpower hunger, which could shed light on why people with anorexia continue to avoid food

despite starvation. The team also found that opioid-producing brainstem cells communicate with the lateral hypothalamus and the ventral tegmental area, which help regulate eating, movement, and motivation. This project seeks to determine how these brain connections contribute to anorexia-like behaviors and test whether blocking opioid signals in these regions can reduce anorexia-like symptoms.

Basic Research

OBESSIVE-COMPULSIVE DISORDER (OCD)

Rachel Bandler, M.D., Ph.D., Yale University, reports research from her lab showing that during development humans have a unique way of using the *Cbln2* gene to assemble extra connections in the prefrontal cortex. *Cbln2* appears to be linked to OCD, helping to organize how brain cells connect. When the gene is missing, mice show compulsive behaviors like excessive nest building. These mice improve when they are given standard OCD medication or a boost of the protein produced by the *Cbln2* gene in the dorsal raphe. Dr. Bandler hypothesizes that OCD might start very early in life if *Cbln2* is not functioning properly, causing the dorsal raphe and prefrontal cortex to misconnect. To test this, the team will use a modified "barcoded" virus to track how individual brain cells connect to each other in a strain of mice genetically modified to mimic human brain circuits. The goal is to better understand how these early brain connections form and potentially miswire in the hope of better understanding OCD pathology.

Basic Research

Jennifer Bussell, Ph.D., Columbia University, is developing a novel approach to uncover circuit mechanisms regulating animals' desire to resolve punishment uncertainty, a state linked by computational psychiatry to OCD, anxiety, and depression. Building on prior work demonstrating that the orbitofrontal cortex (OFC) encodes the intrinsic value of uncertainty reduction in a reward-based information-seeking task for mice, Dr. Bussell designed an aversive information-seeking task in which mice choose whether to receive cues predicting unavoidable shock without altering shock probability. Preliminary evidence shows that mice exhibit stable individual preferences for such aversive information, and that OFC neurons predict reduction of threat-related uncertainty. She seeks to show that the OFC encodes a generalized value signal for reducing uncertainty and that in compulsive states this signal becomes selectively amplified and inflexible for aversive outcomes, leading to compulsive information seeking (i.e., an insatiable desire to reduce uncertainty).

Basic Research

Marina Celestine, Ph.D., Harvard University/McLean Hospital, notes that invasive neurosurgical interventions like Deep Brain Stimulation (DBS) or precise lesion procedures can provide life-changing relief in various disorders and brain-based illnesses including treatment-resistant depression and OCD. This project is part of an effort to significantly improve procedure outcomes by mapping interindividual variability in brain regions involved in symptoms, including the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), ventrolateral prefrontal cortex (vlPFC), amygdala, and insula. The team is utilizing data from a large group of epilepsy patients who underwent stereoelectroencephalography (sEEG) coupled with advanced brain imaging. By aggregating varied electrode trajectories, they aim to reconstruct high-resolution, dense maps of the circuits involved in OCD and depression at a level of detail that standard imaging cannot achieve. After identifying local connections between emotional and decision-making centers, they will use these “seed points” to trace global networks across the brain. The findings will be validated using anatomical data from non-human primates. The ultimate aim is to facilitate personalized neurosurgical strategies.

Next-Generation Therapies

Stephanie Grella, Ph.D., Loyola University Chicago, studies how dysregulated hippocampus (HPC)-prefrontal cortex (PFC) interactions contribute to compulsive behavior. This project will test a mechanistic model, memory hoarding, in which compulsive checking reflects maladaptive persistence and recurrent reactivation of salient HPC-PFC engrams. The hypothesis is that revisiting memories over and over accelerates the loss of contextual detail, pushing memories toward more generalized forms that normally emerge only over long timescales shifting from HPC to PFC dependence. This project, in rodents, will try to establish if this transformation occurs prematurely, leaving memories less vivid but still emotionally intense. This mismatch would heighten uncertainty, further fueling compulsive repetition. It is a direct test of engram persistence and HPC-PFC ensemble coupling as drivers of compulsive behavior, potentially establishing a translational framework for targeting maladaptive memory dynamics in OCD.

Basic Research

Joseph Heffner, Ph.D., Yale University, investigates how prediction error processing contributes to decision-making problems in major depressive disorder (MDD) and obsessive-compulsive disorder (OCD). The research is rooted in the idea that if a person cannot accurately predict how a choice will make them feel, or learn from that feeling afterward, their ability to make adaptive decisions will suffer. Dr. Heffner will combine computational modeling of behavior, clinical interviews, and analysis using AI tools of how participants use language to describe their mental health which he has developed. This research follows participants weekly over a three-week period. This longitudinal

design allows the team to determine if observed computational deficits are stable traits or if they change as symptoms fluctuate. Dr. Heffner hypothesizes a specific “anxious-depression” dimension, identified through language data and validated with standardized questionnaires, which will explain why individuals across both MDD and OCD populations fail to use emotional signals constructively when making choices.

Basic Research

Diagnostic Tools/Early Intervention

Ling-Yu Huang, Ph.D., University of Rochester, suggests cognitive rigidity—a core feature of rumination, which is seen in depression, anxiety, PTSD, OCD, and eating disorders—may arise from distinct mechanisms. One is a failure to appropriately adjust the learning rate in response to informative feedback, resulting in insufficient updating of action–outcome mappings (the “blunted adjustment” account). Another is experience-reinforced negative belief priors, causing negative interpretations to dominate decision processes (the “reinforced negative prior” account). This study seeks to dissociate these candidate mechanisms using complementary behavioral paradigms and multimodal neurophysiological measurements. High-density EEG and concurrent pupillometry will be used to quantify neuromodulatory responses during rule-switching tasks that probe cognitive flexibility under abstract and verbal-emotional contexts. By dissociating candidate mechanisms of cognitive rigidity within the same individuals, the hope is to identify the point(s) of failure underlying rumination-related rigidity.

Basic Research

Alessandro Livi, Ph.D., Washington University, St. Louis, notes many psychiatric illnesses, including OCD and addiction, involve a breakdown in everyday decision making. People may lock into a choice too quickly, struggle to revise when circumstances change, or keep repeating actions even when the outcomes are harmful. These patterns suggest a problem not only with valuing options, but also with when a decision becomes stable enough to drive action. The orbitofrontal cortex (OFC) is central for value-based decision making, yet we still do not understand how OFC activity is converted into a firm, “winner-take-all” decision state that becomes resistant to change. This project will use an all-optical approach to explore whether a layered circuit in the OFC transforms distributed value signals into a stable choice outcome. Mice will perform a value-based decision-making task in which odor cues indicate different reward options. While they deliberate and choose, the team will measure neural activity and deliver time-specific perturbations to targeted neural populations. Seeking to pinpoint how value representations are converted into a committed decision, this work may reveal a circuit-level mechanism that can fail in disorders marked by impulsive commitment, perseveration, and reduced cognitive flexibility.

Basic Research

Maria Picó-Pérez, Ph.D., Universitat Jaume I, Spain, notes that while males and females develop OCD at similar rates, important differences exist in how the disorder begins, how symptoms present, and how the illness progresses over time. This project proposes a new, sex/gender-informed biological model of OCD. The central idea is that stress-related changes in stress hormones and inflammation may alter communication within specific brain circuits, and that these effects differ across sexes. These, together with the exposure to different socioenvironmental stressors, may help explain why OCD symptoms emerge or worsen differently in males and females. To test this, the study will analyze brain imaging, biological and social data from adults in the general population, and those with OCD. Participants have undergone non-invasive brain scans and provided blood samples to measure stress-related hormones and inflammatory markers. By combining brain imaging with biological and social measures, the project will examine how stress systems interact with sex hormones and gender variables to influence brain connectivity and obsessive-compulsive symptoms.

 *Basic Research*

Kathia Ramirez Armenta, Ph.D., University of California, Los Angeles, is interested in how we learn that environmental cues can predict particular forthcoming events. Such memories form the basis of the internal model of environmental relationships (e.g., cue-reward associations) that support the prospective considerations, predictions, and inferences needed for adaptive decision making. Deficits in this process characterize several psychiatric conditions, including substance use and OCD. Studies have established the basolateral amygdala and orbitofrontal cortex as crucial for associative learning and adaptive decision making. This project aims to reveal how the regulation of local brain circuits contributes to adaptive decision making. Evidence suggests dopamine regulation of basolateral amygdala circuitry is likely involved. Basolateral amygdala (BLA) projection neurons to the lateral orbitofrontal cortex (LOFC) not only mediate cue-reward learning but also adaptive decision making. Yet little is known about how this works. One potential mechanism involves dopaminergic modulation, which this research will explore. It aims to reveal how dopamine modulates amygdala microcircuitry to support adaptive decision making.

 *Basic Research*

Robert Seilheimer, M.D., Ph.D., Dell Medical School, University of Texas at Austin, points out that while TMS, DBS, and low-intensity focused ultrasound (LIFU) are promising for treating OCD, at this point none is reliably effective. This project proceeds from the idea that a better understanding of the circuits underlying OCD would help guide neuromodulation targeting and may enhance treatment efficacy. Dr. Seilheimer notes that patients with OCD undergoing EEG recording

display an enhanced response to errors in cognitive tasks, a phenomenon known as error-related negativity (ERN). He seeks to delineate the brain circuits underlying ERN using intracranial EEG. Previous research points to multiple regions including the dorsal anterior cingulate cortex (dACC), dorsomedial prefrontal cortex (dmPFC), and insula as potentially being involved. By conducting tasks that evoke ERN in patients with iEEG electrodes, the project may localize sites that demonstrate ERN or other error-related activity. Once they have identified these sites, the team can analyze the connectivity between these regions. Tracing the neural origin and connectivity of ERN, a well-described and consistent biomarker of OCD, could help guide neuromodulation.

 *Basic Research*

 *Next-Generation Therapies*

Belinda Wang, M.D., Ph.D., University of California, San Francisco/Gladstone Institutes, notes genetic risk in OCD is carried by common and rare variants. Because rare variants point directly to specific genes, they are especially valuable entry points into disease biology. The Wang lab recently identified dozens of such rare variant OCD risk genes, but does not yet know which brain cells these genes act in. They are now positioned to answer this question. Large-scale genetic studies have identified reliable OCD risk genes at a sufficient scale for cellular mapping, and advances in single-cell genomics have produced detailed catalogs of gene activity across hundreds of distinct cell types in the human brain. Together, these tools allow the team to localize OCD genetic risk with unprecedented precision. In this project, they seek to identify which brain cell types most strongly express genes implicated by rare and common variants. They will examine how risk genes relate to one another—whether they converge on shared biological pathways and, if so, in which cell types those pathways are most active. Together, these analyses could produce a map of the cells and molecular processes that underlie OCD genetic risk, helping to advance future research and development of precision treatments.

 *Basic Research*

OTHER PROJECTS

ALZHEIMER'S DISEASE

Jenna Adams, Ph.D., University of California, Irvine, studies biological mechanisms linking depressive symptoms and subtle memory changes in aging, arguing repetitive negative thinking and memory deficits arise from a shared vulnerability of hippocampal circuit dynamics driven by age-related dysregulation of the noradrenergic system. She notes the locus coeruleus (LC), a brainstem nucleus that provides the major noradrenergic input to the hippocampus, begins to accumulate pathology in mid-life, which may disrupt noradrenergic modulation of hippocampal dynamics. The project will test a model in

which age-related disruption of LC-noradrenergic modulation constrains hippocampal circuit dynamics, biasing computations toward persistent, overgeneralized representations that manifest as repetitive negative thinking and reduced memory specificity. The team will leverage a sample of cognitively unimpaired older adults with depressive symptoms who have undergone extensive neuroimaging and behavioral characterization. Establishing a novel hippocampal-noradrenergic circuit signature of depression vulnerability in aging could provide a foundation for studying how LC-driven hippocampal circuit vulnerability interacts with tau accumulation to influence late-life depressive symptom trajectories and Alzheimer's progression.

Basic Research

Nick Corriveau-Lecavalier, Ph.D., Mayo Clinic, Jacksonville, notes that in some instances depressive symptoms may represent a prodromal feature, core manifestation, or consequence of neurodegenerative conditions such as Alzheimer's disease or Lewy body dementia. Early and accurate differential diagnosis is critical. Data-driven diagnostic tools powered by machine learning offer an opportunity to assist clinicians with diagnostically complex decisions. This project expands on StateViewer, a tool developed by the team which combines fluorodeoxyglucose positron emission tomography (FDG-PET) imaging with machine learning. The system is optimized for the differential diagnosis of dementia syndromes and achieves over 90% accuracy across 14 neurodegenerative conditions. This project seeks to extend the tool's utility beyond neurodegenerative diseases to primary psychiatric disorders, with an initial focus on major depression. The team will leverage clinical data from MDD patients who have undergone FDG-PET imaging and use machine learning to compare patterns of cerebral glucose metabolism in MDD (n = 150) with those observed in neurodegenerative dementia syndromes including Alzheimer's, Lewy body dementia, and frontotemporal dementia spectra (n = 2,121).

