BRAIN & BEHAVIOR RESEARCH FOUNDATION

2025 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."

September 2025

We are pleased to present the 2025 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. This program facilitates innovative research through support of early-career basic, translational, and clinical investigators.

We are proud to report that since 1987 BBRF has provided $475 million in research grants to more than 5,700 scientists around the world.

This year, the Foundation's Scientific Council, led by Dr. Judith Ford and comprised of 193 world-renowned scientists with expertise in every area of brain research, reviewed 895 grant applications and selected the 165 meritorious research projects summarized in the pages that follow. This is a 10% increase in the number of grants in order to enhance our support for young scientists.

The 2025 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 (55%) are relevant to the study or treatment of depression or schizophrenia. Many also have relevance for anxiety disorders, addiction/substance-use disorders, PTSD, bipolar disorder, ADHD, OCD, as well as suicide prevention.

Important trends in brain research are reflected in the grants. A dozen projects this year make use of a technology innovated by past grantees and derived from stem cell research. Called induced pluripotent stem cell technology (iPSC), it enables investigators to study pathologies that occur before and just after birth in the developing brain. Some of these pathologies are thought to underlie neurodevelopmental disorders such as autism spectrum disorders and schizophrenia, which are traceable in some cases to genetic mutations or environmental damage to the fetal or early postnatal brain. In iPSC, an investigator samples blood or skin cells from affected patients and reprograms them in the laboratory to redevelop as brain cells. These cells, bearing all the genetic variations of the donor cells, in turn, can be grown in colonies to form "organoids," which have the astonishing capacity to "wire-up" and become functional. Organoids can be transplanted into the brains of living mice, where they integrate into a functioning brain. This provides a window onto how illness-related pathologies first manifest in the brain—as they occur—something that cannot be seen or studied directly in people.

A number of 2025 grantees are seeking to improve or innovate new ways of non-invasively stimulating the brain to treat mental illnesses. TMS (transcranial magnetic stimulation) and related technologies have had a profound impact on the treatment of depression since the FDA's first approval in 2008; many thousands have benefitted from the original technology, pioneered by a past Young Investigator grantee and current member of our Scientific Council. In recent years, BBRF Young Investigators have successfully tested elaborations of the original technology, yielding, for example, a rapid-acting protocol, now FDA-approved, which can bring substantial relief and often remission to those suffering from difficult-to-treat refractory depression. This year's grantees seek to extend the range of illnesses that non-invasive technologies can effectively treat: an application for TMS combined with the drug d-cycloserine for obsessive-compulsive disorder; cTBS (continuous theta-burst stimulation) specifically for postpartum OCD; TMS to modify reward (possibly relevant in addiction and eating disorders); and temporal interference (TI) electrical stimulation for treatment of anxiety.

A number of projects are devoted to better understanding how psychedelic compounds alter neuronal plasticity to generate potentially therapeutic effects, and others to specifically test psilocybin and other agents for possible application in PTSD, depression, anxiety, and addiction. We also note a strong interest across illness categories in studying cognition in the brain, cognitive flexibility, and cognitive impairments. The latter are a key source of functional disability in schizophrenia—but also, as several 2025 grantees note, in bipolar disorder. Other investigators will be studying cognition and cognitive flexibility in the context of OCD, addiction, ADHD, and anxiety.

As always, 100% of every dollar donated for research is invested in our research grants. Our operating expenses are covered by separate foundation grants.

With your donations we can continue to fund innovative scientists across the field of neuropsychiatry. We thank our generous donors for supporting scientists in brain and behavior research so that more people can live full, happy, and productive lives.

Sincerely,

Jeffrey Borenstein, M.D.
President & CEO

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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

AWARDED
6,800+
GRANTS

FUNDED
$475M
GRANTS

THE 2025 YOUNG INVESTIGATOR GRANTEES

The Foundation is pleased to announce over $10.4 million in 150 new two-year grant awards to support the work of promising young scientists with innovative ideas in mental health research.

895
YOUNG INVESTIGATOR APPLICATIONS

165
YOUNG INVESTIGATOR GRANTS AWARDED

$11.4
MILLION AWARDED IN YOUNG INVESTIGATOR GRANTS

RESEARCH CATEGORIES

Basic Research (125 Grants)
To understand what happens in the brain to cause mental illness

Next-Generation Therapies (34 Grants)
To reduce symptoms of mental illness and ultimately cure and prevent brain and behavior disorders

Diagnostic Tools/Early Intervention (23 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 76 percent of the projects funded are **basic research**, the wellspring of innovation in brain research, as in all sciences.

About 21 percent of the projects funded specifically aim to develop **next-generation therapies.**

About 14 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.

Several projects have multiple classifications.

Eighty-two percent of grantees are from the United States (135 grantees). Eighteen percent of grantees come from 13 other countries (30 grantees): Australia, Canada, Denmark, France, Germany, Italy, The Netherlands, Norway, People's Republic of China, South Africa, Spain, Sweden, United Kingdom.

ADDICTION/SUBSTANCE-USE DISORDERS

Gabrielle Agin-Liebes, Ph.D., Yale University, notes the psychedelic drug psilocybin has demonstrated rapid and sustained benefits in some trials for conditions such as depression, alcohol/substance use disorders, anxiety, and PTSD, with emerging evidence suggesting that enhanced cognitive flexibility may be a key mechanism underlying these improvements. This study aims to elucidate the cognitive mechanisms by which psilocybin disrupts rigid thinking and promotes adaptive learning, perhaps thereby optimizing its therapeutic impact across traditional diagnostic boundaries. The trial will enroll people with depression, anxiety, PTSD, or alcohol/substance use disorders who exhibit significant functional impairment. Prior to dosing, participants will attend two preparatory sessions that provide psychoeducation, establish rapport, review personal history, and develop strategies for managing challenging experiences. They will then receive a single 25 mg oral dose of psilocybin, with continuous monitoring for 6 hours. A post-dosing integration session, scheduled 1–3 days later, will support the consolidation of therapeutic insights into actionable strategies for daily life.

Next-Generation Therapies

Kevin Braunscheidel, Ph.D., Icahn School of Medicine at Mount Sinai, seeks more effective drug therapies for smoking cessation. His lab has identified a network of hindbrain regions, including the caudal nucleus of the solitary tract (cNTS), that regulate nicotine aversion. The cNTS receives afferent sensory input from peripheral organs via nodose ganglia (NG) of the vagus nerve. This project will test the hypothesis that nicotine-related sensory information detected by the vagus nerve is transmitted to specific subpoplulations of cNTS neurons to regulate nicotine intake. Altering nicotine intake circuitry in the brain via peripheral manipulation promises unique therapeutic advantages given that it would not require drug permeation across the blood-brain barrier. The project seeks better characterization of periphery-innervated, nicotine-responsive cNTS neurons to promote the development of novel therapeutics.

Basic Research

Next-Generation Therapies

Yusmaris Cariaco, Ph.D., University of Ottawa, Canada, is studying the neurodevelopmental impact of in utero opioid and cannabis exposure. The lab's past research has shown that opioids disrupt placental function, leading to poor fetal growth, with these effects becoming even more severe when cannabis is also used. Testing the theory that damage to the placenta could have lasting consequences on brain development and function, they will study mice exposed to opioids and cannabis during pregnancy, analyzing their brains at embryonic stages, birth, weaning, and adulthood to track how early drug exposure affects brain growth over time. Additionally, they will monitor behavioral changes, such as motor coordination, spatial memory, and social behavior, to identify potential delays or abnormalities.

Basic Research

Ahmet O. Ceceli, Ph.D., Icahn School of Medicine at Mount Sinai, notes that as addiction progresses, motivational control over drug use is posited to shift from being goal-directed (i.e., dependent on the drug's hedonic value and focused in the ventral striatum and prefrontal cortex) to habitual (i.e., cue-triggered, via the dorsal striatum). Rooted in preclinical studies, the evidence for this cortico-striatal basis in human drug addiction is scarce. The neurobiology of motivational control, and its putative fluctuations during recovery, in opioid use disorder are at the focus of this project. It employs naturalistic, longitudinal, and computational methods to inspect the neural substrates of goal-driven behaviors and their contributions to opioid addiction severity and recovery, encompassing craving and relapse, which will be investigated in patients diagnosed with opioid use disorder.

Basic Research

Kurt M. Fraser, Ph.D., University of Minnesota, notes that extensive experience with drugs of abuse produces an over-reliance on rigid, model-free decision systems at the expense of flexible, intricate model-based behavior. Over-reliance on the rigid, model-free system produces deficits in decision-making across domains of behavior—not just pertaining to the acquisition or use of drugs—and represents a significant neurobiological dysregulation impacting those in recovery. This project seeks to 1) identify correlates of each decision-making system in neuromodulator-specific signaling within precise regions of the striatum and 2) rescue model-based decision-making via targeted restoration of activity within striatal acetylcholine-producing neurons. These acetylcholine-producing neurons provide a window into modulating the activity of dopamine axons and in turn dopamine release. This project thus offers a novel approach to identifying and rescuing a dysregulated psychological process via restoration of subregion-specific neuromodulation in the striatum.

Basic Research

Jacqueline Giovanniello, Ph.D., Temple University, notes drugs of abuse like cocaine promote habit formation. One impediment to understanding substance-use disorders is knowing how the neural circuitry controlling habit formation is modulated by drugs of abuse. This project seeks to uncover the neural mechanisms through which drugs of abuse promote habits. The lab's previous work has uncovered a novel circuit mechanism for the potentiation of habits: projections from the central amygdala to the dorsomedial striatum (CeA-DMS). CeA-DMS projections can drive premature habit formation. How drugs of abuse act on these projections to promote habits is unknown. Given evidence that the central amygdala is engaged in cocaine-seeking behavior and cocaine-seeking habits, this project will investigate whether cocaine acts on CeA-DMS projections to promote premature habits.

Basic Research

Joao Guassi Moreira, Ph.D., University of Wisconsin, who studies addiction, notes little is known about which emotion regulation strategies are involved in risky versus non-risky choices, or how these strategies may facilitate or inhibit risk-taking. This project addresses this gap in the effort to help identify intervention targets to mitigate substance use and addiction. The project will first try to identify which strategies are implicated in adolescent risk-taking, using a sample of adolescent participants ages 16–22 years. The team will then use fMRI to mechanistically confirm how the emotion regulation strategies identified in Phase 1 directly affect risky behavior on a decision-by-decision basis. A separate sample of adolescents will complete emotion regulation and risk-taking tasks while undergoing fMRI. Brain activity patterns observed during the emotion regulation task will be used to engineer a neural signature for each relevant regulation strategy. Statistical modelling will quantify how emotion regulation signatures influence risk-taking on a decision-by-decision basis.

Diagnostic Tools/Early Intervention

Kwang-Hyun Hur, Ph.D., McLean Hospital, will investigate the capacity of non-invasive TMS brain stimulation to modulate reward sensitivity, focusing on two reward domains commonly dysregulated in psychiatric populations: food rewards and social rewards. The medial prefrontal cortex (mPFC), a central hub within the fronto-striatal reward circuitry implicated in reward processing, will be targeted. The team will evaluate the bidirectional effects of TMS on reward sensitivity by employing both excitatory (10-Hz) and inhibitory (1-Hz) TMS protocols in a preclinical rodent model over a 4-week period. This experimental design will allow assessment of the long-term effects of TMS on reward-related behavioral responses and corresponding functional and structural alterations within reward-related neural circuits.

Next-Generation Therapies

Anel A. Jaramillo, Ph.D., University of Kentucky, notes that alcohol relapse is often triggered by heightened anxiety and stressful life events. The sexually dimorphic bed nucleus of the stria terminalis (BNST) is a key brain region in modulating stress and anxiety during alcohol abstinence. Projections from the parabrachial nucleus (PBN) release pituitary adenylate cyclase-activating peptide (PACAP) in the BNST. The team's data demonstrate PACAP from the PBN modulates stress and anxiety in alcohol abstinence in females. PACAP inhibitors are in clinical trials for treating migraines and PTSD. Dr. Jaramillo hypothesizes that blocking PACAP within the PBN to BNST circuit will modulate stress and anxiety in abstinence, particularly in females. By measuring neurotransmission in abstinence, these studies will determine if inhibiting PACAP will alleviate dysregulated activity in the PBN to BNST circuit and decrease stress and anxiety. By investigating the role of PACAP the aim is to assess if PACAP inhibitors can sex-specifically treat anxiety in alcohol use disorder.

Next-Generation Therapies

Paul F. Kramer, Ph.D., University of Michigan, is investigating the mechanisms regulating dopaminergic axonal physiology to better understand the neurobiology of nicotine use disorder. Little is known about how nicotine alters axonal excitability, or how nicotine-mediated changes in reward circuit dynamics is processed in the axon. Dr. Kramer has developed a new method using electrophysiology to record the membrane voltage from thin dopaminergic axons. Using this new axonal patch method, his team now hopes to reveal how nicotine controls the excitability of dopaminergic axons in the nucleus accumbens to regulate the amplitude and kinetics of dopamine release. They will also chronically administer nicotine to mice in order to understand how chronic nicotine exposure changes signaling and nicotinic receptor function in axons. The hope is that this will reveal the fundamental biology of how nicotinic receptors control axonal excitability of dopamine neuron axons in the nucleus accumbens, how nicotine hijacks these mechanisms, and what long-term exposure to nicotine does to these processes.

Basic Research

Karolina M. Lempert, Ph.D., Adelphi University, studies "temporal discounting" in the broader context of intertemporal choices, in which individuals decide between smaller, sooner rewards and larger, later rewards. These choices can be mundane (e.g., "do I take an Uber now or wait a few minutes to save money?") or important (e.g., "do I use drugs today or stay clean?"). When making these choices, people display temporal discounting, a tendency to devalue rewards that are delayed in time. Data from animal models suggests persistence and temporal discounting have distinct neural correlates and functional consequences. Dr. Lempert's

team has found that temporal discounting and persistence are uncorrelated across people, and that persistence predicts hazardous drinking, while temporal discounting does not. This project is a pilot functional MRI imaging study to facilitate direct comparison of these key cognitive processes and their neural implementation. Twenty-five healthy young adult participants will be recruited.

Basic Research

Ofir Livne, M.D., Research Foundation for Mental Hygiene, Inc./NYSPI, will (1) examine longitudinal associations between cannabis use and cognitive outcomes in middle-aged and older adults (ages 45 and above); (2) explore age, sex, and health differences in these associations; (3) assess the relationship between cannabis use and structural brain imaging outcomes; and (4) explore the role of brain abnormalities in the relationship between cannabis use and cognitive outcomes. By incorporating detailed measures of cannabis exposure—including frequency, lifetime use, and cannabis use disorder—the project seeks to provide a comprehensive analysis of how cannabis use may accelerate cognitive decline and brain structural abnormalities in aging populations. An array of cognitive domains (e.g., memory, attention, and executive functioning) and brain imaging measures (e.g., cortical thickness, gray matter volume) will be utilized as outcomes.

Diagnostic Tools/Early Intervention

Travis T. Mallard, Ph.D., Massachusetts General Hospital, notes that behavioral disinhibition is present in such conditions as ADHD, conduct disorder, and substance use disorders, each highly heritable and often begin in childhood or adolescence and frequently co-occur. These "externalizing disorders" have been robustly linked to atypical brain development, including altered cortical expansion during these formative periods. Dr. Mallard will test the hypothesis that externalizing disorders are, in part, influenced by genes that shape the timing and patterning of cortical expansion across development. The team will implement novel modeling techniques which will integrate large-scale psychiatric and imaging genetic datasets and identify pleiotropic genetic variants that concurrently influence cortical expansion and externalizing liability. Using data from large databases, they will then try to determine how the identified risk variants disrupt typical neurodevelopment across the lifespan.

Basic Research

Edward H. Nieh, Ph.D., University of Virginia, hypothesizes two interrelated mechanisms underlying the formation of the homeostatic need for a drug—a change in the population neural activity patterns of the lateral hypothalamus (LH), and precise transcriptional changes in specific populations of LH neurons. He proposes that these epigenetic changes are responsible for the long-term neural encoding modifications that cause drug craving to endure, even after long periods of time without the reinforcing effects of the drug itself. To characterize these two mechanisms, he will use machine learning and spatial transcriptomics. The team will train mice to self-administer a drug, like cocaine, and a palatable food, like sucrose, and utilize advanced multi-plane 2-photon calcium imaging techniques to capture neural activity from hundreds of LH neurons simultaneously while they perform the behavior. The goal is to characterize LH changes in the formation of a substance use disorder, which could support development of therapies that target exact neurons with specific genetic profiles to precisely attenuate drug craving without affecting natural reward-seeking behaviors.

Basic Research

Alexios Panoutsopoulos, Ph.D., University of California, Davis, notes prenatal cannabis exposure is linked to an increased risk of neurodevelopmental disorders, including anxiety, attention deficits, and learning impairments. He observes that formation of the neural tube—the start of brain development—relies on tightly regulated cell adhesion, migration, and differentiation. Recent evidence suggests that the body's endocannabinoid system, which includes cannabinoid receptors CB1R and CB2R, plays a role in these developmental processes. If cannabis alters these pathways, it could disrupt early brain formation, potentially increasing susceptibility to neurological disorders later in life. To investigate this, the team will use human neural organoids, which can form neural tube-like structures, allowing study of how cannabis affects key cellular processes. Preliminary data show that CB1R is present in these developing structures and changes dynamically over time, suggesting a crucial role in neural development. The team will expose neural organoids to THC and the natural cannabinoid 2-AG to determine whether these compounds disrupt early brain structure. They will assess structural integrity, examine key proteins such as N-Cadherin and α-catenin that regulate cell-cell interactions, and track neural development by using molecular markers to assess cell proliferation and differentiation.

Basic Research

Kristin Perry, Ph.D., University of Oregon, is interested in the transition to parenthood for fathers who use substances, an understudied and at-risk group. With cannabis use at historic highs and knowing that cannabis affects many of the hormones that change during the transition to parenthood, Dr. Perry will probe whether cannabis use interferes with neurobiological changes that occur during this transition. The project will 1) examine hormone changes for fathers who heavily use cannabis compared to those who do not use cannabis; 2) evaluate postnatal parenting stress and depressed mood for fathers who use cannabis compared to those who

do not use cannabis; and 3) evaluate whether the impact of parenting stress and depressed mood on paternal postnatal cannabis use is moderated by hormone changes. 40 fathers will be recruited into two groups: heavy cannabis users (n = 20) and demographically similar fathers who do not use cannabis (n = 20).

Basic Research

Nicole Petersen, Ph.D., University of California, Los Angeles, studies hormonal modulation of dopamine release as a possible transdiagnostic mechanism of psychiatric risk, involving such illnesses as depression, schizophrenia, and substance use disorders. This study aims to provide a direct test of how estradiol affects dopamine release in the human brain. The team will use advanced brain imaging technology called PET/MR scanning to measure dopamine release in healthy women during two distinct phases of the menstrual cycle: one when estradiol is naturally low and one when it is high. By giving participants a medication that stimulates dopamine release during these two phases, they will test whether estradiol enhances dopamine function. At the same time, they will collect functional MRI data to assess whether these changes can be detected using a more widely available, non-invasive imaging method.

Basic Research

Sema G. Quadir, M.D., Northwestern University, notes that three FDA-approved medications are available for alcohol-use disorder (AUD) but none specifically targets withdrawal symptoms; this underscores the need for targeted interventions addressing AUD-associated negative affect and hyperalgesia. One brain region activated during alcohol withdrawal is the basolateral amygdala (BLA), which contains pyramidal neurons and interneurons, the latter of which includes vasoactive intestinal peptide interneurons (VIP-INs). BLA VIP-INs are activated in response to stress and neuropathic pain, but it is not known if they mediate behavioral symptoms of alcohol withdrawal. Dr. Quadir hypothesizes that alcohol withdrawal enhances BLA VIP-IN activity to promote negative affect and hyperalgesia. The team will use a genetically encoded fluorescent calcium sensor to monitor BLA VIP-IN activity during behavioral tests at baseline and during alcohol withdrawal; and optogenetics to test whether BLA VIP-INs are both necessary and sufficient for alcohol withdrawal-induced hyperalgesia and negative affect.

Basic Research

Siara K. Rouzer, Ph.D., Texas A&M Health Science Center, will use rodent models to systematically examine how alcohol exposure in both parents alters offspring behavior and brain function compared to single-parent exposure. The first objective is to assess behavioral outcomes characteristic of fetal alcohol syndrome, including anxiety-like behaviors, hyperactivity, compulsivity, and alcohol-seeking tendencies. By conducting a range of behavioral tests, the team seeks to determine whether dual-parent exposure leads to more severe or distinct impairments than single-parent exposure. A second objective is to investigate how dual-parental alcohol exposure affects the brain at a molecular level, with a focus on cannabinoid receptor 1 (CNR1), a key component of brain signaling that regulates emotion, impulse control, and reward processing.

Basic Research

Jason M. Tucciarone, M.D., Ph.D., Stanford University, notes that despite the critical role of withdrawal in sustaining opioid use disorder (OUD), it remains unclear whether its physical and affective symptoms arise from distinct neural mechanisms, each contributing uniquely to the disorder's progression. A deeper understanding of the cells and circuits underlying OUD could reveal novel therapeutic targets to treat addiction, prevent relapse, and reduce overdose risk. Given that opioids exert their reinforcing effects through the brain's mu opioid receptor (MOR, Oprm1), his central hypothesis is that circuits and cell types heavily modulated by MOR serve as "first hits" in OUD, with perturbations in these circuits propagating to downstream neuronal systems. His studies focus on subtypes of direct pathway medium spiny neurons (MSNs), specifically those defined by the gene Tshz1, within MOR-rich regions. Here, he aims to investigate their role in modulating dopamine transmission in the striatum and their involvement in opioid reinforcement, withdrawal, and relapse.

Basic Research

Jonathan W. VanRyzin, Ph.D., University of North Carolina at Chapel Hill, cites animal studies showing that social isolation during adolescence leads to long-lasting hyperactivity in the nucleus accumbens (NAc), and is characterized by increased neuronal excitability and excessive synaptic connections. These changes are thought to contribute to behavioral outcomes such as heightened reward sensitivity and increased vulnerability to substance use and mood disorders. Little is known about the role of astrocytes—specialized glial cells that regulate synaptic activity and maintain neural circuit stability—in mediating these effects. This project aims to investigate how adolescent social isolation stress alters astrocyte-neuron interactions and astrocyte physiology within the NAc, and will test the hypothesis that adolescent social isolation stress induces astrocyte withdrawal from circuit-specific synapses and impairs astrocyte synaptic regulatory functions in the NAc core.

Basic Research

Joseph M. Villarin, M.D., Ph.D., Research Foundation for Mental Hygiene, Inc./NYSPI, posits that to develop new biomedical interventions for improving or preventing neurocognitive impairments seen for example in schizophrenia, OCD, and substance use disorders, we must better understand the underlying brain circuits, their networking, and how they coordinate their activity. The neurotransmitter acetylcholine is involved in supporting cognitive functions, and most of the acetylcholine input to cognitive control centers in the brain's cortex and associated structures comes from the basal forebrain. This project seeks to determine how the activity of neural connections from the striatum to the basal forebrain regulates acetylcholine signaling across the brain during reversal learning behavior. Reversal learning is a behavioral paradigm used across species to assess cognitive flexibility. This work will result in a large data set combining simultaneous information about animal behavior and different kinds of neural activity, which will be analyzed to identify neural processes underlying specific computations that animals use in learning and behavioral adaptation.

Basic Research

Leigh C. Walker, Ph.D., University of Melbourne, Australia, notes that sex differences in alcohol consumption remain largely overlooked in preclinical research and drug development. Existing treatments for alcohol use disorder (AUD), predominantly developed in male subjects, are less effective in women, underscoring the urgent need for sex-specific therapeutic strategies. This project will investigate binge drinking-related neurochemical phenotypes and circuits, with a focus on the centrally projecting Edinger-Westphal nucleus (EWcp). The team's recent findings reveal that ghrelin receptor signaling in the EWcp specifically drives binge drinking in female, but not male mice, implicating a sex-specific circuit in excessive alcohol consumption. Additional data suggest a critical interaction between estrogen and ghrelin receptors in this region. Here, they will investigate the role of estrogen receptors in the EWcp and their interaction with the ghrelin system to elucidate mechanisms underlying sex-specific alcohol consumption.

Basic Research

Junshi Wang, Ph.D., Icahn School of Medicine at Mount Sinai, is interested in prolonged emotional abnormalities during opioid abstinence. The interpeduncular nucleus (IPN) is a part of the midbrain that mainly consists of GABAergic neurons. It has a high concentration of μ opioid receptors (MORs), which are responsible for the rewarding and euphoric effects of opioids. During opioid withdrawal, activity, neurotransmission, and gene expression in the IPN are significantly altered, indicating neuroadaptation. This project seeks to characterize chronic opioid exposure-induced neuroadaptation among IPN-derived circuits and to identify the circuits responsible for persistent negative affective states that arise during abstinence. Dr. Wang will measure the strength of connections between IPN neurons and their numerous projected areas with single-neuron resolution in both control and oxycodone-dependent mice. By selectively manipulating synaptic transmission in one of these circuits, the team will examine its role in somatic and affective components of withdrawal symptoms in oxycodone-dependent mice

Basic Research

Lu Wang, Ph.D., Yale University School of Medicine, has led two recently completed, largest-to-date whole-exome sequencing (WES) studies on alcohol use disorder (AUD) and opioid use disorder (OUD), using biobank-based cohorts across multiple ancestries. To date, genome-wide association studies (GWAS) have identified common variants linked to AUD, but their effects are relatively small and vary across different populations. AUD is influenced by a complex interplay of genetic and environmental factors, with the contributions of rare variants remaining largely unexplored. Whole-genome sequencing (WGS) presents a powerful opportunity to investigate the full spectrum of genetic variants, including rare variants that often have larger effect sizes but are missing in GWAS. This project will use large-scale WGS data across multiple ancestries from population-based biobanks including UK Biobank (UKB), All of Us (AoU), and the Million Veteran Program (MVP). Novel rare variants will be identified and analyzed. The team also plans to construct a novel risk prediction model.

Basic Research

Diagnostic Tools/Early Intervention

Heather B. Ward, M.D., Vanderbilt University Medical Center, thinks the vulnerability of people with schizophrenia (SZ) to cannabis use is based in brain pathology. In cannabis users, the default mode network (DMN) is chronically hyperconnected, but cannabis use transiently corrects this network pathology. This suggests some cannabis users may be using cannabis to self-medicate a DMN pathology problem. Dr. Ward proposes that if this network problem is corrected, it will reduce the need to self-medicate with cannabis. This project will test if DMN pathology can be corrected via non-invasive transcranial magnetic stimulation (rTMS). The treatments will target a network problem specific to cannabis use (via network-targeted rTMS) to see if it can outperform conventional rTMS targets used in depression treatments (typically, the DLPFC). The team will compare the effects of these two rTMS interventions on functional connectivity, cannabis craving, and use, in a randomized, crossover design with pre/post neuroimaging people with schizophrenia with cannabis use (n=20).

Next-Generation Therapies

Belgin Yalcin, Ph.D., Stanford University, will investigate how opioid exposure during the most critical stages of brain development affects myelin, potentially disrupting brain functions that require myelin plasticity. Myelin is a fatty substance that wraps around axons to enhance the transmission of electrical signals across neurons. Minor changes in myelin structure can greatly impact the speed of these signals and the behaviors that are regulated by related neural circuits. This project's first goal is to determine how prenatal opioid exposure impacts myelin health and function by assessing myelination changes and dynamic regulation of myelin-forming cell states, and the myelin-forming cell response to changing dopaminergic neuron activity. The second goal is to determine the behavioral consequences of prenatal opioid exposure on memory, attention, and sociability. Genetic and pharmacological modulation of myelination will be used to assess the contribution of myelin to these behavioral changes.

Basic Research

Junhua Yang, Ph.D., Texas A&M University, aims to: 1) determine the effects of acute and chronic cocaine exposure on ventral tegmental area (VTA) astrocyte Ca2+ (a type of calcium ion) signaling in vivo; and 2) determine the consequences of manipulating VTA astrocyte Ca2+ signaling on cocaine-induced cellular and behavioral changes in mice. The team will employ confocal Ca2+ imaging, in vivo fiber photometry Ca2+ recording, brain slice electrophysiology, chemogenetic ("designer receptors exclusively activated by designer drugs," DREADDs) and optogenetic manipulation, astrocyte Ca2+ depletion using a PMCA2 Ca2+ pump (CalEx), transgenic mice, and a cocaine-related animal behavior paradigm. The aim is to provide a comprehensive understanding of the critical role of astrocyte Ca2+ signaling in regulating tonic inhibition and neuronal activity, perhaps establishing increased astrocyte Ca2+ signaling as a novel mechanism for cocaine addiction. Findings could lay groundwork for the development of potential new addiction therapies that target astrocyte Ca2+ signaling and its downstream effectors, such as SWELL1 channels.

Basic Research

Lynn Yap, Ph.D., Columbia University, notes that dysfunction of valuation systems underpins psychiatric conditions, particularly addiction, depression, and PTSD. Addiction and depression are characterized by the over- and undervaluation of reward-related cues, whereas PTSD manifests as a resistance of threat-related cues to extinction. The medial prefrontal cortex (mPFC) plays a key role in the consolidation of long-term associative memories and in the integration of sensory inputs to guide flexible goal-directed behaviors. The mechanisms by which it maintains synaptic stability despite behavioral flexibility remain enigmatic. Dr. Yap has used high-density electrophysiological recordings in mice to observe the emergence of two distinct yet spatially intermingled populations of neurons encoding rewarded (conditioned stimuli, CS+) and unrewarded (CS-) odors. The hypothesis in this project is that this dual-population system may provide a circuit-level solution for the stability-flexibility problem. The project will investigate whether the CS- population is diminished and inhibition weakened in models of substance-use disorders. Dr. Yap predicts recruitment of the CS- population during extinction is diminished, which may account for compulsive reward-seeking.

Basic Research

ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

Camila S.A. Cosmo, M.D., Ph.D., Ocean State Research Institute, Inc., will assess the feasibility and effectiveness of high-dose iTBS non-invasive brain stimulation for ADHD in a placebo-controlled pilot trial involving 20 patients. The project proceeds from the hypothesis that an accelerated and extended single-day iTBS regimen, guided by fcMRI, and delivered at 90% of motor threshold, totaling 7,200 pulses, over the right inferior frontal gyrus will be feasible and well tolerated, and will enhance inhibition and reduce impulsivity compared to sham stimulation. The study could provide a foundation for future, larger mechanistic clinical trials using non-invasive brain stimulation to improve symptoms, function, and quality of life in patients afflicted with ADHD and at heightened risk of suicide.

Next-Generation Therapies

Nicholas D. Fogleman, Ph.D., University of North Carolina at Chapel Hill, is studying deficits in emotion regulation (ER) in youths with and without ADHD, to fill knowledge gaps regarding how differences in brain network organization underlie ER on a group level and how heterogeneity in brain network organization predicts adverse outcomes in adolescence on an individual level. He will use network neuroscience to fill these gaps by characterizing ER-related network function in youths with and without ADHD, and determining how ER ability and academic, behavioral, and social outcomes in individuals differ based on differences in ER-related brain network organization. Deficits in ER were once considered a core feature of ADHD, but were not included in the diagnostic criteria of the DSM manual. This decision—which this research may help to modify—paved the way for how we assess and treat youth with ADHD, focusing only on symptoms of inattention, hyperactivity, and impulsivity.

Basic Research

Travis T. Mallard, Ph.D., Massachusetts General Hospital, notes that behavioral disinhibition is present in such conditions as ADHD, conduct disorder, and substance use disorders, each highly heritable and often begin in childhood or adolescence and frequently co-occur. These "externalizing disorders" have been robustly linked to atypical brain development, including altered cortical expansion during these formative periods. Dr. Mallard will test the hypothesis that externalizing disorders are, in part, influenced by genes that shape the timing and patterning of cortical expansion across development. The team will implement novel modeling techniques which will integrate large-scale psychiatric and imaging genetic datasets and identify pleiotropic genetic variants that concurrently influence cortical expansion and externalizing liability. Using data from large databases, they will then try to determine how the identified risk variants disrupt typical neurodevelopment across the lifespan.

Basic Research

Xiangling Meng, Ph.D., Baylor College of Medicine, has identified a gene, CSDE1, as playing a critical role in the production of inhibitory neurons. Patients with CSDE1 mutations often experience ADHD, autism, and epilepsy, suggesting that disruptions in this gene may lead to improper brain development, especially in inhibitory neurons. The team will use brain organoids grown from cells of patients and controls to examine in the lab how CSDE1 mutations impact the formation and movement of inhibitory neurons in the developing brain. By comparing organoids with normal and mutated CSDE1, they can determine whether fewer inhibitory neurons are produced or if they migrate improperly. To understand how these altered neurons affect brain function and behavior, organoids will be transplanted into developing rat brains, to observe if animals with transplanted mutated neurons display hyperactivity, anxiety, or social impairments—behaviors that resemble ADHD symptoms in humans.

Basic Research

Nadezhda (Nadya) N. Modyanova, Ph.D., Montana State University, notes children with ADHD, autism spectrum disorder (ASD), and developmental language disorder (DLD) face unique challenges with communication that require intervention, especially in rural areas with limited access to speech and language pathologists. Extant literature indicates hand gestures support comprehension and production of language for individuals with typical development (TD), ASD, and DLD; but little is known about gestures in ADHD, and also about the brain basis of how gestures support language comprehension. This project seeks to investigate rural Montana children's brain responses during comprehension of a story told by their caregivers using speech with hand gestures. In combination with recording children's brain activity, the team aims to understand how aspects of caregiver gestures can affect children's language comprehension. The goal is to determine children's language comprehension processes during social interaction and engagement with caregivers, and how gestures can better support communication.

Basic Research

Next-Generation Therapies

Ali Mohebi, Ph.D., University of Wisconsin, investigates multi-timescale reward processing, which directly addresses core pathophysiological mechanisms underlying ADHD and schizophrenia. While distinct, these illnesses share fundamental computational disturbances in how the brain integrates reward information across time—a process essential for adaptive decision-making and motivated behavior. The lab characterizes how dopaminergic dysregulation within specific prefrontal circuits compromises the maintenance of extended reward representations, potentially illuminating why individuals with ADHD struggle to sustain goal-directed behavior despite intact immediate reward processing. For schizophrenia, negative symptoms—including anhedonia and avolition—may emerge from impairments in the prefrontal network dynamics that support persistent representations of reward contexts. By mapping the spatial organization of reward timescales within prefrontal subregions, Dr. Mohebi seeks to identify the specific circuit elements whose dysfunction leads to the fragmentation of temporal continuity in reward processing.

Basic Research

Tadaaki Nishioka, Ph.D., Icahn School of Medicine at Mount Sinai, suggests attentional dysfunction in depression may share mechanisms with neurodevelopmental disorders such as ADHD. However, while medial prefrontal cortex (mPFC) parvalbumin-expressing interneurons (PVIs) are crucial for attention control via gamma oscillations, their developmental trajectory and susceptibility to stress remain poorly understood. A key challenge in studying attentional development in adolescent mice is the technical limitation in assessing attentional behavior, as conventional tasks require extensive training, making them unsuitable for rapid developmental studies. To address this, this study employs a novel fast attentional testing protocol that enables efficient assessment of mPFC-PVI activity in adolescent mice. Given that PVI dysfunction is implicated in multiple psychiatric conditions, this study may provide key insights into novel therapeutic approaches targeting PVI maturation to mitigate stress-related attention deficits.

Basic Research

Alexios Panoutsopoulos, Ph.D., University of California, Davis, notes prenatal cannabis exposure is linked to an increased risk of neurodevelopmental disorders, including anxiety, attention deficits, and learning impairments. He observes that formation of the neural tube—the start of brain development—relies on tightly regulated cell adhesion, migration, and differentiation. Recent evidence suggests that the body's endocannabinoid system, which includes cannabinoid receptors CB1R and CB2R, plays a role in these developmental processes. If cannabis alters these pathways, it could disrupt early brain formation, potentially increasing susceptibility to neurological disorders later in life. To investigate this, the team will use human neural organoids, which can form neural tube-like structures, allowing study of how cannabis affects key cellular processes. Preliminary data show that CB1R is present in these developing structures and changes dynamically over time, suggesting a crucial role in neural development. The team will expose neural organoids to THC and the natural cannabinoid 2-AG to determine whether these compounds disrupt early brain structure. They will assess structural integrity, examine key proteins such as N-Cadherin and α-catenin that regulate cell-cell interactions, and track neural development by using molecular markers to assess cell proliferation and differentiation.

Basic Research

Lisa Pavinato, Ph.D., Università della Svizzera Italiana, Italy, focuses on alterations in the CAPRIN1 gene, which she has associated with a rare genetic neurodevelopmental disorder with affected individuals manifesting language impairment, ADHD, ASD, intellectual disability (ID), and seizures. She wants to understand the biological pathway leading from the genetic variants in CAPRIN1 to disease manifestations. This project seeks to define the role of CAPRIN1 in neurogenesis, neuronal differentiation, and the underlying process of gene regulation. The team will use patient-derived and control-derived human induced pluripotent stem cells (hiPSCs) and differentiate them into brain organoids. Using these neural models, they will investigate the impact of CAPRIN1 downregulation on neuronal development, proliferation, and cell-fate commitment.

Basic Research

Ashley Song, Ph.D., Johns Hopkins University School of Medicine, studies the impacts of early-life exposure to mixtures of organic pollutants on early brain development and neurodevelopment. Early postnatal changes of cortical surface areas may play an important role in the development of neurodevelopmental disorders. It is well documented that early-life exposure to environmental pollutants is linked to poor birth outcomes and neurodevelopmental deficits. This project explores the relationship between innovative dental biomarkers of organic pollutants, longitudinal measures of infant brain structure, cognitive and behavior traits, and neurodevelopmental disorders. The team will leverage existing dentine exposure, structural MRI, and phenotypic data of 152 participants in the Infant Brain Imaging Study (IBIS). Specific goals are to: (1) investigate the effect of early life phthalates and PCBs mixtures on early infant longitudinal brain development; (2) evaluate the effect of early life phthalates and PCBs mixtures on early trajectory of cognitive abilities and adaptive function; (3) investigate whether the effect of exposure to a mixture of phthalates and PCBs on early brain development and cognitive behavior development varies by ASD and ADHD risk.

Basic Research

ANXIETY DISORDERS

Gabrielle Agin-Liebes, Ph.D., Yale University, notes the psychedelic drug psilocybin has demonstrated rapid and sustained benefits in some trials for conditions such as depression, alcohol/substance use disorders, anxiety, and PTSD, with emerging evidence suggesting that enhanced cognitive flexibility may be a key mechanism underlying these improvements. This study aims to elucidate the cognitive mechanisms by which psilocybin disrupts rigid thinking and promotes adaptive learning, perhaps thereby optimizing its therapeutic impact across traditional diagnostic boundaries. The trial will enroll people with depression, anxiety, PTSD, or alcohol/substance use disorders who exhibit significant functional impairment. Prior to dosing, participants will attend two preparatory sessions that provide psychoeducation, establish rapport, review personal history, and develop strategies for managing challenging experiences. They will then receive a single 25 mg oral dose of psilocybin, with continuous monitoring for 6 hours. A post-dosing integration session, scheduled 1–3 days later, will support the consolidation of therapeutic insights into actionable strategies for daily life.

Next-Generation Therapies

Sophie Bagur, Ph.D., ESPCI Paris, France, studies interoception—our ability to perceive our own internal states, manifest, for example, in signals for hunger, thirst, or perception of heart rate. This project seeks to establish the tools to measure and manipulate cardiac interoception at the neural and behavioral level in the mouse and then use these tools to explore whether anxiety modifies interoception and whether an increase in interoceptive sensitivity can cause anxiety. Among other features, the research will optogenetically modify the gain in the insular or prefrontal cortex to either increase or decrease interoceptive sensitivity at the neural level. The team will observe whether such manipulations increase or decrease anxiety levels in classical anxiety tasks.

Basic Research

Ritchie Chen, Ph.D., University of California, San Francisco, notes that emotional experiences are strongly influenced by signals from within the body ("interoception"), yet the neural mechanisms by which these interoceptive signals shape affective states remain incompletely understood. The insular cortex is centrally positioned to integrate internal physiological cues—such as heart rate, hunger, and thirst—with salient external stimuli to guide adaptive, goal-directed behaviors. Recent evidence supports a predictive coding framework wherein the insula compares expected internal states with actual physiological inputs, generating "prediction errors" that can trigger changes in emotional tone and behavior. The precise neural circuits and downstream targets mediating these error signals remain unclear. Building on preliminary findings that artificially elevated heart rates exacerbate anxiety-like behaviors through the posterior insula, Dr. Chen seeks to define how cardiogenic interoceptive signals modulate insular activity and drive affective states.
Basic Research

María del Carmen Camarena Delgado, Ph.D., University of Cadiz, Spain, notes that anxiety is a natural response to stress, but when excessive and persistent, it can become a disabling disorder. Its frequent comorbidity with chronic neuropathic pain (NP) represents a major public health concern. She studies the brain's anterior cingulate cortex (ACC) and basolateral amygdala (BLA), brain regions involved in emotion regulation and pain processing and highly interconnected. This project will explore the interactions between glutamatergic neurons in the BLA-ACC circuit and astrocytes in NP-induced anxiety, with a focus on sex differences in glial function and neuroinflammation. By investigating neuron-glia communication in NP-induced anxiety, this study aims to identify new therapeutic targets.
Basic Research

Josepheen De Asis-Cruz, M.D., Ph.D., Children's National Medical Center, will use non-invasive, resting-state functional MRI (rsfMRI) to investigate hypothalamic connectivity in healthy, term neonates and neonates who were exposed to maternal anxiety in the womb. The hypothalamus is critical in regulating the brain and the body's responses to anxiety. The broader goal is to provide a comprehensive picture of how fetal in utero exposure to maternal anxiety influences developing brain circuits. By identifying early brain markers of risk, this research could inform innovative precision medicine approaches in perinatal mental health. Specific goals include: investigation of how prenatal anxiety alters hypothalamic connectivity to the limbic network; assessment of whether newborns exposed to higher maternal anxiety show stronger hypothalamic-amygdala connections (suggesting heightened stress reactivity) and weaker hypothalamic-prefrontal connectivity (potentially indicating reduced emotional regulation); and examination of how exposure to anxiety in the womb affects neonatal hypothalamic connectivity to large-scale brain networks.
Basic Research

Raoni C. dos Santos, Ph.D., University of South Carolina, notes that the neurotransmitter norepinephrine (NE) is involved in the stress response. NE neurons in the nucleus of the solitary tract (NTS) send axonal projections to brain regions such as the prefrontal cortex and hippocampus involved in regulating behavior and motivation. This project is about disruption of the NE system in depression and social anxiety disorders. In mouse models, it will explore the hypotheses that: 1) NTS-NE neurons are essential for regulation of depression-like and social behaviors; 2) sustained hyperactivity of these neurons will disrupt the NE system and cause long-lasting behavioral alterations; and 3) inhibition of NTS-NE neurons during stress exposure will protect against the development of stress-induced depression.
Basic Research

Kyle Harrington Flippo, Ph.D., University of Iowa College of Medicine, is studying neural mechanisms underlying maladaptive fear responses, which are central to numerous psychiatric disorders, including PTSD and anxiety disorders. Specifically, the focus is on how threat intensity modulates neuropeptide signaling within the basolateral (BLA) and central (CeA) amygdala to drive either adaptive or maladaptive fear responses. Dysregulated fear generalization—where fear extends beyond actual threats to neutral stimuli—is a hallmark of PTSD and anxiety disorders, contributing to persistent hypervigilance and avoidance behaviors. The project seeks to elucidate how gastrin-releasing peptide (Grp) signaling in a BLA-CeA circuit facilitates excessive fear responses, a process that may also be relevant to psychiatric comorbidities observed in neurodevelopmental (e.g., autism spectrum disorder) and neurodegenerative (e.g., Alzheimer's disease) conditions, where altered amygdala function has been implicated in anxiety and emotional dysregulation.
Basic Research

Rodolfo Flores Garcia, Ph.D., University of Texas at El Paso, focuses on the infralimbic cortex, which helps regulate emotional responses, and its connection with the basal forebrain, which produces acetylcholine, a chemical messenger critical for attention and learning. In mice, the team will track the activity of basal forebrain-to-infralimbic cortex connections during approach-avoidance conflicts, measure how acetylcholine levels change in real-time during decision making, and examine how psychological stress alters these brain circuits. Preliminary findings show that neurons in the infralimbic cortex respond to both reward and threat cues during these conflicts. This research directly

examines the circuit mechanisms that enable flexible decision-making during emotional conflict and establishes a concrete link between stress exposure, disruption of specific brain circuits, and the behavioral patterns seen in anxiety disorders, depression, and PTSD.

Basic Research

Pegah Kassraian, Ph.D., Columbia University, notes that schizophrenia is often accompanied by comorbidities such as social anxiety disorder (SAD), which affects approximately 35% of patients relative to a prevalence of around 12% in the general population. Social withdrawal and generalization of social fears are hallmarks of SAD, yet the neural mechanisms underlying these behavioral phenotypes are not understood. This project investigates the hippocampal basis of social fear processing, focusing on the CA2 region, which is critical for social memory and critical for threat-associated social learning. The team will use Df(16)A+/- mice, a model of the 22q11.2 deletion syndrome, one of the strongest known genetic risk factors for schizophrenia, which exhibits CA2-selective deficits in social novelty memory and reduced CA2 activity during social interactions.

Basic Research

Annelise A. Madison, Ph.D., University of Michigan, will assess physiological and psychological responses among 100 college sorority recruits to the stress of recruitment. By comparing those actively seeking sorority membership and those already in a sorority, the study aims to understand how the threat of exclusion, or relative social safety, impacts immune responses and depression risk. This study's main objectives are to observe differences in stress responses between recruits and existing members, and investigate whether inflammatory responses to a recruitment event predict social behavior. Dr. Madison hypothesizes that recruits will show higher physiological stress responses, including increased heart rate, cortisol, and inflammatory responses. Recruits over the entire recruitment period may show increased intestinal permeability, systemic inflammation, symptoms of anhedonia, and overall psychological distress (i.e., depression and anxiety).

Basic Research

Laura Modol, Ph.D., Fundacio Institut Mar d'Investigacions Mediques, Spain, notes that we do not yet understand exactly how early-life stress (ELS) alters brain development and contributes to the development of anxiety disorders. One key brain region affected by ELS is the prefrontal cortex (PFC). Changes in PFC development may help explain why females exposed to early stress are more likely to experience anxiety disorders. A crucial but understudied factor in this process is the role of interneurons. This project will use imaging to track how the PFC develops from early life to adulthood in animal models exposed to stress. The hope is to uncover how changes in interneurons contribute to anxiety-related disorders.

Basic Research

Jessie Muir, Ph.D., Princeton University, aims to identify how psilocybin, a psychedelic that has been shown to drive sustained antidepressant effects, modulates nucleus accumbens (NAc) circuitry and whether this may drive protective effects against future stress and symptoms of depression. Dr. Muir will image single cell activity in the NAc following an injection of psilocybin as mice are freely moving, then expose them to a stress protocol. The hypothesis is that psilocybin will increase activity in the NAc and induce a protective effect, reducing the impact of stress on the treated mice. The project will also tag neurons activated by psilocybin, then sequence the NAc to determine what cell types are activated by the drug and what genes are over-expressed in these cell types and may contribute to its antidepressant effects.

Next-Generation Therapies

Kally C. O'Reilly Sparks, Ph.D., Research Foundation for Mental Hygiene, Inc./NKI, is exploring how juvenile social experiences and neuronal development reciprocally shape later social competence, dominance, and aggression. The hypothesis is that social competence is gained through juvenile peer interactions. The team will deprive juvenile mice of peer interactions during a sensitive developmental period , then assess the home cage activity of mice during peer-deprivation, measure associated stress, and examine cells activated by juvenile social novelty in transiently activated cell populations (TRAP2). They anticipate that peer-deprivation will result in atypical juvenile social interactions, namely decreased sociability, which may indicate increased social anxiety, and increased aggression toward novel conspecifics. Longitudinally, they expect that juvenile peer-deprivation will result in increased aggression and dominance behavior in brief social interactions. The ultimate aim is to uncover specific aspects of social competence impacted by juvenile peer-deprivation or neuronal silencing, to provide a foundation to examine the role of development in refining social flexibility, social decision making, social learning, and social reinforcement.

Basic Research

Alexios Panoutsopoulos, Ph.D., University of California, Davis, notes prenatal cannabis exposure is linked to an increased risk of neurodevelopmental disorders, including anxiety, attention deficits, and learning impairments. He observes that formation of the neural tube—the start of brain development—relies on tightly regulated cell adhesion, migration, and differentiation. Recent evidence suggests that the body's endocannabinoid system, which includes cannabinoid receptors CB1R and CB2R, plays a role in these

developmental processes. If cannabis alters these pathways, it could disrupt early brain formation, potentially increasing susceptibility to neurological disorders later in life. To investigate this, the team will use human neural organoids, which can form neural tube-like structures, allowing study of how cannabis affects key cellular processes. Preliminary data show that CB1R is present in these developing structures and changes dynamically over time, suggesting a crucial role in neural development. The team will expose neural organoids to THC and the natural cannabinoid 2-AG to determine whether these compounds disrupt early brain structure. They will assess structural integrity, examine key proteins such as N-Cadherin and ß-catenin that regulate cell-cell interactions, and track neural development by using molecular markers to assess cell proliferation and differentiation.

Basic Research

Puja K. Parekh, Ph.D., University of Texas at Dallas, notes the precise function of discrete circuits in encoding reward and cost-related information to drive behavior is incompletely understood; and that it has been established that stressful experiences predispose some individuals to develop neuropsychiatric conditions, likely as a consequence of morphological and functional adaptations within key brain regions which inhibit plasticity mechanisms and neurotrophic signaling. The goal of this research is to delineate the roles of cell types and pathways critical in supporting motivated behaviors and how these are affected by stress in vulnerable individuals, and to ultimately inform novel candidates for therapeutic development. Using animal models, Dr. Parekh will make use of improved behavioral assays which capture anticipatory, consummatory and learning-related aspects of effortful motivation. To explore the how chronic stress modulates the activity of the nucleus accumbens (NAc), a critical integrator of limbic and cognitive information for the regulation of goal-directed actions, he will target neurons expressing D1- and D2-type dopamine receptors and measure levels of extracellular dopamine while animals perform tasks engaging effortful motivated behavior; and apply spatially-resolved RNA-sequencing methods to assay all cell types of the NAc and determine whether a unique transcriptional profile is associated with susceptibility or resilience to motivational deficits of stress.

Basic Research

Payam Piray, Ph.D., University of Southern California, notes anxiety is characterized by profound intolerance of uncertainty, with ambiguous situations triggering significant distress. The specific computations supporting this general notion of uncertainty and how they go wrong in anxiety remain unclear. Dr. Piray will address these questions by drawing on the lab's recent theoretical work, which identifies computational hypotheses about how uncertainty processes may become disrupted when faced with two types of noise: moment-to-moment stochasticity of observations and volatility (how quickly they change). Using a paradigm that manipulates both factors simultaneously, the team will combine behavior, computational modeling, neuroimaging, and pupillometry, seeking to identify the neurocomputational processes shaping learning under uncertainty in anxiety and determine whether and how these processes link to pupil-related arousal systems.

Basic Research

Nicole R. Provenza, Ph.D., Baylor College of Medicine, notes that researchers have seen observable changes in OCD patients treated with experimental deep-brain stimulation (DBS)—talkativeness, being more social, smiling more, and being more willing to move or do things that were difficult before. Such "approach behavior" often makes individuals more likely to approach other people, situations, and activities. But if the electrical stimulation is a little too much for an individual, "we sometimes see these behaviors go from healthy and positive to overly energetic and even impulsive or reckless." DBS devices allow not only the electrical stimulation of the brain, but also recording of the electrical signals that are actively happening in the brain. The team will use these data together with data from wearable sensors, like Oura rings and Apple watches, to continuously measure patient behavior. This could allow them to assess how day-to-day changes in sleep, stress, physical activity, and socialization affect OCD symptoms, and how these may change in response to DBS treatment.

Next-Generation Therapies

Luis E. Rosas-Vidal, M.D., Ph.D., Northwestern University, notes that patients with PTSD and anxiety disorders experience overgeneralization even to safe stimuli, thus triggering symptoms during daily living. Avoidance generalization to non-threat predictive stimuli is thought to play a key role in the pathogenesis of PTSD. Little is known about the mechanisms mediating avoidance generalization. Using a modified platform-mediated avoidance task in combination with immunohistochemistry against the activity marker cFos, the team has discovered that activity in the infralimbic prefrontal cortex (IL) and the anterior hypothalamus (AH) is inversely correlated with avoidance generalization. They will use local and projection-specific single-cell in vivo calcium imaging and optogenetic approaches to address 1) how IL and the IL-AH projection neurons engage during uncertain threat stimuli to represent and mediate reductions in avoidance generalization and 2) whether these neurons are sufficient and necessary to reduce avoidance generalization in the presence of an uncertain threat.

Basic Research

Fangmiao Sun, Ph.D., University of California, Los Angeles, notes that prosocial behaviors play a crucial role in fostering social cohesion by enabling individuals to recognize and respond to the needs or distress of others. Impairments in emotion recognition and prosocial behaviors are common in neuropsychiatric and neuro-developmental disorders, including depression, social anxiety disorder, and autism spectrum disorder. Understanding the neural mechanisms underlying empathy-like prosocial behaviors is essential for advancing knowledge of sensory perception, decision-making systems, and social motivation in the brain, and for developing targeted therapeutic interventions. Dr. Sun hypothesizes that dopamine (DA) plays a critical role in reinforcing these prosocial behaviors and that chronic stress causes changes in the DA system, leading to impairments of prosocial behaviors. To test this, the team will investigate DA dynamics in nucleus accumbens core (NAcc) and ventral tegmental area (VTA) DA neuronal activity during rescue-like prosocial behaviors; will try to determine the functional role of VTA DA neurons in rescue-like prosocial behaviors; and explore the impact of chronic stress on rescue-like behaviors and DA dynamics.
Basic Research

Tomoki Suzuki, M.D., Ph.D., The Rockefeller University, notes face perception is essential for social communication and mental well-being, enabling individuals to recognize identities, interpret facial expressions, and properly infer social situations. Impairments in this ability are hallmark features of several neuropsychiatric conditions, including schizophrenia, social anxiety disorders, and autism spectrum disorder. This project will investigate hierarchical processing within the macaque face-processing system in the inferior temporal cortex, a network of three interconnected nodes with well-defined hierarchical relationships. The overall objective is the identification of the neural mechanisms underlying the qualitative transformation of face representations across two levels of the hierarchy. The central hypothesis is that face processing occurs through a sequence of incremental steps along the feedforward pathway, within and between face-selective areas.
Basic Research

Kristin L. Szuhany, Ph.D., New York University School of Medicine, notes elevated levels of chronic stress contribute to "high allostatic load"—markers of the impact of wear and tear on the body. Markers of allostatic load include inflammatory cytokines (e.g., IL-6) and metabolic markers such as acetyl-L-carnitine (LAC), involved in fatty acid oxidation. Exercise may contribute to successful allostasis, protect mitochondrial metabolism, decrease inflammation, and improve psychiatric symptoms. This project seeks to learn more about how exercise may affect LAC and its association with inflammation, in adults with chronic stress and anxiety disorders. A pilot study will assess 1) differences in neuronal markers of mitochondrial metabolism (LAC) and inflammation (IL-6) in individuals with anxiety disorders compared to controls; and 2) if exercise can increase LAC and decrease IL-6 across and within diagnostic groups. Participants will be 30 sedentary adults: 15 with a primary DSM-5 anxiety disorder and 15 controls.
Basic Research
Next-Generation Therapies

Sarah M. Tashjian, Ph.D., University of Melbourne, Australia, is interested in avoidance behaviors, a common response in individuals with anxiety. While avoidance may provide temporary relief from discomfort, it undermines a core developmental goal of adolescence: exploration. Little is known about the neural mechanisms of adolescent anxiety and the underlying neural systems that contribute to avoidance and exploration. This study will use ultra-high field 7-Tesla neuroimaging to identify neural circuits that contribute to avoidance and exploration preferences in adolescents with heightened anxiety. It seeks to examine how neural circuits are altered by anxiety during adolescence. This could help to differentiate between the neural systems that support maladaptive coping strategies, such as avoidance, and those that underlie adaptive strategies, like exploration.
Basic Research

Michael Totty, Ph.D., Johns Hopkins University School of Medicine, notes impaired fear regulation presents a major barrier to effective interventions and may stem, in part, from dysregulated interactions between the amygdala and prefrontal cortex (mPFC), brain regions involved in fear processing and extinction. While some molecular consequences of stress in the amygdala are known, we still lack a clear understanding of which cell types are disproportionately affected by stress, and an even larger gap exists in translating circuit-level findings from rodent models to human disease. Dr. Totty's long-term goal is to define how trauma alters cellular and molecular function within neural circuits that regulate fear, and to leverage these insights to develop targeted therapeutics for PTSD. In this project he seeks to determine if parallel amygdala projections to the mPFC that bidirectionally regulate fear and extinction are distinctly impacted by traumatic stress, using a mouse model relevant for PTSD.
Basic Research

Sebnem N. Tuncdemir, Ph.D., University of Connecticut Health Center, notes that impaired discrimination of sensory cues associated with traumatic experiences is a hallmark of trauma-related disorders, including PTSD. A patient may experience distress when reminded of a traumatic event, such as a fire, by encountering related sensory cues like its smell. The hippocampus, specifically the dentate gyrus (DG), is crucial for integrating sensory information into episodic memories, and its dysfunction is implicated in PTSD. This project investigates the

cellular mechanisms underlying DG dysfunction in a mouse model of PTSD-like symptoms, focusing on the distinct roles of developmentally defined granule cell (GC) subtypes. The team's previous work demonstrated that sensory and spatial information is encoded in largely non-overlapping neural channels within mature GCs of the dorsal DG, enhancing the DG's ability to remap sensory cues across different contexts. This heterogeneity suggests specialized roles in information processing, a hypothesis largely unexplored in trauma-related memory research. To investigate the cellular basis of PTSD-like discrimination deficits in the DG, the team will use innovative neurogenesis-based targeting methods to specifically label, monitor, and manipulate the activity of embryonically (eGCs) and neonatally (nGCs) born granule cells. They also hope to study the therapeutic potential of manipulating eGC and nGC activity using chemogenetic techniques.