Diagnostic Tools/Early Intervention

Basic Research

Chenfeng He, Ph.D., University of Wisconsin-Madison, notes that in Alzheimer's disease (AD) patients, depression worsens cognitive decline, reduces life quality, and complicates care. Clinically, depression in Alzheimer's (dAD) often looks similar to major depressive disorder (MDD) in people without dementia, yet treatments for MDD show limited benefit in dAD patients. This suggests underlying biological mechanisms may differ. This project seeks to define shared and distinct mechanisms to enable more precise diagnosis and more effective, mechanism-based treatments. Advances in single-cell genomics make it possible to measure gene activity in millions of cells from human postmortem brain tissues. Large single-cell datasets for both dAD and MDD are accumulating. This project will build on Dr. He's recently developed AI framework, PASCode, designed

to identify "phenotype-associated cells"—subpopulations most strongly linked to a given clinical phenotype. Using PASCode models trained on each disorder, the team hopes to identify cell populations and gene programs that converge and diverge between the two disorders, providing a map of their shared versus distinct biology.

Basic Research

Diagnostic Tools/Early Intervention

Victoria Marshe, Ph.D., Columbia University, notes the co-morbidity of neuropsychiatric symptoms presents a significant challenge for Alzheimer's disease treatment. One of the most common symptoms is depression. Cognitive decline is accelerated in individuals with increasing late-life depressive symptoms and those with comorbid psychiatric disorders. This project seeks to expand understanding of molecular signatures across different cell types, as well as genetic signatures associated with the presence of depression in late-life and in individuals with Alzheimer's disease. Using single-cell transcriptomics, the team will create an atlas across different cell types in the brain to understand which genetic signatures are associated with depression in Alzheimer's independently of neurodegenerative pathology; whether these signatures are affected before or after cognitive decline; and whether these signatures are driven by genetic variation. This may help expand the understanding of the overlapping risk between depression and Alzheimer's disease and support the identification of novel pathways and targets.

Basic Research

Michael Thornton, Ph.D., Salk Institute for Biological Studies, cites genetic and clinical evidence implicating synaptic dysfunction in neurodegenerative and neuropsychiatric disorders, including Alzheimer's and schizophrenia. Scalable methods to quantify synaptic plasticity across large populations of living human neurons remain limited. This project seeks to develop a next-generation platform to measure and control synaptic weights across hundreds of neurons in patient-derived biological networks. Among other aims, spike timing-dependent plasticity kernels will be systematically quantified across hundreds of monosynaptically connected human neuronal pairs, enabling classification of distinct plasticity phenotypes within the network. The team will apply this platform to human disease-relevant models to identify disorder-specific signatures of plasticity deficits. They hypothesize that Alzheimer's neurons will exhibit impaired synapse stabilization, whereas schizophrenia neurons will demonstrate altered timing dependence and increased variability of synaptic modification. Comparative analysis could determine whether shared or distinct plasticity vulnerabilities emerge. By defining quantitative functional signatures of synaptic dysfunction in human neurons, this work seeks to establish a scalable framework for identifying therapeutic strategies aimed at restoring adaptive circuit dynamics in brain disease.

Basic Research

DEMENTIA

Nick Corriveau-Lecavalier, Ph.D., Mayo Clinic, Jacksonville, notes that in some instances depressive symptoms may represent a prodromal feature, core manifestation, or consequence of neurodegenerative conditions such as Alzheimer's disease or Lewy body dementia. Early and accurate differential diagnosis is critical. Data-driven diagnostic tools powered by machine learning offer an opportunity to assist clinicians with diagnostically complex decisions. This project expands on StateViewer, a tool developed by the team which combines fluorodeoxyglucose positron emission tomography (FDG-PET) imaging with machine learning. The system is optimized for the differential diagnosis of dementia syndromes and achieves over 90% accuracy across 14 neurodegenerative conditions. This project seeks to extend the tool's utility beyond neurodegenerative diseases to primary psychiatric disorders, with an initial focus on major depression. The team will leverage clinical data from MDD patients who have undergone FDG-PET imaging and use machine learning to compare patterns of cerebral glucose metabolism in MDD (n = 150) with those observed in neurodegenerative dementia syndromes including Alzheimer's, Lewy body dementia, and frontotemporal dementia spectra (n = 2,121).

 *Diagnostic Tools/Early Intervention*

 *Basic Research*

Ari Cuperfain, M.D., University of Toronto/Centre for Addiction and Mental Health, Canada, notes older adults with alcohol use disorder (AUD) are at elevated risk for cognitive impairment and dementia. Abstinence may help, but the extent of improvement varies widely and mechanisms underlying this variability remain poorly understood. Evidence suggests chronic alcohol exposure disrupts the brain's balance between excitatory and inhibitory signaling (E/I balance), perhaps dysregulating brain circuits and increasing vulnerability to cognitive dysfunction and neuronal injury. The team has demonstrated in older adult drinkers increased "interference intrusions," i.e., errors in which previously learned information intrudes during new learning tasks, which may reflect impaired inhibitory control within the prefrontal cortex (PFC). They will now use TMS and EEG to measure E/I inhibitory imbalance in the PFC. By quantifying these responses in older adults with AUD they hope to determine if signaling balance is disrupted following alcohol withdrawal and whether this predicts cognitive outcomes during abstinence.

 *Diagnostic Tools/Early Intervention*

 *Basic Research*

PANIC DISORDER

Michael Schappe, Ph.D., University of Illinois at Urbana-Champaign, notes that anxiety and panic attacks can be accompanied by debilitating and powerful internal sensations

including sudden shortness of breath, chest tightness, or a frightening sense of gasping for air. Scientists have proposed panic disorders may begin due to heightened sensitivity of the body's "suffocation alarm system," but we still do not know exactly which cells in the body detect breathing problems, how they send signals to the brain, or how those signals are transformed into feelings of fear and anxiety. Breathing is monitored by sensory nerves that directly connect airways to the brain through the vagus nerve. The team has identified mechanisms of an airway-sensing circuit that reflexively triggers a gasping reflex, distressed breathing, and panic-like behaviors resembling respiratory crisis. It senses airway closure in the lungs through a rare group of sensory cells and the vagus nerve, which can be turned on and off with neurobiological tools. The team will investigate how this specific internal sense contributes to and influences panic-related symptoms and behaviors in real-time, focusing on discovering how these "airway alarms" are represented in the brain and relate to other panic-inducing signals. Moving beyond broad theories about interoception, they hope to indicate concrete biological mechanisms that will establish whether a specific breathing-sensing circuit can directly drive anxiety.

 *Basic Research*

PARKINSON'S DISEASE

Ellen Bradley, M.D., University of California, San Francisco/Gladstone Institutes, notes standard antidepressants are often ineffective for depression that occurs in Parkinson's disease (PD), potentially because PD involves widespread neurodegenerative changes that disrupt glutamate and other neurotransmitter systems implicated in mood regulation. It is currently unknown if ketamine might help in PD depression. Leveraging an ongoing, clinical trial of ketamine for PD depression, this project will add MRI at baseline and 24 hours post-treatment to identify functional connectivity changes and white-matter microstructural changes that may be markers of ketamine-induced neuroplastic remodeling. The team will evaluate whether greater changes in these neuroimaging metrics correlate with greater improvement in participants' depression symptoms. The project will also generate neuroimaging data for future trials aimed at predicting and optimizing ketamine response among people with PD and related neurodegenerative conditions.

 *Next-Generation Therapies*

PREVENTING AI-ENABLED RESEARCH CORRUPTIONS

Veith Weinhhammer, M.D., Ph.D., University of London/University College London, UK, notes that surveys of depression, anxiety, schizophrenia, and other psychiatric conditions routinely collect symptom ratings, treatment feedback, and quality-of-life assessments through web-based questionnaires. But artificial intelligence (AI) systems can now fill out surveys

automatically, generating responses that look human but are entirely fabricated. Even a small percentage of fake responses (3%–5%) can meaningfully distort study results, potentially leading to incorrect conclusions about how common a disorder is, whether a treatment works, or which risk factors matter most. There is no broadly available, scientifically validated tool designed to address survey pollution by AI. This project proposes a new approach. Instead of analyzing what a respondent answers, the team will measure how they interact with the survey via mouse movements, touchscreen gestures, and typing patterns. Genuine human motor behavior has a richness and complexity that current AI agents cannot fully replicate. The team will build a survey interface called SPRITE that captures physical interaction patterns and uses them to compute a confidence score indicating whether a response is likely from a real person.

 *Diagnostic Tools/Early Intervention*

POST-TRAUMATIC STRESS DISORDER (PTSD)

David Clewett, Ph.D., University of California, Los Angeles, is interested in “event segmentation,” where the brain relies on detecting moments of change, such as shifts in location, activity, or goals, that help to structure memories and make them last. Emotional arousal also shapes this process. Dr. Clewett proposes that in PTSD, chronic hyperarousal alters this organizing system. Rather than simply weakening memory, heightened arousal may shift the brain’s boundary detection system away from meaningful contextual changes and toward emotionally intense transitions, perhaps causing individuals to segment experience and memory around the wrong moments, leading to disorganized memory and poorer recall. This project explores if this bias arises from dysfunction in the locus coeruleus-norepinephrine (LC-NE) system, a core regulator of arousal and memory function. It includes a mechanistic test of whether altered LC dynamics drive memory disorganization in PTSD. Trauma-exposed control participants and those with PTSD will watch a TV episode during brain imaging, followed by detailed recall and boundary identification, or event segmentation. The team will examine how arousal-related brain activity shapes detection of emotional and neutral transitions and how emotion-biased segmentation influences the content and structure of memory.

 *Basic Research*

Michael Conoscenti, Ph.D., University of Utah, studies the neurobiology of aggression. The dorsal aspect of the bed nucleus of the stria terminalis (dBNST) has known roles in stress, anxiety, and social behavior, making it well-suited for the orchestration of defensive social behavior. The dBNST

contains a unique population of cells that co-express the neuropeptides tachykinin 2 (Tac2) and corticotropin-releasing hormone (CRH). This project seeks to discover the function of these two genetically defined neuronal populations. Dr. Conoscenti has shown that these genetically defined dBNST cell populations control distinct aspects of stress-like defensive social behaviors. Photostimulation of dBNST CRH+, Tac2+, or CRH+Tac2+ cells increased antisocial behavior, aggression, and social avoidance, respectively. These cells project to the ventromedial hypothalamus (VMH), which has known roles in defensive social behavior. The functional role of this circuit has never been explored. This study will test the hypothesis that neuropeptide dBNST neurons mediate defensive social behavior via their projections to the VMH, potentially revealing a neurobiological mechanism for stress-induced aggression and avoidance seen in PTSD patients exhibiting violent behavior and social withdrawal.

 *Basic Research*

Boushra Dalile, Ph.D., KU Leuven, Belgium, notes gut bacteria produce molecules that can enter the bloodstream and reach the brain, where they can affect gene expression, inflammation, and emotional learning. One such molecule, butyrate, can influence gene expression to promote synaptic plasticity. It is produced when gut bacteria ferment dietary fiber found in complex carbohydrate-rich foods and in animals, and has been shown to enhance the brain’s capacity to “unlearn” fear and strengthen extinction memories. This project seeks to learn more about how butyrate affects fear related processes in humans. Dr. Dalile will investigate how butyrate shapes communication between key brain regions involved in fear and safety including the amygdala, hippocampus, and prefrontal cortex, and how it alters HDAC activity and histone acetylation in the blood, molecular switches that regulate memory formation. These mechanisms mirror those disrupted in PTSD and anxiety disorders. By identifying how a naturally occurring microbial metabolite can boost the brain’s ability to regulate fear, this research has the potential to guide the development of novel treatment-enhancing strategies.

 *Basic Research*

 *Next-Generation Therapies*

Ana Verónica Domingues, Ph.D., University of Minho, Portugal, notes the ventral tegmental area (VTA) and its dopamine projections to the nucleus accumbens (NAc) contribute to aversive learning and extinction updating, yet dopamine operates within a neuromodulatory environment that can reshape these computations under stress. A strong candidate is the endogenous opioid neuropeptide dynorphin, acting via kappa-opioid receptors (KORs). Dynorphin terminals are dense in the VTA and KORs and broadly expressed on VTA neurons and presynaptic compartments, positioning dynorphin/KOR signaling to powerfully tune

MTA microcircuit function and dopamine output. This project will leverage newly developed genetically encoded sensors to provide real-time, event-resolved monitoring of dynorphin/KOR engagement during aversive conditioning and extinction, alongside simultaneous measurements of NAc dopamine dynamics. By establishing the temporal and circuit logic of dynorphin/KOR recruitment, this research may provide a mechanistic bridge from stress-opioid neuromodulation to PTSD-like phenotypes, highlighting concrete circuit targets and learning phases for future intervention.

Basic Research

Josh Greene, M.D., Ph.D., Columbia University, observes that despite the clear connection between adrenaline and PTSD symptoms, we do not understand which brain circuits control adrenaline release during threat, or how adrenaline (epinephrine) might feed back to the brain to keep the body in a prolonged state of alarm. Focusing on a specific brain-to-body pathway that may be central to this process, Dr. Greene developed an approach for measuring adrenaline in mice which revealed that the brain's paraventricular nucleus of the hypothalamus (PVH), known to coordinate the body's stress response, sends direct connections to the spinal neurons that control the adrenal gland. This identifies a specific population of brain cells that could act as a switch for adrenaline release. This project will record brain activity in the PVH-to-spinal pathway, circulating adrenaline, heart rate, and behavior during threat to determine how these signals relate in time. Optogenetics will be used to turn this pathway on or off, testing whether it is both necessary and sufficient to drive adrenaline release and the sustained defensive state.