Basic Research

Milenna T. van Dijk, Ph.D., Columbia University, notes that only some children, who may be less genetically resilient, develop psychopathology after adversity, suggesting neurobiological and genetic differences. One researcher recently found key hippocampal genetic pathways that lead to resilience in mice exposed to stress. This project will determine whether similar genetic pathways in human adolescents can increase resilience to adversity and thereby mitigate the likelihood that youth will develop psychopathology. The team will leverage a novel "expression-based polygenic score (ePGS)", which gives a measure of individual variation in predicted hippocampal expression of the resilience-related genes for youths in the Adolescent Brain Cognitive Development Study (ABCD). The team will then test if individual differences in expression of resilience-related genes predict anxiety and depression and compare it to how well standard genetic scores for depression and anxiety predict psychopathology. To elucidate gene by environment interactions, they will test how these genetic scores interact with early adversity to predict risk for depression and anxiety in response to adversity.

Basic Research

Diagnostic Tools/Early Intervention

Weizhen Xie, Ph.D., University of Maryland, will test new technique called temporal interference (TI) electrical stimulation, a non-invasive method for targeting deep brain structures involved in anxiety. Unlike conventional brain stimulation methods, which struggle to reach deeper brain regions, TI uses two high-frequency electrical currents with a slight frequency offset to generate lower-frequency modulation within deep brain areas, such as the amygdala, a central hub for fear and anxiety responses. This project is a double-blinded, sham-controlled study involving over 100 participants, who will complete a laboratory task designed to induce anxiety. This will allow the team to measure self-reported anxiety levels and objective physiological responses, such as pupil dilation—a reliable marker of anxiety-related arousal—during threat anticipation. While participants perform this task, TI stimulation will be applied to the amygdala to assess its potential for reducing anxiety-related responses.

New Technologies

Next-Generation Therapies

Rongzhen Yan, Ph.D., New York University School of Medicine, notes that post-stress social support has shown promise in mitigating symptoms associated with various psychiatric disorders, such as anxiety and depression. This phenomenon, known as social buffering, underscores the crucial role of interpersonal relationships in boosting resilience and attenuating the negative impact of stress. Despite its proven efficacy, the neural pathways and mechanisms underpinning social buffering remain poorly understood. This study focuses on oxytocin receptor-expressing cells in the anterior ventrolateral part of the ventromedial hypothalamus (aVMHvl OXTR) as a key player in mediating social avoidance after defeat (the basis of an animal model to study stress and depression). The team aims to unravel the dynamic responses of aVMHvl OXTR cells to repeated "defeat" experiences and investigate how social buffering modulates these responses. Preliminary findings suggest that prolonged defeat experiences lead to heightened excitability in aVMHvl OXTR cells, culminating in generalized social avoidance behaviors. Conversely, pair-housed mice exhibit resilience to such changes, implicating social buffering in modulating neural plasticity in response to stress.

Basic Research

Bohan Zhao, Ph.D., Scripps Research, notes that while emotional regulation is traditionally attributed to the brain, emerging research suggests that adipose (fatty) tissue communicates metabolic information directly to the brain through sensory neurons. This project seeks to uncover how this adipose-brain signaling influences mood and whether disruptions in this pathway contribute to psychiatric disorders such as eating disorders, anxiety, and depression. Dr. Zhao will use brain-wide dynamic recording and whole-brain profiling to study how sensory neurons in fat tissue transmit metabolic information to the brain. Functional ultrasound imaging (fUS) which enables whole-brain, high-resolution activity tracking, will be used to measure how the brain responds to metabolic stimulation of adipose tissue. By selectively eliminating sensory input from adipose tissue unilaterally, Dr. Zhao will compare brain activity between two hemispheres. This will help to identify the specific brain regions that rely on adipose sensory signaling. Preliminary data demonstrate that unilateral adipose denervation causes asymmetric brain activity, with changes observed in key

regions such as the thalamus, somatosensory cortex, and insular cortex, areas known to process sensory and emotional information. These results suggest a critical role of adipose sensory input in brain function.

Basic Research

AUTISM SPECTRUM DISORDERS (ASD)

Kyle Harrington Flippo, Ph.D., University of Iowa College of Medicine, is studying neural mechanisms underlying maladaptive fear responses, which are central to numerous psychiatric disorders, including PTSD and anxiety disorders. Specifically, the focus is on how threat intensity modulates neuropeptide signaling within the basolateral (BLA) and central (CeA) amygdala to drive either adaptive or maladaptive fear responses. Dysregulated fear generalization—where fear extends beyond actual threats to neutral stimuli—is a hallmark of PTSD and anxiety disorders, contributing to persistent hypervigilance and avoidance behaviors. The project seeks to elucidate how gastrin-releasing peptide (Grp) signaling in a BLA→CeA circuit facilitates excessive fear responses, a process that may also be relevant to psychiatric comorbidities observed in neurodevelopmental (e.g., autism spectrum disorder) and neurodegenerative (e.g., Alzheimer's disease) conditions, where altered amygdala function has been implicated in anxiety and emotional dysregulation.

Basic Research

Xiangling Meng, Ph.D., Baylor College of Medicine, has identified a gene, CSDE1, as playing a critical role in the production of inhibitory neurons. Patients with CSDE1 mutations often experience ADHD, autism, and epilepsy, suggesting that disruptions in this gene may lead to improper brain development, especially in inhibitory neurons. The team will use brain organoids grown from cells of patients and controls to examine in the lab how CSDE1 mutations impact the formation and movement of inhibitory neurons in the developing brain. By comparing organoids with normal and mutated CSDE1, they can determine whether fewer inhibitory neurons are produced or if they migrate improperly. To understand how these altered neurons affect brain function and behavior, organoids will be transplanted into developing rat brains, to observe if animals with transplanted mutated neurons display hyperactivity, anxiety, or social impairments—behaviors that resemble ADHD symptoms in humans.

Basic Research

Nadezhda (Nadya) N. Modyanova, Ph.D., Montana State University, notes children with ADHD, autism spectrum disorder (ASD), and developmental language disorder (DLD) face unique challenges with communication that require intervention, especially in rural areas with limited access to speech and language pathologists. Extant literature indicates hand gestures support comprehension and production of language for individuals with typical development (TD), ASD, and DLD; but little is known about gestures in ADHD, and also about the brain basis of how gestures support language comprehension. This project seeks to investigate rural Montana children's brain responses during comprehension of a story told by their caregivers using speech with hand gestures. In combination with recording children's brain activity, the team aims to understand how aspects of caregiver gestures can affect children's language comprehension. The goal is to determine children's language comprehension processes during social interaction and engagement with caregivers, and how gestures can better support communication.

Basic Research

Next-Generation Therapies

Hemanth Mohan, Ph.D., University of Texas Health Science Center at Houston, notes impaired sensorimotor coordination and fine motor control are key features of autism spectrum disorder (ASD) and schizophrenia (SZ), driven in part by aberrant cortical-subcortical circuit connectivity and dynamics. Understanding how these circuits govern normal behavior is essential for investigating their dysfunction and causal links to symptoms. This project aims to investigate cortical circuits governing sensorimotor coordination at cell-type resolution and provide an alternative framework for studying circuit dysfunction in ASD and SZ by integrating state-of-the-art approaches from mouse genetics, behavior, systems, and computational neuroscience. Dr. Mohan hopes to build on his findings to extend investigations into mouse models of ASD and SZ by assessing sensorimotor deficits in the Df(h22q11)/+ schizophrenia mouse model.

Basic Research

Mohammed A. Mostajo-Radji, Ph.D., University of California, Santa Cruz, will use organoids and high-density microelectrode arrays (HD-MEAs) to examine how SHANK3 mutations impair communication in human and mouse models, as s way of advancing knowledge of how neurodevelopmental disorders like schizophrenia and autism are caused. He will measure differences in synchronized network activity and signal transmission to identify human-specific deficits. A single-cell transcriptomic analyses will determine whether human neurons lack compensatory pathways that mouse neurons use to mitigate SHANK3 loss. A distinctive aspect of this work is its evolutionary perspective: by comparing species, the aim is to reveal how genetic

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—Barbara Toll, Board Member & Research Partner

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changes over millions of years may have inadvertently made human neural circuits more susceptible to SHANK3-related disorders. By integrating 3D neuronal models, HD-MEAs, and evolutionary genomics, this work may identify human-specific mechanisms of SHANK3-related dysfunction, which could help to inform new therapeutic strategies.
Basic Research

Mauricio M. Oliveira, Ph.D., New York University Medical Center, points out that a complex population of neurons aids in intricate cognitive tasks, but it is unclear how they cooperate in dynamic settings such as activity-induced plasticity to output proper behavior, hindering our understanding of molecular aspects of memory and its disruption in severe brain disorders such as PTSD. Part of this problem is the lack of approaches to integrate the multiple molecular layers that cooperate to form a flexible molecular environment in the cell. He believes the likelihood of an mRNA being translated by a neuron during threat memory consolidation relies on the combination of cis-elements inserted in the mature version of the mRNA. With the aid of a self-developed tool to isolate specific cell types from the brain, he seeks to combine simultaneous characterization of the neuron type-specific transcriptome and the translatome using long-read RNA sequencing technology. The goal is to reveal the molecular underpinnings of threat memory consolidation, crucial in the identification of novel therapeutic targets in PTSD and perhaps also dementia and autism.
Basic Research

Lisa Pavinato, Ph.D., Università della Svizzera Italiana, Italy, focuses on alterations in the CAPRIN1 gene, which she has associated with a rare genetic neurodevelopmental disorder with affected individuals manifesting language impairment, ADHD, ASD, intellectual disability (ID), and seizures. She wants to understand the biological pathway leading from the genetic variants in CAPRIN1 to disease manifestations. This project seeks to define the role of CAPRIN1 in neurogenesis, neuronal differentiation, and the underlying process of gene regulation. The team will use patient-derived and control-derived human induced pluripotent stem cells (hiPSCs) and differentiate them into brain organoids. Using these neural models, they will investigate the impact of CAPRIN1 downregulation on neuronal development, proliferation, and cell-fate commitment.
Basic Research

Giorgia Picci, Ph.D., Boys Town National Research Hospital, notes that while puberty has been identified as a potentially sensitive period for the emergence and progression of internalizing symptoms in autism, the neurobiological mechanisms remain largely unexplored in this population. Dr. Picci hypothesizes that the hormonal surges, neural reorganization, and increasing social demands of puberty amplify mental health risks for youths with autism, potentially interfering with their transition to adult social roles. To address existing scientific gaps and inform future treatment, this project seeks to investigate how pubertal factors affect neural function and structure in networks supporting behavioral domains affected in autism and internalizing disorders (i.e., social-affective, executive control). Among the objectives is to identify longitudinal associations by comparing youths with and without autism to determine if and how baseline neural function and structure predict changes in pubertal progression and internalizing symptoms over a 1-year period.
Basic Research

Ashley Song, Ph.D., Johns Hopkins University School of Medicine, studies the impacts of early-life exposure to mixtures of organic pollutants on early brain development and neurodevelopment. Early postnatal changes of cortical surface areas may play an important role in the development of neurodevelopmental disorders. It is well documented that early-life exposure to environmental pollutants is linked to poor birth outcomes and neurodevelopmental deficits. This project explores the relationship between innovative dental biomarkers of organic pollutants, longitudinal measures of infant brain structure, cognitive and behavior traits, and neurodevelopmental disorders. The team will leverage existing dentine exposure, structural MRI, and phenotypic data of 152 participants in the Infant Brain Imaging Study (IBIS). Specific goals are to: (1) investigate the effect of early life phthalates and PCBs mixtures on early infant longitudinal brain development; (2) evaluate the effect of early life phthalates and PCBs mixtures on early trajectory of cognitive abilities and adaptive function; (3) investigate whether the effect of exposure to a mixture of phthalates and PCBs on early brain development and cognitive behavior development varies by ASD and ADHD risk.
Basic Research

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Basic Research

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Basic Research

BIOLOGY OF THE BRAIN

MARKERS OF PRENATAL ENVIRONMENTAL UNPREDICTABILITY

Annie Aitken, Ph.D., New York University, seeks to better understand how prenatal exposure to environmental unpredictability shapes stress biology, particularly the immunoendocrine pathways influencing maternal mental health. Advances in remote biospecimen sampling and experimental methods provide a promising opportunity to examine immunoendocrine signatures of environmental unpredictability in hard-to-reach populations. These advancements are critical because maternal stress physiology serves as a key mediator between environmental conditions and infant development. This project will test the hypothesis that prenatal immunoendocrine dysregulation and postnatal autonomic nervous system (ANS) function are key mechanisms in the intergenerational transmission of psychopathology during the perinatal period. Using a prospective longitudinal design, the team will integrate new data collection with an existing study, leveraging remote methods to assess prenatal stress reactivity and inflammation, predictive analytics to identify biomarkers of risk, and longitudinal measures of infant physiological and behavioral regulation.

Basic Research

Diagnostic Tools/Early Intervention

ANHEDONIA, IMMUNE MARKERS & MENOPAUSAL TRANSITION

Erin M. Bondy, Ph.D., University of North Carolina at Chapel Hill, is studying anhedonia in the "menopause transition" (MT). The team will utilize neuroimaging to provide insight into the MT. Anhedonia is treated with exogenous estradiol (E2), a primary ovarian hormone that plays a modulatory role in neuroimmune signaling and naturally declines in the MT. Data suggests exogenous E2 reduces striatal myo-inositol (myo-Ins), a metabolite linked to glial activation and neuroimmune signaling that is correlated with peripheral inflammation and sensitive to immune stimulation challenges. This project will test whether E2 and anhedonia in the MT is linked to myo-Ins, in 23 pre-menopausal and 23 age-matched post-menopausal participants, ages 44-55, stratified based on anhedonia severity. The goal is to discover how ovarian hormones are linked to neuroimmunological markers and related psychopathology, to inform future precision medicine initiatives.

Basic Research

INTEROCEPTION, THE INSULA, & EMOTIONS

Ritchie Chen, Ph.D., University of California, San Francisco, notes that emotional experiences are strongly influenced by signals from within the body ("interoception"), yet the neural mechanisms by which these interoceptive signals shape affective states remain incompletely understood. The insular cortex is centrally positioned to integrate internal physiological cues—such as heart rate, hunger, and thirst—with salient external stimuli to guide adaptive, goal-directed behaviors. Recent evidence supports a predictive coding framework wherein the insula compares expected internal states with actual physiological inputs, generating "prediction errors" that can trigger changes in emotional tone and behavior. The precise neural circuits and downstream targets mediating these error signals remain unclear. Building on preliminary findings that artificially elevated heart rates exacerbate anxiety-like behaviors through the posterior insula, Dr. Chen seeks to define how cardiogenic interoceptive signals modulate insular activity and drive affective states.

Basic Research

PREDICTIVE PROCESSING & COGNITIVE DYSFUNCTION

Steven P. Errington, Ph.D., University of Newcastle, UK, seeks to provide new insights into how the brain detects and adapts to unexpected events. EEG reveals a characteristic brain response called mismatch negativity (MMN) when an unexpected event disrupts an expected pattern. Variations in MMN have been linked to schizophrenia, and Alzheimer's and Parkinson's diseases, suggesting impairments in predictive processing may underlie certain cognitive dysfunctions. This

project focuses on better understanding how individual neurons generate the MMN signal and how it emerges from underlying brain circuits. He will combine EEG with direct neural recordings from the auditory cortex to investigate how violations of expectation are processed within the brain, at the single-neuron level; and will try to manipulate these signals using optogenetics to investigate the causal relationship between intracortical and EEG activity.

Basic Research

MODULATION OF SYNAPTIC STRENGTH

Linlin Fan, Ph.D., Massachusetts Institute of Technology, is motivated by the fact that very few approaches exist to measure and control synaptic strength and synaptic plasticity in vivo under behaviorally relevant conditions. Using novel technologies involving optical tools, Dr. Fan seeks to provide fundamental insight into synaptic and circuit mechanisms underlying learning and memory in behaving mammals based on precise readout and control of synaptic and circuit pathways. This project focuses on how the brain balances the plasticity of learning new information and the stability of maintaining stored information. The hypothesis is that neuromodulation may regulate learning rates and balance flexibility and stability, for instance, by giving a 'when-to-learn' signal. To test this, the team will focus on the serotonin system, which has been implicated in modulating learning speed, and the hippocampus, which plays crucial roles in spatial and contextual memories.

New Technologies

PSYCHEDELICS & THE SEROTONIN 2-A RECEPTOR

Ryan H. Gumpper, Ph.D., University of North Carolina at Chapel Hill, notes that while the induction of spinogenesis and neuroplasticity is thought to be a potential therapeutic mechanism of psychedelic compounds, the molecular mechanisms behind what makes the serotonin 2-A receptor (5-HT2A) hallucinogenic/non-hallucinogenic remain a mystery. This project will examine four non-hallucinogenic 5-HT2A agonists and reveal the molecular mechanisms, signaling patterns, and receptor interactions that lead to non-hallucinogenic/hallucinogenic phenotypes. The team will accomplish this through in vitro biochemical and pharmacological characterization, and reveal the ligand-receptor interactions using structural biology and cryoelectron microscopy, while investigating receptor dynamics using in silico approaches. This approach may support developing a comprehensive hypothesis on how these ligands work at the receptor and molecular levels.

Basic Research

PSYCHEDELIC-INDUCED PLASTICITY

Sarah J. Jefferson, M.D., Ph.D., Yale University, has previously shown that the serotonin receptor-activating psychedelic 5-MeO-DMT, with rapid, prolonged antidepressant effects in early studies, produces long-lasting increases in structural plasticity in the mouse medial frontal cortex after a single dose. This occurs through the formation of new dendritic spines, the structures at which synaptic communication occurs. In contrast, she has demonstrated that MDMA, another psychedelic with distinct pharmacology, has rapid but shorter-lived neuroplastic effects. The project seeks to elucidate mechanisms that drive the rapid and persistent neuroplastic changes seen with psychedelic drugs. The team will measure and manipulate cAMP activity in live animals with spatial and temporal precision. They predict that the cAMP pathway mediates the rapid neuroplastic effects of both 5-MeO-DMT and MDMA, but that different downstream factors regulate the maintenance of new dendritic spines and thus duration of therapeutic effects.

Basic Research

EPIDEMIOLOGY OF GENETIC RISK

Sonja LaBianca, M.D., Ph.D., Psychiatric Center Ballerup, Mental Health Services of the Capital Region of Denmark, will conduct a population-wide epidemiological characterization of those at both extremes of the spectrum of genetic risk for psychiatric disorders. She will provide a genetic epidemiological characterization of individuals at high and low psychiatric genetic risk, with or without a major psychiatric disorder, hoping in this way to distinguish protective genetic and environmental factors from non-canonical genetic and large environmental risk factors. By comparing results across disorders, the hope is to obtain insights into disorder-specific or general risk and protective factors. Such factors may indicate markers for prevention or intervention. A unique large data resource from Denmark will be employed.

Diagnostic Tools/Early Intervention

INFERRING COGNITIVE STATES FROM SPEECH

Baihan Lin, Ph.D., Icahn School of Medicine at Mount Sinai, performs research that seeks to infer psychiatric cognition from speech. Dr. Lin notes that while computational methods to perform such analysis exist, current approaches lack systematic ways to quantify how thought patterns evolve during illness and treatment. The premise of this project is that without a structured, objective framework to measure these changes, psychiatric assessment remains inconsistent and limited in predictive power. Existing speech-based tools in psychiatry primarily measure word choice, sentiment, and fluency, offering broad correlations with symptoms but fail to explain why or how thought processes become disorganized. This research seeks to establish a computational

psychiatry framework that systematically tracks speech-based cognitive markers to quantify thought structure, to track how speech patterns reflect cognitive shifts over time. By modeling these changes, Dr. Lin aims to create a structured, mechanistic understanding of psychiatric symptoms and treatment response.

Diagnostic Tools/Early Intervention

Basic Research

MUSCLE IMAGING & EMOTIONAL STATES

Timothy A. Machado, Ph.D., University of Pennsylvania School of Medicine, seeks to provide a better understanding of how emotional states are encoded at the level of muscle activity. Facial expressions, for example, convey rich emotional information key to studying mental illnesses in both humans and rodent models. Objectively measuring emotional state in rodent models can be achieved by applying computer vision algorithms to videos of mouse orofacial movements. But only some expressions are conveyed through overt movement—likely because subtle contractions of the facial muscles are not captured by video-based approaches. This project supports development of a new optical population muscle recording approach that permits recording from across dozens of muscles in the face simultaneously. This technique should enable real-time, non-invasive tracking of muscle dynamics at a level of detail that was previously unattainable, making it possible to distinguish between subtle muscle activations that movement-based approaches cannot resolve. Dr. Machado hypothesizes that this method will reveal novel patterns of orofacial muscle recruitment associated with both positive- and negative-valence stimuli, and that it will uncover how chronic stress reshapes these activation patterns.

New Technologies

Basic Research

EARLY SOCIAL EXPERIENCE & NEURONAL DEVELOPMENT

Kally C. O'Reilly Sparks, Ph.D., Research Foundation for Mental Hygiene, Inc./NKI, is exploring how juvenile social experiences and neuronal development reciprocally shape later social competence, dominance, and aggression. The hypothesis is that social competence is gained through juvenile peer interactions. The team will deprive juvenile mice of peer interactions during a sensitive developmental period , then assess the home cage activity of mice during peer-deprivation, measure associated stress, and examine cells activated by juvenile social novelty in transiently activated cell populations (TRAP2). They anticipate that peer-deprivation will result in atypical juvenile social interactions, namely decreased sociability, which may indicate increased social anxiety, and increased aggression toward novel conspecifics. Longitudinally, they expect that juvenile peer-deprivation will result in increased aggression and dominance behavior in brief social interactions. The ultimate aim is to uncover specific aspects of social competence impacted by juvenile peer-deprivation or neuronal silencing, to provide a foundation to examine the role of development in refining social flexibility, social decision making, social learning, and social reinforcement.

Basic Research

SOCIAL FACTORS & MATERNAL MENTAL HEALTH

Elizabeth Sahagun, Ph.D., University of California, Davis, proceeds from the premise that social determinants of health (SDH), including race, insurance type, education level, and birthplace, significantly impact maternal mental health (MH) and contribute to poor pregnancy outcomes. Disorders in mothers such as depression, anxiety, ADHD, substance abuse, schizophrenia, and bipolar disorder have long been linked to adverse outcomes, but underlying biological functions linking social and psychological factors to maternal health remain poorly understood. This study aims to investigate MH as a mediator between SDH and pregnancy complications, and to identify changes in maternal immune patterns during pregnancy within socially disadvantaged groups that may be driving health disparities. Building upon the team's previous work with the Immune and Metabolic Markers during Pregnancy and Child DevelopmenT (IMPaCT) cohort (n=2569), they hypothesize that MH mediates the adverse effects of SDH on pregnancy outcomes, and that socially disadvantaged individuals with MH diagnoses will exhibit heightened immune dysregulation.

Basic Research

NEURAL ACTIVITY PATTERNS IN PSYCHIATRIC ILLNESSES

Ethan A. Solomon, M.D., Ph.D., Stanford University, notes some neurosurgical patients, mainly for treatment of refractory epilepsy, have undergone in vivo recordings via electrodes implanted within the brain (intracranial EEG; iEEG), providing exceptionally high-resolution signals even from structures deep in the brain. Up to 50% are affected by co-morbid psychiatric disorders. These patients present a rare opportunity to study the neural basis of psychiatric diseases. This project supports the creation of a database that links previously collected intracranial EEG data with information about co-morbid psychiatric diagnoses and neuro-psychological testing. Dr. Solomon will use the Restoring Active Memory (RAM) dataset, assembled over 10 years and involving ~ 600 patients with co-morbidities that include depression, anxiety, bipolar disorder, schizophrenia, substance use, PTSD, and suicidality. The relationship between these diagnoses and underlying neural activity will be probed, testing among other things the hypothesis that disordered activity in the hippocampus, a locus for learning, memory, and navigation, contributes to schizophrenia.

Diagnostic Tools/Early Interventions

BIPOLAR DISORDER

Clara Albinana, Ph.D., Aarhus University, Denmark, seeks to link depressive symptoms with disruption of daily 24-hour circadian rhythms. She intends to investigate circadian disruption from a molecular perspective to provide insight into biological reasons for such disruption. This study will generate a circadian proteomics reference dataset to accurately model the 24-hour patterns of proteins in plasma, based on biological samples from international collaborators. The hope is to generate a circadian "time-stamp" for biobank cross-sectional data. This will enable exploration of the association of depression and psychiatric-relevant phenotypes (e.g., bipolarity) with inferred measures of circadian disruption in biobank data. The association models will be performed at the population-level and thus will be based on thousands of cases.

Basic Research

Natalie Bareis, Ph.D., Research Foundation for Mental Hygiene, Inc./NKI, seeks to help personalize treatments for bipolar disorder (BD). She notes that people with BD often have multiple trials of psychotropic treatments with mixed results and only partial symptom reduction. It can take up to 10 years before an effective regimen is established. She believes computational psychiatry using machine learning (ML) can help identify treatments more fit for each patient. This study, drawing upon electronic health record data, will use ML to cluster individuals with BD and then use ML-driven pharmaco-epidemiologic methods to compare effectiveness of treatments they receive to identify the most effective regimens for these clusters. It is hoped that these analyses will shed light on the comparative effectiveness of data-driven regimens that will inform personalized treatment rules.

Next-Generation Therapies

Natalia E. Fares-Otero, Ph.D., Institut D'investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Spain, notes research exploring associations between childhood maltreatment (CM), cognitive functioning, and social information processing in bipolar disorder (BD) is limited. There has been some indication that CM is associated with impairments in processing speed, working memory, executive functions, and poor social relationships in BD, although results are unclear regarding social cognition. This project will test whether CM exposure is associated with initial and updating beliefs about friends and strangers in patients with BD. The team will also examine the efficacy of a tailored intervention in improving updating beliefs and increasing selective flexibility to social relations among patients with CM in a randomized controlled trial. Findings could help inform psychotherapeutic approaches targeting personality and advanced training to help those affected cope with social issues in their lives that may be preventing them from achieving or maintaining recovery.

Basic Research

Yang Ge, Ph.D., The Broad Institute of MIT and Harvard University, notes schizophrenia (SZ) and bipolar disorder (BD) share genetic risk factors and both involve motivation. People with BD may feel overly driven to seek rewards during manic episodes but lack motivation during depressive episodes. Similarly, individuals with SZ may experience reduced motivation as part of the condition's negative symptoms. A recent landmark genetic study identified mutations in a gene called AKAP11 as a strong risk factor for both disorders. Dr. Ge studied genetically modified mice that lack one or both copies of AKAP11 and found these mutant mice show dramatically increased levels of a protein called protein kinase A (PKA). PKA is known to play a key role in brain signaling, particularly in response to dopamine, a chemical that regulates motivation and reward. Because dopamine can either activate or suppress PKA in different brain cells, Dr. Ge now seeks to test whether PKA activity is out of balance in different cell types of AKAP11-mutant mice, leading to changes in motivation.

Basic Research

Kwang-Hyun Hur, Ph.D., McLean Hospital, will investigate the capacity of non-invasive TMS brain stimulation to modulate reward sensitivity, focusing on two reward domains commonly dysregulated in psychiatric populations: food rewards and social rewards. The medial prefrontal cortex (mPFC), a central hub within the fronto-striatal reward circuitry implicated in reward processing, will be targeted. The team will evaluate the bidirectional effects of TMS on reward sensitivity by employing both excitatory (10-Hz) and inhibitory (1-Hz) TMS protocols in a preclinical rodent model over a 4-week period. This experimental design will allow assessment of the long-term effects of TMS on reward-related behavioral responses and corresponding functional and structural alterations within reward-related neural circuits.

Next-Generation Therapies

Giacomo Maddaloni, Ph.D., Harvard University, notes depressive episodes in bipolar disorder (BD) peak in the fall/winter and manic episodes in the spring/summer, with mood cycling frequently triggered at the transition between long and short days (and vice versa). Underlying mechanisms are largely unknown. His research is aimed at identifying molecules, cell types, and brain circuits that regulate adaptation to seasonal changes in the 24-hour light/dark cycle (photoperiod), with the ultimate goal of identifying novel intervention points for disorders characterized by seasonality, including BD. The team has identified in mice a brain circuit that regulates sleep/wake

and circadian synchronization to changes in day length. This project aims to delineate the dual function of a distinct subgroup of serotonin-glutamate neurons, called mrEn1-Pet1 neurons, by analyzing dynamics and relative contribution of serotonin vs. glutamate signaling to activity and sleep/wake adaptation to seasonal photoperiods. The goal is to find a way to accelerate sleep/wake synchronization to photoperiod changes.

Basic Research

Lindsay M. Melhuish Beaupre, Ph.D., Mayo Clinic, Jacksonville, seeks to uncover biological markers that can distinguish bipolar disorder (BD) from major depression (MDD) early on to help with the longstanding problem of misdiagnosis. The project's hypothesis is that markers of mitochondrial dysfunction may help differentiate the two disorders. Mitochondria are cellular components responsible for a variety of critical functions, including energy production and metabolism, and have been implicated in both BD and MDD. Past research has revealed that there are alterations in metabolites involved in energy production and metabolism, as well as in mitochondrial DNA (mtDNA), in BD and MDD. Growth-differentiation factor 15 (GDF-15) is another marker of mitochondrial dysfunction that plays a role in metabolism and inflammation. This project will assess GDF-15 and mtDNA markers in individuals with BD and MDD with the goal of identifying biological markers that can differentiate the two mood disorders.