Basic Research

Julianne Griffith, Ph.D., University of Pittsburgh, notes alterations in neurobehavioral processes related to motivation and reward, known as the positive valence systems (PVS), in anhedonia. Among children of anhedonic mothers, reduced activation in PVS may emerge in early childhood before the onset of symptoms and interfere with important developmental tasks, such as play, social approach, and exploration, conferring risk for persistent psychopathology. This study will investigate associations between maternal anhedonia, mother PVS function, and child PVS function, as well as the role of maternal positive emotion socialization behaviors in moderating these associations. In 75 mother-child pairs, it will test a model in which maternal invalidating and discouraging responses to children's positive affect ("dampening") strengthen biological risk pathways linking maternal anhedonia and reduced maternal PVS activation to child reduced PVS activation, whereas maternal responsive and encouraging responses to children's positive affect ("enhancing") weaken them. Mother and child PVS activation will be assessed using EEG during a reward task and happy-faces viewing task.

Basic Research

Ling-Yu Huang, Ph.D., University of Rochester, suggests cognitive rigidity—a core feature of rumination, which is seen in depression, anxiety, PTSD, OCD, and eating disorders—may arise from distinct mechanisms. One is a failure to appropriately adjust the learning rate in response to informative feedback, resulting in insufficient updating of action–outcome mappings (the “blunted adjustment” account). Another is experience-reinforced negative belief priors, causing negative interpretations to dominate decision processes (the “reinforced negative prior” account). This study seeks to dissociate these candidate mechanisms using complementary behavioral paradigms and multimodal neurophysiological measurements. High-density EEG and concurrent pupillometry will be used to quantify neuromodulatory responses during rule-switching tasks that probe cognitive flexibility under abstract and verbal-emotional contexts. By dissociating candidate mechanisms of cognitive rigidity within the same individuals, the hope is to identify the point(s) of failure underlying rumination-related rigidity.

Basic Research

Anthony Jang, M.D., University of California, Los Angeles, proposes that pathological anxiety may reflect a disruption in the ability to flexibly balance pursuit of goals with avoidance of potential threats, known as approach–avoidance decision-making. This project seeks to uncover the fear-related brain activity involved in approach–avoidance decisions by studying behavior in naturalistic environments. The team will use virtual reality (VR) technology to mimic real-life situations. Participants will wear a VR headset and freely walk through virtual environments containing desirable goals and locations associated with potential threat, requiring them to continuously balance reward-seeking with avoidance. The team will directly record brain activity during these tasks in participants already implanted with a clinically approved neural device for epilepsy or PTSD. Readings will be made from the amygdala and hippocampus. By identifying the neural circuits that govern fear-guided decisions, this work seeks to inform the development of targeted neuromodulation strategies for treatment-resistant anxiety disorders.

Basic Research

Jineun Kim, Ph.D. California Institute of Technology, seeks better understanding of how the brain integrates energy needs with environmental information to guide appropriate behavior. This project investigates how the brain normally balances these competing signals and why this balance can break down in eating and mood disorders. Dr. Kim focuses on the hypothalamus, which receives information from the body about energy status while also processing social and emotional cues from the environment. By integrating these signals, it helps animals prioritize behaviors that support survival. This project aims to understand how hypothalamic neural circuits

compute behavioral priorities when animals face competing needs, such as feeding versus responding to social stress. The team will record the activity of individual neurons in freely moving mice while they navigate such competing situations. They hope to reveal whether distinct groups of neurons represent competing drives and how interactions between these groups shape behavioral choices. They will also examine how signals related to metabolic imbalance or chronic stress alter these neural circuits.

Basic Research

Ukbong Kwon, Ph.D., Baylor College of Medicine, is interested in how non-neuronal plasticity contributes to the persistence, specificity, and inappropriate generalization of fear memories. His recent work explored the concept of learning-associated astrocytes (LAAs) as experience-tagged astrocyte ensembles that couple to engram neurons and can trigger memory recall upon reactivation. How epigenetic programs shape durable LAA ensembles and support recall competence is at the focus of this project. Preliminary data indicate astrocyte ensemble allocation can bias later memory expression: mismatched recruitment of previously tagged LAAs during fear conditioning is sufficient to drive later fear expression upon reactivation of that ensemble, consistent with context-inappropriate (“false”) recall. These findings support the hypothesis that fear learning installs durable epigenomic programs in LAAs that support recall competence and context specificity. The team will test this by defining LAA epigenomic states across learning and recall, perturbing candidate epigenetic pathways in astrocytes to determine whether they regulate recruitment into LAAs and preserve recall specificity, and selectively manipulating epigenetic regulators within tagged LAAs to test whether ensemble-intrinsic epigenetic programming is sufficient to alter recall and false recall.

Basic Research

Songjun Li, M.D., Ph.D., Yale University, notes that in individuals with cluster B personality disorder and trauma-related conditions, socio-affective flexibility is severely impaired, leading to rigid, maladaptive interpersonal patterns and poor decision making. A major developmental risk factor for these disorders is early life stress (ELS). This project utilizes a naturalistic behavioral paradigm in pairs of rats that requires them to engage in a series of complex decisions to either compete or cooperate for reward. Preliminary data suggest ELS behaviorally disrupts prosocial-specific decision-making, leading to the hypothesis that this is driven by perturbation of the neuronal balance between the normally coordinated activity of prefrontal brain networks connecting the anterior cingulate cortex to basolateral amygdala and anterior cingulate cortex to anterior insula, which together promote prosocial behavior. One part of this project will test whether ELS chronically restricts the network to a self-focused state and

therefore prevents the acquisition of cooperative strategies in susceptible animals. Another part seeks proof-of-principle data exploring how this dysregulation is sustained at the molecular level and whether it can be therapeutically reversed.

Basic Research

Xiaotang Lu, Ph.D., University of Illinois at Urbana-Champaign, wants to know, at synaptic resolution, how extinction learning suppresses fear expression. The basolateral amygdala (BLA) contains neuronal ensembles engaged during fear retrieval and during extinction. What is still missing is the wiring logic: how these ensembles are coupled, and which inhibitory microcircuits impose control at the point where behavior is expressed. The team seeks to generate an ensemble-resolved, cell-type-annotated synaptic map of BLA microcircuits that links fear and extinction ensembles within the same tissue volume. The hypothesis is that local inhibitory circuits implement the critical control between extinction and fear ensembles through a set of definable motifs. The wiring diagram obtained could help distinguish between competing models by reading out the synaptic architecture directly. By identifying specific inhibitory motifs and their cellular constituents, this work will nominate concrete circuit elements for subsequent causal tests. More broadly, it establishes a general strategy for translating clinically relevant brain states into mechanistic, synapse-level circuit hypotheses that can guide targeted intervention development.

Basic Research

Farzaneh Najafi, Ph.D., Georgia Institute of Technology, notes that disorders including schizophrenia may involve problems in how the brain updates beliefs in response to unexpected events. This project will investigate how the cerebellum and posterior parietal cortex work together to support belief updating. Imaging studies in patients with psychiatric disorders suggest that communication between the cerebellum and cortex may be disrupted, but we do not yet understand how this affects learning at the level of brain circuits. The team has developed a behavioral task in mice that requires animals to learn patterns in the timing of events and to adjust when those patterns change. This provides a controlled way to measure how quickly and accurately beliefs are updated. Using advanced optical imaging techniques, they will record the activity of specific types of neurons in the cortex while animals perform this task, and selectively manipulate signals coming from the cerebellum to determine whether they influence how strongly the cortex responds to unexpected events. The hypothesis is that cerebellar output regulates how much weight the cortex gives to surprising events, which might shed light on disorders characterized by disrupted perception and belief formation.

Basic Research

Rose Olson, M.D., Harvard University/Brigham and Women's Hospital, notes that dysregulation of autonomic nervous system function, including reduced heart rate variability, heightened sympathetic arousal, and reduced sleep quality, are known to occur in PTSD. Although digital interventions can expand access to evidence-based psychotherapies such as Written Exposure Therapy (WET), a first-line treatment for PTSD, the mechanisms underlying treatment response remain poorly defined. This study will test whether improvement in autonomic regulation is associated with reductions in PTSD symptom severity during WET, using continuous, clinical-grade wearable data collected during an open pilot of a digital WET intervention. Participants (N=15–20) will complete a 5-week, 5-session digital WET-based intervention with continuous wearable monitoring. Biomarkers of autonomic regulation—including heart rate variability, electrodermal activity, peripheral temperature, and sleep disruption—obtained via wearable devices will be analyzed to characterize within-person physiologic trajectories and their association with pre/post PTSD symptom change.

 *Basic Research*

 *Next-Generation Therapies*

Caitlin Paquet, Ph.D., Harvard Medical School, notes the conceptual model of “sleep health” involves related domains such as sleep duration, regularity, efficiency, timing, and circadian robustness. Multidimensional sleep health in the context of PTSD enables identification of heterogeneous sleep profiles that are obscured by singular sleep metrics and has been shown to improve prediction of adverse outcomes, including all-cause mortality and incident cardiovascular disease. Actigraphy—measuring rest and sleep cycles, often via wearable devices—provides an objective, longitudinal method to capture these dimensions and rest-activity rhythms (RAR), with preliminary evidence suggesting its utility in distinguishing PTSD from trauma-exposed controls and identifying suicide risk. This project will leverage data from 103,712 UK biobank participants who completed actigraphy assessment and mental health questionnaires to examine how multidimensional sleep relates to PTSD and suicide risk. The hypothesis is that sleep phenotypes characterized by poorer sleep quality and greater circadian irregularity will be associated with increased risk for PTSD and suicide.

 *Diagnostic Tools/Early Intervention*

Zachary Pennington, Ph.D., University of British Columbia, Canada, notes that only a small proportion of individuals who experience a traumatic event go on to develop PTSD. How variability in the brain's stress circuits confers susceptibility to stress-related illnesses is poorly understood. The team has identified a brain region that regulates stress vulnerability in mice, the anterior hypothalamic nucleus, or AHN. AHN neuron activity was found to reflect stress severity,

and stress-vulnerable animals possessed a larger number of stress-responsive AHN neurons. Dampening AHN activity led to a blunting of stress responses. The specific cell types within the AHN that regulate stress remain unknown. The team seeks to identify these neurons. They will permanently tag the specific subset of neurons in the AHN that respond to stress. They will then bi-directionally manipulate these neurons' activity to test their behavioral function. The overarching hypothesis is that this specific subset of neurons within the AHN titrates the magnitude of the stress response.

 *Basic Research*

Andrea Putica, Ph.D., University of Melbourne, Australia, notes that in PTSD, learning signals that should update beliefs and reduce feelings of threat may become misallocated to brain regions that control bodily sensations and physical responses, reinforcing feelings of danger rather than resolving them. The severity of functional neurological symptoms (FNS) such as paralysis or sensory loss without an identifiable physical cause, which are experienced by some with PTSD, may reflect the degree of this misallocation. To test this, 50 individuals with PTSD will complete a validated threat learning task during MRI scanning, with comparison to 50 healthy controls. The team will examine deep brain structures involved in threat and bodily processing that standard imaging cannot reliably resolve. Computational modelling will be used to track individual learning signals and map which brain systems they engage. The team will test whether FNS severity predicts the degree to which learning signals shift toward bodily brain systems, and will also examine whether heightened attention to bodily sensations, both as a stable personal trait and measured moment-to-moment during the task itself, amplifies this shift.

 *Basic Research*

Nicole Rigney, Ph.D., University of California, Los Angeles, notes that in PTSD the failure to appropriately modulate behavior in social contexts manifests as irritable behavior and reactive aggression. Emotional dysregulation also drives impulsive aggression in borderline personality disorder, and irritability is increasingly recognized as a prominent feature of treatment-resistant depression. Despite the transdiagnostic significance of impaired social sensitivity, the neural circuits that detect distress in others and modulate behavior accordingly remain poorly understood. A significant barrier has been a lack of behavioral paradigms that capture this socially modulated behavioral response. Dr. Rigney's team has discovered a clear example of social sensitivity in mice: when a male mouse encounters an acutely stressed intruder, it robustly suppresses its own aggression and increases affiliative allogrooming toward the stressed individual. This behavioral shift is driven by olfactory stress cues. They identified a neuronal population in the lateral septum that is both necessary and sufficient for this response. They now seek to determine the molecular

identity and projection targets of stress-responsive lateral septum neurons, and to test whether chronic corticosterone exposure impairs both the behavioral response to stressed conspecifics and the activation of the underlying circuit.

Basic Research

Nina Rouhani, Ph.D., University of Southern California, notes that PTSD is characterized by altered behavioral responding, hyperarousal, and intrusive memories of trauma, yet the computational mechanisms linking maladaptive learning patterns to episodic memory remain unclear. Contrary to cue-triggered accounts, emerging work suggests PTSD may reflect reduced flexibility in updating internal ('latent') models of the environment. This process relies on discriminating between prediction errors (PEs) that signal a true shift in the environment (volatility), requiring a model update, vs. model stability. This project explores a neurocomputational account of PTSD wherein diminished updating of latent models for volatility-driven PEs impairs memory segmentation, potentially driving the overgeneralized and decontextualized memories observed clinically. The team will recruit trauma-exposed veterans with and without PTSD (N=60) to complete a behavioral paradigm testing the relationship between learning rates and memory segmentation during fMRI, allowing characterization of neural uncertainty signals and their effect on neural representations of the task. They expect that PTSD will be characterized by blunted neural differentiation between volatility and stochasticity, along with reduced representational distance between distinct task states, which may, in turn, predict diminished memory segmentation in behavior.

Basic Research

Next-Generation Therapies

Megha Sehgal, Ph.D., Ohio State University, notes that when neutral experiences become inappropriately linked to trauma, individuals may develop fear responses to harmless stimuli, a core feature of PTSD. The team has identified a key role for the retrosplenial cortex (RSC) in linking neutral events to fearful experiences. The RSC is a brain region involved in episodic memory retrieval across species, and hyperactivity within the RSC is observed in PTSD patients. They have shown that microglia are required for linking neutral events to traumatic memories in the RSC. Blocking microglial P2Y12 receptors, either locally in the RSC or systemically using the FDA-approved drug clopidogrel, disrupted memory linking. They discovered that linked memories are stored within shared dendritic branches on individual neurons. When two memories are linked, new clusters of spines are formed on the same dendritic branches following each of the two memories. They were able to artificially link two independent memories by forcing them to be encoded within the same dendritic branches. This indicates a previously unrecognized role for

highly compartmentalized dendritic plasticity in organizing memories across time. This project will use imaging to determine how inhibiting microglial P2Y12 receptors alters neuronal activity patterns in the RSC during the formation of linked fear memories. They will also test whether these receptors are necessary for the formation of clustered dendritic spines that support memory linking, aiming to identify how microglia shape fear memory organization at the level of neural circuits and dendrites.

Basic Research

Melanie Stearns, Ph.D., University of South Florida, is exploring how circadian rhythm and brain circuits that govern stress reactivity interact to shape daily functioning in adolescents with PTSD. This PTSD-CLOCKS study will recruit 50 adolescents ages 13-17, comparing those with PTSD to a group without PTSD. The team will examine whether "social jetlag," a mismatch between an individual's internal circadian clock and their externally imposed schedule, is a hidden driver of heightened physiological stress reactivity in adolescents with PTSD. Participants will wear wrist monitors (actigraphy) and complete daily sleep diaries for 10 days. The protocol also includes Dim Light Melatonin Onset (DLMO) testing, which requires collecting saliva samples in low-light conditions to determine when melatonin production begins. The team will also measure physiological stress reactivity using markers of autonomic and neuroendocrine function. The hypothesis is that PTSD not only makes sleep more difficult but also disrupts synchronization of the circadian clock and the body's stress-regulation systems. Such circadian misalignment is expected to amplify physiological stress reactivity, making adolescents more easily startled, less able to recover from stress, and more vulnerable to daily challenges. Understanding these interlocking biological and neural mechanisms could support moving beyond "one-size-fits-all" approaches to trauma treatment.

Basic Research

PRENATAL BRAIN DEVELOPMENT

Sarah Banker, Ph.D., New York University, will explore biological pathways through which symptoms of depression and anxiety in pregnancy might alter fetal brain development. Using a combination of tools, the team will test whether changes in the mother's physiology help explain how her mood and anxiety symptoms might impact the fetal brain. For example, disruptions to normal changes in sleep and nervous system regulation during pregnancy could influence how the fetal brain develops before birth. This study will draw on two independent cohorts of pregnant women, examining how self-reported depression and anxiety symptoms relate to patterns of fetal brain development, particularly in brain areas involved in emotions and mental health, such as the hippocampus and the amygdala. It will also investigate whether poor sleep or altered nervous system regulation (as indexed by heart-rate variability) in the mother help explain these patterns. Finally, the study will explore whether there are specific weeks of pregnancy when these associations are strongest.

 *Basic Research*

Cristine Casingal, Ph.D., University of North Carolina at Chapel Hill, studies primary cilia, a signaling hub in neurons that modulate the formation and function of cortical neural circuits. Disruption of primary cilia signaling in human ciliopathies, resulting from genetic mutations or environmental insults, causes disorders including schizophrenia and mood and eating disorders. This project seeks to delineate neurodevelopmental pathways and mechanisms underpinning the emergence of circuit malformations linked to primary cilia dysfunction, using a multimodal approach based on cortical organoids, CRISPR-Cas9-based ciliopathy gene manipulation, genetic barcode-based mapping of brain developmental trajectories, and proteomic mapping of cilia-driven signaling networks.

 *Basic Research*

Mattia Chini, M.D., Ph.D., University of Liege, Belgium, studies the complement system, molecules involved in immunity. In the brain, this system can also tag synaptic connections for removal during early development. This research seeks to learn more about how early synapse loss leads to the circuit-level problems that define schizophrenia. If synapse loss reduces excitatory connectivity, pyramidal output drops. This reduction should affect parvalbumin (PV) interneurons, inhibitory neurons that depend on excitatory input to mature and stabilize network activity. Many studies implicate PV dysfunction in schizophrenia. This project tests whether shifting complement tagging changes the timing of PV maturation during early development, thereby linking synapse pruning to circuit dysfunction. The team hopes to produce a developmental map of prefrontal circuit maturation and test whether complement loss accelerates PV recruitment.

This could clarify how complement can shape early prefrontal circuit development in a schizophrenia-relevant context and pave the way to larger studies testing complement gain-of-function and inflammatory microglial priming.

 *Basic Research*

Lindsay Hayes, Ph.D., The University of Oklahoma Health Sciences Center, is interested mechanisms by which developmental immune activation programs long-term alterations in brain development and contributes to risk for neurodevelopmental disorders like schizophrenia and ASD. This project focuses on disruption of microglial maturation, which can profoundly alter neuronal connectivity and behavioral outcomes. The team will use a maternal immune activation (MIA) mouse model in which pregnant dams are delivered an immune stimulus during pregnancy and the offspring are then evaluated. The team hypothesizes that DNA methylation serves as an epigenetic imprint of prenatal immune stress in microglia, driving altered maturation and developmental functions. Among other objectives, they seek to determine the necessity and sufficiency of DNA methylation in regulating microglial maturation and phagocytosis in MIA and control offspring. This may demonstrate that disrupted epigenetic imprinting underlies aberrant microglial developmental functions and which DNA methylation machinery may underlie the imprinting.

 *Basic Research*

Claudia Lopes, Ph.D., Harvard University/McLean Hospital, focuses on how inflammation during pregnancy may disturb the early development of the hippocampus, a brain region important for memory, stress regulation, and mood. Using stem cells from individuals with schizophrenia and controls, the team will grow miniature placentas (trophoblast organoids, hTOs) and hippocampi (hippocampal organoids, hHOs), focusing on male-derived cells. Hippocampal organoids generated from schizophrenia patient cells show reduced growth and overactive networks, even without an inflammatory insult. The team will briefly expose schizophrenia-derived and control hTOs to the inflammatory signal IL-6, then collect the proteins and molecules they release (the "secretome"). They will apply these placental secretomes to control hippocampal organoids at a time point that mimics mid-gestation. The hope is to isolate the effects of placenta-encoded inflammatory signals on an otherwise genetically typical developing brain, without directly exposing the brain tissue itself to IL-6. By comparing how control hippocampal organoids respond to secretomes from inflamed versus non-inflamed, and genetically typical versus schizophrenia-derived placentas, they seek to determine if a vulnerable placenta is sufficient to slow hippocampal growth, disrupt the balance of developing nerve cells, and push brain circuits into an overly active state like that in overactive hippocampi in people with schizophrenia.

 *Basic Research*

Ana Soraia Lourenco Barao, Ph.D., Algarve Biomedical Center, Portugal, will test the hypothesis that a subset of progenitor-enriched schizophrenia risk genes disrupts progenitor proliferative capacity and division, leading to altered specification and connectivity of brain cells called ULNs. The team's findings suggest schizophrenia-associated genetic variation may converge on progenitor-specific regulatory programs rather than act solely on post-mitotic neuronal dysfunction. To test this, the team will follow a single mechanistic path from progenitor function to circuit outcomes and human validation. They will define the cellular and molecular mechanisms by which specific risk genes regulate progenitor proliferation and fate decisions. They seek to determine how progenitor-stage perturbations alter ULN identity and long-range connectivity. Risk genes with validated function in progenitors will be examined. Human induced pluripotent stem cell-derived cortical neurospheroids will be engineered with the same gene perturbations defined in mouse. This model will enable assessment of effects on human progenitor dynamics and downstream neuronal network activity using high-density microelectrode arrays.

Basic Research

Jagadeesh Puvvula, Ph.D., University of Pennsylvania, notes flame retardants and plasticizers (phthalates) are synthetic compounds that are widely used in food packaging and consumer products. These compounds structurally and functionally mimic the role of natural hormones essential for neurodevelopment. Exposure to these chemicals during a susceptible period, such as pregnancy, can interfere with the endocrine system and may affect how an offspring's brain develops and how they behave. In addition, some newborns inherit genetic traits that increase their vulnerability to behavioral problems, and complex interactions between these genetic risks and environmental exposures may heighten the risk of adverse neurobehavioral outcomes. This study aims to examine the joint effects of genetic and environmental risks on the offspring's brain structure and behavior. The team also will evaluate gene-environment interactions using genetic markers that influence neurotransmission pathways in the offspring's brain and their effects on brain structure and behavior. Using data collected from 256 mother-child dyads, this prospective study seeks to elucidate the contributions of genetic and environmental risk factors towards offspring neurobehavior.

Basic Research

Federico Salas-Lucia, Ph.D., University of Chicago, notes that children with ADHD, schizophrenia, epilepsy, autism, and related disorders commonly present changes in the size and connectivity of specific brain regions. These defects may originate from selective neuronal vulnerability to external challenges during critical developmental periods, when neurons acquire their final identity and establish the connectivity and functionality of neuronal networks. One of these challenges could be inadequate exposure to thyroid hormone (T3). This

project explores whether unregulated T3 level is important in the etiology of neurodevelopmental conditions and seeks to discover mechanisms involved in appropriate T3 signaling in neurons and their role in neuronal identity acquisition and functional connectivity. The team will study new iPSCs genetically deficient in DIO3 (neuronal enzyme type 3 deiodinase, which reduces T3 action in neural cells) and genetically normal control cells to define the effect of increased T3 action on real-time gene expression during neuronal identity acquisition and functional maturation. This may capture real-time gene expression changes associated with neuronal differentiation and identify developmental periods in which altered T3 states affect critical molecular and cellular processes in the developing human brain, leading to altered populations of neuronal subtypes, with functional brain consequences of relevance to neurodevelopmental disorders.

Basic Research

Huili Sun, Ph.D., University of Pennsylvania School of Medicine, cites evidence suggesting children with prenatal cannabis exposure (PCE) face higher risks of psychiatric conditions, including ADHD, anxiety, and depression. This project hopes to uncover underlying brain mechanisms during development through which PCE shapes these transdiagnostic vulnerabilities. The project seeks to clarify when PCE-related brain alterations emerge, how these changes evolve across early life, and how strongly they affect risks for emerging psychopathology. The team will use the large-scale developmental neuroimaging datasets with the recent release of infant data from the HEALthy Brain and Child Development (HBCD) Study to determine whether PCE-related brain alterations are detectable in infancy, whether they persist across development, and whether early brain deviations predict later psychiatric risks. They will quantify how the brain structural network shapes its dynamic activities. Controllability, measuring the brain's capacity to support dynamic brain functions, has been implicated in multiple neurodevelopmental psychiatric disorders, offering a sensitive tool for detecting transdiagnostic psychiatric risk following PCE. Demonstrating that brain network deviations are detectable in the first months of life, and that they predict dimensional psychiatric risk years later, would establish infancy as a sensitive window for early intervention.

Basic Research

Lisanne van Houtum, Ph.D., University Medical Center Rotterdam/Erasmus Medical Center, The Netherlands, notes that having a parent with severe mental illness (SMI), e.g., bipolar disorder, schizophrenia, or major depressive disorder, is the most important risk factor for developing mental illness. This project is part of a larger study ("PANDA") exploring the earliest neurodevelopmental and socioemotional consequences related to this risk. The perinatal period, specifically, is a critical developmental window, making it the optimal time for

interventions. Perinatal brain characteristics (e.g., intracranial volume [ICV] growth, connectome development) and infant socioemotional development may mediate how genetic and environmental factors ultimately translate into mental illness. The team is investigating if familial risk for SMI influences fetal and neonatal ICV growth and resting-state functional connectivity; and if fetal and neonatal ICV growth and resting-state functional connectivity relates to infant socioemotional development, in children of parents with vs. without SMI. The hope is that such data findings will inform development, implementation, and/or adaptation of early-life, low-threshold preventive strategies for families at risk.

 *Diagnostic Tools/Early Intervention*

 *Basic Research*

Shaoyuan Zhu, Ph.D., Stanford University, studies neuronal wiring processes that go awry in neurodevelopmental conditions including ADHD, autism (ASD), and intellectual disability, specifically, molecular instructions that tell specific neurons which partners to connect to. This project investigates a family of proteins called Latrophilins and their binding partners, the Teneurins, which together act as a molecular “address code” guiding the formation of hippocampal circuits. Genetic studies have identified LPHN3 (ADGRL3)—the gene encoding Latrophilin-3—as an ADHD risk gene; related TENEURIN genes have been linked to ASD and intellectual disability. It remains unknown how disruption of Latrophilin–Teneurin signaling damages hippocampal circuits and produces cognitive symptoms. To address this, the team has generated mice lacking all three Latrophilin proteins in forebrain neurons. They will map when and where hippocampal architecture breaks down during development after Latrophilin loss, characterize resulting synapse defects at nanometer resolution, and perform a behavioral assessment to link circuit disruption to cognitive impairment. They will also test whether the physical binding between Latrophilins and Teneurins is what encodes the wiring specificity of two major hippocampal output pathways.