Diagnostic Tools/Early Intervention

Caitlin E. Millett, Ph.D., The Feinstein Institute for Medical Research/Northwell Health, seeks to learn more about cognitive impairment in bipolar disorder (BD) and ways to treat it. This project seeks to test the hypothesis that blood-brain barrier (BBB) dysfunction and consequent brain damage are most pronounced during manic episodes. The team will employ MRI techniques to evaluate the permeability and perfusion of the BBB. The BBB maintains the delicate ionic balance of the interstitial milieu necessary for the activity of neurons. Dr. Millett posits that cognitive performance is substantially influenced by the permeability and perfusion of the BBB. Increased permeability may facilitate the entry of peripheral toxins, ions, and fluid into the brain, thereby disrupting neuronal signaling and damaging the parenchyma. The team will analyze BBB metrics in relation to cognitive performance across the entire manic spectrum and track changes within each study participant over time.

Basic Research

Jean-Paul G. Noel, Ph.D., University of Minnesota, will examine the updating of expectations driving hallucination-like behaviors in mouse models of different psychiatric conditions such as schizophrenia, bipolar disorder, and depression. The project will take a transdiagnostic and genetically informed approach in bridging from computational psychiatry to systems neuroscience, building foundations for precision psychiatry. To study hallucination-like behaviors in mice the team will develop two tasks, one measuring how quickly expectations are updated, and another measuring how strongly expectations influence behavior. They will then have mice expressing genetic profiles associated with schizophrenia, bipolar disorder, severe depression, Parkinson's, or substance abuse perform these tasks. They will record neural activity from neurons in areas associated with the updating of expectations and/or driving hallucination-like behaviors in mice (i.e., primary visual area, anterior cingulate, and striatum). They hypothesize that individual-specific neural responses across brain regions associated with updating expectations and driving hallucination-like behaviors will be better descriptors of behavior than medical taxonomy (i.e., whether the genetic profile was associated with schizophrenia or depression, for example).

Basic Research

Anthony D. Ramnauth, Ph.D., Research Foundation for Mental Hygiene, Inc./NKI, is interested in atrophy of hippocampus (HPC) tissue seen in schizophrenia, depression, and bipolar disorder. Does this phenomenon have a unique molecular footprint in each disorder? The team will use spatial transcriptomics and proteomics to study postmortem hippocampal tissue from decedents who had these psychiatric conditions. They will use spatial transcriptomics to map molecular changes onto HPC subfields within intact tissue, including the synaptic-rich molecular layer, the neural-rich granule cell layer, and the myelin-rich white matter. Assaying these different HPC subfields, they hope to identify gene expression changes at the RNA and protein level that are correlated with volumetric changes seen in structural magnetic resonance imaging across diagnoses. This approach provides a powerful way to investigate molecular dysfunction and its topographical distribution in specific cell types of the hippocampus in each disorder. Such transdiagnostic molecular profiling of the HPC may uncover pathways associated with the etiology of hippocampal atrophy and aid in discovering biomarkers.

Basic Research

Jennifer E. Siegel-Ramsay, Ph.D., University of Texas at Austin, will explore how long-term stress affects the brain and stress response system in teenagers and young adults who have a family history of bipolar disorder. By studying both chronic stress levels and brain activity, this research aims to identify early warning signs of bipolar disorder and develop better ways to support at-risk youth before symptoms appear. The team will work with young people (ages 14–21) who are already part of a long-term mental health study. Half have a parent with bipolar disorder I (high-risk). Each participant will provide hair samples to measure long-term stress hormone levels, saliva samples to track how their body responds to stress in the moment, and complete a brain scan (fMRI) while solving

challenging math problems under pressure to see how their brain reacts to stress. The study will test whether those with a family history have increases in long-term stress hormone levels and whether early-life stress makes this worse, and examine whether those with higher long-term stress levels show stronger emotional reactions and less ability to control those reactions during stressful situations, which could explain why they are at greater risk for mood disorders.

Basic Research

Shivang Sullere, Ph.D., Harvard Medical School, notes genome wide association studies have identified mutations in the CACNA1C gene, which encodes the Cav1.2 L-type voltage-gated calcium channel, as a significant risk factor for bipolar disorder (BD). Cav1.2 channels are crucial for regulating calcium flux in many cell types, including neurons and vascular smooth muscle cells (vSMCs). Previous research has also suggested a link between Cav1.2 mutations and working memory deficits. This project will explore the consequences of Cav1.2 dysfunction on cognitive outcomes in the context of BD pathophysiology. The team has created a mouse line that allows conditional knockdown Cav1.2 in a cell-type specific manner. Knocking down Cav1.2 in vascular Smooth Muscle Cells (vSMCs) of the brain impairs neurovascular coupling (NVC), needed for matching local blood flow to neuronal energy demands, especially during periods of heightened neuronal activity, e.g., during tasks requiring attention, memory, and decision-making. Cognitive deficits in BD often include impairments in working memory and executive function during periods of heightened cognitive demand, along with vascular comorbidities. This project will try to determine if Cav1.2-driven vascular deficits cause similar pathophysiological outcomes to those observed in BD.

Basic Research

Brittany J. Wolff, Ph.D., University of California, Los Angeles, aims to establish biologically validated endophenotypes (heritable traits) that predict functional outcomes in bipolar disorder (BD). This project will leverage the BD2 Integrated Network cohort to propose a convergent multi-systems approach integrating four key domains: immunometabolic biomarkers, cognitive intra-individual variability, clinical symptoms, and quantitative speech features. The approach moves beyond the traditional deficit model to capture both vulnerability and resilience patterns, capable of revealing protective mechanisms in subgroups of individuals with BD who maintain functional capacity despite illness burden. The novel integration of natural language processing (NLP) with biological markers represents a contribution to psychiatric classification. This work seeks to demonstrate the feasibility of a biologically informed dimensional framework that can guide personalized treatment selection.

Basic Research

CHILDHOOD & ADOLESENCE

Lorenza Dall'Aglio, Ph.D., Massachusetts General Hospital, is exploring how changing lifestyle habits like reducing screen time and getting more sleep may help lower the risk of depression in young people. Among other things, it is unclear when lifestyle changes should occur to have the greatest potential benefit. This project seeks to estimate how changing lifestyle habits (screen time, sleep) at different stages of development (late childhood, early, mid, late adolescence) can reduce depression in early adulthood; and to identify brain characteristics that make different people respond differently to lifestyle changes for reducing depression. Data from the Brazilian High-Risk Cohort (n = 2,512), a large study that followed children with a family history of mental illness from childhood to adulthood, will be used.

Next-Generation Therapies

Nicholas D. Fogleman, Ph.D., University of North Carolina at Chapel Hill, is studying deficits in emotion regulation (ER) in youths with and without ADHD, to fill knowledge gaps regarding how differences in brain network organization underlie ER on a group level and how heterogeneity in brain network organization predicts adverse outcomes in adolescence on an individual level. He will use network neuroscience to fill these gaps by characterizing ER-related network function in youths with and without ADHD, and determining how ER ability and academic, behavioral, and social outcomes in individuals differ based on differences in ER-related brain network organization. Deficits in ER were once considered a core feature of ADHD, but were not included in the diagnostic criteria of the DSM manual. This decision—which this research may help to modify—paved the way for how we assess and treat youth with ADHD, focusing only on symptoms of inattention, hyperactivity, and impulsivity.

Basic Research

Joao Guassi Moreira, Ph.D., University of Wisconsin, who studies addiction, notes little is known about which emotion regulation strategies are involved in risky versus non-risky choices, or how these strategies may facilitate or inhibit risk-taking. This project addresses this gap in the effort to help identify intervention targets to mitigate substance use and addiction. The project will first try to identify which strategies are implicated in adolescent risk-taking, using a sample of adolescent participants ages 16–22 years. The team will then use fMRI to mechanistically confirm how the emotion regulation strategies identified in Phase 1 directly affect risky behavior on a decision-by-decision basis. A separate sample of adolescents will complete emotion regulation and risk-

taking tasks while undergoing fMRI. Brain activity patterns observed during the emotion regulation task will be used to engineer a neural signature for each relevant regulation strategy. Statistical modelling will quantify how emotion regulation signatures influence risk-taking on a decision-by-decision basis.

Diagnostic Tools/Early Intervention

Clotilde Guidetti, M.D., Massachusetts General Hospital, notes deficiencies of micronutrients (e.g., B vitamins) have been associated with neuropsychiatric disorders, including depression. Although vitamin B1 (thiamine) deficiency has been implicated in depression in adults, its relationship to pediatric depression is unknown. This project aims to: 1) evaluate the association between thiamine levels and pediatric depressive symptoms, and 2) assess the effect of thiamine supplementation on pediatric depressive symptoms through an exploratory open-label pilot trial involving ~120 patients with depressive symptoms (ages 8-17). Approximately 30 patients with elevated depressive symptoms will enter the trial, receiving 100 mg thiamine for 60 days. Thiamine levels will be measured at baseline and after treatment completion. Participants will be assessed weekly for safety and biweekly for efficacy with self- and parent-report depression severity scales and global functioning scales. Analyses will be conducted to assess the relationship between thiamine levels and depression severity as well as the effect of thiamine administration.

Next-Generation Therapies

Carina Heller, Ph.D., University of Minnesota, notes that ~ 1 in 5 female adolescents initiates hormonal contraceptive (HC) use during adolescence, a process that suppresses endogenous hormone production of estradiol and progesterone, while introducing more potent exogenous derivatives. It is unknown how their suppression, combined with the introduction of exogenous derivatives, impacts brain maturation and mental health. Emerging evidence suggests that HC use during adolescence is associated with an increased risk of mood disorders, particularly depression and anxiety, in adulthood. This project will characterize structural and functional brain developmental trajectories in adolescents initiating HC use in a large longitudinal, heterogeneous sample drawn from the Adolescent Brain Cognitive Development (ABCD) study. The team will assess brain volume, cortical thickness, and functional connectivity in networks implicated in mood disorders, from baseline through five follow-up assessments and map neurodevelopmental trajectories following HC initiation. They will investigate whether brain neurodevelopmental trajectories mediate the relationship between HC use and internalizing symptoms.

Basic Research

Nicole R. Karcher, Ph.D., Washington University School of Medicine, notes that recent resilience research indicates that factors including familial support may help mitigate the negative effect of adverse life events (ALEs) on psychotic-like experiences (PLEs). The latter are unusual thoughts or perceptions that don't reach the level of a diagnosable mental health condition but can still be distressing and raise risk for onset of psychosis. This study seeks to test this concept. The project will investigate whether ALEs lead to worsening of PLEs, examine brains regions that may partially account for these associations, and identify resilience factors that may mitigate these associations. This study will use data from the Adolescent Brain Cognitive Development (ABCD) Study, which follows nearly 11,800 children over time. Analyses will use data from baseline (ages 9-10) through 5-year follow-up (ages 14-16) assessment waves.

Diagnostic Tools/Early Intervention

Basic Research

Christina A.G. Laurenzi, Ph.D., Stellenbosch University, South Africa, will conduct a pilot study of a culturally adapted intervention to reduce depressive symptoms among adolescent mothers (AM) in South Africa. The premise is that contextually relevant interventions addressing interpersonal, cultural, and sociological factors contributing to depression and suicide risk are needed—especially in low-resource settings with no psychiatric services. Phase 1 will include collaborative adaptation of the WHO's interpersonal therapy intervention (IPT) adapted for delivery by non-specialists and in group settings over 2 individual and 8 group sessions. In Phase 2, adapted IPT will be tested in an open pilot, with AM screened and recruited during postpartum visits. Due to the sensitivities regarding postpartum depression, suicidality risk in the postpartum period, and the additional vulnerability for younger mothers, an open pilot is most scientifically appropriate. Data will be collected at two timepoints to investigate preliminary directionality of effects on depressive symptoms and suicidality, alongside other quantitative and qualitative data ascertaining study safety, feasibility, and acceptability.

Next-Generation Therapies

Bochao D. Lin, Ph.D., Maastricht University, The Netherlands, notes that 80% of adolescent psychotic experiences (PEs) are transient, 20% persist into adulthood, with 7% progressing to psychotic disorders. The dynamic interplay of genetic and environmental factors across generations, mediated by neurodevelopmental changes, remains poorly understood, hindering early detection and preventive strategies. Recent research emphasizes the role of early-life stressors and altered cortical development in PE onset and progression. This project employs a novel

transgenerational and longitudinal approach to address key gaps. By integrating genetic, environmental, and neuroimaging data across two large prospective cohorts, Dr. Lin will systematically investigate how parental exposures, genetic predispositions, and brain developmental trajectories interact to shape the risk and persistence of PEs. The long-term goal is to be able to identify modifiable parental/early-life risks and neurodevelopmental biomarkers, providing actionable targets for family-centered prevention strategies.

Diagnostic Tools/Early Intervention

Travis T. Mallard, Ph.D., Massachusetts General Hospital, notes that behavioral disinhibition is present in such conditions as ADHD, conduct disorder, and substance use disorders, each highly heritable and often begin in childhood or adolescence and frequently co-occur. These "externalizing disorders" have been robustly linked to atypical brain development, including altered cortical expansion during these formative periods. Dr. Mallard will test the hypothesis that externalizing disorders are, in part, influenced by genes that shape the timing and patterning of cortical expansion across development. The team will implement novel modeling techniques which will integrate large-scale psychiatric and imaging genetic datasets and identify pleiotropic genetic variants that concurrently influence cortical expansion and externalizing liability. Using data from large databases, they will then try to determine how the identified risk variants disrupt typical neurodevelopment across the lifespan.

Basic Research

Lluís Miquel Rio, Ph.D., Institute of Biomedicine & Biotechnology of Cantabria, Spain, seeks to advance understanding of the neurobiology of suicidal behavior (SB) in adolescents. Dr. Rio hypothesizes that adolescents with SB will exhibit a distinct miRNA expression profile in their circulating extracellular vesicles (EVs) compared to healthy controls, potentially revealing changes in brain function associated with SB pathophysiology. This project will test whether administration of EVs isolated from adolescents with SB to mice will induce behavioral and molecular changes in brain circuits relevant to SB. The team will isolate and characterize plasma EVs from 30 adolescents (aged 12-17 years) with SB and 30 age- and sex-matched controls. To investigate the functional role of dysregulated miRNAs, isolated EVs will be used to develop a preclinical mouse model.

Basic Research

Laura Modol, Ph.D., Fundacio Institut Mar d'Investigacions Mediques, Spain, notes that we do not yet understand exactly how early-life stress (ELS) alters brain development and contributes to the development of anxiety disorders. One key brain region affected by ELS is the prefrontal cortex (PFC). Changes in PFC development may help explain why females exposed to early stress are more likely to experience anxiety disorders. A crucial but understudied factor in this process is the role of interneurons. This project will use imaging to track how the PFC develops from early life to adulthood in animal models exposed to stress. The hope is to uncover how changes in interneurons contribute to anxiety-related disorders.

Basic Research

Nadezhda (Nadya) N. Modyanova, Ph.D., Montana State University, notes children with ADHD, autism spectrum disorder (ASD), and developmental language disorder (DLD) face unique challenges with communication that require intervention, especially in rural areas with limited access to speech and language pathologists. Extant literature indicates hand gestures support comprehension and production of language for individuals with typical development (TD), ASD, and DLD; but little is known about gestures in ADHD, and also about the brain basis of how gestures support language comprehension. This project seeks to investigate rural Montana children's brain responses during comprehension of a story told by their caregivers using speech with hand gestures. In combination with recording children's brain activity, the team aims to understand how aspects of caregiver gestures can affect children's language comprehension. The goal is to determine children's language comprehension processes during social interaction and engagement with caregivers, and how gestures can better support communication.

Basic Research

Next-Generation Therapies

Kally C. O'Reilly Sparks, Ph.D., Research Foundation for Mental Hygiene, Inc./NKI, is exploring how juvenile social experiences and neuronal development reciprocally shape later social competence, dominance, and aggression. The hypothesis is that social competence is gained through juvenile peer interactions. The team will deprive juvenile mice of peer interactions during a sensitive developmental period , then assess the home cage activity of mice during peer-deprivation, measure associated stress, and examine cells activated by juvenile social novelty in transiently activated cell populations (TRAP2). They anticipate that peer-deprivation will result in atypical juvenile social interactions, namely decreased sociability, which may indicate increased social anxiety, and increased aggression toward novel conspecifics. Longitudinally, they expect that juvenile peer-deprivation will result in increased aggression and dominance behavior in brief social interactions. The ultimate aim is to uncover specific aspects of social competence impacted by juvenile

peer-deprivation or neuronal silencing, to provide a foundation to examine the role of development in refining social flexibility, social decision making, social learning, and social reinforcement.

Basic Research

Giorgia Picci, Ph.D., Boys Town National Research Hospital, notes that while puberty has been identified as a potentially sensitive period for the emergence and progression of internalizing symptoms in autism, the neurobiological mechanisms remain largely unexplored in this population. Dr. Picci hypothesizes that the hormonal surges, neural reorganization, and increasing social demands of puberty amplify mental health risks for youths with autism, potentially interfering with their transition to adult social roles. To address existing scientific gaps and inform future treatment, this project seeks to investigate how pubertal factors affect neural function and structure in networks supporting behavioral domains affected in autism and internalizing disorders (i.e., social-affective, executive control). Among the objectives is to identify longitudinal associations by comparing youths with and without autism to determine if and how baseline neural function and structure predict changes in pubertal progression and internalizing symptoms over a 1-year period.

Basic Research

Reza Rahimian, Ph.D., McGill University, Canada, notes there is a life-course association between childhood adversity and elevated peripheral inflammatory markers in adulthood, suggesting inflammation as a possible mediator linking adverse experiences in early life to psychopathology in adulthood. The choroid plexus (CP), a highly vascularized tissue that produces cerebrospinal fluid, is an interface between peripheral and central immune responses that participates in regulating neurogenesis, inflammatory signals, and plasticity. It is among the least studied structures in psychiatric conditions, particularly in depression. This project investigates the cellular and molecular profiles of the CP of the lateral ventricle in postmortem samples from age- and sex-matched depressed suicide victims with and without a history of childhood abuse, and psychiatrically healthy controls (3 groups; n=32 per group, with at least 50% of subjects female). The goal is to expand what is known about depression pathology in suicide subjects who were exposed to severe childhood adversity.

Basic Research

Prithviraj Rajebhosale, Ph.D., National Institute of Mental Health (NIMH/NIH), is investigating the role of semilunar granule cells (SGC) in susceptibility to psychotic disorders. The lab has explored how a psychosis-associated mutation in the Neuregulin1 (Nrg1) gene alters the composition of dentate gyrus granule cell (GC) subtypes, which may underlie hippocampal dysfunction in schizophrenia. The DG is a part of the hippocampus. This mutation leads to an overabundance of SGCs, a rare GC subtype that possess unique circuit properties allowing them to potently regulate hippocampal network activity. This study examines how SGC circuit properties mature during adolescence and will contrast their development in Nrg1 mutant mice versus wild-type mice. The team will test the hypothesis that SGC overabundance leads to hyperactivity in downstream hippocampal regions such as CA3, potentially altering the way sensory information is processed. One consequence of hyperactivity may be deficits in sensorimotor gating, a cognitive function often impaired in schizophrenia. The team will investigate whether manipulating SGC activity can rescue sensorimotor gating deficits in Nrg1 mutant mice.

Basic Research

Siara K. Rouzer, Ph.D., Texas A&M Health Science Center, will use rodent models to systematically examine how alcohol exposure in both parents alters offspring behavior and brain function compared to single-parent exposure. The first objective is to assess behavioral outcomes characteristic of fetal alcohol syndrome, including anxiety-like behaviors, hyperactivity, compulsivity, and alcohol-seeking tendencies. By conducting a range of behavioral tests, the team seeks to determine whether dual-parent exposure leads to more severe or distinct impairments than single-parent exposure. A second objective is to investigate how dual-parental alcohol exposure affects the brain at a molecular level, with a focus on cannabinoid receptor 1 (CNR1), a key component of brain signaling that regulates emotion, impulse control, and reward processing.

Basic Research

Jennifer E. Siegel-Ramsay, Ph.D., University of Texas at Austin, will explore how long-term stress affects the brain and stress response system in teenagers and young adults who have a family history of bipolar disorder. By studying both chronic stress levels and brain activity, this research aims to identify early warning signs of bipolar disorder and develop better ways to support at-risk youth before symptoms appear. The team will work with young people (ages 14–21) who are already part of a long-term mental health study. Half have a parent with bipolar disorder I (high-risk). Each participant will provide hair samples to measure long-term stress hormone levels, saliva samples to track how their body responds to stress in the moment, and complete a brain scan (fMRI) while solving challenging math problems under pressure to see how their brain reacts to stress. The study will test whether those with a family history have increases in long-term stress hormone levels and whether early-life stress makes this worse, and examine whether those with higher

long-term stress levels show stronger emotional reactions and less ability to control those reactions during stressful situations, which could explain why they are at greater risk for mood disorders.

Basic Research

Ashley Song, Ph.D., Johns Hopkins University School of Medicine, studies the impacts of early-life exposure to mixtures of organic pollutants on early brain development and neurodevelopment. Early postnatal changes of cortical surface areas may play an important role in the development of neurodevelopmental disorders. It is well documented that early-life exposure to environmental pollutants is linked to poor birth outcomes and neurodevelopmental deficits. This project explores the relationship between innovative dental biomarkers of organic pollutants, longitudinal measures of infant brain structure, cognitive and behavior traits, and neurodevelopmental disorders. The team will leverage existing dentine exposure, structural MRI, and phenotypic data of 152 participants in the Infant Brain Imaging Study (IBIS). Specific goals are to: (1) investigate the effect of early life phthalates and PCBs mixtures on early infant longitudinal brain development; (2) evaluate the effect of early life phthalates and PCBs mixtures on early trajectory of cognitive abilities and adaptive function; (3) investigate whether the effect of exposure to a mixture of phthalates and PCBs on early brain development and cognitive behavior development varies by ASD and ADHD risk.

Basic Research

Sarah M. Tashjian, Ph.D., University of Melbourne, Australia, is interested in avoidance behaviors, a common response in individuals with anxiety. While avoidance may provide temporary relief from discomfort, it undermines a core developmental goal of adolescence: exploration. Little is known about the neural mechanisms of adolescent anxiety and the underlying neural systems that contribute to avoidance and exploration. This study will use ultra-high field 7-Tesla neuroimaging to identify neural circuits that contribute to avoidance and exploration preferences in adolescents with heightened anxiety. It seeks to examine how neural circuits are altered by anxiety during adolescence. This could help to differentiate between the neural systems that support maladaptive coping strategies, such as avoidance, and those that underlie adaptive strategies, like exploration.

Basic Research

Milenna T. van Dijk, Ph.D., Columbia University, notes that only some children, who may be less genetically resilient, develop psychopathology after adversity, suggesting neurobiological and genetic differences. One researcher recently found key hippocampal genetic pathways that lead to resilience in mice exposed to stress. This project will determine whether similar genetic pathways in human adolescents can increase resilience to adversity and thereby mitigate the likelihood that youth will develop psychopathology. The team will leverage a novel "expression-based polygenic score (ePGS)", which gives a measure of individual variation in predicted hippocampal expression of the resilience-related genes for youths in the Adolescent Brain Cognitive Development Study (ABCD). The team will then test if individual differences in expression of resilience-related genes predict anxiety and depression and compare it to how well standard genetic scores for depression and anxiety predict psychopathology. To elucidate gene by environment interactions, they will test how these genetic scores interact with early adversity to predict risk for depression and anxiety in response to adversity.

Basic Research

Diagnostic Tools/Early Intervention

Alecia C. Vogel, M.D., Ph.D., Washington University, St. Louis, notes that emotion dysregulation generally and irritability, or dysregulated negative affect, specifically, are significant risk factors for depression in adolescence. This project investigates the biological and developmental mechanisms underlying this association and specifically, the role of adrenarche in the initial phase of pubertal hormone changes, in the development of emotion dysregulation. The hypothesis is that adrenarche, indexed by dehydroepiandrosterone (DHEA) levels, influences the neural circuitry of emotion regulation and contributes to the trajectory of irritability and emotion dysregulation in children. Utilizing data from an ongoing study, the team will analyze hair DHEA levels in 100 children ages 7-10 years, enriched for parent-reported emotion dysregulation, at baseline and one-year follow-up. They will examine the relationship between DHEA levels and questionnaire-based measures of irritability and emotion dysregulation, as well as neural activation patterns during an fMRI emotion regulation task.

Basic Research

DEPRESSION

Gabrielle Agin-Liebes, Ph.D., Yale University, notes the psychedelic drug psilocybin has demonstrated rapid and sustained benefits in some trials for conditions such as depression, alcohol/substance use disorders, anxiety, and PTSD, with emerging evidence suggesting that enhanced cognitive flexibility may be a key mechanism underlying these improvements. This study aims to elucidate the cognitive mechanisms by which psilocybin disrupts rigid thinking and promotes adaptive learning, perhaps thereby optimizing its therapeutic impact across traditional diagnostic boundaries.

The trial will enroll people with depression, anxiety, PTSD, or alcohol/substance use disorders who exhibit significant functional impairment. Prior to dosing, participants will attend two preparatory sessions that provide psychoeducation, establish rapport, review personal history, and develop strategies for managing challenging experiences. They will then receive a single 25 mg oral dose of psilocybin, with continuous monitoring for 6 hours. A post-dosing integration session, scheduled 1–3 days later, will support the consolidation of therapeutic insights into actionable strategies for daily life.

Next-Generation Therapies

Clara Albinana, Ph.D., Aarhus University, Denmark, seeks to link depressive symptoms with disruption of daily 24-hour circadian rhythms. She intends to investigate circadian disruption from a molecular perspective to provide insight into biological reasons for such disruption. This study will generate a circadian proteomics reference dataset to accurately model the 24-hour patterns of proteins in plasma, based on biological samples from international collaborators. The hope is to generate a circadian "time-stamp" for biobank cross-sectional data. This will enable exploration of the association of depression and psychiatric-relevant phenotypes (e.g., bipolarity) with inferred measures of circadian disruption in biobank data. The association models will be performed at the population-level and thus will be based on thousands of cases.

Basic Research

Benedetta Bigio, Ph.D., New York University, notes a dearth of mechanistic pathway data and a lack of easily accessible brain-molecular markers of depressive symptoms in Alzheimer's Disease (AD). Debilitating depression, which is not uncommon in AD, significantly adds to the challenges of care. Research relevant to pathways and markers has largely been limited to postmortem brain measures. Rigorous understanding of such factors requires they be examined in vivo, Dr. Bigio says. This project funds a translational study of molecular determinants of mitochondrial metabolism for programming of key neuroinflammatory pathways assayed in neuronal exosomes of AD subjects with/without depressive symptoms (N=60). It promises to lay the groundwork for new personalized interventions using exosomes as delivery vehicles to treat debilitating depressive symptoms in people with AD.

Basic Research

Gustavo Costa Medeiros, M.D., University of Maryland, Baltimore, notes there is individual variability in benefit to antidepressant treatment with intranasally delivered esketamine, a variant of the ketamine molecule; and that there are no well-accepted means to differentiate individuals who are more likely to respond. One predictor of response to ketamine is change in gamma power during/after its administration, which can be captured by electroencephalogram (EEG). Gamma waves are one of four primary brainwave types measured by EEG. Increases in gamma power, especially in the pre-frontal cortex, are associated with greater antidepressant effects in the week after a ketamine infusion. Dr. Costa Medeiros will measure changes in gamma power during and after the administration of esketamine and analyze whether changes in gamma oscillations after initial treatments predict antidepressant response 24 hours after induction. This will be an open-label trial with 22 participants with treatment-resistant depression who will receive eight esketamine treatments.

Next-Generation Therapies

Iris Dalhuisen, Ph.D., University of Nijmegen, The Netherlands, proposes one way to make rTMS non-invasive brain stimulation more effective may be to combine it with cognitive control training (CCT), a type of computer-based brain training that helps strengthen brain networks involved in attention, memory, and problem-solving—functions often affected in people with depression. Studies suggest that combining rTMS with CCT could enhance treatment effects by making the brain more receptive to change. It is not yet understood how this combination would work on a biological level. To explore this, the team will conduct a study alongside the DIRECT-TMS trial, which is testing whether rTMS combined with CCT improves depression symptoms more than rTMS alone. This project will use electroencephalography (EEG) to measure brain activity before and directly after treatment, as well as 6 months later, to assess how the brain responds to rTMS and CCT, whether the combination leads to lasting changes, and how brain activity differs between people with depression and healthy individuals.

Next-Generation Therapies

Lorenza Dall'Aglio, Ph.D., Massachusetts General Hospital, is exploring how changing lifestyle habits like reducing screen time and getting more sleep may help lower the risk of depression in young people. Among other things, it is unclear when lifestyle changes should occur to have the greatest potential benefit. This project seeks to estimate how changing lifestyle habits (screen time, sleep) at different stages of development (late childhood, early, mid, late adolescence) can reduce depression in early adulthood; and to identify brain characteristics that make different people respond differently to lifestyle changes for reducing depression. Data from the Brazilian High-Risk Cohort (n = 2,512), a large study that followed children with a family history of mental illness from childhood to adulthood, will be used.

Next-Generation Therapies

Raoni C. dos Santos, Ph.D., University of South Carolina, notes that the neurotransmitter norepinephrine (NE) is involved in the stress response. NE neurons in the nucleus of the solitary tract (NTS) send axonal projections to brain regions such as the prefrontal cortex and hippocampus involved in regulating behavior and motivation. This project is about disruption of the NE system in depression and social anxiety disorders. In mouse models, it will explore the hypotheses that: 1) NTS-NE neurons are essential for regulation of depression-like and social behaviors; 2) sustained hyperactivity of these neurons will disrupt the NE system and cause long-lasting behavioral alterations; and 3) inhibition of NTS-NE neurons during stress exposure will protect against the development of stress-induced depression.