 *Basic Research*

PSYCHOSIS

Bodily Brand, Ph.D., University of Oxford, UK, notes that in women, fluctuations and decline in estradiol are associated with predictable changes in psychosis symptom severity, relapse risk, and treatment response. Periods of low estradiol, including the last week of the menstrual cycle (the premenstrual phase) and the menopausal transition, represent clinically meaningful windows of increased vulnerability. Emerging evidence indicates that estradiol modulates cortical excitation–inhibition (E/I) balance, disruption of which is a well-established candidate mechanism underlying psychosis. This research seeks to learn whether this relationship contributes to clinical deterioration in women with

schizophrenia spectrum disorder during periods of estradiol decline. By integrating endocrine, electrophysiological, and clinical measures, this study seeks to clarify if estradiol decline is a driver of psychosis symptom destabilization in women. The findings have the potential to inform biologically grounded, sex-specific approaches to relapse prediction and intervention across key hormonal transitions.

 *Diagnostic Tools/Early Intervention*

Jaime Castellon, Ph.D., University of California, Los Angeles, has shown that dopamine shapes how the brain represents subjective reward value, and that the link between dopamine and reward-related decisions appears in different directions across different clinical populations. This suggests the brain’s value computations reorganize in disorder-specific ways. This project uses functional MRI to map how the brain represents subjective reward value when people make decisions for themselves versus for another person. Adults varying in subclinical anhedonia and psychotic-like experiences will make decisions to discount monetary rewards by delay, effort, and probability for both themselves and another person while the team measures brain activity patterns. The central question is whether anhedonia and psychotic-like experiences produce distinct disruptions in the brain’s value code. Dr. Castellon hypothesizes that anhedonia compresses subjective value representations so that rewarding options become indistinguishable across both self- and other-directed decisions, and psychotic-like experiences selectively disorganize the relationship between self and other value representations due to impaired perspective-taking. Results may inform targeted approaches to improving reward valuation and social functioning in schizophrenia and lay the groundwork for interventions targeted at specific disruptions to the computation of reward value.

 *Basic Research*

Rebecca Cooper, Ph.D., Harvard University/Boston Children’s Hospital, studies psychotic-like experiences (PLEs), a transdiagnostic risk factor for adverse psychiatric, educational and functional outcomes. Emotion dysregulation is considered a predisposing factor for PLEs, but current assessments rely on retrospective self-report or lab-based paradigms that lack scalability and ecological validity. Linguistic distancing—use of language that creates psychological distance from an emotive event—is an emotion regulation strategy that can be expressed through smartphone communication, providing an opportunity to measure emotion regulation at scale in a real-world setting. Dr. Cooper aims to validate language expressed in real-world smartphone communication as a digital marker for emotion regulation, using data from 500 early adolescents, quantifying its potential predictive value for emerging PLEs, over and above self-report measures of emotion regulation.

 *Diagnostic Tools/Early Intervention*

Deborah Luessen, Ph.D., Emory University, cites evidence implicating pathological striatal dopamine signaling as a central driver of psychosis and motivational dysfunction, underscoring the need for therapeutic strategies that normalize dopamine transmission without broadly suppressing dopaminergic circuits. Metabotropic glutamate receptor mGlu1 is a promising regulator of striatal function. Positive allosteric modulators (PAMs) of this receptor suppress dopamine release and reverse psychostimulant-induced behavioral phenotypes in preclinical models. The cell-type-specific mechanisms through which mGlu1 regulates dopamine transmission remain undefined. mGlu1 is expressed in multiple striatal populations, yet D1-expressing medium spiny neurons (D1-MSNs) are uniquely positioned to influence dopamine release through local circuits and retrograde signaling mechanisms. Determining whether mGlu1 in D1-MSNs mediates dopamine suppression is critical to understanding the circuit basis of mGlu1-based therapeutic effects. This project seeks to define how mGlu1 signaling within D1-MSNs regulates striatal dopamine release and shapes behaviorally relevant dopamine dynamics. The team hypothesizes that mGlu1 expressed in D1-MSNs constrains dopamine release and that this mechanism underlies the behavioral effects of mGlu1 PAMs.

Basic Research

Kate Merritt, Ph.D., University College London, UK, will use a new neuroimaging method called three-dimensional magnetic resonance spectroscopic imaging (3D-MRSI) to measure glutamate levels across the entire brain in a single scan. This will enable the team to create detailed maps showing how glutamate is altered throughout the brain in people experiencing psychosis. By combining these whole-brain glutamate maps with information about brain structure, this study aims to identify distinct glutamatergic network patterns that may represent meaningful biological subtypes of psychosis. These network differences could help explain why some individuals respond to antipsychotic medication while others do not. They may also clarify which patients are most likely to benefit from emerging glutamatergic treatments. Together, these impacts could guide more precise and personalized treatment strategies.

Diagnostic Tools/Early Intervention

New Technologies

Next-Generation Therapies

Aubrey Moe, Ph.D., Ohio State University, notes one of the most impactful challenges for people with psychosis is impaired mentalizing, the ability to figure out what other people may be thinking or feeling. Mentalizing difficulties are closely tied to poor social functioning, and are difficult to address. New research suggests that the posterior cerebellum (PCb) plays a key role in mentalizing and social understanding. It may act as a real-time interpersonal coordination regulator. Though promising, this has not yet been tested in real-world social behavior. To measure how well two people coordinate

with one another during conversation it may be possible to use interpersonal linguistic synchrony (ILS), which captures how much conversational partners naturally adjust to and match each other's speaking styles. This project seeks to connect brain activation during mentalizing, naturalistic conversational behavior, and social outcomes in youth with psychotic disorders. Using data from an existing study of 54 adolescents and young adults with psychosis and 39 matched controls, the team will examine whether disruptions in ILS help explain why PCb dysfunction leads to social difficulties.

Basic Research

Deepa Purushothaman, M.D., Yale University, has found that the right temporoparietal region junction (rTPJ) shows reduced activity in first episode psychosis, along with a weakening of theta-band oscillations, which may be related to deficits in people with psychosis and schizophrenia in accurately analyzing facial expressions to grasp the meaning of a social interaction. This project will test the hypothesis that after a "gentle reset" of the relevant circuit (centering on the right temporoparietal junction) individuals with early schizophrenia will be able to analyze facial expressions better. For the reset, the team will use non-invasive intermittent theta burst stimulation (iTBS) to directly target the rTPJ. Since the magnetic pulsations are delivered at the frequency of the theta rhythm, the team believes that weakened theta rhythms will be re-engaged. Twenty-four young adults with first-episode psychosis will participate. Each will be receiving both the targeted stimulation and a control condition on separate visits.

Next-Generation Therapies

Basic Research

Rida Rehman, Ph.D., Stanford University, observes that patients with psychosis lose up to 30% of their synapses, a loss that begins before psychotic symptoms appear, suggesting it may be a root cause rather than an effect. One of the strongest common genetic risk factors for schizophrenia is the number of copies a person has of a gene called C4A. More copies mean more C4A protein, which tags synapses for removal by the brain's immune cells, called microglia. But C4A-driven synaptic loss has only been shown in mice and in cells grown in a dish. Mouse brains do not process C4A as human brains do, and cells in a dish lack the complexity of a living brain. No one has tested whether too much C4A actually drives synaptic loss in human brain tissue. Using stem-cell technology and patient-derived cells, Dr. Rehman will grow organoids and transplant them into a mouse brain, creating a compartment of living human brain tissue. The team will test if excess C4A causes microglia to strip away too many human synapses; and compare two treatments: an antibody called anti-C1q, and clozapine. Anti-C1q, already in clinical trials, might rescue synapses. If so, it would be the first evidence that targeting complement can protect synapses. If complement-mediated synaptic loss is confirmed as a cause

in human tissue, it may open an entirely new class of treatment for psychotic disorders.

 *Basic Research*

 *Next-Generation Therapies*

SCHIZOPHRENIA

Larissa Albantakis, Ph.D., University of Wisconsin, notes thalamocortical dysfunction is a core neurobiological deficit in schizophrenia spectrum disorder (SSD), contributing to cognitive impairment, symptom severity, and sleep disturbances marked by abnormal sleep oscillations, of which a notable biomarker is reduction of sleep spindles—brief 10–16 Hz oscillations generated by thalamocortical circuits during NREM sleep. Spindle deficits have been associated with greater positive and negative symptom severity, cognitive impairment, and poorer functional outcome in first-episode SSD. Non-invasive brain stimulation techniques are unable to directly target deep brain structures like the thalamus, where sleep spindles are generated. This project will use temporal interference transcranial electric stimulation (TI-TES) to stimulate the thalamus, testing whether repeated thalamic TI-TES can produce lasting changes in thalamocortical network organization. A cohort of healthy adults will be recruited. This work aims to provide safety, feasibility, and effect-size estimates needed to design patient trials aimed at targeting thalamocortical dysfunction and its downstream consequences for sleep and cognition in schizophrenia.

 *Basic Research*

 *Next-Generation Therapies*

André Bastos, Ph.D., Vanderbilt University, who focuses on schizophrenia, studies predictive processing—the brain's capacity to use internal models to anticipate incoming information. He proposes a framework called Predictive Routing that links inhibitory interneurons and brain rhythms to processing of predictions brain-wide. This project tests the hypothesis that somatostatin-positive (SST+) interneurons are involved in computing predictions (what you think you will see next) using slower alpha-beta band neural oscillations; and that parvalbumin-positive (PV+) interneurons are involved in computing prediction errors (the difference between expectation and experience) using fast gamma oscillations. The team will study PV/SST+ cell activity using high-density recordings across the brain while animal subjects play a video game that taps into their cognitive ability to make predictions of visual sequences. This may reveal how specific inhibitory interneurons are involved in prediction. Dr. Bastos hopes this will shed light on how clinical biomarkers in patients with schizophrenia relate to circuit-level brain mechanisms.

 *Basic Research*

Upasana Bhattacharyya, Ph.D., Feinstein Institute for Medical Research/Northwell Health, is interested in specific biological pathways—such as neuroinflammation or synaptic pruning—in individual cases of schizophrenia and bipolar 1 disorder (BD), which share approximately 70% of genetic risk factors. The team aims to deconstruct shared genetic risk into specific, biologically interpretable components; and map these onto clinically meaningful outcomes. They hypothesize the shared genetic foundation of these disorders is composed of distinct biological axes that influence outcomes such as treatment response, illness severity, and physical health. They seek to integrate data on these biological axes with medical data derived from large-scale electronic health records of over 15,000 genetically characterized patients from Singapore and Finland. They will track how well these genetic risk scores derived from biologically grounded genetic components align with outcomes such as treatment resistance, risk for severe hospitalizations, and cardiometabolic complications. Benchmarking these refined polygenic scores against traditional genome-wide polygenic risk scores will support evaluation of whether a more granular approach provides the accuracy and inclusivity needed to better understand patient trajectories.

 *Basic Research*

Guy Bouvier, Ph.D., University Pierre & Marie Curie/Centre National de la Recherche Scientifique (CNRS), France, notes people with schizophrenia often struggle to distinguish events they cause themselves from events caused by the outside world. These symptoms are poorly understood. His research targets how the brain decides whether the visual world is moving, or whether we are. Doing so requires our brain to combine what we see with information about how we moved, so that self-generated and world-generated visual signals can be told apart. He believes this basic computation is affected in schizophrenia, and that understanding where and how it fails will reveal new insights into why psychotic symptoms emerge and future treatments. The hypothesis tested here is whether this breakdown originates from disrupted connections between the pulvinar thalamus—a relay hub deep in the brain—and the visual cortex, the very first stage at which the brain begins to build a picture of the world. The experiments will be conducted in mice carrying the 22q11.2 genetic deletion. Ultimately, this research may help us understand schizophrenia, not only as a disorder of thought, but as a fundamental disruption in how the brain knows what it has caused itself.

 *Basic Research*

Mazdak Bradberry, M.D., Ph.D., Columbia University, seeks to provide an understanding of schizophrenia biology using proximity-labeling proteomics, an analytical chemical technique that enables the measurement of thousands of proteins specifically at brain synapses in both human and rodent brain tissue. In this project, brain tissue from rodents with three

different schizophrenia-associated genetic variants will be analyzed, and changes in the proteins measured at presynaptic and postsynaptic neurons independently. The proteins of neurons that release dopamine, which has been implicated in some schizophrenia symptoms, will also be analyzed. Because the proteins at the synapse are responsible for its function, changes in the proteins will provide insight into how these schizophrenia-associated genetic changes are related to the composition and function of the synapse. Importantly, studying three different genetic models will allow for the determination of the common factors among them, which may represent biological changes pertinent to schizophrenia causation.

Basic Research

Bodyl Brand, Ph.D., University of Oxford, UK, notes that in women, fluctuations and decline in estradiol are associated with predictable changes in psychosis symptom severity, relapse risk, and treatment response. Periods of low estradiol, including the last week of the menstrual cycle (the premenstrual phase) and the menopausal transition, represent clinically meaningful windows of increased vulnerability. Emerging evidence indicates that estradiol modulates cortical excitation–inhibition (E/I) balance, disruption of which is a well-established candidate mechanism underlying psychosis. This research seeks to learn whether this relationship contributes to clinical deterioration in women with schizophrenia spectrum disorder during periods of estradiol decline. By integrating endocrine, electrophysiological, and clinical measures, this study seeks to clarify if estradiol decline is a driver of psychosis symptom destabilization in women. The findings have the potential to inform biologically grounded, sex-specific approaches to relapse prediction and intervention across key hormonal transitions.

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Basic Research

Swastik De, Ph.D., Columbia University, studies circular RNAs (circRNAs), a class of covalently closed transcripts highly enriched in the mammalian brain and which have emerged as regulators of gene expression and, in many cases, as templates for protein synthesis through cap-independent internal ribosome entry site (IRES)-driven translation. CircRNAs are robustly dysregulated in schizophrenia and major depressive disorder (MDD). Whether such dysregulation has functional consequences at the protein level is not known. The structural mechanisms by which circRNA IRES elements recruit the ribosomal initiation machinery are

undefined, limiting biological understanding and therapeutic exploitation of this RNA class. This project will test whether three circRNAs implicated in MDD and schizophrenia function as authentic IRES-driven translational templates in human neuronal cells and will map their protein interaction networks. It will also determine the first cryo-EM structure of a psychiatrically relevant circRNA IRES bound to human ribosomal initiation complexes. Findings may establish circRNA translation as a previously unrecognized molecular layer in psychiatric disease.

 *Basic Research*

Marc Dos Santos, Ph.D., Northwestern University, notes that while schizophrenia is often described as a disorder with fewer synapses in adulthood, several genetic risk factors show the opposite pattern in youth. Some high-risk genetic variants are linked to excessive connectivity during adolescence. This indicates a transient phase of hyperconnectivity during peri-adolescence which could lay the basis for altered brain function and cognitive problems in adulthood. To find molecules that might guide new synaptic treatments, the team found people with schizophrenia have lower CSF levels of synaptic protein PTPRD, a cell-adhesion and signaling protein at synapses that can be cleaved at the cell surface, releasing its outer portion into the extracellular fluid. The team believes the soluble extracellular portion of PTPRD may act as a normalizing signal for brain connectivity. In genetic mouse models of schizophrenia that show excessive connectivity during adolescence, a precisely timed dose during early adolescence could restore brain activity to healthy levels, a theory that will be tested in this project. It will also test if giving soluble PTPRD during adolescence improves brain activity and behavior in rodents. This could open a path to novel circuit-normalizing therapies based on endogenous brain-fluid proteins for schizophrenia.

 *Basic Research*

 *Next-Generation Therapies*

Travis Faust, Ph.D., University of Massachusetts Medical School, cites evidence that in schizophrenia, synaptic pruning is disrupted during adolescence in the prefrontal cortex, leading to excessive synapse loss. This research is driven by the question of how certain synapses are selected for removal and why particular brain regions and developmental periods are vulnerable. Dr. Faust has identified a mechanism that helps explain this selective vulnerability, involving communication and contacts between microglia and astrocytes. This project will test if genetic and environmental risk factors for schizophrenia disrupt astrocyte-based control of synapse vulnerability during adolescence in the prefrontal cortex, using mouse models linked to schizophrenia risk. The team will measure whether certain risk factors increase synapse vulnerability by altering astrocyte contact and whether restoring astrocyte contact can prevent abnormal synapse loss; they also seek to identify differences in the proteins present at synapses closely contacted by astrocytes compared to those that are not.

 *Basic Research*

Ariel Gilad, Ph.D., The Hebrew University of Jerusalem, Israel, is thinking about schizophrenia as a disorder of large-scale circuit dysfunction rather than isolated regional abnormalities. Human imaging and computational studies have revealed widespread dysconnectivity across prefrontal, striatal, hippocampal, thalamic, and limbic systems. Using a high-density 24-site multi-fiber photometry platform enabling simultaneous recording of neural dynamics across cortical and subcortical regions in freely moving mice, which they developed, the team plans to identify brain-wide dopamine and serotonin network dysfunction in schizophrenia-model mice; and use clozapine as a mechanistic probe to determine whether restoration of neuromodulatory topology governs circuit-level rescue. By establishing quantitative neuromodulatory network metrics as mechanistic readouts of pathological and restored circuit states, this project seeks to create a scalable platform for testing additional disease models, neuronal subtypes, neuromodulators, and novel pharmacological interventions.

 *Basic Research*

 *New Technologies*

Lindsay Hayes, Ph.D., The University of Oklahoma Health Sciences Center, is interested mechanisms by which developmental immune activation programs long-term alterations in brain development and contributes to risk for neurodevelopmental disorders like schizophrenia and ASD. This project focuses on disruption of microglial maturation, which can profoundly alter neuronal connectivity and behavioral outcomes. The team will use a maternal immune activation (MIA) mouse model in which pregnant dams are delivered an immune stimulus during pregnancy and the offspring are then evaluated. The team hypothesizes that DNA methylation serves as an epigenetic imprint of prenatal immune stress in microglia, driving altered maturation and developmental functions. Among other objectives, they seek to determine the necessity and sufficiency of DNA methylation in regulating microglial maturation and phagocytosis in MIA and control offspring. This may demonstrate that disrupted epigenetic imprinting underlies aberrant microglial developmental functions and which DNA methylation machinery may underlie the imprinting.

 *Basic Research*

Stephanie Herrlinger, Ph.D., Columbia University, notes that while inhibition has long been implicated in schizophrenia, few of the many GABAergic cell types have been examined and thus the circuit-level mechanisms linking characteristic microdeletions to episodic memory dysfunction remain poorly understood. She will use a mouse model of the 22q11.2 deletion syndrome strongly linked with schizophrenia. To definitively determine whether disinhibition is a bottleneck for spatial learning deficits, she will use advanced 2-photon imaging and closed-loop optogenetic experiments to determine precisely when, where, and how disinhibition fails during learning. Each

of these questions is independently addressable and stands to significantly impact the field's understanding of both neural mechanisms during learning and memory in the hippocampus and deficits in neuropsychiatric disorders.

Basic Research

Maltesh Kambali, Ph.D., University of Illinois at Urbana-Champaign, cites evidence implicating mitochondrial dysfunction as a potential unifying mechanism linking genetic variation to neuronal and cognitive deficits in schizophrenia. Mitochondrial pathways have not yet been firmly established as reliable biomarkers or therapeutic targets for the illness, however. This project will test the hypothesis that diverse schizophrenia-linked genetic mutations converge on mitochondrial deficits as a shared mechanistic substrate and that pharmacological correction of these deficits can restore neuronal, circuit, and behavioral function. Using genetically defined mouse models, cell-type-specific mitochondrial assays, and in vivo circuit and behavioral analyses, the team aims to determine whether mitochondrial impairments are cell-type dependent and whether metformin rescues mitochondrial function and associated neural ensemble dynamics across models. The study seeks to mechanistically link mitochondrial bioenergetics to excitatory-inhibitory balance, neural dynamics, and cognition, perhaps providing validation for mitochondrial pathways as therapeutic targets.

Basic Research

Next-Generation Therapies

Kangjoo Lee, Ph.D., Florida International University, seeks better understanding of how neural circuit dynamics map to symptom fluctuations in schizophrenia across timescales from moments to years. The team will collect a 10-month longitudinal neuroimaging and digital phenotyping dataset in patients (N=20; ages 18–45) and integrate monthly 30-minute multi-echo resting-state fMRI sessions with structured clinical assessments, quarterly neuropsychological testing, and twice-daily smartphone-based ecological momentary assessment (EMA) for 14 days following each quarterly visit. They will examine trait-level network architecture, month-to-month reorganization, and moment-to-moment neural state dynamics. Aims include quantifying within- versus between-person variance and defining confidence intervals for expected session-to-session fluctuation; and testing whether, within individuals, reduced between-network segregation and decreased occupancy of a segregated whole-brain co-activation pattern (CAP) state predict worsening negative symptoms and cognitive decline. By integrating dense neuroimaging with high-frequency EMA, this study shifts beyond static case-control contrasts to identify time-resolved, within-person neural signatures of symptom change.

Basic Research

Diagnostic Tools/Early Intervention

Emi Ling, Ph.D., RIKEN Brain Science Institute, Japan, has compared cellular differences between people with and without schizophrenia, work that revealed a coordinated conversation between neurons and astrocytes that Dr. Ling calls the synaptic neuron-astrocyte program (SNAP). In people with schizophrenia this conversation is dramatically muted, and many of the genes involved are known to increase risk for the disorder. This research seeks to eavesdrop on the SNAP signal outside the brain, using a simple blood draw. If a blood test could detect the loss of SNAP activity in the brain, clinicians might have a minimally invasive way to diagnose schizophrenia early. Using postmortem brain tissue and matching blood drawn while donors were alive, the team will look for RNA fingerprints in the Japan biobank cohort: patterns of gene activity in blood cells that track the weakening of SNAP in the brain; and identify lipid and protein clues of changes in SNAP activity in the brain. The goal is to uncover blood-based markers that faithfully reflect the disrupted neuronal-astrocyte communication in the brain that occurs in schizophrenia.

Basic Research

Diagnostic Tools/Early Intervention

Claudia Lopes, Ph.D., Harvard University/McLean Hospital, focuses on how inflammation during pregnancy may disturb the early development of the hippocampus, a brain region important for memory, stress regulation, and mood. Using stem cells from individuals with schizophrenia and controls, the team will grow miniature placentas (trophoblast organoids, hTOs) and hippocampi (hippocampal organoids, hHOs), focusing on male-derived cells. Hippocampal organoids generated from schizophrenia patient cells show reduced growth and overactive networks, even without an inflammatory insult. The team will briefly expose schizophrenia-derived and control hTOs to the inflammatory signal IL-6, then collect the proteins and molecules they release (the “secretome”). They will apply these placental secretomes to control hippocampal organoids at a time point that mimics mid-gestation. The hope is to isolate the effects of placenta-encoded inflammatory signals on an otherwise genetically typical developing brain, without directly exposing the brain tissue itself to IL-6. By comparing how control hippocampal organoids respond to secretomes from inflamed versus non-inflamed, and genetically typical versus schizophrenia-derived placentas, they seek to determine if a vulnerable placenta is sufficient to slow hippocampal growth, disrupt the balance of developing nerve cells, and push brain circuits into an overly active state like that in overactive hippocampi in people with schizophrenia.

Basic Research

Ana Soraia Lourenco Barao, Ph.D., Algarve Biomedical Center, Portugal, will test the hypothesis that a subset of progenitor-enriched schizophrenia risk genes disrupts progenitor proliferative capacity and division, leading to altered specification and connectivity of brain cells called ULNs. The team's findings suggest schizophrenia-associated genetic variation may converge on progenitor-specific regulatory programs rather than act solely on post-mitotic neuronal dysfunction. To test this, the team will follow a single mechanistic path from progenitor function to circuit outcomes and human validation. They will define the cellular and molecular mechanisms by which specific risk genes regulate progenitor proliferation and fate decisions. They seek to determine how progenitor-stage perturbations alter ULN identity and long-range connectivity. Risk genes with validated function in progenitors will be examined. Human induced pluripotent stem cell-derived cortical neurospheroids will be engineered with the same gene perturbations defined in mouse. This model will enable assessment of effects on human progenitor dynamics and downstream neuronal network activity using high-density microelectrode arrays.

 **Basic Research**

Deborah Luessen, Ph.D., Emory University, cites evidence implicating pathological striatal dopamine signaling as a central driver of psychosis and motivational dysfunction, underscoring the need for therapeutic strategies that normalize dopamine transmission without broadly suppressing dopaminergic circuits. Metabotropic glutamate receptor mGlu1 is a promising regulator of striatal function. Positive allosteric modulators (PAMs) of this receptor suppress dopamine release and reverse psychostimulant-induced behavioral phenotypes in preclinical models. The cell-type-specific mechanisms through which mGlu1 regulates dopamine transmission remain undefined. mGlu1 is expressed in multiple striatal populations, yet D1-expressing medium spiny neurons (D1-MSNs) are uniquely positioned to influence dopamine release through local circuits and retrograde signaling mechanisms. Determining whether mGlu1 in D1-MSNs mediates dopamine suppression is critical to understanding the circuit basis of mGlu1-based therapeutic effects. This project seeks to define how mGlu1 signaling within D1-MSNs regulates striatal dopamine release and shapes behaviorally relevant dopamine dynamics. The team hypothesizes that mGlu1 expressed in D1-MSNs constrains dopamine release and that this mechanism underlies the behavioral effects of mGlu1 PAMs.

 **Basic Research**

Sara Mederos, Ph.D., Hospital del Mar Research Institute, Barcelona, Spain, notes that during periods of rest, groups of hippocampal neurons briefly fire together in coordinated bursts known as sharp wave ripples (SWR) which are thought to replay recent experiences and help reorganize stored

information. Evidence suggests these coordinated activity patterns may also help update internal representations in ways that support flexible behavioral adaptation. Hippocampal activity supporting contextual representation and memory reactivation is disrupted in schizophrenia. This project tests the hypothesis that in the mouse model of schizophrenia-related 22q11.2 deletion syndrome, hippocampal SWR activity fails to appropriately support contextual updating following transient internal state perturbations, leading to persistent and inflexible behavioral strategies. By linking genetic risk to specific alterations in hippocampal network dynamics and measurable deficits in contextual updating, this research seeks to define a circuit-level mechanism underlying cognitive inflexibility in schizophrenia.