Basic Research

Rand Eid, Ph.D., McGill University, Canada, is studying circuit dysregulation in perinatal depression (PND). Because the perinatal period involves profound hormonal fluctuations, depression that emerges during this time may involve brain mechanisms distinct from those underlying depression occurring at other times. This project seeks to address this gap by investigating alterations in brain circuits associated with PND-like states in mouse models. Dr. Eid's stress-based model of PND reveals significant molecular changes in key regions of the mesocorticolimbic circuit—specifically, the prefrontal cortex (PFC), nucleus accumbens (NAc), and ventral tegmental area (VTA)—which regulate mood, reward processing, and maternal behavior. These changes suggest disrupted dopamine signaling and broader impairments in synaptic plasticity and communication within these circuits. This project will directly examine how mesocorticolimbic circuit function is reshaped during the perinatal period, and how it can become dysregulated in PND-like states.

Basic Research

Meghan E. Flanigan, Ph.D., Medical University of South Carolina, notes studies in humans and animal models indicating hyperactivity of the lateral habenula (LHb) is a critical mechanism promoting major depression that can be counteracted by both SSRIs and ketamine. She also notes evidence that dual therapy with ketamine and SSRIs produces more robust and longer lasting antidepressant effects than either monotherapy, suggesting that ketamine and SSRIs may have synergistic therapeutic mechanisms. Preclinical studies have recently illustrated that chronic stress enhances LHb burst firing, a rapid pattern of neuronal activation critical for network synchronization and synaptic plasticity. Both acute ketamine treatment and serotonin rapidly suppress LHb bursting, suggesting that ketamine and SSRIs may exert additive antidepressant effects through this mechanism in patients with major depression. This project seeks to evaluate the effects of ketamine, SSRIs, and dual therapy on LHb bursting, excitability, and responses to serotonin in naïve and chronically stressed male and female mice.

Next-Generation Therapies

Rodolfo Flores Garcia, Ph.D., University of Texas at El Paso, focuses on the infralimbic cortex, which helps regulate emotional responses, and its connection with the basal forebrain, which produces acetylcholine, a chemical messenger critical for attention and learning. In mice, the team will track the activity of basal forebrain-to-infralimbic cortex connections during approach-avoidance conflicts, measure how acetylcholine levels change in real-time during decision making, and examine how psychological stress alters these brain circuits. Preliminary findings show that neurons in the infralimbic cortex respond to both reward and threat cues during these conflicts. This research directly examines the circuit mechanisms that enable flexible decision-making during emotional conflict and establishes a concrete link between stress exposure, disruption of specific brain circuits, and the behavioral patterns seen in anxiety disorders, depression, and PTSD.

Basic Research

Clotilde Guidetti, M.D., Massachusetts General Hospital, notes deficiencies of micronutrients (e.g., B vitamins) have been associated with neuropsychiatric disorders, including depression. Although vitamin B1 (thiamine) deficiency has been implicated in depression in adults, its relationship to pediatric depression is unknown. This project aims to: 1) evaluate the association between thiamine levels and pediatric depressive symptoms, and 2) assess the effect of thiamine supplementation on pediatric depressive symptoms through an exploratory open-label pilot trial involving ~120 patients with depressive symptoms (ages 8-17). Approximately 30 patients with elevated depressive symptoms will enter the trial, receiving 100 mg thiamine for 60 days. Thiamine levels will be measured at baseline and after treatment completion. Participants will be assessed weekly for safety and biweekly for efficacy with self- and parent-report depression severity scales and global functioning scales. Analyses will be conducted to assess the relationship between thiamine levels and depression severity as well as the effect of thiamine administration.

Next-Generation Therapies

Carina Heller, Ph.D., University of Minnesota, notes that ~ 1 in 5 female adolescents initiates hormonal contraceptive (HC) use during adolescence, a process that suppresses endogenous hormone production of estradiol and progesterone, while introducing more potent exogenous derivatives. It is unknown how their suppression, combined with the introduction of exogenous derivatives, impacts brain maturation and mental

health. Emerging evidence suggests that HC use during adolescence is associated with an increased risk of mood disorders, particularly depression and anxiety, in adulthood. This project will characterize structural and functional brain developmental trajectories in adolescents initiating HC use in a large longitudinal, heterogeneous sample drawn from the Adolescent Brain Cognitive Development (ABCD) study. The team will assess brain volume, cortical thickness, and functional connectivity in networks implicated in mood disorders, from baseline through five follow-up assessments and map neurodevelopmental trajectories following HC initiation. They will investigate whether brain neurodevelopmental trajectories mediate the relationship between HC use and internalizing symptoms.

Basic Research

Kwang-Hyun Hur, Ph.D., McLean Hospital, will investigate the capacity of non-invasive TMS brain stimulation to modulate reward sensitivity, focusing on two reward domains commonly dysregulated in psychiatric populations: food rewards and social rewards. The medial prefrontal cortex (mPFC), a central hub within the fronto-striatal reward circuitry implicated in reward processing, will be targeted. The team will evaluate the bidirectional effects of TMS on reward sensitivity by employing both excitatory (10-Hz) and inhibitory (1-Hz) TMS protocols in a preclinical rodent model over a 4-week period. This experimental design will allow assessment of the long-term effects of TMS on reward-related behavioral responses and corresponding functional and structural alterations within reward-related neural circuits.

Next-Generation Therapies

Jenessa N. Johnston, Ph.D., National Institute of Mental Health (NIMH/NIH), will use stem cell and organoid technologies to distinguish the effects of chronic stress on cell lines derived from individuals with treatment-resistant depression (TRD) vs. healthy controls. One key aim is to determine the impact of ketamine on cortical organoids from these populations. Direct comparisons of neural molecular changes and clinical response have the potential to uncover key biosignatures underlying ketamine's effects, possibly contributing to the development of new rapid-acting antidepressants and a deeper understanding of depressive pathophysiology.

Basic Research

Next-Generation Therapies

Miranda Koloski, Ph.D., University of California, San Diego, in pursuit of biomarkers that reliably signal symptoms of depression to help predict treatment response, accelerate diagnoses, and offer more effective treatments, seeks to develop large-scale, network-level measures of brain activity in preclinical models of depression. Communication from the prefrontal cortex to the striatum (cortico-striatal pathways) is important for reward processing. People with depression, who lack motivation for reward, show reduced cortico-striatal activity. The lab has previously found that high frequency beta oscillations carry information about reward and may compute value estimations. The value of a reward is dependent on its attributes (magnitude, likelihood) and motivation for the reward. Extending this work, this project focuses on the neural basis of effort valuation in the context of depression.

Basic Research

Christina A.G. Laurenzi, Ph.D., Stellenbosch University, South Africa, will conduct a pilot study of a culturally adapted intervention to reduce depressive symptoms among adolescent mothers (AM) in South Africa. The premise is that contextually relevant interventions addressing interpersonal, cultural, and sociological factors contributing to depression and suicide risk are needed—especially in low-resource settings with no psychiatric services. Phase 1 will include collaborative adaptation of the WHO's interpersonal therapy intervention (IPT) adapted for delivery by non-specialists and in group settings over 2 individual and 8 group sessions. In Phase 2, adapted IPT will be tested in an open pilot, with AM screened and recruited during postpartum visits. Due to the sensitivities regarding postpartum depression, suicidality risk in the postpartum period, and the additional vulnerability for younger mothers, an open pilot is most scientifically appropriate. Data will be collected at two timepoints to investigate preliminary directionality of effects on depressive symptoms and suicidality, alongside other quantitative and qualitative data ascertaining study safety, feasibility, and acceptability.

Next-Generation Therapies

Younga H. Lee, Ph.D., Massachusetts General Hospital, notes that in spite of the well-established association between depression and metabolic dysfunction, underlying biological mechanisms remain unclear, partly due to the heterogeneity of depressive symptoms. This project takes a novel approach by examining distinct clusters of depression symptoms (affective versus somatic) rather than broad diagnostic definitions that potentially obscure specific biological signals linking depression to metabolic syndrome. Using large-scale genetic data from diverse populations, Dr. Lee seeks to identify specific genetic pathways connecting genetically informed depression symptom clusters with metabolic syndrome (Aim 1). Mechanistic insights from Aim 1 will directly inform the development of clinically applicable prediction models to identify depression patients at elevated risk for metabolic syndrome in real-world clinical settings (Aim 2).

Diagnostic Tools/Early Intervention

Long Li, Ph.D., Chinese Academy of Sciences, People's Republic of China, notes that those chronically exposed to or who experience violent events are prone to developing mental illnesses or violent behaviors. There are significant differences in individual responses to violent events: some individuals exhibit strong empathy, which may lead to depressive or social avoidance behaviors, while others may develop violent inclinations. Dr. Li is investigating the neural basis of the disparity between aggression and depression after witnessing violence. Using mouse models they have developed, the team will investigate the neural circuit dynamics underlying these phenotypes from two dimensions: real time whole-brain functional connectivity mapping and whole-time-scale neural activity dynamics along chronic violence exposure. Following unbiased imaging they aim to find critical neural circuits that can divergently regulate depressive and violent tendencies. This research may help shed light on various mental health conditions, including antisocial personality disorder, major depressive disorder, and PTSD.

Basic Research

Andrea Locarno, Ph.D., Stockholm University, Sweden, is studying sexual dysfunction (SD) as a side effect of SSRI antidepressants. A key regulator of sexual and reproductive function is the pituitary hormone prolactin (Prl). Elevated Prl levels are strongly linked to reduced fertility, diminished libido, menstrual irregularities, and erectile dysfunction. Prl secretion is tightly controlled by dopamine (DA), which is released by hypothalamic tuberoinfundibular dopaminergic (TIDA) neurons. The TIDA-pituitary cross-talk, through highly regulated feedback mechanisms, is in charge of maintaining Prl levels within an optimal range. This project seeks to elucidate how chronic SSRI administration alters TIDA physiology and Prl secretion. It will try to establish a direct link between TIDA neuron activity and SSRI-induced sexual dysfunction via recording and manipulating TIDA activity during chronic SSRI treatment by combining fiber-photometry and chemogenetics in behaving rats.

Basic Research

Annelise A. Madison, Ph.D., University of Michigan, will assess physiological and psychological responses among 100 college sorority recruits to the stress of recruitment. By comparing those actively seeking sorority membership and those already in a sorority, the study aims to understand how the threat of exclusion, or relative social safety, impacts immune responses and depression risk. This study's main objectives are to observe differences in stress responses between recruits and existing members, and investigate whether inflammatory responses to a recruitment event predict social behavior. Dr. Madison hypothesizes that recruits will show higher physiological stress responses, including increased heart rate, cortisol, and inflammatory responses. Recruits over the entire recruitment period may show increased intestinal permeability, systemic inflammation, symptoms of anhedonia, and overall psychological distress (i.e., depression and anxiety).

Basic Research

Magdalena Martinez Garcia, Ph.D., University of California, Santa Barbara, seeks ways of preventing or detecting postpartum depression early. She has been experimenting with a precision imaging approach that tracks MRI-based brain changes alongside peripheral biomarkers across gestation and postpartum in healthy women (parent study). Here, she will expand this to track neurobiological and peripheral blood-derived changes preceding the onset of PPD symptoms. The team will enroll primiparous women with and without a history of depressive episodes—the strongest predictor of PPD relapse—for multimodal MRI, blood sampling, and neuropsychological assessments across 17 longitudinal visits, spanning pre-conception to 1 year postpartum. Key measures include structural and functional neuroimaging, white matter microstructure, cerebral blood perfusion, steroid hormone profiling, and high-throughput proteomic analyses, with a focus on immune signaling pathways. By capturing brain and peripheral changes before clinical symptoms emerge, this study seeks to identify early biomarkers of PD vulnerability that could inform future risk prediction and intervention efforts.

Diagnostic Tools/Early Intervention

Lindsay M. Melhuish Beaupre, Ph.D., Mayo Clinic, Jacksonville, seeks to uncover biological markers that can distinguish bipolar disorder (BD) from major depression (MDD) early on to help with the longstanding problem of misdiagnosis. The project's hypothesis is that markers of mitochondrial dysfunction may help differentiate the two disorders. Mitochondria are cellular components responsible for a variety of critical functions, including energy production and metabolism, and have been implicated in both BD and MDD. Past research has revealed that there are alterations in metabolites involved in energy production and metabolism, as well as in mitochondrial DNA (mtDNA), in BD and MDD. Growth-differentiation factor 15 (GDF-15) is another marker of mitochondrial dysfunction that plays a role in metabolism and inflammation. This project will assess GDF-15 and mtDNA markers in individuals with BD and MDD with the goal of identifying biological markers that can differentiate the two mood disorders.

Diagnostic Tools/Early Intervention

Christina Metcalf, Ph.D., University of Colorado Anschutz Medical Campus, focuses on changes associated with the

menopause transition that create increased risk for depression and cognitive issues, particularly among women who have experienced significant levels of adverse childhood experiences (ACEs; e.g., abuse, neglect). This may be because brain regions relevant to mood and certain aspects of cognition are commonly impacted by exposure to childhood adversity and are further implicated in the menopause transition due to the important role of estradiol in these brain regions. ACEs are linked with worse perimenopausal mood and cognitive function in the context of higher levels of HPA axis- and immune markers. This project seeks to test in a higher-risk population (women in perimenopause with high levels of ACE) whether psychological interventions such as mindfulness-based stress reduction are able to reduce levels of HPA axis and immune markers.

Next-Generation Therapies

Akiko Mizuno, Ph.D., University of Pittsburgh, is interested in learning more about how various factors may influence individual risk for depression. Dr. Mizuno is now focusing on "privilege awareness," or recognizing unearned advantages or disadvantages in life, noting privilege can take different forms, but structural privilege—advantages shaped by systems like wealth and access to education—plays a key role in mental health. Processing this type of privilege relies on social cognition, which is the brain's ability to understand and navigate social structures and relationships. This study explores how privilege awareness connects to depression by studying its effects on the brain. To investigate this, the team will use a computer-based social competition game that mimics real-world privilege dynamics and allows measurement of how people react to these differences and whether they recognize unfair advantages. They will also use fMRI to scan 40 adults (ages 18–65) with different levels of depression, to examine how their brains process privilege and focus on brain areas involved in social thinking and decision-making, and how these brain responses relate to depression symptoms and personal life experiences.

Basic Research

Daniel P. Moriarity, Ph.D., University of Pennsylvania School of Medicine, hopes to illustrate fundamental aspects of clinical trial design that are often overlooked in traditional clinical trial methodologies. He seeks to conduct an intensive longitudinal, placebo-controlled pharmacological probe of adalimumab, a tumor necrosis factor (TNF) blocking agent with preliminary evidence supporting its use as an antidepressant, administered every 14 days for two months. This will serve as a proof-of-principle study of the clinical efficacy of a promising new treatment, but also, a new approach to clinical trial design. Novel features include demonstrating how to use phenotyping pharmacological probes to guide a) screening procedures tailored to symptoms and biological profiles predictive of treatment efficacy, b) registration of specific symptoms as primary trial outcomes (instead of total depression symptoms), and c) empirically informed trial durations and assessment frequencies to maximize causal relevance in subsequent trials.

Next-Generation Therapies

Jessie Muir, Ph.D., Princeton University, aims to identify how psilocybin, a psychedelic that has been shown to drive sustained antidepressant effects, modulates nucleus accumbens (NAc) circuitry and whether this may drive protective effects against future stress and symptoms of depression. Dr. Muir will image single cell activity in the NAc following an injection of psilocybin as mice are freely moving, then expose them to a stress protocol. The hypothesis is that psilocybin will increase activity in the NAc and induce a protective effect, reducing the impact of stress on the treated mice. The project will also tag neurons activated by psilocybin, then sequence the NAc to determine what cell types are activated by the drug and what genes are over-expressed in these cell types and may contribute to its antidepressant effects.

Next-Generation Therapies

Tadaaki Nishioka, Ph.D., Icahn School of Medicine at Mount Sinai, suggests attentional dysfunction in depression may share mechanisms with neurodevelopmental disorders such as ADHD. However, while medial prefrontal cortex (mPFC) parvalbumin-expressing interneurons (PVIs) are crucial for attention control via gamma oscillations, their developmental trajectory and susceptibility to stress remain poorly understood. A key challenge in studying attentional development in adolescent mice is the technical limitation in assessing attentional behavior, as conventional tasks require extensive training, making them unsuitable for rapid developmental studies. To address this, this study employs a novel fast attentional testing protocol that enables efficient assessment of mPFC-PVI activity in adolescent mice. Given that PVI dysfunction is implicated in multiple psychiatric conditions, this study may provide key insights into novel therapeutic approaches targeting PVI maturation to mitigate stress-related attention deficits.

Basic Research

Jean-Paul G. Noel, Ph.D., University of Minnesota, will examine the updating of expectations driving hallucination-like behaviors in mouse models of different psychiatric conditions such as schizophrenia, bipolar disorder, and depression. The project will take a transdiagnostic and genetically informed approach in bridging from computational psychiatry to systems neuroscience, building foundations for

precision psychiatry. To study hallucination-like behaviors in mice the team will develop two tasks, one measuring how quickly expectations are updated, and another measuring how strongly expectations influence behavior. They will then have mice expressing genetic profiles associated with schizophrenia, bipolar disorder, severe depression, Parkinson's, or substance abuse perform these tasks. They will record neural activity from neurons in areas associated with the updating of expectations and/or driving hallucination-like behaviors in mice (i.e., primary visual area, anterior cingulate, and striatum). They hypothesize that individual-specific neural responses across brain regions associated with updating expectations and driving hallucination-like behaviors will be better descriptors of behavior than medical taxonomy (i.e., whether the genetic profile was associated with schizophrenia or depression, for example).

Basic Research

Jessica A. Osterhout, Ph.D., University of Utah, notes that sickness symptoms such as lethargy, social withdrawal, and mood alterations, are essential physiological responses to infection, aiding in energy conservation and immune function. But chronic inflammation often leads to maladaptive sickness behaviors, including major depressive disorder (MDD), as seen in patients with inflammatory diseases and those undergoing immunotherapies. Despite strong correlations between immune activation and depression, the precise mechanisms linking inflammation to depressive symptoms remain unclear, perhaps due to the limitations of inflammatory models. This proposal explores the role of social environments in modulating sickness-induced depressive behaviors. The hypothesis is that social isolation exacerbates sickness severity and prolongs recovery, contributing to depression-like symptoms not typically found in acute inflammation models. The team will assess sickness responses, including body temperature fluctuations and depressive behaviors, in both isolated and group-housed conditions.

Basic Research

Puja K. Parekh, Ph.D., University of Texas at Dallas, notes the precise function of discrete circuits in encoding reward and cost-related information to drive behavior is incompletely understood; and that it has been established that stressful experiences predispose some individuals to develop neuropsychiatric conditions, likely as a consequence of morphological and functional adaptations within key brain regions which inhibit plasticity mechanisms and neurotrophic signaling. The goal of this research is to delineate the roles of cell types and pathways critical in supporting motivated behaviors and how these are affected by stress in vulnerable individuals, and to ultimately inform novel candidates for therapeutic development. Using animal models, Dr. Parekh will make use of improved behavioral assays which capture anticipatory, consummatory and learning-related aspects of effortful motivation. To explore the how chronic stress modulates the activity of the nucleus accumbens (NAc), a critical integrator of limbic and cognitive information for the regulation of goal-directed actions, he will target neurons expressing D1- and D2-type dopamine receptors and measure levels of extracellular dopamine while animals perform tasks engaging effortful motivated behavior; and apply spatially-resolved RNA-sequencing methods to assay all cell types of the NAc and determine whether a unique transcriptional profile is associated with susceptibility or resilience to motivational deficits of stress.

Basic Research

Nicole Petersen, Ph.D., University of California, Los Angeles, studies hormonal modulation of dopamine release as a possible transdiagnostic mechanism of psychiatric risk, involving such illnesses as depression, schizophrenia, and substance use disorders. This study aims to provide a direct test of how estradiol affects dopamine release in the human brain. The team will use advanced brain imaging technology called PET/MR scanning to measure dopamine release in healthy women during two distinct phases of the menstrual cycle: one when estradiol is naturally low and one when it is high. By giving participants a medication that stimulates dopamine release during these two phases, they will test whether estradiol enhances dopamine function. At the same time, they will collect functional MRI data to assess whether these changes can be detected using a more widely available, non-invasive imaging method.

Basic Research

Mohsen Poorganji, Ph.D., University of California, San Diego, says that standard iTBS treatment (a form of non-invasive brain stimulation) "does not work" for many people with treatment-resistance depression (TRD), possibly because the number of pulses given is not tailored to each individual's brain needs. To address this, the team will test whether adjusting the number of iTBS pulses can improve brain function and depression symptoms. The study will involve 75 people with TRD, who will be divided into three groups: (1) personalized iTBS with tailored pulse numbers, (2) standard iTBS with a fixed number of pulses, and (3) a sham (placebo) treatment. The hypothesis is that tailoring the number of pulses will lead to stronger brain responses and better depression outcomes compared to the standard treatment.

Next-Generation Therapies

Reza Rahimian, Ph.D., McGill University, Canada, notes there is a life-course association between childhood

adversity and elevated peripheral inflammatory markers in adulthood, suggesting inflammation as a possible mediator linking adverse experiences in early life to psychopathology in adulthood. The choroid plexus (CP), a highly vascularized tissue that produces cerebrospinal fluid, is an interface between peripheral and central immune responses that participates in regulating neurogenesis, inflammatory signals, and plasticity. It is among the least studied structures in psychiatric conditions, particularly in depression. This project investigates the cellular and molecular profiles of the CP of the lateral ventricle in postmortem samples from age- and sex-matched depressed suicide victims with and without a history of childhood abuse, and psychiatrically healthy controls (3 groups; n=32 per group, with at least 50% of subjects female). The goal is to expand what is known about depression pathology in suicide subjects who were exposed to severe childhood adversity.

Basic Research

Anthony D. Ramnauth, Ph.D., Research Foundation for Mental Hygiene, Inc./NKI, is interested in atrophy of hippocampus (HPC) tissue seen in schizophrenia, depression, and bipolar disorder. Does this phenomenon have a unique molecular footprint in each disorder? The team will use spatial transcriptomics and proteomics to study postmortem hippocampal tissue from decedents who had these psychiatric conditions. They will use spatial transcriptomics to map molecular changes onto HPC subfields within intact tissue, including the synaptic-rich molecular layer, the neural-rich granule cell layer, and the myelin-rich white matter. Assaying these different HPC subfields, they hope to identify gene expression changes at the RNA and protein level that are correlated with volumetric changes seen in structural magnetic resonance imaging across diagnoses. This approach provides a powerful way to investigate molecular dysfunction and its topographical distribution in specific cell types of the hippocampus in each disorder. Such transdiagnostic molecular profiling of the HPC may uncover pathways associated with the etiology of hippocampal atrophy and aid in discovering biomarkers.

Basic Research

Zachary P. Rosenthal, M.D., Ph.D., University of Pennsylvania School of Medicine, notes that electroconvulsive therapy (ECT) is the gold standard for severe, medication-resistant depression, achieving rapid symptom improvement in 60%-80% of patients and reducing suicide risk by 50%. No one yet knows exactly why electrically-induced seizures are therapeutic. Immediately after seizure, ECT in mice induces a second event called cortical spreading depolarization (CSD), a slow-propagating, high-amplitude inhibitory wave that resets neuronal electrochemical gradients. CSD waves are undetectable with routine brain activity monitoring and have never been described in ECT. To determine if this occurs in humans, he developed a novel method for non-invasive optical neuroimaging of cerebral hemodynamics during ECT, revealing that postictal CSD also occurs in patients during ECT. This project deploys optical CSD detection throughout a 4-week ECT course in a closely-monitored patient cohort, testing for relationships between CSD occurrence and stimulation parameters, seizure characteristics, treatment response, and neuroimaging.

New Technologies

Mohammad S.E. Sendi, Ph.D., McLean Hospital, is studying how non-invasive TMS brain stimulation influences brain function. Identifying distinct biotypes of depression in pre-TMS resting-state functional MRI (fMRI) is now seen as a pathway to more personalized and effective treatments. By tailoring interventions to the specific neural patterns of individuals, Dr. Sendi hopes to substantially enhance the therapeutic outcomes for those suffering from major depression (MDD). This project aims to clarify how TMS-induced changes in emotion and cognition circuits and identified pre-TMS biotypes map to clinical outcomes in MDD. Among other things, the project seeks to assess how TMS modulates resting-state fMRI connectivity in emotion and cognition circuits, using a dataset of 576 MDD patients provided by ENIGMA Neuromodulation Working Group. Another aspect will study baseline brain connectivity, employing unsupervised clustering to define subtypes of depression that may predict individual TMS responses.

Next-Generation Therapies

Tsvetan Serchov, Ph.D., Centre National de la Recherche Scientifique, France, notes acute sleep deprivation (SD) has been found to induce rapid but short-lived antidepressant effects. The mechanisms remain unclear, though some evidence points to a potential role of the circadian clock. This project will investigate how the circadian clock contributes to the putative antidepressant effect of SD and potentially identify new therapeutic targets for MDD. It will test the hypothesis that resetting the molecular clock is a potential mechanism for the rapid antidepressant and sustained therapeutic effect of acute SD. Dr. Serchov proposes the molecular clock plays a critical role in mood regulation via direct modulation of homeostatic plasticity and glutamatergic signaling. He will investigate the effects of acute SD and the following recovery sleep period on the expression of canonical clock genes in different mood-controlling brain regions; then, test directly the role of the circadian clock on SD antidepressant efficacy and duration by targeted genetic or pharmacological manipulation of the molecular clockworks.

Basic Research

Christopher V. Sikes-Keilp, M.D., University of North Carolina at Chapel Hill, seeks to better characterize the pathophysiological basis of premenstrual exacerbations of depression (PME). PME responds poorly to treatments that are effective for other menstrually related mood disorders, suggesting there may be unique neuro-hormonal mechanisms contributing to PME. Recent work implicates the late luteal phase withdrawal of ovarian hormones estradiol (E2) and progesterone (P4) in premenstrual increases in anhedonia. The well established effects of E2 and P4 on neural reward systems suggest that dysregulation of brain reward processing may underlie anhedonia in the setting of cycle-based ovarian hormone withdrawal, though this has yet to be experimentally tested. This study seeks to identify the role of ovarian hormones in the neural and behavioral reward mechanisms of anhedonia symptoms in PME. Among the outcomes may be an ability to define effects of neurophysiologic and clinical predictors, including stress-axis function and EEG-based network activity, in a model of deficient reward processing and anhedonia in PME.

Basic Research

Kunmi Sobowale, M.D., University of California, Los Angeles, is motivated by inadequate detection of perinatal depression, particularly among Black women. This project seeks to test whether patient portal messages from patients to clinicians can be leveraged for detecting perinatal depression. A retrospective cohort study will analyze English-language patient portal messages from perinatal patients (ages 16–50) to clinicians at UCLA clinics from 2013–2024. The primary outcome is peripartum depression diagnosis via ICD codes or antidepressant medication dispensing. Linguistic distancing markers will be extracted using Linguistic Inquiry and Word Count software. Models will be developed using clinical, demographic, and linguistic features. Model performance will be evaluated, with equal opportunity difference assessing fairness in prediction outcomes between race-stratified models for Non-Hispanic White and Non-Hispanic Black women.

Diagnostic Tools/Early Intervention

Fangmiao Sun, Ph.D., University of California, Los Angeles, notes that prosocial behaviors play a crucial role in fostering social cohesion by enabling individuals to recognize and respond to the needs or distress of others. Impairments in emotion recognition and prosocial behaviors are common in neuropsychiatric and neuro-developmental disorders, including depression, social anxiety disorder, and autism spectrum disorder. Understanding the neural mechanisms underlying empathy-like prosocial behaviors is essential for advancing knowledge of sensory perception, decision-making systems, and social motivation in the brain, and for developing targeted therapeutic interventions. Dr. Sun hypothesizes that dopamine (DA) plays a critical role in reinforcing these prosocial behaviors and that chronic stress causes changes in the DA system, leading to impairments of prosocial behaviors. To test this, the team will investigate DA dynamics in nucleus accumbens core (NAcc) and ventral tegmental area (VTA) DA neuronal activity during rescue-like prosocial behaviors; will try to determine the functional role of VTA DA neurons in rescue-like prosocial behaviors; and explore the impact of chronic stress on rescue-like behaviors and DA dynamics.

Basic Research

Kristin L. Szuhany, Ph.D., New York University School of Medicine, notes elevated levels of chronic stress contribute to "high allostatic load"—markers of the impact of wear and tear on the body. Markers of allostatic load include inflammatory cytokines (e.g., IL-6) and metabolic markers such as acetyl-L-carnitine (LAC), involved in fatty acid oxidation. Exercise may contribute to successful allostasis, protect mitochondrial metabolism, decrease inflammation, and improve psychiatric symptoms. This project seeks to learn more about how exercise may affect LAC and its association with inflammation, in adults with chronic stress and anxiety disorders. A pilot study will assess 1) differences in neuronal markers of mitochondrial metabolism (LAC) and inflammation (IL-6) in individuals with anxiety disorders compared to controls; and 2) if exercise can increase LAC and decrease IL-6 across and within diagnostic groups. Participants will be 30 sedentary adults: 15 with a primary DSM-5 anxiety disorder and 15 controls.

Basic Research

Next-Generation Therapies

Joshua R. Tatz, Ph.D., University of Iowa, is studying negative thought patterns as a major source of emotional distress in many psychiatric conditions, ranging from negative rumination in depression to intrusive memories in PTSD. As an alternative to invasive deep brain stimulation, he is focusing on low-intensity, focused ultrasound (FUS), an emerging, non-invasive brain stimulation technique that can precisely target deep brain regions with longevity after stimulation. Given that the subgenual anterior cingulate cortex (sgACC) inhibits activity in the basolateral and central amygdala, the team will target sgACC with an FUS protocol, hypothesizing this will lead to net suppression of amygdala activity at rest. They will further examine negative thoughts as they occur in humans 1) spontaneously after viewing personally aversive images, and 2) when neutral images prompt memory intrusions of associated aversive images (e.g. a car crash scene) despite attempted memory suppression. These will provide human models that could shed light on how negative thoughts occur in ruminative depression and PTSD.

Basic Research

Ye E. Tian, Ph.D., University of Melbourne, Australia, cites emerging evidence suggesting that chronic physical illness comorbidity and somatic symptoms in depression may be linked to the brain-immunometabolic axis, i.e., the interaction between the brain and the immune and metabolic systems. Dysfunctional brain circuits, chronic low-grade inflammation, oxidative stress, and imbalanced energy homeostasis commonly co-occur in people with depression. Treating immunometabolic dysregulation is generally not considered in mental health care. To facilitate holistic clinical care, a necessary first step, taken up in this project, is to characterize individual immunometabolic profiles in depression and understand how they relate to the prognosis and illness course of depression and depression-related brain changes. Dr. Tian seeks to develop a comprehensive immunometabolic profile to quantify immunometabolic dysfunction in depression. This will involve integrating a vast set of blood-based inflammatory markers and metabolic biomarkers of glucose and lipid metabolism, with data supplementing a related concurrent major neuroimaging study.

Diagnostic Tools/Early Intervention

Milenna T. van Dijk, Ph.D., Columbia University, notes that only some children, who may be less genetically resilient, develop psychopathology after adversity, suggesting neurobiological and genetic differences. One researcher recently found key hippocampal genetic pathways that lead to resilience in mice exposed to stress. This project will determine whether similar genetic pathways in human adolescents can increase resilience to adversity and thereby mitigate the likelihood that youth will develop psychopathology. The team will leverage a novel "expression-based polygenic score (ePGS)", which gives a measure of individual variation in predicted hippocampal expression of the resilience-related genes for youths in the Adolescent Brain Cognitive Development Study (ABCD). The team will then test if individual differences in expression of resilience-related genes predict anxiety and depression and compare it to how well standard genetic scores for depression and anxiety predict psychopathology. To elucidate gene by environment interactions, they will test how these genetic scores interact with early adversity to predict risk for depression and anxiety in response to adversity.

Basic Research

Diagnostic Tools/Early Intervention

Cassis Varlow, Ph.D., Centre for Addiction and Mental Health, University of Toronto, Canada, seeks to better understand how psilocybin works. This psychedelic drug has gained attention as a possible new treatment for depression, including treatment-resistant major depression (TRD). Clinical studies show that when psilocybin is used along with psychological support, it can significantly reduce symptoms of depression. These positive effects can last for several weeks or even months. This project will study the connection between psilocybin binding to the 5-HT2A (serotonin 2-A) receptor and its antidepressant effects. The team will use positron emission tomography (PET) to image the brains of living patients, to measure how much psilocybin binds to the receptors. The study will include 15 adults with TRD, who will receive different doses of psilocybin: 5 mg, 10 mg, or 1 mg. Brain scans will be taken before the treatment and one hour afterward and changes in depression symptoms will be monitored for one week after treatment.

Next-Generation Therapies

Alecia C. Vogel, M.D., Ph.D., Washington University, St. Louis, notes that emotion dysregulation generally and irritability, or dysregulated negative affect, specifically, are significant risk factors for depression in adolescence. This project investigates the biological and developmental mechanisms underlying this association and specifically, the role of adrenarche in the initial phase of pubertal hormone changes, in the development of emotion dysregulation. The hypothesis is that adrenarche, indexed by dehydroepiandrosterone (DHEA) levels, influences the neural circuitry of emotion regulation and contributes to the trajectory of irritability and emotion dysregulation in children. Utilizing data from an ongoing study, the team will analyze hair DHEA levels in 100 children ages 7-10 years, enriched for parent-reported emotion dysregulation, at baseline and one-year follow-up. They will examine the relationship between DHEA levels and questionnaire-based measures of irritability and emotion dysregulation, as well as neural activation patterns during an fMRI emotion regulation task.

Basic Research

Lauren N. Woodie, Ph.D., George Washington University, notes that those who work late-night and other non-conventional shifts often eat at the "wrong" time of day and can be affected by many mental and behavioral disorders including depression. Depression-like behavior includes disrupted sleep patterns and results in disrupted sleep/wake cycles in rodents and humans. It is associated with depression-like behavior, but the neural correlates and molecular mechanisms have yet to be established. Dr. Woodie's prior work indicates the lateral hypothalamus (LH) is specifically activated in mice fed during the light phase (mistimed food intake), but the molecular identity of these neurons remains to be determined. Orexin neurons in the LH promote wakefulness and arousal while also stimulating food intake and have established roles in the pathophysiology of depression. This project will test the hypothesis that mistimed eating induces depression-like behaviors through

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the aberrant activation of LH orexin neurons. The investigator proposes that mistimed eating-sensitive (MES) cells in the LH are orexin neurons and that chronic activation of MES LH neurons induces the depression-like behaviors of sleep disruption, anhedonia, and impaired coping.

Basic Research

Rongzhen Yan, Ph.D., New York University School of Medicine, notes that post-stress social support has shown promise in mitigating symptoms associated with various psychiatric disorders, such as anxiety and depression. This phenomenon, known as social buffering, underscores the crucial role of interpersonal relationships in boosting resilience and attenuating the negative impact of stress. Despite its proven efficacy, the neural pathways and mechanisms underpinning social buffering remain poorly understood. This study focuses on oxytocin receptor-expressing cells in the anterior ventrolateral part of the ventromedial hypothalamus (aVMHvl OXTR) as a key player in mediating social avoidance after defeat (the basis of an animal model to study stress and depression). The team aims to unravel the dynamic responses of aVMHvl OXTR cells to repeated "defeat" experiences and investigate how social buffering modulates these responses. Preliminary findings suggest that prolonged defeat experiences lead to heightened excitability in aVMHvl OXTR cells, culminating in generalized social avoidance behaviors. Conversely, pair-housed mice exhibit resilience to such changes, implicating social buffering in modulating neural plasticity in response to stress.

Basic Research

Bohan Zhao, Ph.D., Scripps Research, notes that while emotional regulation is traditionally attributed to the brain, emerging research suggests that adipose (fatty) tissue communicates metabolic information directly to the brain through sensory neurons. This project seeks to uncover how this adipose-brain signaling influences mood and whether disruptions in this pathway contribute to psychiatric disorders such as eating disorders, anxiety, and depression. Dr. Zhao will use brain-wide dynamic recording and whole-brain profiling to study how sensory neurons in fat tissue transmit metabolic information to the brain. Functional ultrasound imaging (fUS) which enables whole-brain, high-resolution activity tracking, will be used to measure how the brain responds to metabolic stimulation of adipose tissue. By selectively eliminating sensory input from adipose tissue unilaterally, Dr. Zhao will compare brain activity between two hemispheres. This will help to identify the specific brain regions that rely on adipose sensory signaling. Preliminary data demonstrate that unilateral adipose denervation causes asymmetric brain activity, with changes observed in key regions such as the thalamus, somatosensory cortex, and insular cortex, areas known to process sensory and emotional information. These results suggest a critical role of adipose sensory input in brain function.

Basic Research

EATING DISORDERS

Melissa L. Cooper, Ph.D., New York University, notes that astrocytes, involved in memory formation and synaptic plasticity, communicate as interconnected networks of cells linked by gap junctions. Dr. Cooper's past work demonstrates that after a period of metabolic deficit, astrocyte networks contract to preserve local metabolic stores. In this work, she will test a novel vector to infect astrocytes in any brain region and study each cell as it communicates through gap junctions by biotinylating gap-junction fluxed molecules. Mass spectrometry of the fluxed molecules has already enabled the lab to identify over 200 peptides, hormones, metabolites, and antioxidants fluxed by astrocyte networks. In this project, the aim is to understand how disordered eating can change the structure and function of astrocyte networks, how astrocyte networks recover from a period of disordered eating, and how modulating astrocyte network function impacts that recovery.

Basic Research

Kwang-Hyun Hur, Ph.D., McLean Hospital, will investigate the capacity of non-invasive TMS brain stimulation to modulate reward sensitivity, focusing on two reward domains commonly dysregulated in psychiatric populations: food rewards and social rewards. The medial prefrontal cortex (mPFC), a central hub within the fronto-striatal reward circuitry implicated in reward processing, will be targeted. The team will evaluate the bidirectional effects of TMS on reward sensitivity by employing both excitatory (10-Hz) and inhibitory (1-Hz) TMS protocols in a preclinical rodent model over a 4-week period. This experimental design will allow assessment of the long-term effects of TMS on reward-related behavioral responses and corresponding functional and structural alterations within reward-related neural circuits.

Next-Generation Therapies

Salvador Valencia Sanchez, Ph.D., University of Colorado, Boulder, aims to explore the role of specific striatal cell types, particularly dopamine and glutamate receptor-expressing neurons, in the onset and maintenance of anorexia nervosa (AN) using an activity-based anorexia (ABA) rodent model. ABA, characterized by excessive running during food restriction, mimics behavioral aspects of AN. The hypothesis is that differential activation of D1- and D2-expressing neurons in the nucleus accumbens (NAc) modulates reward processing and abnormal behaviors seen in AN. The team will test whether D1 neurons in the NAc shell exhibit heightened

activation and D2 neurons display suppressed activity in ABA mice compared to controls. Neuronal activity will be recorded during running and feeding. Data will be analyzed to assess neuronal dynamics, dendritic branching, axon morphology, and neuronal firing rates. They will also investigate whether D1 and D2 neurons in the NAc are essential for ABA onset and maintenance. Chemogenetic tools (DREADDs) will be used to selectively inhibit or activate these populations to determine their causal role in behavior.

Basic Research

Elizabeth A. Velkoff, Ph.D., Drexel University, notes that patients with anorexia nervosa (AN) struggle to follow regular eating, due to factors including ambivalence about recovery, habitual avoidance of eating, and poor interoception for hunger cues. Tracking completion of a prescribed meal plan relies on patients self-monitoring their eating episodes. Self-monitoring logs may be inaccurate. This study will test the feasibility and acceptability of a novel means of passive data collection in patients with AN, continuous glucose monitoring (CGM). It will compare the validity of these data against traditional ecological momentary assessment (EMA), a form of data collection in which participants complete brief assessments several times a day. The team will recruit 30 patients ages 18-35 with the restricting subtype of AN. At a baseline session, the participant will insert a CGM sensor and then provide CGM data for 28 days, and will report eating episodes using EMA during this period, after which comparisons will be made.

Diagnostic Tools/Early Intervention

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Basic Research

OBSESSIVE-COMPUSIVE DISORDER (OCD)

Rebecca C. Cox, Ph.D., Washington University, St. Louis, notes the perinatal period is associated with heightened risk for the development of obsessive-compulsive disorder (OCD). Given that postpartum OCD is associated with poor outcomes for mothers and infants, she believes it is important to identify predictors of postpartum OCD that could be targeted for treatment. One potential predictor is sleep and circadian rhythm disruption. This study will examine whether sleep and circadian rhythm disruption in the third trimester of pregnancy predicts increased OCD symptoms at 2 months postpartum in a sample of 55 women with elevated OCD symptoms in pregnancy. In the third trimester, participants will complete 1 week of sleep monitoring using wrist-worn actigraphy and a sleep diary and will complete a self-report measure of insomnia symptoms, and complete a dim-light melatonin onset assessment, which will measure the time at which melatonin levels begin to sharply rise in the evening (this provides a biomarker of the timing of the circadian clock). At 2 months postpartum, participants will complete a self-report measure of postpartum OCD symptoms. The team will examine whether sleep disruption and circadian misalignment predict postpartum OCD symptoms

Basic Research

Diagnostic Tools/Early Intervention

Meghan J. Kulak, M.D., Butler Hospital, will test TMS non-invasive brain stimulation in postpartum OCD. The current FDA-cleared protocol for OCD, which involves stimulation to the dorsomedial prefrontal cortex, is only modestly effective. Other brain areas such as the orbitofrontal cortex are of interest as alternative TMS targets due to their central role in OCD pathology. Small studies of 1Hz repetitive TMS to the orbitofrontal cortex have shown signs of efficacy in OCD in the general population, and a recent pilot study of an accelerated TMS type called continuous theta burst (cTBS) stimulation, to the frontal pole, produced responses in 4 of 7 participants within 14 days. This approach may be highly advantageous in the postpartum OCD population where individuals have high symptom burdens and significant challenges with childcare logistics. This project seeks to assess the feasibility and acceptability of an accelerated course of cTBS to the right orbitofrontal cortex in 12 women with postpartum OCD.

Next-Generation Therapies

Elizabeth E. Manning, Ph.D., University of Newcastle, Australia, seeks to optimize non-invasive transcranial magnetic stimulation (TMS) for obsessive compulsive disorder (OCD). This project weeks to determine how different TMS protocols influence specific cortico-striatal pathways that are implicated in OCD. Her research in a rodent model of OCD has shown that a specific striatal output pathway, the "indirect" pathway, is hyperactive during compulsive behavior. This leads to the research question: can TMS targeting superficial cortical areas be optimized to selectively turn down the activity of downstream striatal indirect pathway neurons and relieve compulsive behavior? She will compare TMS treatment with different protocols and characterize their effects on striatal indirect pathway activity using fluorescent activity sensors. These studies will compare a new protocol recently used in a promising OCD TMS trial combining TMS with the plasticity- enhancing drug d-cycloserine to other widely used protocols, to determine effects on compulsive behavior and striatal indirect pathway activity

Next-Generation Therapies

Nicole R. Provenza, Ph.D., Baylor College of Medicine, notes that researchers have seen observable changes in OCD patients treated with experimental deep-brain stimulation (DBS)—talkativeness, being more social, smiling more, and being more willing to move or do things that were difficult before. Such "approach behavior" often makes individuals more likely to approach other people, situations, and activities. But if the electrical stimulation is a little too much for an individual, "we sometimes see these behaviors go from healthy and positive to overly energetic and even impulsive or reckless." DBS devices allow not only the electrical stimulation of the brain, but also recording of the electrical signals that are actively happening in the brain. The team will use these data together with data from wearable sensors, like Oura rings and Apple watches, to continuously measure patient behavior. This could allow them to assess how day-to-day changes in sleep, stress, physical activity, and socialization affect OCD symptoms, and how these may change in response to DBS treatment.

Next-Generation Therapies

Joseph M. Villarin, M.D., Ph.D., Research Foundation for Mental Hygiene, Inc./NYSPI, posits that to develop new biomedical interventions for improving or preventing neurocognitive impairments seen for example in schizophrenia, OCD, and substance use disorders, we must better understand the underlying brain circuits, their networking, and how they coordinate their activity. The neurotransmitter acetylcholine is involved in supporting cognitive functions, and most of the acetylcholine input to cognitive control centers in the brain's cortex and associated structures comes from the basal forebrain. This project seeks to determine how the activity of neural connections from the striatum to the basal forebrain regulates acetylcholine signaling across the brain during reversal learning behavior. Reversal learning is a behavioral paradigm used across species to assess cognitive flexibility. This work will result in a large data set combining simultaneous information about animal behavior and different kinds of neural activity, which will be analyzed to identify neural processes underlying specific computations that animals use in learning and behavioral adaptation.

Basic Research

OTHER DISORDERS

ALZHEIMER'S DISEASE

Benedetta Bigio, Ph.D., New York University, notes a dearth of mechanistic pathway data and a lack of easily accessible brain-molecular markers of depressive symptoms in Alzheimer's Disease (AD). Debilitating depression, which is not uncommon in AD, significantly adds to the challenges of care. Research relevant to pathways and markers has largely been limited to postmortem brain measures. Rigorous understanding of such factors requires they be examined in vivo, Dr. Bigio says. This project funds a translational study of molecular determinants of mitochondrial metabolism for programming of key neuroinflammatory pathways assayed in neuronal exosomes of AD subjects with/without depressive symptoms (N=60). It promises to lay the groundwork for new personalized interventions using exosomes as delivery vehicles to treat debilitating depressive symptoms in people with AD.

Basic Research

Lorenzo Pasquini, Ph.D., University of California, San Francisco, will test the psychedelic psilocybin in cognitively healthy participants with positive FDA-approved biomarkers of Alzheimer's Disease (AD) pathology and low well-being. The team will investigate whether psilocybin increases structural integrity of prefrontal-subcortical white matter tract and whether it reduces markers of neuroinflammation typically increased in preclinical AD. They will conduct a Stage 1b double blind, 1:1 randomized placebo-controlled pilot trial in 40 cognitively healthy participants with low well-being and positive FDA-approved biomarkers of AD pathology. 20 participants will receive one oral dose of psilocybin (up to 25 mg); 20 will receive placebo. Neuroimaging and plasma will be collected at baseline (three weeks before dosing) and at the primary endpoint (three weeks after dosing) to assess for longitudinal structural brain changes and reductions in neuroinflammation.

Next-Generation Therapies

ANTISOCIAL PERSONALITY DISORDER

Long Li, Ph.D., Chinese Academy of Sciences, People's Republic of China, notes that those chronically exposed to or who experience violent events are prone to developing mental illnesses or violent behaviors. There are significant differences in individual responses to violent events: some individuals exhibit strong empathy, which may lead to depressive or social avoidance behaviors, while others may develop violent inclinations. Dr. Li is investigating the neural basis of the disparity between aggression and depression after witnessing violence. Using mouse models they have developed, the team will investigate the neural circuit dynamics underlying these phenotypes from two dimensions: real time whole-brain functional connectivity mapping and whole-time-scale neural activity dynamics along chronic violence exposure. Following unbiased imaging they aim to find critical neural circuits that can divergently regulate depressive and violent tendencies. This research may help shed light on various mental health conditions, including antisocial personality disorder, major depressive disorder, and PTSD.

Basic Research

CONDUCT DISORDER

Travis T. Mallard, Ph.D., Massachusetts General Hospital, notes that behavioral disinhibition is present in such conditions as ADHD, conduct disorder, and substance use disorders, each highly heritable and often begin in childhood or adolescence and frequently co-occur. These "externalizing disorders" have been robustly linked to atypical brain development, including altered cortical expansion during these formative periods. Dr. Mallard will test the hypothesis that externalizing disorders are, in part, influenced by genes that shape the timing and patterning of cortical expansion across development. The team will implement novel modeling techniques which will integrate large-scale psychiatric and imaging genetic datasets and identify pleiotropic genetic variants that concurrently influence cortical expansion and externalizing liability. Using data from large databases, they will then try to determine how the identified risk variants disrupt typical neurodevelopment across the lifespan.

Basic Research

MORAL INJURY & FORENSIC PSYCHIATRIC SERVICES

Ilvy Goossens, Ph.D., McMaster University, Canada, explores the concept of moral injury (MI) in individuals found not criminally responsible due to mental illness (NCRMD), a population that has received limited research attention. Offenses committed by NCRMD individuals are often linked to mental illness, leading to a dissonance between their self-identity and the criminal act. These individuals may experience significant guilt, shame, and moral injury upon realizing the harm they have caused, especially when victims are family members or close acquaintances. This disconnect between the individual's illness-related behavior and their moral values can result in deep emotional distress. The primary objective of this project is to finalize and validate the Moral Injury Screener in the Offending Population NCR (MIO-NCR), a tool developed to assess MI in NCRMD individuals. Dr. Goossens proposes that by recognizing MI as a distinct and critical treatment target, services can shift toward more comprehensive and compassionate care, improving engagement and reducing recidivism.

Diagnostic Tools/Early Intervention

POST-TRAUMATIC STRESS DISORDER (PTSD)

Gabrielle Agin-Liebes, Ph.D., Yale University, notes the psychedelic drug psilocybin has demonstrated rapid and sustained benefits in some trials for conditions such as depression, alcohol/substance use disorders, anxiety, and PTSD, with emerging evidence suggesting that enhanced cognitive flexibility may be a key mechanism underlying these improvements. This study aims to elucidate the cognitive mechanisms by which psilocybin disrupts rigid thinking and promotes adaptive learning, perhaps thereby optimizing its therapeutic impact across traditional diagnostic boundaries. The trial will enroll people with depression, anxiety, PTSD, or alcohol/substance use disorders who exhibit significant functional impairment. Prior to dosing, participants will attend two preparatory sessions that provide psychoeducation, establish rapport, review personal history, and develop strategies for managing challenging experiences. They will then receive a single 25 mg oral dose of psilocybin, with continuous monitoring for 6 hours. A post-dosing integration session, scheduled 1–3 days later, will support the consolidation of therapeutic insights into actionable strategies for daily life.

Next-Generation Therapies

Ariana Anderson, Ph.D., University of California, Los Angeles, notes PTSD significantly affects cognitive function, and can impair memory, attention, executive function, and emotional regulation. These impairments can produce difficulties in recalling events, intrusive flashbacks, poor concentration, decision-making challenges, and a heightened negativity bias, which disrupt daily life. This project entails open-source software development via a web app called the Auditory Core Test (ACT) to remotely measure affect and cognition, deploying standard screeners for PTSD symptoms as well as novel verbal-response neurocognitive tasks. The app will remove the need for patients to travel to provide data for researchers, and could provide a more accurate snapshot of their daily affect and cognition. Measuring PTSD symptoms remotely opens the possibility, also, of quicker and more precise insights into the effectiveness of interventions.

Diagnostic Tools/Early Intervention

Victor Cazares, Ph.D., Williams College, notes the need to improve the long-term effectiveness of exposure-based treatments

for PTSD and ensure their stability across time and different environments. This project aims to identify how brain activity patterns in the prefrontal cortex are linked to better outcomes in exposure-based therapies, as well as to patterns associated with fear relapse. The team will focus on two areas of the prefrontal cortex—the prelimbic and infralimbic regions—known to play roles, respectively, in promoting and inhibiting fear. The team will use live brain imaging in mice to track the activity of individual cells in both regions simultaneously, during the formation of a fear memory and its subsequent suppression. They will also examine how other brain areas, beyond the prefrontal cortex, contribute to the success of exposure-based treatments. This could result in a model to study the effects of both standard and enhanced exposure procedures on prefrontal brain activity in the same animal over time.

Basic Research

Next-Generation Therapies

Jennifer J. Donegan, Ph.D., Dell Medical School, University of Texas at Austin, proceeds from preliminary data suggesting chronic stress specifically increases activity in the hippocampal-to-prefrontal cortex pathway. Whether this chronic stress-induced pathway activation underlies the excessive or persistent fear and anxiety that characterize PTSD has not been fully examined. The team hypothesizes that stress-induced alterations in the pathway promote fear and anxiety. To test this, they will further characterize the effect of chronic stress on the hippocampal-to-prefrontal cortex pathway; then, manipulate pathway activity to determine whether the stress-induced hyperactivity is necessary and sufficient to drive fear and anxiety. These studies may provide new insights into the neurobiological mechanisms of PTSD risk and help identify potential molecular targets for therapeutic intervention.

Basic Research

Kyle Harrington Flippo, Ph.D., University of Iowa College of Medicine, is studying neural mechanisms underlying maladaptive fear responses, which are central to numerous psychiatric disorders, including PTSD and anxiety disorders. Specifically, the focus is on how threat intensity modulates neuropeptide signaling within the basolateral (BLA) and central (CeA) amygdala to drive either adaptive or maladaptive fear responses. Dysregulated fear generalization—where fear extends beyond actual threats to neutral stimuli—is a hallmark of PTSD and anxiety disorders, contributing to persistent hypervigilance and avoidance behaviors. The project seeks to elucidate how gastrin-releasing peptide (Grp) signaling in a BLA-CeA circuit facilitates excessive fear responses, a process that may also be relevant to psychiatric comorbidities observed in neurodevelopmental (e.g., autism spectrum disorder) and neurodegenerative (e.g., Alzheimer's disease) conditions, where altered amygdala function has been implicated in anxiety and emotional dysregulation.

Basic Research

Rodolfo Flores Garcia, Ph.D., University of Texas at El Paso, focuses on the infralimbic cortex, which helps regulate emotional responses, and its connection with the basal forebrain, which produces acetylcholine, a chemical messenger critical for attention and learning. In mice, the team will track the activity of basal forebrain-to-infralimbic cortex connections during approach-avoidance conflicts, measure how acetylcholine levels change in real-time during decision making, and examine how psychological stress alters these brain circuits. Preliminary findings show that neurons in the infralimbic cortex respond to both reward and threat cues during these conflicts. This research directly examines the circuit mechanisms that enable flexible decision-making during emotional conflict and establishes a concrete link between stress exposure, disruption of specific brain circuits, and the behavioral patterns seen in anxiety disorders, depression, and PTSD.

Basic Research

Long Li, Ph.D., Chinese Academy of Sciences, People's Republic of China, notes that those chronically exposed to or who experience violent events are prone to developing mental illnesses or violent behaviors. There are significant differences in individual responses to violent events: some individuals exhibit strong empathy, which may lead to depressive or social avoidance behaviors, while others may develop violent inclinations. Dr. Li is investigating the neural basis of the disparity between aggression and depression after witnessing violence. Using mouse models they have developed, the team will investigate the neural circuit dynamics underlying these phenotypes from two dimensions: real time whole-brain functional connectivity mapping and whole-time-scale neural activity dynamics along chronic violence exposure. Following unbiased imaging they aim to find critical neural circuits that can divergently regulate depressive and violent tendencies. This research may help shed light on various mental health conditions, including antisocial personality disorder, major depressive disorder, and PTSD.

Basic Research

Mauricio M. Oliveira, Ph.D., New York University Medical Center, points out that a complex population of neurons aids in intricate cognitive tasks, but it is unclear how they cooperate in dynamic settings such as activity-induced plasticity to output proper behavior, hindering our understanding of molecular aspects of memory and its disruption in severe brain disorders such as PTSD. Part of this problem is the lack of approaches to integrate the multiple molecular layers that cooperate to form a flexible molecular environment in the cell. He believes the likelihood of an mRNA being translated by a neuron during threat memory consolidation relies on the combination of cis-elements inserted in the mature version of the mRNA. With the aid of a self-developed tool to isolate specific cell types from the brain, he seeks to combine simultaneous characterization of the neuron type-specific transcriptome and the translatome using

long-read RNA sequencing technology. The goal is to reveal the molecular underpinnings of threat memory consolidation, crucial in the identification of novel therapeutic targets in PTSD and perhaps also dementia and autism.

Basic Research

Luis E. Rosas-Vidal, M.D., Ph.D., Northwestern University, notes that patients with PTSD and anxiety disorders experience overgeneralization even to safe stimuli, thus triggering symptoms during daily living. Avoidance generalization to non-threat predictive stimuli is thought to play a key role in the pathogenesis of PTSD. Little is known about the mechanisms mediating avoidance generalization. Using a modified platform-mediated avoidance task in combination with immunohistochemistry against the activity marker cFos, the team has discovered that activity in the infralimbic prefrontal cortex (IL) and the anterior hypothalamus (AH) is inversely correlated with avoidance generalization. They will use local and projection-specific single-cell in vivo calcium imaging and optogenetic approaches to address 1) how IL and the IL-AH projection neurons engage during uncertain threat stimuli to represent and mediate reductions in avoidance generalization and 2) whether these neurons are sufficient and necessary to reduce avoidance generalization in the presence of an uncertain threat.

Basic Research

Adam Steel, Ph.D., University of Illinois at Urbana-Champaign, wants to better understand how, in PTSD, the brain switches from processing the present moment to being overwhelmed by traumatic memories. Recent research has discovered special areas in the brain that dynamically integrate the visual information currently in view with memories of the wider visuospatial environment. This project will use powerful MRI technology to examine these areas in great detail. Typical brain scanning methods cannot achieve sufficient spatial resolution to see exactly how these regions interact, but high-powered scanning technology (7-Tesla MRI) can reveal these details. This project has three goals: to create detailed maps of where memory and perception regions meet in the brain; to understand how these areas communicate with other brain regions; and to examine how information flows between these visual and memory brain areas in different directions (i.e., from perception to memory and vice versa). The study will work intensively with seven participants, each spending about 10 hours in the scanner across multiple sessions.

Basic Research

Weinan Sun, Ph.D., Cornell University, aims to understand exactly how the hippocampus normally creates accurate mental maps, and how this process becomes impaired in psychiatric conditions such as schizophrenia and PTSD. Dr. Sun's team will record the activity of thousands of individual neurons in the hippocampus of awake mice as they navigate through virtual environments. By observing how the brain organizes and differentiates similar experiences into distinct memories, they hope to see how precise cognitive maps develop over time. Such observations in healthy animals can then be compared with those in animal models designed to reflect symptoms of PTSD and schizophrenia. The hope is to discover specific changes in brain activity that lead to either overly general or fragmented memory representations. This research could provide insights into how memory works—and how it goes wrong—in psychiatric illness.

Basic Research

Joshua R. Tatz, Ph.D., University of Iowa, is studying negative thought patterns as a major source of emotional distress in many psychiatric conditions, ranging from negative rumination in depression to intrusive memories in PTSD. As an alternative to invasive deep brain stimulation, he is focusing on low-intensity, focused ultrasound (FUS), an emerging, non-invasive brain stimulation technique that can precisely target deep brain regions with longevity after stimulation. Given that the subgenual anterior cingulate cortex (sgACC) inhibits activity in the basolateral and central amygdala, the team will target sgACC with an FUS protocol, hypothesizing this will lead to net suppression of amygdala activity at rest. They will further examine negative thoughts as they occur in humans 1) spontaneously after viewing personally aversive images, and 2) when neutral images prompt memory intrusions of associated aversive images (e.g. a car crash scene) despite attempted memory suppression. These will provide human models that could shed light on how negative thoughts occur in ruminative depression and PTSD.