 **Basic Research**

Kate Merritt, Ph.D., University College London, UK, will use a new neuroimaging method called three-dimensional magnetic resonance spectroscopic imaging (3D-MRSI) to measure glutamate levels across the entire brain in a single scan. This will enable the team to create detailed maps showing how glutamate is altered throughout the brain in people experiencing psychosis. By combining these whole-brain glutamate maps with information about brain structure, this study aims to identify distinct glutamatergic network patterns that may represent meaningful biological subtypes of psychosis. These network differences could help explain why some individuals respond to antipsychotic medication while others do not. They may also clarify which patients are most likely to benefit from emerging glutamatergic treatments. Together, these impacts could guide more precise and personalized treatment strategies.

 **Diagnostic Tools/Early Intervention**

 **New Technologies**

 **Next-Generation Therapies**

Jorge Miranda-Barrientos, Ph.D., Johns Hopkins University/Lieber Institute for Brain Development, is interested in sustained attention, the ability to focus on an activity or stimulus over time. Attention is impaired across multiple neuropsychiatric disorders, including ADHD and schizophrenia. The team seeks to better understand the cellular mechanisms of sustained attention to support development of targeted, mechanism-based interventions to ameliorate attentional deficits and improve functional outcomes. This project focuses on the cellular and molecular mechanisms by which projection-defined medial prefrontal cortex (mPFC) circuits to catecholaminergic nuclei regulate sustained attention. To enhance translational impact, they hope to molecularly characterize mPFC-LC (locus coeruleus) projectors using single-nucleus RNA sequencing, which can facilitate identification of potential pharmacological targets for this cellular population. Overall, the aim is to link cellular mechanisms underlying circuit dynamics to molecular identity,

providing a framework for the development of novel, targeted therapies for attentional impairments.

Basic Research

Aubrey Moe, Ph.D., Ohio State University, notes one of the most impactful challenges for people with psychosis is impaired mentalizing, the ability to figure out what other people may be thinking or feeling. Mentalizing difficulties are closely tied to poor social functioning, and are difficult to address. New research suggests that the posterior cerebellum (PCb) plays a key role in mentalizing and social understanding. It may act as a real-time interpersonal coordination regulator. Though promising, this has not yet been tested in real-world social behavior. To measure how well two people coordinate with one another during conversation it may be possible to use interpersonal linguistic synchrony (ILS), which captures how much conversational partners naturally adjust to and match each other's speaking styles. This project seeks to connect brain activation during mentalizing, naturalistic conversational behavior, and social outcomes in youth with psychotic disorders. Using data from an existing study of 54 adolescents and young adults with psychosis and 39 matched controls, the team will examine whether disruptions in ILS help explain why PCb dysfunction leads to social difficulties.

Basic Research

Arghya Mukherjee, Ph.D., University of Pennsylvania/Children's Hospital of Philadelphia, notes dysfunctional GABAergic inhibitory signaling is a key cellular deficit thought to underlie cognitive symptoms and impairments in schizophrenia and substance-use disorders. Beyond inhibitory neurons, the postsynaptic molecular machinery that makes inhibition possible is dysfunctional in mouse models of psychosis and substance use disorders, Dr. Mukherjee's work has shown. GABA signaling depends on neurons maintaining low levels of intracellular chloride. A protein called KCC2 performs this essential function. Using RNA expression data from patients with schizophrenia, the team discovered that KCC2 is selectively depleted in prefrontal excitatory neurons. Remarkably, OV350, a small molecule activator of KCC2, rescued deficits in working memory and attentional flexibility in animals. This project focuses on the mechanistic specificity needed to translate this discovery into a genuine clinical strategy. It seeks to identify precisely which prefrontal neuron populations are most vulnerable to chloride dysregulation, establish causal proof that KCC2 loss drives cognitive failure, and determine which cell types respond most powerfully to OV350.

Basic Research

Next-Generation Therapies

Farzaneh Najafi, Ph.D., Georgia Institute of Technology, notes that disorders including schizophrenia may involve problems in how the brain updates beliefs in response to unexpected events. This project will investigate how the cerebellum and posterior parietal cortex work together to support belief updating. Imaging studies in patients with psychiatric disorders suggest that communication between the cerebellum and cortex may be disrupted, but we do not yet understand how this affects learning at the level of brain circuits. The team has developed a behavioral task in mice that requires animals to learn patterns in the timing of events and to adjust when those patterns change. This provides a controlled way to measure how quickly and accurately beliefs are updated. Using advanced optical imaging techniques, they will record the activity of specific types of neurons in the cortex while animals perform this task, and selectively manipulate signals coming from the cerebellum to determine whether they influence how strongly the cortex responds to unexpected events. The hypothesis is that cerebellar output regulates how much weight the cortex gives to surprising events, which might shed light on disorders characterized by disrupted perception and belief formation.

Basic Research

Marco Niello, Ph.D., Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy, is studying deficits in emotion recognition, a core feature of schizophrenia whose underlying circuit mechanisms remain largely unresolved. Evidence implicates somatostatin-expressing (SOM) interneurons in the medial prefrontal cortex (mPFC) as key regulators of emotion discrimination, and highlights serotonin (5HT) system modulation as a major influence on prefrontal inhibitory circuit function. In past research the team showed d-Fenfluramine (dFen) preferentially elevates 5HT levels in SOM interneurons, restoring inhibitory balance and rescuing impairments in emotion recognition caused by SOM hypoactivity. This project tests the hypothesis that molecularly and functionally distinct SOM interneuron subtypes—defined by specific 5HT receptor expression—mediate positive-emotion discrimination and are selectively recruited by dFen-evoked serotonergic signaling. They hope to define the molecular and circuit principles by which 5HT shapes socio-emotional behavior, identifying 5HT-responsive inhibitory microcircuits as promising therapeutic entry points for impairments seen in schizophrenia.

Basic Research

Mary Patton, Ph.D., University of Tennessee Health Science Center, will investigate a circuit underlying attentional deficits in a mouse model of 22q11 deletion syndrome (22q11DS), a genetic disorder that significantly predisposes individuals to psychiatric disorders characterized by attentional deficits, notably schizophrenia and ADHD. Results stand to further

understanding of the neural circuits underlying attention deficits across psychiatric disorders and may help generate novel treatment options for this symptom. Thalamic signaling onto dorsal striatal cholinergic interneurons (CHIs) is necessary for identifying and filtering out relevant information from background noise. Following a salient environmental cue, excitatory synaptic transmission from the thalamus drives CHIs to fire in a characteristic “burst-pause” manner, in which CHIs increase their firing rate before entering a prolonged silent period. In a mouse model of 22q11DS, the team finds increased thalamic-CHI synaptic transmission and an increase in CHI firing activity, suggesting altered burst-pause firing in these mice. They will test the hypothesis that enhanced thalamic-CHI synaptic transmission alters burst-pause activity in CHIs of 22q11DS mice and causes attentional deficits.

Basic Research

Deepa Purushothaman, M.D., Yale University, has found that the right temporoparietal region junction (rTPJ) shows reduced activity in first episode psychosis, along with a weakening of theta-band oscillations, which may be related to deficits in people with psychosis and schizophrenia in accurately analyzing facial expressions to grasp the meaning of a social interaction. This project will test the hypothesis that after a “gentle reset” of the relevant circuit (centering on the right temporoparietal junction) individuals with early schizophrenia will be able to analyze facial expressions better. For the reset, the team will use non-invasive intermittent theta burst stimulation (iTBS) to directly target the rTPJ. Since the magnetic pulsations are delivered at the frequency of the theta rhythm, the team believes that weakened theta rhythms will be re-engaged. Twenty-four young adults with first-episode psychosis will participate. Each will be receiving both the targeted stimulation and a control condition on separate visits.

Next-Generation Therapies

Basic Research

Rida Rehman, Ph.D., Stanford University, observes that patients with psychosis lose up to 30% of their synapses, a loss that begins before psychotic symptoms appear, suggesting it may be a root cause rather than an effect. One of the strongest common genetic risk factors for schizophrenia is the number of copies a person has of a gene called C4A. More copies mean more C4A protein, which tags synapses for removal by the brain’s immune cells, called microglia. But C4A-driven synaptic loss has only been shown in mice and in cells grown in a dish. Mouse brains do not process C4A as human brains do, and cells in a dish lack the complexity of a living brain. No one has tested whether too much C4A actually drives synaptic loss in human brain tissue. Using stem-cell technology and patient-derived cells, Dr. Rehman will grow organoids and transplant them into a mouse brain, creating a compartment of living human brain tissue. The team will test if excess C4A

causes microglia to strip away too many human synapses; and compare two treatments: an antibody called anti-C1q, and clozapine. Anti-C1q, already in clinical trials, might rescue synapses. If so, it would be the first evidence that targeting complement can protect synapses. If complement-mediated synaptic loss is confirmed as a cause in human tissue, it may open an entirely new class of treatment for psychotic disorders.

Basic Research

Next-Generation Therapies

Anna Sunshine, M.D., Ph.D., University of Washington, has identified and characterized a de novo nonsense mutation in the chromatin remodeling gene INO80D, which is critical to maintenance of pluripotency in stem cells. In INO80D, which is intolerant to loss of function, the mutation triggers nonsense mediated decay, leading to haploinsufficiency. The team modeled similarly decreased INO80D function in neural stem cells and neurons by knocking down expression of INO80D in WTC-11 cells using CRISPRi, and by differentiation of patient-derived induced pluripotent stem cells (iPSCs) into neural stem cells and neurons. Decreased expression of INO80D preferentially altered expression of schizophrenia-related genes. In this project, they will further investigate the effects of the INO80D mutation on neuronal firing, then test if it is possible to reverse these effects. The hope is to elucidate the morphology and signaling mechanisms by which INO80D p.Q568X alters the activity of neurons derived from a schizophrenia patient.

Basic Research

Michael Thornton, Ph.D., Salk Institute for Biological Studies, cites genetic and clinical evidence implicating synaptic dysfunction in neurodegenerative and neuropsychiatric disorders, including Alzheimer’s and schizophrenia. Scalable methods to quantify synaptic plasticity across large populations of living human neurons remain limited. This project seeks to develop a next-generation platform to measure and control synaptic weights across hundreds of neurons in patient-derived biological networks. Among other aims, spike timing-dependent plasticity kernels will be systematically quantified across hundreds of monosynaptically connected human neuronal pairs, enabling classification of distinct plasticity phenotypes within the network. The team will apply this platform to human disease-relevant models to identify disorder-specific signatures of plasticity deficits. They hypothesize that Alzheimer’s neurons will exhibit impaired synapse stabilization, whereas schizophrenia neurons will demonstrate altered timing dependence and increased variability of synaptic modification. Comparative analysis could determine whether shared or distinct plasticity vulnerabilities emerge. By defining quantitative functional signatures of synaptic dysfunction in human neurons, this work seeks to establish a scalable framework for identifying therapeutic strategies aimed at

restoring adaptive circuit dynamics in brain disease.

Basic Research

Hayley Thorpe, Ph.D., Western University, Canada, notes that in the context of comorbid schizophrenia and cannabis use, disruption of shared neural pathways and networks may partially explain comorbidity. Most neuroimaging research on cannabis' role in schizophrenia occurs after its emergence and does not consider genetic sharedness. It is thus unclear if brain divergences existed before or because of the disorder and substance use, or how much genetics contributes to developmental trajectories. Dr. Thorpe will analyze neuroimaging phenotypes in genetically at-risk adolescents (N=11,632; ages 9–17) without schizophrenia or cannabis use. Using youth genetic data and trait-partitioned GWAS, the team will develop cannabis-only, schizophrenia-only, and shared schizophrenia-cannabis biomarkers (i.e., polygenic scores) and analyze their associations with brain structure and function before and after cannabis use and psychosis onset. The hypothesis is that neurodevelopmental variance in cannabis use and schizophrenia-related brain regions of interest is a function of genetic biomarkers, and variance will be more pronounced in those who also use cannabis and/or report psychotic-like experiences.

Basic Research

Samara Walpole, Ph.D., University of Wollongong, Australia, notes that while most currently available schizophrenia treatments target dopamine, they don't address disturbances in glutamate-related brain circuits nor interactions between dopamine and glutamate that are critical for cognition. mGluR7 plays a critical role in neural circuits underlying cognition and is uniquely positioned to regulate communication between dopamine and glutamate systems. The team's data demonstrate a selective reduction of mGluR7 expression in the midbrain of individuals with high-inflammation schizophrenia. In rodents, activation of mGluR7 influences glutamate and dopamine levels but it remains unknown whether mGluR7 directly regulates dopamine release. Defining the ability of mGluR7 to regulate both dopamine and glutamate release might reveal a mechanism to potentially stabilize dysfunctional signaling in schizophrenia, particularly under inflammatory conditions. This project directly addresses this by exploring mGluR7 cellular architecture in the human brain across regions involved in cognition, motivation, and reward processing. The team will examine whether positively or negatively influencing the activity of mGluR7 can restore signaling deficits, particularly in the context of inflammation.

Basic Research

Next-Generation Therapies

Jessica Wojtalik, Ph.D., Case Western Reserve University, studies neurobiological predictors and cognitive effects of community-based psychosocial rehabilitation in schizophrenia. Her prior research established that significant cognitive impairments and underlying fronto-limbic neurobiological abnormalities in schizophrenia are critical predictors of functional outcome. Still unknown are the impacts of functionally effective interventions in the community, such as the Clubhouse Model (CM) of Psychosocial Rehabilitation on cognition and fronto-limbic neurobiology that support functional recovery, as well as cognitive and neurobiological predictors of functional response. This project will use a 6-month non-randomized clinical trial design to examine the effect of the CM (n = 11), relative to usual community-based mental health care (n = 11), on cognition and fronto-limbic activation and connectivity. It also seeks to identify objective baseline cognitive and fronto-limbic activation and connectivity predictors of CM functional response, with the goal of determining which individuals are most likely to benefit from the intervention.