Basic Research

Michael Totty, Ph.D., Johns Hopkins University School of Medicine, notes impaired fear regulation presents a major barrier to effective interventions and may stem, in part, from dysregulated interactions between the amygdala and prefrontal cortex (mPFC), brain regions involved in fear processing and extinction. While some molecular consequences of stress in the amygdala are known, we still lack a clear understanding of which cell types are disproportionately affected by stress, and an even larger gap exists in translating circuit-level findings from rodent models to human disease. Dr. Totty's long-term goal is to define how trauma alters cellular and molecular function within neural circuits that regulate fear, and to leverage these insights to develop targeted therapeutics for PTSD. In this project he seeks to determine if parallel amygdala projections to the mPFC that bidirectionally regulate fear and extinction are distinctly impacted by traumatic stress, using a mouse model relevant for PTSD.

Basic Research

Sebnem N. Tuncdemir, Ph.D., University of Connecticut Health Center, notes that impaired discrimination of sensory

cues associated with traumatic experiences is a hallmark of trauma-related disorders, including PTSD. A patient may experience distress when reminded of a traumatic event, such as a fire, by encountering related sensory cues like its smell. The hippocampus, specifically the dentate gyrus (DG), is crucial for integrating sensory information into episodic memories, and its dysfunction is implicated in PTSD. This project investigates the cellular mechanisms underlying DG dysfunction in a mouse model of PTSD-like symptoms, focusing on the distinct roles of developmentally defined granule cell (GC) subtypes. The team's previous work demonstrated that sensory and spatial information is encoded in largely non-overlapping neural channels within mature GCs of the dorsal DG, enhancing the DG's ability to remap sensory cues across different contexts. This heterogeneity suggests specialized roles in information processing, a hypothesis largely unexplored in trauma-related memory research. To investigate the cellular basis of PTSD-like discrimination deficits in the DG, the team will use innovative neurogenesis-based targeting methods to specifically label, monitor, and manipulate the activity of embryonically (eGCs) and neonatally (nGCs) born granule cells. They also hope to study the therapeutic potential of manipulating eGC and nGC activity using chemogenetic techniques.

Basic Research

PRENATAL BRAIN DEVELOPMENT

Annie Aitken, Ph.D., New York University, seeks to better understand how prenatal exposure to environmental unpredictability shapes stress biology, particularly the immunoendocrine pathways influencing maternal mental health. Advances in remote biospecimen sampling and experimental methods provide a promising opportunity to examine immunoendocrine signatures of environmental unpredictability in hard-to-reach populations. These advancements are critical because maternal stress physiology serves as a key mediator between environmental conditions and infant development. This project will test the hypothesis that prenatal immunoendocrine dysregulation and postnatal autonomic nervous system (ANS) function are key mechanisms in the intergenerational transmission of psychopathology during the perinatal period. Using a prospective longitudinal design, the team will integrate new data collection with an existing study, leveraging remote methods to assess prenatal stress reactivity and inflammation, predictive analytics to identify biomarkers of risk, and longitudinal measures of infant physiological and behavioral regulation.

Basic Research

Diagnostic Tools/Early Intervention

Yusmaris Cariaco, Ph.D., University of Ottawa, Canada, is studying the neurodevelopmental impact of in utero opioid and cannabis exposure. The lab's past research has shown that opioids disrupt placental function, leading to poor fetal growth, with these effects becoming even more severe when cannabis is also used. Testing the theory that damage to the placenta could have lasting consequences on brain development and function, they will study mice exposed to opioids and cannabis during pregnancy, analyzing their brains at embryonic stages, birth, weaning, and adulthood to track how early drug exposure affects brain growth over time. Additionally, they will monitor behavioral changes, such as motor coordination, spatial memory, and social behavior, to identify potential delays or abnormalities.

Basic Research

Josepheen De Asis-Cruz, M.D., Ph.D., Children's National Medical Center, will use non-invasive, resting-state functional MRI (rsfMRI) to investigate hypothalamic connectivity in healthy, term neonates and neonates who were exposed to maternal anxiety in the womb. The hypothalamus is critical in regulating the brain and the body's responses to anxiety. The broader goal is to provide a comprehensive picture of how fetal in utero exposure to maternal anxiety influences developing brain circuits. By identifying early brain markers of risk, this research could inform innovative precision medicine approaches in perinatal mental health. Specific goals include: investigation of how prenatal anxiety alters hypothalamic connectivity to the limbic network; assessment of whether newborns exposed to higher maternal anxiety show stronger hypothalamic-amygdala connections (suggesting heightened stress reactivity) and weaker hypothalamic-prefrontal connectivity (potentially indicating reduced emotional regulation); and examination of how exposure to anxiety in the womb affects neonatal hypothalamic connectivity to large-scale brain networks.

Basic Research

Claudia Z. Han, Ph.D., Washington University, St. Louis, seeks to discover how early-life immune challenges shape long-term brain function, potentially revealing new molecular targets for therapeutic intervention. Dr. Han's work has indicated that human microglia express many of the risk genes associated with schizophrenia throughout development. Environmental triggers during pregnancy such as stress and infection can also be a risk factor for schizophrenia. Microglia integrate genetic and environmental influences through enhancers—small DNA regions that act as molecular switches—turning genes on and off in specific moments. Using mouse models, the team will explore how in utero infection leaves lasting "memories" in microglia that impact brain function later in life; and seeks to identify which enhancers of such processes contain risk variants associated with schizophrenia. They will also investigate whether

microglia are the primary drivers of brain pathology or if they primarily respond to and amplify damage caused by other cell types.

Basic Research

Deepak A. Kaji, M.D., Ph.D., Icahn School of Medicine at Mount Sinai, notes that while acute ketamine exposure likely reproduces some of the glutamatergic dysfunction seen in schizophrenia, this model omits the neurodevelopmental impact of NMDA receptor (NMDAR) inhibition in the embryo. Dr. Kaji believes it is possible that omitting this critical component from the ketamine model has led scientists to develop drugs that do not reverse the consequence of chronic (neurodevelopmentally damaging) NMDAR inhibition and that fail clinical trials. He will use induced pluripotent stem cells (iPSCs) to generate 3D neocortical organoids that model the development of the cortex. To untangle the temporal contributions of NMDAR dysfunction to schizophrenia, he will compare neocortical organoids from 4 experimental conditions: healthy control lines exposed to ketamine throughout differentiation (chronic ketamine exposure), control lines exposed to ketamine for 24 hours upon the completion of the differentiation (acute ketamine exposure), control lines without ketamine (negative control), and lines from 22q11.2 deletion patients with diagnosed schizophrenia (an established model for schizophrenia).

Basic Research

Next-Generation Therapies

Xiangling Meng, Ph.D., Baylor College of Medicine, has identified a gene, CSDE1, as playing a critical role in the production of inhibitory neurons. Patients with CSDE1 mutations often experience ADHD, autism, and epilepsy, suggesting that disruptions in this gene may lead to improper brain development, especially in inhibitory neurons. The team will use brain organoids grown from cells of patients and controls to examine in the lab how CSDE1 mutations impact the formation and movement of inhibitory neurons in the developing brain. By comparing organoids with normal and mutated CSDE1, they can determine whether fewer inhibitory neurons are produced or if they migrate improperly. To understand how these altered neurons affect brain function and behavior, organoids will be transplanted into developing rat brains, to observe if animals with transplanted mutated neurons display hyperactivity, anxiety, or social impairments—behaviors that resemble ADHD symptoms in humans.

Basic Research

Mohammed A. Mostajo-Radji, Ph.D., University of California, Santa Cruz, will use organoids and high-density microelectrode arrays (HD-MEAs) to examine how SHANK3 mutations impair communication in human and mouse models, as s way of advancing knowledge of how neurodevelopmental disorders like schizophrenia and autism are caused. He will measure differences in synchronized network activity and signal transmission to identify human-specific deficits. A single-cell transcriptomic analyses will determine whether human neurons lack compensatory pathways that mouse neurons use to mitigate SHANK3 loss. A distinctive aspect of this work is its evolutionary perspective: by comparing species, the aim is to reveal how genetic changes over millions of years may have inadvertently made human neural circuits more susceptible to SHANK3-related disorders. By integrating 3D neuronal models, HD-MEAs, and evolutionary genomics, this work may identify human-specific mechanisms of SHANK3-related dysfunction, which could help to inform new therapeutic strategies.

Basic Research

Alexios Panoutsopoulos, Ph.D., University of California, Davis, notes prenatal cannabis exposure is linked to an increased risk of neurodevelopmental disorders, including anxiety, attention deficits, and learning impairments. He observes that formation of the neural tube—the start of brain development—relies on tightly regulated cell adhesion, migration, and differentiation. Recent evidence suggests that the body's endocannabinoid system, which includes cannabinoid receptors CB1R and CB2R, plays a role in these developmental processes. If cannabis alters these pathways, it could disrupt early brain formation, potentially increasing susceptibility to neurological disorders later in life. To investigate this, the team will use human neural organoids, which can form neural tube-like structures, allowing study of how cannabis affects key cellular processes. Preliminary data show that CB1R is present in these developing structures and changes dynamically over time, suggesting a crucial role in neural development. The team will expose neural organoids to THC and the natural cannabinoid 2-AG to determine whether these compounds disrupt early brain structure. They will assess structural integrity, examine key proteins such as N-Cadherin and α-catenin that regulate cell-cell interactions, and track neural development by using molecular markers to assess cell proliferation and differentiation.

Basic Research

Belgin Yalcin, Ph.D., Stanford University, will investigate how opioid exposure during the most critical stages of brain development affects myelin, potentially disrupting brain functions that require myelin plasticity. Myelin is a fatty substance that wraps around axons to enhance the transmission of electrical signals across neurons. Minor changes in myelin structure can greatly impact the speed of these signals and the behaviors that are regulated by related neural circuits. This project's first goal is to determine how prenatal opioid exposure impacts myelin health and function by assessing myelination changes and dynamic regulation of myelin-forming cell states, and the myelin-forming cell response to changing dopaminergic neuron activity. The second goal is to determine the behavioral consequences of prenatal opioid exposure on memory, attention,

and sociability. Genetic and pharmacological modulation of myelination will be used to assess the contribution of myelin to these behavioral changes.

Basic Research

PSYCHOSIS

Sidhant Chopra, Ph.D., Orygen, Australia, is interested in synaptic loss, which has emerged as a fundamental pathophysiological mechanism in schizophrenia, and may present a promising target for novel disease-modifying treatments. While several synaptogenic compounds are entering clinical trials, their effective implementation requires identifying which patients may benefit most and when intervention would be most effective, Dr. Chopra notes. This project will include synaptic density PET imaging in a large cohort of early psychosis patients. By integrating PET-based synaptic density measures with detailed clinical and cognitive assessments, the team hopes to establish whether a synaptic deficit subgroup (SDS) is detectable at first illness presentation, and, if so, to identify potential clinical correlates. This could support determination of whether early synaptic loss predicts distinct illness trajectories, and provide insights into the role of synaptic deficits in disease progression.

Basic Research

Diagnostic Tools/Early Intervention

Danique Jeurissen, Ph.D., New York University, notes current treatments for psychiatric disorders including schizophrenia, such as cognitive behavioral therapy and pharmacology, can either target the underlying pathology or promote compensatory mechanisms in other brain regions. Neural mechanisms enabling compensation for disrupted neural signals in psychiatric disorders remain poorly understood and are targeted in this project. The team has established a primate model of disrupted higher cognitive function followed by compensatory mechanisms to restore behavior. They now seek to learn how compensatory mechanisms can be triggered and how changes in activity across the entire brain lead to behavioral compensation. In macaque monkeys they will disrupt persistent activity in parietal cortical regions while the animal performs a decision-making task. By leveraging large-scale population recordings across parietal and frontal regions, they aim to elucidate the neural basis of behavioral compensation.

Basic Research

Nicole R. Karcher, Ph.D., Washington University School of Medicine, notes that recent resilience research indicates that factors including familial support may help mitigate the negative effect of adverse life events (ALEs) on psychotic-like experiences (PLEs). The latter are unusual thoughts or perceptions that don't reach the level of a diagnosable mental health condition but can still be distressing and raise risk for onset of psychosis. This study seeks to test this concept. The project will investigate whether ALEs lead to worsening of PLEs, examine brains regions that may partially account for these associations, and identify resilience factors that may mitigate these associations. This study will use data from the Adolescent Brain Cognitive Development (ABCD) Study, which follows nearly 11,800 children over time. Analyses will use data from baseline (ages 9-10) through 5-year follow-up (ages 14-16) assessment waves.

Diagnostic Tools/Early Intervention

Basic Research

Benson S. Ku, M.D., Ph.D., Emory Clinic, notes environmental factors measured by neighborhood characteristics (e.g., air pollutants and social fragmentation) contribute to a greater risk of subclinical psychosis symptoms called psychotic-like experiences (PLEs) above and beyond individual-level socioeconomic factors. Dr. Ku's preliminary studies have shown that county-level social fragmentation, as measured by the high levels of population turnover and non-nuclear families, is one of the strongest predictors of reduction of gray matter (GM) volume in regions of the cortex, perigenual anterior cingulate cortex (pACC), and hippocampus, which have been associated with the onset of psychosis. This project seeks to determine the role of neighborhood social fragmentation in structural brain changes and how it may, in turn, be associated with trajectories of PLEs; and how polygenic scores may moderate these relationships. The hope is to clarify the nature of the association between the social environment and trajectories of distressing psychotic-like experiences, while advancing understanding of the structural brain changes that contribute to psychotic-like experiences.

Basic Research

Baihan Lin, Ph.D., Icahn School of Medicine at Mount Sinai, performs research that seeks to infer psychiatric cognition from speech. Dr. Lin notes that while computational methods to perform such analysis exist, current approaches lack systematic ways to quantify how thought patterns evolve during illness and treatment. The premise of this project is that without a structured, objective framework to measure these changes, psychiatric assessment remains inconsistent and limited in predictive power. Existing speech-based tools in psychiatry primarily measure word choice, sentiment, and fluency, offering broad correlations with symptoms but fail to explain why or how thought processes become disorganized. This research seeks to establish a computational psychiatry framework that systematically tracks speech-based cognitive markers to quantify thought structure, to track how speech patterns reflect cognitive shifts over time. By

modeling these changes, Dr. Lin aims to create a structured, mechanistic understanding of psychiatric symptoms and treatment response.

Diagnostic Tools/Early Intervention

Basic Research

Bochao D. Lin, Ph.D., Maastricht University, The Netherlands, notes that 80% of adolescent psychotic experiences (PEs) are transient, 20% persist into adulthood, with 7% progressing to psychotic disorders. The dynamic interplay of genetic and environmental factors across generations, mediated by neurodevelopmental changes, remains poorly understood, hindering early detection and preventive strategies. Recent research emphasizes the role of early-life stressors and altered cortical development in PE onset and progression. This project employs a novel transgenerational and longitudinal approach to address key gaps. By integrating genetic, environmental, and neuroimaging data across two large prospective cohorts, Dr. Lin will systematically investigate how parental exposures, genetic predispositions, and brain developmental trajectories interact to shape the risk and persistence of PEs. The long-term goal is to be able to identify modifiable parental/early-life risks and neurodevelopmental biomarkers, providing actionable targets for family-centered prevention strategies.

Diagnostic Tools/Early Intervention

Basic Research

Lauren Luther, Ph.D., University of Alabama at Birmingham, will probe the idea of enhancing treatment of negative symptoms seen in psychosis and schizophrenia via mechanism-based digital therapeutics that can be made widely available to clinics and first-episode psychosis (FEP) patients over the internet or mobile phones. It will test Optimizing Your Success and Mood (OYSM), a program that directly targets reward-processing components to improve negative symptoms. OYSM uses a hybrid approach by focusing on skill development through a web-based program combined with a mobile application focused on translating the skills learned in the web-based program into patients' daily lives. The primary aim is to test whether OYSM is effective for remediating negative symptoms and associated clinical outcomes in 25 individuals with FEP. Secondary aims include trying to identify neural and behavioral mechanisms involved in therapeutic outcomes in OYSM.

Next-Generation Therapies

Katie F.M. Marwick, M.D., Ph.D., University of Edinburgh, UK, seeks to improve understanding of risk factors and long-term outcomes of postpartum psychosis. High quality nationwide electronic health records have been kept in Wales for two decades. They will be used to ask whether having postpartum psychosis increases the chances of having certain physical health disorders (misdirected immune system, heart disease, diabetes) a different pattern of use of hormonal medications, significant mental health problems around the time of menopause, or altered life expectancy. This project, says Dr. Marwick, would be the first to assess the long-term physical health outcomes of postpartum psychosis, the first to look at health information in both hospital and primary care (family doctor) records, and have the longest follow-up period of any study to date.

Diagnostic Tools/Early Intervention

Christina Mo, Ph.D., University of Melbourne, Australia, notes a hallmark of schizophrenia is disrupted self-perception, where individuals may feel that their thoughts or actions are controlled by an external force. Despite how frightening and disabling these symptoms can be, we still do not fully understand what happens in the brain to cause them—the focus of this project. Dr. Mo explains that connections between the cortex and thalamus play a key role in how the brain predicts and processes self-generated movements. She has identified a cortico-thalamo-cortical (transthalamic) pathway that is critical for perception which may be responsible for generating internal copies of motor commands. Its role in encoding self-generated actions remains unexplored. This research will address this gap by dissecting the circuitry during sophisticated behavioral tasks to understand how transthalamic pathways contribute to perceptual learning and efference in the mouse brain. It may in this way offer insights into circuit mechanisms that cannot be obtained by studying the human brain.

Basic Research

Weibo Niu, Ph.D., Emory University, aims to develop a novel drug discovery platform targeting disease-associated gene regulatory networks (regulons) for 22q11.2 Deletion Syndrome (22q11DS), the most prevalent chromosomal microdeletion disorder in humans and linked with schizophrenia in 20%-30% of cases. Dr. Niu will do so by integrating cutting-edge human iPSC-derived brain organoids, single-cell multiomics analyses, and advanced computational tools, having derived iPSC lines from healthy controls and individuals with 22q11DS with extensive clinical assessments. Preliminary work showed neuronal hyperexcitability and altered synaptic transmission in 22q11DS neurons, which is significantly associated with psychosis-related clinical phenotypes in patients. The team will delineate the genetically-driven regulons associated with 22q11DS in patient-derived cortical organoids by single cell multi-omics analyses. They then will try to identify candidate FDA-approved drugs targeting the regulons dysregulated in 22q11DS using network-based computational approaches. This could lead to a unique stem-cell technology platform for developing and testing next-generation therapeutics for schizophrenia and other neuropsychiatric disorders.

Basic Research

Next-Generation Therapies

Jean-Paul G. Noel, Ph.D., University of Minnesota, will examine the updating of expectations driving hallucination-like behaviors in mouse models of different psychiatric conditions such as schizophrenia, bipolar disorder, and depression. The project will take a transdiagnostic and genetically informed approach in bridging from computational psychiatry to systems neuroscience, building foundations for precision psychiatry. To study hallucination-like behaviors in mice the team will develop two tasks, one measuring how quickly expectations are updated, and another measuring how strongly expectations influence behavior. They will then have mice expressing genetic profiles associated with schizophrenia, bipolar disorder, severe depression, Parkinson's, or substance abuse perform these tasks. They will record neural activity from neurons in areas associated with the updating of expectations and/or driving hallucination-like behaviors in mice (i.e., primary visual area, anterior cingulate, and striatum). They hypothesize that individual-specific neural responses across brain regions associated with updating expectations and driving hallucination-like behaviors will be better descriptors of behavior than medical taxonomy (i.e., whether the genetic profile was associated with schizophrenia or depression, for example).

Basic Research

Prithviraj Rajebhosale, Ph.D., National Institute of Mental Health (NIMH/NIH), is investigating the role of semilunar granule cells (SGC) in susceptibility to psychotic disorders. The lab has explored how a psychosis-associated mutation in the Neuregulin1 (Nrg1) gene alters the composition of dentate gyrus granule cell (GC) subtypes, which may underlie hippocampal dysfunction in schizophrenia. The DG is a part of the hippocampus. This mutation leads to an overabundance of SGCs, a rare GC subtype that possess unique circuit properties allowing them to potently regulate hippocampal network activity. This study examines how SGC circuit properties mature during adolescence and will contrast their development in Nrg1 mutant mice versus wild-type mice. The team will test the hypothesis that SGC overabundance leads to hyperactivity in downstream hippocampal regions such as CA3, potentially altering the way sensory information is processed. One consequence of hyperactivity may be deficits in sensorimotor gating, a cognitive function often impaired in schizophrenia. The team will investigate whether manipulating SGC activity can rescue sensorimotor gating deficits in Nrg1 mutant mice.

Basic Research

Alfredo L. Sklar, M.D., Ph.D., University of Pittsburgh, notes impaired selective attention is a core clinical feature of schizophrenia that manifests early and contributes significantly to disease burden. As opposed to a general deficit of attention, individuals with schizophrenia exhibit a narrowed, intense focus on a restricted segment of the visual scene, a phenomenon referred to as hyperfocusing. This project focuses on potential contributions of impaired emotional processing networks. Individuals with schizophrenia even at their first psychotic episode exhibit a negativity bias, or a tendency to evaluate neutral facial expressions as negative. The goal of this study is to determine if negativity bias in first-episode psychosis (FEP) contributes to attentional hyperfocusing at this early stage of the disorder. In healthy adults, viewing happy emotional facial expressions can induce a positive affective state leading to a broadened field of attention and global processing of visual scenes as opposed to individual stimulus features with the opposite true of negative facial expressions. Individuals with schizophrenia even at their first psychotic episode exhibit a negativity bias. This study seeks to determine if negativity bias in FEP contributes to attentional hyperfocusing.

Basic Research

Joseph M. Villarin, M.D., Ph.D., Research Foundation for Mental Hygiene, Inc./NYSPI, posits that to develop new biomedical interventions for improving or preventing neurocognitive impairments seen for example in schizophrenia, OCD, and substance use disorders, we must better understand the underlying brain circuits, their networking, and how they coordinate their activity. The neurotransmitter acetylcholine is involved in supporting cognitive functions, and most of the acetylcholine input to cognitive control centers in the brain's cortex and associated structures comes from the basal forebrain. This project seeks to determine how the activity of neural connections from the striatum to the basal forebrain regulates acetylcholine signaling across the brain during reversal learning behavior. Reversal learning is a behavioral paradigm used across species to assess cognitive flexibility. This work will result in a large data set combining simultaneous information about animal behavior and different kinds of neural activity, which will be analyzed to identify neural processes underlying specific computations that animals use in learning and behavioral adaptation.

Basic Research

SCHIZOPHRENIA

Jamie A. Abbott, Ph.D., Research Foundation for the State University of New York (SUNY)/University at Buffalo, notes newly developed positive allosteric modulators (PAMs) have been shown to enhance signaling at excitatory NMDA receptors (NMDARs) in various model systems. Such signaling has been observed to be reduced in schizophrenia. It is hypothesized that NMDAR PAMs may help to alleviate schizophrenia symptoms. This project uses cellular and single-molecule electrophysiology to explore the therapeutic potential of new NMDAR PAMs in treating schizophrenia. Among the aims is to define how drug interactions may favorably enhance reduced NMDAR activity.

Basic Research

Next-Generation Therapies

Novin Balafkan, Ph.D., Haukeland University Hospital, Norway, notes evidence that rare, high-impact genetic mutations may underlie treatment-resistant schizophrenia, calling attention to the need for more personalized treatment strategies. This study aims to solve two mysteries: (1) why clozapine works when other drugs don't, and (2) how genetic risks in schizophrenia disrupt brain cell communication, leading to symptoms. In reprogrammed lab-grown neurons based on cells sampled from patients, the team will study how rare mutations disrupt glutamate signaling. Focus will be on schizophrenia-associated high-risk genes that control glutamate receptors and calcium balance in brain cells. Using CRISPR, the team will disable these genes and note impact on cell communication. They will then test how a clozapine metabolite, NDMC, repairs these disruptions. Drug databases will be probed to identify existing medications that mimic NDMC's repair effects.

Next-Generation Therapies

Basic Research

Samuel T. Barlow, Ph.D., University of Maryland, Baltimore, notes researchers have long hypothesized that NMDA receptor dysfunction could be playing a causal role in schizophrenia pathophysiology. Given this, it is striking that a neurochemical that disrupts NMDA receptor signaling, kynurenic acid (KYNA), is elevated in schizophrenia patients. Indeed, patient KYNA levels seem to predict the severity of schizophrenia symptoms. This project will use imaging to investigate how KYNA impacts synaptic function and protein expression in cell types relevant to schizophrenia pathology. The work will define the properties of synapses which make them vulnerable to impairment by KYNA. It will test the model that increased levels of KYNA can weaken and eliminate synapses in mouse models with genetically modified KYNA levels, to determine if increased KYNA levels can increase the expression of proteins which tag synapses for elimination. This is a potential molecular mechanism for excessive synapse elimination in schizophrenia.

Basic Research

Kynon J. Benjamin, Ph.D., Northwestern University, observes that much research on schizophrenia has focused on the prefrontal cortex, leaving other important regions like the caudate nucleus and hippocampus underexplored. This project will use advanced computational techniques to analyze existing brain data, allowing the team to estimate cell type-specific gene expression in the caudate nucleus, dorsolateral prefrontal cortex, and hippocampus. The goal is to pinpoint genes altered in specific schizophrenia-affected cell types and understand how these changes disrupt brain function. By integrating this analysis with large-scale genetic studies, the team also hopes to identify key schizophrenia risk genes within these brain cell types.

Basic Research

Alexandra S. Bova, Ph.D., University of Iowa, notes neurons expressing the D1 and D2 dopamine receptors in the striatum play a key role in cognitive functions which are impaired in schizophrenia. She seeks to better understand how these neurons regulate cognitive function, in order to design better therapies. Dr. Bova's past work shows that striatal neurons expressing dopamine receptors are essential for how the brain estimates time, a process that is markedly abnormal in schizophrenia. Dopamine can predict changes in activity of striatal neurons, but it is not known how dopamine regulates striatal neurons during timing. In this project, she will test the hypothesis that striatal dopamine has opposing control over neurons expressing D1- and D2-dopamine receptors during timing. This will be tested by imaging dopamine release, manipulating dopamine neuron activity, recording from large populations of striatal neurons, and computational modeling.

Basic Research

Philip D. Campbell, M.D., Ph.D., University of Pennsylvania, noting that individuals with schizophrenia are highly heterogenous in terms of their clinical presentations, treatment response, and outcomes, suggests they may have diverse underlying disease mechanisms. Perhaps as a result, it has been difficult to identify effective treatments and biomarkers that apply to the entire population. Ultimately working toward the design of treatment, biomarker, and outcomes trials that are more likely to succeed, Dr. Campbell seeks a way to subgroup individuals based on their underlying disease mechanisms. Patient genetic information provides one possible way. Recently, ultra-rare genetic coding variants (URVs) conferring substantial risk for schizophrenia have been identified in 32 human genes. He hypothesizes that

these URVs converge on specific molecular and/or cellular mechanisms to generate brain and behavioral phenotypes. Working in part with zebrafish animal models, he hopes that identifying which aberrant genes converge on similar mechanisms will be the starting point for subgrouping individuals based on mechanism.

Basic Research

Runnan Cao, Ph.D., Washington University School of Medicine, is interested in an underexplored social function in people with schizophrenia, first impressions, which arise rapidly from making social trait judgments (e.g. trustworthiness and competence) based on facial appearance. It is hypothesized that the illness influences trait inferences, associated with symptoms such as paranoia and affective ambivalence, which may lead to heightened suspiciousness and social avoidance. Dr. Cao will investigate how individuals with schizophrenia perceive and interpret social traits in faces compared to neurotypical individuals. The project will test the hypothesis that individuals with schizophrenia make social trait judgments of faces with reduced specificity, which may be a factor in psychiatric symptoms such as paranoia and affective ambivalence; and that these changes are causally linked to altered neural representations of faces in face-processing areas, including the fusiform face area (FFA) and amygdala, which may be driven by increased reliance on low-level visual features (e.g., contour, texture) and reduced utilization of high-level facial features (e.g., eyes, mouth).

Basic Research

Sidhant Chopra, Ph.D., Orygen, Australia, is interested in synaptic loss, which has emerged as a fundamental pathophysiological mechanism in schizophrenia, and may present a promising target for novel disease-modifying treatments. While several synaptogenic compounds are entering clinical trials, their effective implementation requires identifying which patients may benefit most and when intervention would be most effective, Dr. Chopra notes. This project will include synaptic density PET imaging in a large cohort of early psychosis patients. By integrating PET-based synaptic density measures with detailed clinical and cognitive assessments, the team hopes to establish whether a synaptic deficit subgroup (SDS) is detectable at first illness presentation, and, if so, to identify potential clinical correlates. This could support determination of whether early synaptic loss predicts distinct illness trajectories, and provide insights into the role of synaptic deficits in disease progression.

Basic Research

Diagnostic Tools/Early Intervention

Dibyadeep Datta, Ph.D., Yale University, aims to explore a novel role of M4Rs within the primate dorsolateral prefrontal cortex (DLPFC), a brain region crucial for higher-order cognitive functions, including working memory and executive processing. M4Rs are the M4 muscarinic receptors, which are targeted, along with the M1Rs, by the newly approved schizophrenia medicine Cobenfy. Some studies have suggested that this medicine not only treats positive and negative symptoms of schizophrenia but also has cognitive benefits for some patients. Dr. Datta focuses on elucidating the molecular and cellular mechanisms by which M1R and M4R contribute to DLPFC function. Given the profound cognitive impairments in schizophrenia, which often precede psychotic symptoms, Dr. Datta aims to provide a comprehensive understanding of how M1R/M4R modulation can ameliorate cognitive dysfunctions in schizophrenia.