Next-Generation Therapies

Diagnostic Tools/Early Intervention

Anna Yoney, Ph.D., Columbia University, notes that human neuronal models based on stem-cell technology generally reflect early embryonic or neonatal stages of neuronal maturation, while the effects and therapeutic windows for treating schizophrenia are in mature or adult neurons. The team has developed a new method to produce large numbers of mature human induced neurons of specific subtypes (Fast-iNs). This system produces neurons without transiting through all developmental intermediates, opening the door to in-depth and rapid analysis. In this project they will apply this system to identify the effects of the schizophrenia risk gene SETD1A on different mature neuronal subtypes, including subtypes strongly implicated in disease. Results could establish a pipeline that can be applied to other risk genes and additional neuronal subtypes. The goal is to identify and validate therapeutic targets across many cell types.

New Technologies

Basic Research

SUICIDE PREVENTION

Brenda Cabrera-Mendoza, M.D., Ph.D., Yale University, notes women report higher rates of suicidal ideation and attempts, whereas men exhibit substantially higher suicide mortality. Although genetic factors substantially contribute to suicidal behavior, genomic studies assume genetic liability operates similarly in males and females. Yet emerging evidence implicates immune-inflammatory processes and hormone-related biology—both with well-established sex differences—in mood disorders and suicidal behavior. This study seeks to characterize how biological sex modifies polygenic liability to suicidal behavior and to identify immune-inflammatory and hormone-related mechanisms underlying this sex-dependent genetic risk expression. Using data from the All of Us Research Program (n=414,840, 62% female), with genomic, electronic health records and biomarker data, the team will construct genome-wide polygenic risk scores (PRS). They will test whether sex modifies the association between suicide PRS and suicidality phenotypes; and whether immune-inflammatory biomarkers and hormone-related proxies reflect biological pathways through which sex modifies genetic liability to suicidal behavior.

Basic Research

Ka Ip, Ph.D., University of Minnesota, studies social disconnection in the context of teens with depressive symptoms. Such youths often struggle to sustain engagement during peer interaction and report diminished feelings of belonging. This project will examine whether patterns of “peer neural coupling” differentiate adolescents whose depressive symptoms persist from those who show clinically meaningful improvement over time. Peer neural coupling refers to the degree to which two individuals’ brain activity becomes aligned during shared interaction. Adolescents ages 12–17 with elevated depressive symptoms will participate in Imagination Studio, a 12-week creative arts after-school program providing structured opportunities for peer engagement. The team will test whether trajectories of peer neural coupling track depressive symptom trajectories across the 12 weeks. This project, a longitudinal functional near-infrared spectroscopy (fNIRS) hyperscanning study to examine peer interaction in adolescents with depressive symptoms, seeks to shift focus from individual brain markers to interpersonal neural dynamics, distinguishing phenomena associated with symptom persistence versus improvement.

Next-Generation Therapies

Caitlin Paquet, Ph.D., Harvard Medical School, notes the conceptual model of “sleep health” involves related domains such as sleep duration, regularity, efficiency, timing, and circadian robustness. Multidimensional sleep health in the context of PTSD enables identification of heterogeneous sleep profiles that are obscured by singular sleep metrics and has been shown to improve prediction of adverse outcomes, including all-cause mortality and

incident cardiovascular disease. Actigraphy—measuring rest and sleep cycles, often via wearable devices—provides an objective, longitudinal method to capture these dimensions and rest-activity rhythms (RAR), with preliminary evidence suggesting its utility in distinguishing PTSD from trauma-exposed controls and identifying suicide risk. This project will leverage data from 103,712 UK biobank participants who completed actigraphy assessment and mental health questionnaires to examine how multidimensional sleep relates to PTSD and suicide risk. The hypothesis is that sleep phenotypes characterized by poorer sleep quality and greater circadian irregularity will be associated with increased risk for PTSD and suicide.

Diagnostic Tools/Early Intervention

Manivel Rengasamy, M.D., University of Pittsburgh School of Medicine, is interested in mechanisms behind ketamine’s effects on suicidality in adolescents. One theory is that ketamine’s prophylactic effects on stress reactivity lead to downstream reductions in suicidal thoughts and behaviors. Ketamine, administered before a stressor, protects against maladaptive reactions to the stressor. The drug may reduce stress-induced inflammation, seen in the increase in peripheral inflammatory markers such as IL-6 and TNF α that follows a stress response. This study will examine effects of a single dose of IV ketamine over 1 week while measuring stress reactivity at different timepoints in a cohort of adolescents with recent suicidal thoughts and behaviors (STBs). Among the objects is to determine if baseline stress reactivity predicts ketamine’s treatment effects on STBs. Findings may provide a foundation for a future randomized controlled trial in adolescents that can rigorously probe whether changes in stress reactivity, across a range of biological mediators, act as a mediator between ketamine treatment and STBs.

Basic Research

Next-Generation Therapies

Katherine Schafer, Ph.D., Vanderbilt University Medical Center, notes that although nearly 20% of adolescents in primary care clinics report suicidal ideation (SI), most do not receive evidence-based care due to stigma, cost, limited provider availability, long wait times, and insufficient family support. Single session interventions (SSIs) offer a potential scalable solution. This project will test a text message-delivered SSI for adolescents presenting to primary care who report SI. The team will conduct a randomized controlled trial comparing this to treatment as usual. The hypothesis is that adolescents receiving the SSI will show greater reductions in SI and related symptoms (depression and anxiety) and that the intervention will demonstrate strong reach, appropriateness, acceptability, and feasibility when embedded within routine primary-care workflows. Participants will include 300 adolescents ages 15–17 who have SI added to their problems list during a primary care visit and have an electronic health record and phone number on file.

Diagnostic Tools/Early Intervention

Rammohan Shukla, Ph.D., University of Wyoming, works to translate human gene-family molecular signatures of suicidality into behavioral models. The team will integrate systems-level transcriptomic analysis with in vivo behavioral phenotyping to test whether partial, targeted perturbation of suicidality-associated ribosomal protein gene families (RPGs) preferentially alters stress-sensitive impulsivity and response inhibition linked to suicide risk, relative to depression-like anhedonia. To prioritize the strongest candidates for experimental testing, the team will identify the RPGs most strongly associated with suicidality in their human brain data. They hope to determine which RPGs show coordinated expression patterns that best distinguish suicidality from non-suicidal depression at the functional pathway level. In mice, top-ranked RPGs will be partially downregulated in the ventromedial prefrontal cortex (infralimbic region) and anhedonia will be assessed and impulsive action and response inhibition will be measured. By linking ribosomal signatures that differentiate suicidality from depression in the human brain to domain-specific behaviors in animals, this project seeks to establish a mechanistic bridge between transcriptomic polygenicity and measurable behavioral vulnerability.

Basic Research

Delainey Wescott, Ph.D., University of Pittsburgh, notes disrupted sleep-wake rhythms can precipitate suicidal thoughts and behaviors (STBs) and are a promising modifiable treatment target to rapidly reduce suicide risk. Self-reports do not capture perturbations in circadian physiology that may underlie risk for suicide. Triple Chronotherapy is a rapid-acting and non-pharmacological circadian intervention with demonstrated efficacy for rapid and sustained antidepressant effects, entailing sleep deprivation followed by shifting sleep timing earlier plus morning bright light. This project will integrate with the first randomized controlled trial of Triple Chronotherapy in acutely suicidal individuals. The team will add novel circadian rhythm assessments prior to treatment and at follow-up to characterize circadian dysregulation underlying STBs and identify for whom Triple Chronotherapy may be most indicated. Circadian rhythms will be measured using behavioral, biological, and genetically determined markers for a global assessment of circadian functioning. Behavioral rest-activity rhythms from actigraphy will calculate the circadian functioning index (robustness), biological assessments of core body temperature will measure circadian phase (timing), and circadian gene expression in fibroblasts will determine circadian period (duration). They will also assess retinal light sensitivity non-invasively using the post-illumination pupil response. The team will further examine how changes in circadian phase and rhythm robustness following Triple Chronotherapy contributes to reduced STBs.

Next-Generation Therapies

Institutions of the 2026 Young Investigators, at the time of grant award*

Aarhus University, Denmark	Medical College of Wisconsin	University of Minho, Portugal
Algarve Biomedical Center, Portugal	Moser Research Institute	University of Minnesota (5)
Allen Institute for Brain Science	at Kennedy Krieger	University of Minnesota Medical
Baylor College of Medicine	Nanjing University, People's	Center – Fairview (2)
Beth Deaconess Medical Center (2)	Republic of China	University of North Carolina
Boston Children's Hospital (2)	New York Genome Center	at Chapel Hill (3)
Boston University (2)	New York University (4)	University of Oklahoma
Brigham and Women's Hospital	Northwestern University	Health Sciences Center
California Institute of Technology	Ohio State University (2)	University of Oregon
Case Western Reserve University	Ottawa Hospital Research	University of Oxford, UK
Children's Hospital of Philadelphia	Institute, Canada	University of Pennsylvania (3)
Children's National Hospital	QIMR Berghofer Medical	University of Pennsylvania
Columbia University (9)	Research Institute, Australia	School of Medicine (2)
Dalhousie University, Canada (2)	Research Foundation for	University Pierre & Marie Curie/
Dell Medical School, University	Mental Hygiene, Inc./NKI	Centre National de la Recherche
of Texas at Austin (2)	Research Foundation for the	Scientifique (CNRS), France
Drexel University	State University of New York,	University of Pittsburgh (4)
Emory University (2)	Stony Brook University (2)	University of Pittsburgh
Feinstein Institute for Medical	RIKEN Brain Science Institute, Japan	School of Medicine
Research/Northwell Health	Rutgers University	University of Rochester
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Ospedale Maggiore Policlinico, Italy	Stanford University (3)	University of Tennessee
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University Medicine Berlin, Germany	University College London, UK (2)	University of Texas Health
Georgia Institute of Technology	Universitat Jaume I, Spain	Science Center at Houston
Georgia State University	University of Alabama at Birmingham	University of Texas Medical
Harvard Medical School (2)	University of Arizona/Barrow	Branch at Galveston
Harvard University (9)	Neurological Institute	University of Texas Southwestern
Hebrew University of Jerusalem, Israel	University of British	Medical Center at Dallas
Hospital del Mar Research	Columbia, Canada	University of Toronto/
Institute, Barcelona, Spain	University of California, Irvine (3)	Centre for Addiction and
Hugo W. Moser Research	University of California,	Mental Health, Canada
Institute at Kennedy Krieger	Los Angeles (5)	University of Toronto/Sunnybrook
Icahn School of Medicine	University of California, Riverside	Health Sciences Centre, Canada
at Mount Sinai (4)	University of California San Diego	University of Utah
Indiana University	University of California, San	University of Virginia
Indiana University	Francisco/Gladstone Institutes (3)	University of Washington (2)
School of Medicine	University of Chicago	University of Wisconsin
Institut du Cerveau /Paris	University of Illinois at	University of Wisconsin, Madison
Brain Institute, France	Urbana-Champaign (3)	University of Wollongong, Australia
IRCCS Centro San Giovanni	University of Iowa (2)	University of Wyoming
di Dio Fatebenefratelli, Italy	University of Liege, Belgium	University of Zurich, Switzerland (2)
Johns Hopkins University (4)	University of London, UK	Vanderbilt University
King's College London, UK (2)	University of Maryland	Vanderbilt University Medical Center
KU Leuven, Belgium	University of Massachusetts	Virginia Commonwealth University
Lieber Institute for Brain Development	Medical School (2)	Wake Forest University
Loyola University, Chicago	University Medical Center	Washington University, St. Louis (2)
Massachusetts General Hospital	Rotterdam/Erasmus Medical	Wayne State University
Mayo Clinic, Jacksonville	Center, The Netherlands (2)	Weill Cornell Medical College
McLean Hospital (3)	University of Melbourne, Australia (2)	Western University, Canada
	University of Milan, Italy	Yale University (6)

*Some grantees are affiliated with more than one institution



BENEFITS OF BECOMING A RESEARCH PARTNER

Barbara Toll

BBRF Board Member & Research Partner

Many BBRF donors have a very personal interest in brain and behavior research. They know from often difficult, first-hand experience the devastation mental illness can bring upon family and friends, and they know that research will ultimately bring about better understanding and treatments.

Our **Research Partners Program** offers donors the opportunity to personally select and support scientists based on various criteria, including, but not limited to, illness specialty area or specific institutions, or a combination of these. Researchers are selected by the donor (our Research Partner) after members of our all-volunteer Scientific Council have conducted an independent peer review of the submitted applications and have made their recommendations for grant awards.

The **Research Partners Program** enables donors to choose among the best and brightest scientists and the most promising, cutting-edge proposals in mental illness research.

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To date the BBRF **Research Partners Program** has funded more than 1,500 research grants.

To learn more about the Research Partners Program, please contact us at **646-681-4889** or **researchpartner@bbrfoundation.org**.

Visit us at bbrfoundation.org/researchpartners.

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