Basic Research

Steven P. Errington, Ph.D., University of Newcastle, UK, seeks to provide new insights into how the brain detects and adapts to unexpected events. EEG reveals a characteristic brain response called mismatch negativity (MMN) when an unexpected event disrupts an expected pattern. Variations in MMN have been linked to schizophrenia, and Alzheimer's and Parkinson's diseases, suggesting impairments in predictive processing may underlie certain cognitive dysfunctions. This project focuses on better understanding how individual neurons generate the MMN signal and how it emerges from underlying brain circuits. He will combine EEG with direct neural recordings from the auditory cortex to investigate how violations of expectation are processed within the brain, at the single-neuron level; and will try to manipulate these signals using optogenetics to investigate the causal relationship between intracortical and EEG activity.

Basic Research

Pawan Sirwan Faris, Ph.D., University of Pavia, Italy, seeks to define the role of cerebellar dysfunction at the local microcircuit level in schizophrenia-related cognitive deficits and determine whether clozapine can restore altered network dynamics. One question to be resolved is whether cerebellar alterations are a primary driver of schizophrenia pathology, or a compensatory response. This project aims to provide the first evidence addressing this by investigating cerebellar microcircuit dynamics in the 22q11.2 microdeletion mouse model, based on a well-established genetic risk factor for schizophrenia. To determine the onset and progression of cerebellar alterations and whether they precede cognitive deficits, the study will assess cerebellar microcircuit dynamics at key developmental stages: the premorbid stage (P18–P21) and the prodromal to chronic stage (P60). Behavioral assays targeting working memory, executive function, and decision-making will correlate cerebellar alterations with cognitive impairments. The study also will examine whether clozapine can normalize such deficits at specific disease stages.

Basic Research

Marc Forrest, Ph.D., Northwestern University, focuses on high-confidence risk genes in schizophrenia. The largest exome sequencing study to date identified 10 genes robustly associated with schizophrenia, including TRIO, which encodes large multi-domain guanine-nucleotide exchange factor (GEF), involved in regulating the actin cytoskeleton and neuron morphology. Functional analysis of TRIO in the nervous system may uncover novel biological mechanisms related to the illness and provide novel avenues for therapeutic development. But the TRIO gene locus contains 57 exons and produces numerous distinct isoforms. Thus, the exact identity, expression patterns and functions of specific isoforms in the brain remain elusive. The objective of this project is to create a comprehensive repertoire of TRIO isoforms in the mouse brain, combined with functional analysis. The hope is to obtain novel insights into TRIO gene function and schizophrenia pathogenesis.

Basic Research

Yang Ge, Ph.D., The Broad Institute of MIT and Harvard University, notes schizophrenia (SZ) and bipolar disorder (BD) share genetic risk factors and both involve motivation. People with BD may feel overly driven to seek rewards during manic episodes but lack motivation during depressive episodes. Similarly, individuals with SZ may experience reduced motivation as part of the condition's negative symptoms. A recent landmark genetic study identified mutations in a gene called AKAP11 as a strong risk factor for both disorders. Dr. Ge studied genetically modified mice that lack one or both copies of AKAP11 and found these mutant mice show dramatically increased levels of a protein called protein kinase A (PKA). PKA is known to play a key role in brain signaling, particularly in response to dopamine, a chemical that regulates motivation and reward. Because dopamine can either activate or suppress PKA in different brain cells, Dr. Ge now seeks to test whether PKA activity is out of balance in different cell types of AKAP11-mutant mice, leading to changes in motivation.

Basic Research

Claudia Z. Han, Ph.D., Washington University, St. Louis, seeks to discover how early-life immune challenges shape long-term brain function, potentially revealing new molecular targets for therapeutic intervention. Dr. Han's work has indicated that human microglia express many of the risk genes associated with schizophrenia throughout development. Environmental triggers during pregnancy such as stress and infection can also be a risk factor for schizophrenia. Microglia integrate genetic and environmental influences through enhancers—small DNA regions that act as molecular switches—turning genes on and off in specific moments. Using mouse models, the team will explore how in utero infection leaves lasting "memories" in microglia that impact brain function later in life; and seeks to identify which enhancers of such processes contain risk variants associated with schizophrenia. They will also investigate whether microglia are the primary drivers of brain pathology or if they primarily respond to and amplify damage caused by other cell types.

Basic Research

Benxia Hu, Ph.D., University of Texas Health Science Center at Houston, seeks to develop therapeutically useful silencer (transcription repressor) inhibitors for the clinical treatment of schizophrenia (SZ). The overall objectives in this project are to (1) prioritize silencers implicated in SZ using deep learning and single-cell CRISPR interference, and (2) elucidate the molecular mechanisms by which silencers can be implicated in SZ. The central hypothesis is that silencers regulate SZ risk genes by recruiting transcription repressors and forming silencer-promoter interactions. The rationale for this research is that a determination of the preclinical therapeutical efficacy and associated mechanisms of silencer (transcription repressor) inhibitors may offer a strong scientific framework for development of new therapies for schizophrenia.

Basic Research

Kwang-Hyun Hur, Ph.D., McLean Hospital, will investigate the capacity of non-invasive TMS brain stimulation to modulate reward sensitivity, focusing on two reward domains commonly dysregulated in psychiatric populations: food rewards and social rewards. The medial prefrontal cortex (mPFC), a central hub within the fronto-striatal reward circuitry implicated in reward processing, will be targeted. The team will evaluate the bidirectional effects of TMS on reward sensitivity by employing both excitatory (10-Hz) and inhibitory (1-Hz) TMS protocols in a preclinical rodent model over a 4-week period. This experimental design will allow assessment of the long-term effects of TMS on reward-related behavioral responses and corresponding functional and structural alterations within reward-related neural circuits.

Next-Generation Therapies

Alison R. Hwong, M.D., Ph.D., Stanford University, notes the potential role of social factors, such as homelessness and social isolation, in predicting dementia risk among older adults with schizophrenia. Prior studies have examined the role of clinical and behavioral risk factors (e.g., heart disease, substance use, anticholinergic medications) for dementia among persons with schizophrenia, but social factors have been challenging to study because they are not systematically collected in clinical records. This project links multiple sources of data on social factors for a large, diverse cohort of over 90,000 adults over 50 years of age with schizophrenia. The team will examine the relative predictive value of social factors for dementia risk, in the context of traditional clinical and behavioral risk factors, in this population. This work

will link several comprehensive VA and Medicare databases that capture diagnoses, encounters, homelessness history, incarceration history, geocoded residence, health factors, and sociodemographic data.

Diagnostic Tools/Early Intervention

Danique Jeurissen, Ph.D., New York University, notes current treatments for psychiatric disorders including schizophrenia, such as cognitive behavioral therapy and pharmacology, can either target the underlying pathology or promote compensatory mechanisms in other brain regions. Neural mechanisms enabling compensation for disrupted neural signals in psychiatric disorders remain poorly understood and are targeted in this project. The team has established a primate model of disrupted higher cognitive function followed by compensatory mechanisms to restore behavior. They now seek to learn how compensatory mechanisms can be triggered and how changes in activity across the entire brain lead to behavioral compensation. In macaque monkeys they will disrupt persistent activity in parietal cortical regions while the animal performs a decision-making task. By leveraging large-scale population recordings across parietal and frontal regions, they aim to elucidate the neural basis of behavioral compensation.

Basic Research

Deepak A. Kaji, M.D., Ph.D., Icahn School of Medicine at Mount Sinai, notes that while acute ketamine exposure likely reproduces some of the glutamatergic dysfunction seen in schizophrenia, this model omits the neurodevelopmental impact of NMDA receptor (NMDAR) inhibition in the embryo. Dr. Kaji believes it is possible that omitting this critical component from the ketamine model has led scientists to develop drugs that do not reverse the consequence of chronic (neurodevelopmentally damaging) NMDAR inhibition and that fail clinical trials. He will use induced pluripotent stem cells (iPSCs) to generate 3D neocortical organoids that model the development of the cortex. To untangle the temporal contributions of NMDAR dysfunction to schizophrenia, he will compare neocortical organoids from 4 experimental conditions: healthy control lines exposed to ketamine throughout differentiation (chronic ketamine exposure), control lines exposed to ketamine for 24 hours upon the completion of the differentiation (acute ketamine exposure), control lines without ketamine (negative control), and lines from 22q11.2 deletion patients with diagnosed schizophrenia (an established model for schizophrenia).

Basic Research

Next-Generation Therapies

Nicole R. Karcher, Ph.D., Washington University School of Medicine, notes that recent resilience research indicates that factors including familial support may help mitigate the negative effect of adverse life events (ALEs) on psychotic-like experiences (PLEs). The latter are unusual thoughts or perceptions that don't reach the level of a diagnosable mental health condition but can still be distressing and raise risk for onset of psychosis. This study seeks to test this concept. The project will investigate whether ALEs lead to worsening of PLEs, examine brains regions that may partially account for these associations, and identify resilience factors that may mitigate these associations. This study will use data from the Adolescent Brain Cognitive Development (ABCD) Study, which follows nearly 11,800 children over time. Analyses will use data from baseline (ages 9-10) through 5-year follow-up (ages 14-16) assessment waves.

Diagnostic Tools/Early Intervention

Basic Research

Pegah Kassraian, Ph.D., Columbia University, notes that schizophrenia is often accompanied by comorbidities such as social anxiety disorder (SAD), which affects approximately 35% of patients relative to a prevalence of around 12% in the general population. Social withdrawal and generalization of social fears are hallmarks of SAD, yet the neural mechanisms underlying these behavioral phenotypes are not understood. This project investigates the hippocampal basis of social fear processing, focusing on the CA2 region, which is critical for social memory and critical for threat-associated social learning. The team will use Df(16)A+/- mice, a model of the 22q11.2 deletion syndrome, one of the strongest known genetic risk factors for schizophrenia, which exhibits CA2-selective deficits in social novelty memory and reduced CA2 activity during social interactions.

Basic Research

Bas Lendemeijer, Ph.D., Columbia University, notes that loss-of-function mutations in a gene called SETD1A have been causally linked to schizophrenia, but how these mutations lead to symptoms remains unclear. Using patient-derived cells reprogrammed using stem cell technology, the team will integrate cells bearing the mutation into the mouse brain, where they will be integrated and begin to function; these will be compared with transplanted cells derived from people without the mutation. The team will track neuronal integration and participation into brain circuits over time while animals are awake and exposed to sensory stimuli. This and other experiments should provide an opportunity to compare the development and integration of SETD1A mutant and wildtype neurons into sensory brain networks. The team also will examine the in vivo therapeutic potential of an epigenetic regulator, LSD1, previously shown to rescue multiple phenotypes in SETD1A mutant neurons.

Basic Research

Baihan Lin, Ph.D., Icahn School of Medicine at Mount Sinai, performs research that seeks to infer psychiatric cognition from

speech. Dr. Lin notes that while computational methods to perform such analysis exist, current approaches lack systematic ways to quantify how thought patterns evolve during illness and treatment. The premise of this project is that without a structured, objective framework to measure these changes, psychiatric assessment remains inconsistent and limited in predictive power. Existing speech-based tools in psychiatry primarily measure word choice, sentiment, and fluency, offering broad correlations with symptoms but fail to explain why or how thought processes become disorganized. This research seeks to establish a computational psychiatry framework that systematically tracks speech-based cognitive markers to quantify thought structure, to track how speech patterns reflect cognitive shifts over time. By modeling these changes, Dr. Lin aims to create a structured, mechanistic understanding of psychiatric symptoms and treatment response.

Diagnostic Tools/Early Intervention

Basic Research

Christina Mo, Ph.D., University of Melbourne, Australia, notes a hallmark of schizophrenia is disrupted self-perception, where individuals may feel that their thoughts or actions are controlled by an external force. Despite how frightening and disabling these symptoms can be, we still do not fully understand what happens in the brain to cause them—the focus of this project. Dr. Mo explains that connections between the cortex and thalamus play a key role in how the brain predicts and processes self-generated movements. She has identified a cortico-thalamo-cortical (transthalamic) pathway that is critical for perception which may be responsible for generating internal copies of motor commands. Its role in encoding self-generated actions remains unexplored. This research will address this gap by dissecting the circuitry during sophisticated behavioral tasks to understand how transthalamic pathways contribute to perceptual learning and efference in the mouse brain. It may in this way offer insights into circuit mechanisms that cannot be obtained by studying the human brain.

Basic Research

Hemanth Mohan, Ph.D., University of Texas Health Science Center at Houston, notes impaired sensorimotor coordination and fine motor control are key features of autism spectrum disorder (ASD) and schizophrenia (SZ), driven in part by aberrant cortical-subcortical circuit connectivity and dynamics. Understanding how these circuits govern normal behavior is essential for investigating their dysfunction and causal links to symptoms. This project aims to investigate cortical circuits governing sensorimotor coordination at cell-type resolution and provide an alternative framework for studying circuit dysfunction in ASD and SZ by integrating state-of-the-art approaches from mouse genetics, behavior, systems, and computational neuroscience. Dr. Mohan hopes to build on his findings to extend investigations into mouse models of ASD and SZ by assessing sensorimotor deficits in the Df(h22q11)/+ schizophrenia mouse model.

Basic Research

Ali Mohebi, Ph.D., University of Wisconsin, investigates multi-timescale reward processing, which directly addresses core pathophysiological mechanisms underlying ADHD and schizophrenia. While distinct, these illnesses share fundamental computational disturbances in how the brain integrates reward information across time—a process essential for adaptive decision-making and motivated behavior. The lab characterizes how dopaminergic dysregulation within specific prefrontal circuits compromises the maintenance of extended reward representations, potentially illuminating why individuals with ADHD struggle to sustain goal-directed behavior despite intact immediate reward processing. For schizophrenia, negative symptoms—including anhedonia and avolition—may emerge from impairments in the prefrontal network dynamics that support persistent representations of reward contexts. By mapping the spatial organization of reward timescales within prefrontal subregions, Dr. Mohebi seeks to identify the specific circuit elements whose dysfunction leads to the fragmentation of temporal continuity in reward processing.

Basic Research

Mohammed A. Mostajo-Radji, Ph.D., University of California, Santa Cruz, will use organoids and high-density microelectrode arrays (HD-MEAs) to examine how SHANK3 mutations impair communication in human and mouse models, as s way of advancing knowledge of how neurodevelopmental disorders like schizophrenia and autism are caused. He will measure differences in synchronized network activity and signal transmission to identify human-specific deficits. A single-cell transcriptomic analyses will determine whether human neurons lack compensatory pathways that mouse neurons use to mitigate SHANK3 loss. A distinctive aspect of this work is its evolutionary perspective: by comparing species, the aim is to reveal how genetic changes over millions of years may have inadvertently made human neural circuits more susceptible to SHANK3-related disorders. By integrating 3D neuronal models, HD-MEAs, and evolutionary genomics, this work may identify human-specific mechanisms of SHANK3-related dysfunction, which could help to inform new therapeutic strategies.

Basic Research

Weibo Niu, Ph.D., Emory University, aims to develop a novel drug discovery platform targeting disease-associated gene regulatory networks (regulons) for 22q11.2 Deletion Syndrome (22q11DS), the most prevalent chromosomal microdeletion disorder in humans and linked with

schizophrenia in 20%-30% of cases. Dr. Niu will do so by integrating cutting-edge human iPSC-derived brain organoids, single-cell multiomics analyses, and advanced computational tools, having derived iPSC lines from healthy controls and individuals with 22q11DS with extensive clinical assessments. Preliminary work showed neuronal hyperexcitability and altered synaptic transmission in 22q11DS neurons, which is significantly associated with psychosis-related clinical phenotypes in patients. The team will delineate the genetically-driven regulons associated with 22q11DS in patient-derived cortical organoids by single cell multi-omics analyses. They then will try to identify candidate FDA-approved drugs targeting the regulons dysregulated in 22q11DS using network-based computational approaches. This could lead to a unique stem-cell technology platform for developing and testing next-generation therapeutics for schizophrenia and other neuropsychiatric disorders.

Basic Research

Next-Generation Therapies

Jean-Paul G. Noel, Ph.D., University of Minnesota, will examine the updating of expectations driving hallucination-like behaviors in mouse models of different psychiatric conditions such as schizophrenia, bipolar disorder, and depression. The project will take a transdiagnostic and genetically informed approach in bridging from computational psychiatry to systems neuroscience, building foundations for precision psychiatry. To study hallucination-like behaviors in mice the team will develop two tasks, one measuring how quickly expectations are updated, and another measuring how strongly expectations influence behavior. They will then have mice expressing genetic profiles associated with schizophrenia, bipolar disorder, severe depression, Parkinson's, or substance abuse perform these tasks. They will record neural activity from neurons in areas associated with the updating of expectations and/or driving hallucination-like behaviors in mice (i.e., primary visual area, anterior cingulate, and striatum). They hypothesize that individual-specific neural responses across brain regions associated with updating expectations and driving hallucination-like behaviors will be better descriptors of behavior than medical taxonomy (i.e., whether the genetic profile was associated with schizophrenia or depression, for example).

Basic Research

Nicole Petersen, Ph.D., University of California, Los Angeles, studies hormonal modulation of dopamine release as a possible transdiagnostic mechanism of psychiatric risk, involving such illnesses as depression, schizophrenia, and substance use disorders. This study aims to provide a direct test of how estradiol affects dopamine release in the human brain. The team will use advanced brain imaging technology called PET/MR scanning to measure dopamine release in healthy women during two distinct phases of the menstrual cycle: one when estradiol is naturally low and one when it is high. By giving participants a medication that stimulates dopamine release during these two phases, they will test whether estradiol enhances dopamine function. At the same time, they will collect functional MRI data to assess whether these changes can be detected using a more widely available, non-invasive imaging method.

Basic Research

Prithviraj Rajebhosale, Ph.D., National Institute of Mental Health (NIMH/NIH), is investigating the role of semilunar granule cells (SGC) in susceptibility to psychotic disorders. The lab has explored how a psychosis-associated mutation in the Neuregulin1 (Nrg1) gene alters the composition of dentate gyrus granule cell (GC) subtypes, which may underlie hippocampal dysfunction in schizophrenia. The DG is a part of the hippocampus. This mutation leads to an overabundance of SGCs, a rare GC subtype that possess unique circuit properties allowing them to potently regulate hippocampal network activity. This study examines how SGC circuit properties mature during adolescence and will contrast their development in Nrg1 mutant mice versus wild-type mice. The team will test the hypothesis that SGC overabundance leads to hyperactivity in downstream hippocampal regions such as CA3, potentially altering the way sensory information is processed. One consequence of hyperactivity may be deficits in sensorimotor gating, a cognitive function often impaired in schizophrenia. The team will investigate whether manipulating SGC activity can rescue sensorimotor gating deficits in Nrg1 mutant mice.

Basic Research

Anthony D. Ramnauth, Ph.D., Research Foundation for Mental Hygiene, Inc./NKI, is interested in atrophy of hippocampus (HPC) tissue seen in schizophrenia, depression, and bipolar disorder. Does this phenomenon have a unique molecular footprint in each disorder? The team will use spatial transcriptomics and proteomics to study postmortem hippocampal tissue from decedents who had these psychiatric conditions. They will use spatial transcriptomics to map molecular changes onto HPC subfields within intact tissue, including the synaptic-rich molecular layer, the neural-rich granule cell layer, and the myelin-rich white matter. Assaying these different HPC subfields, they hope to identify gene expression changes at the RNA and protein level that are correlated with volumetric changes seen in structural magnetic resonance imaging across diagnoses. This approach provides a powerful way to investigate molecular dysfunction and its topographical distribution in specific cell types of the hippocampus in each disorder. Such transdiagnostic molecular profiling of the HPC may uncover pathways associated with the etiology of hippocampal atrophy and aid in discovering biomarkers.

Basic Research

Paul K. Reardon, M.D., Ph.D., Massachusetts General Hospital, is intrigued by emerging evidence pointing to the cerebellum as a critical hub in the pathophysiology of cognitive symptoms in schizophrenia. Non-invasive transcranial magnetic stimulation of the cerebellum has shown promise in improving cognitive performance in patients. Focusing on the cerebellum represents a paradigm shift in schizophrenia research, which has traditionally centered on cortical dysfunction. Building on these promising findings, Dr. Reardon seeks to identify molecular mechanisms underlying cognitive impairment in schizophrenia by using patient-derived cortical and cerebellar brain organoids. In concert with network electrophysiology, spatially resolved transcriptomics, and neuromodulation, the team seeks to characterize the cellular and molecular correlates of cognitive impairment in the organoids. By identifying disease-specific differences in functional neural networks and exploring the potential of electrical and chemical stimulation to restore network function, new therapeutic targets could be identified.

Basic Research

Tal Sharf, Ph.D., University of California, Santa Cruz, will use patient-derived brain organoids carrying the 22q11.2 microdeletion—one of the strongest genetic predictors of schizophrenia—to study how neuronal circuits malfunction and contribute to schizophrenia pathology. The team will track how the mutation alters neuronal activity over different timescales, from milliseconds to months, to determine how early developmental changes lead to long-term dysfunction. By integrating electrophysiology and computational modeling, they will analyze how these brain circuits are affected, laying the foundation for human-based preclinical models to improve therapeutic targeting and drug testing. The project entails development of a brain-organoid machine interface, combining high-density neuroelectronics and computational tools to observe these networks in real time, to identify how imbalances in cortical-thalamic-midbrain signaling contribute to early circuit disruptions in a genetic model of schizophrenia. The team will also create connectoids—organoids linked using microfluidic chips—to study how dopamine circuits in the midbrain interact with the cortex and thalamus, to uncover how dopamine misregulation affects cognitive function and psychosis risk.

Basic Research

New Technologies

Alfredo L. Sklar, M.D., Ph.D., University of Pittsburgh, notes impaired selective attention is a core clinical feature of schizophrenia that manifests early and contributes significantly to disease burden. As opposed to a general deficit of attention, individuals with schizophrenia exhibit a narrowed, intense focus on a restricted segment of the visual scene, a phenomenon referred to as hyperfocusing. This project focuses on potential contributions of impaired emotional processing networks. Individuals with schizophrenia even at their first psychotic episode exhibit a negativity bias, or a tendency to evaluate neutral facial expressions as negative. The goal of this study is to determine if negativity bias in first-episode psychosis (FEP) contributes to attentional hyperfocusing at this early stage of the disorder. In healthy adults, viewing happy emotional facial expressions can induce a positive affective state leading to a broadened field of attention and global processing of visual scenes as opposed to individual stimulus features with the opposite true of negative facial expressions. Individuals with schizophrenia even at their first psychotic episode exhibit a negativity bias. This study seeks to determine if negativity bias in FEP contributes to attentional hyperfocusing.

Basic Research

Weinan Sun, Ph.D., Cornell University, aims to understand exactly how the hippocampus normally creates accurate mental maps, and how this process becomes impaired in psychiatric conditions such as schizophrenia and PTSD. Dr. Sun's team will record the activity of thousands of individual neurons in the hippocampus of awake mice as they navigate through virtual environments. By observing how the brain organizes and differentiates similar experiences into distinct memories, they hope to see how precise cognitive maps develop over time. Such observations in healthy animals can then be compared with those in animal models designed to reflect symptoms of PTSD and schizophrenia. The hope is to discover specific changes in brain activity that lead to either overly general or fragmented memory representations. This research could provide insights into how memory works—and how it goes wrong—in psychiatric illness.

Basic Research

Tomoki Suzuki, M.D., Ph.D., The Rockefeller University, notes face perception is essential for social communication and mental well-being, enabling individuals to recognize identities, interpret facial expressions, and properly infer social situations. Impairments in this ability are hallmark features of several neuropsychiatric conditions, including schizophrenia, social anxiety disorders, and autism spectrum disorder. This project will investigate hierarchical processing within the macaque face-processing system in the inferior temporal cortex, a network of three interconnected nodes with well-defined hierarchical relationships. The overall objective is the identification of the neural mechanisms underlying the qualitative transformation of face representations across two levels of the hierarchy. The central hypothesis is that face processing occurs through a sequence of incremental steps along the feedforward pathway, within and between face-selective areas.

Basic Research

Joseph M. Villarin, M.D., Ph.D., Research Foundation for Mental Hygiene, Inc./NYSPI, posits that to develop new biomedical interventions for improving or preventing neurocognitive impairments seen for example in schizophrenia, OCD, and substance use disorders, we must better understand the underlying brain circuits, their networking, and how they coordinate their activity. The neurotransmitter acetylcholine is involved in supporting cognitive functions, and most of the acetylcholine input to cognitive control centers in the brain's cortex and associated structures comes from the basal forebrain. This project seeks to determine how the activity of neural connections from the striatum to the basal forebrain regulates acetylcholine signaling across the brain during reversal learning behavior. Reversal learning is a behavioral paradigm used across species to assess cognitive flexibility. This work will result in a large data set combining simultaneous information about animal behavior and different kinds of neural activity, which will be analyzed to identify neural processes underlying specific computations that animals use in learning and behavioral adaptation.

Basic Research

Heather B. Ward, M.D., Vanderbilt University Medical Center, thinks the vulnerability of people with schizophrenia (SZ) to cannabis use is based in brain pathology. In cannabis users, the default mode network (DMN) is chronically hyperconnected, but cannabis use transiently corrects this network pathology. This suggests some cannabis users may be using cannabis to self-medicate a DMN pathology problem. Dr. Ward proposes that if this network problem is corrected, it will reduce the need to self-medicate with cannabis. This project will test if DMN pathology can be corrected via non-invasive transcranial magnetic stimulation (rTMS). The treatments will target a network problem specific to cannabis use (via network-targeted rTMS) to see if it can outperform conventional rTMS targets used in depression treatments (typically, the DLPFC). The team will compare the effects of these two rTMS interventions on functional connectivity, cannabis craving, and use, in a randomized, crossover design with pre/post neuroimaging in people with schizophrenia with cannabis use (n=20).

Next-Generation Therapies

Hui Yang, Ph.D., Icahn School of Medicine at Mount Sinai, notes that previous studies have identified schizophrenia-associated genetic risk variants and transcriptional changes, but leave open the question of how these alterations affect brain cell maturation and spatial organization across adulthood. This project will generate and integrate single-nucleus RNA sequencing and high-resolution spatial transcriptomics from schizophrenia and neurotypical donors across multiple adult age groups to construct an age-stratified spatial framework of schizophrenia pathology. By mapping disease-associated disruptions in neuronal and glial maturation, cortical architecture, and intercellular communication, this study hopes to uncover critical windows of vulnerability and trajectory-specific molecular mechanisms. It could help establish a spatially resolved reference for schizophrenia across different stages of adulthood, possibly bridging molecular and anatomical insights to identify novel therapeutic targets.

Basic Research

Marco Zierhut, M.D., Charité - University Medicine Berlin, Germany, notes that treatments for schizophrenia spectrum disorders (SSD) remain ineffective in addressing negative symptoms (NS), leaving impairments to social functioning and quality of life unaddressed. Dysfunctional connectivity between the mesocorticolimbic dopamine system and socioemotional networks may underly NS, Dr. Zierhut suggests. Oxytocin (OXT) enhances connectivity between these networks, improving social cognition and promoting social activation. Lower plasma OXT levels correlate with greater NS severity in SSD, suggesting its therapeutic potential. However, findings on intranasal OXT administration in SSD remain inconsistent. The team's pilot studies indicate that combining intranasal OXT with mindfulness-based group psychotherapy (MBGT) improves NS, stress, depression, social functioning, and quality of life, with high treatment fidelity and satisfaction. This triple-blind, randomized, placebo-controlled trial aims to extend prior findings on NS by assessing the efficacy of 4-week MBGT combined with a higher OXT dose (48 I.U.) compared to 24 I.U. and placebo. The team hypothesizes that the higher dose will enhance treatment efficacy.

Next-Generation Therapies

SUICIDE PREVENTION

Christina A.G. Laurenzi, Ph.D., Stellenbosch University, South Africa, will conduct a pilot study of a culturally adapted intervention to reduce depressive symptoms among adolescent mothers (AM) in South Africa. The premise is that contextually relevant interventions addressing interpersonal, cultural, and sociological factors contributing to depression and suicide risk are needed—especially in low-resource settings with no psychiatric services. Phase 1 will include collaborative adaptation of the WHO's interpersonal therapy intervention (IPT) adapted for delivery by non-specialists and in group settings over 2 individual and 8 group sessions. In Phase 2, adapted IPT will be tested in an open pilot, with AM screened and recruited during postpartum visits. Due to the sensitivities regarding postpartum depression, suicidality risk in the postpartum period, and the additional vulnerability for younger mothers, an open pilot is most scientifically appropriate. Data will be collected at two timepoints to investigate preliminary directionality of effects on depressive symptoms and suicidality, alongside other quantitative and qualitative data ascertaining study safety, feasibility, and acceptability.

Next-Generation Therapies

Lluís Miquel Rio, Ph.D., Institute of Biomedicine & Biotechnology of Cantabria, Spain, seeks to advance understanding of the neurobiology of suicidal behavior (SB) in adolescents. Dr. Rio hypothesizes that adolescents with SB will exhibit a distinct miRNA expression profiles in their circulating extracellular vesicles (EVs) compared to healthy controls, potentially revealing changes in brain function associated with SB pathophysiology. This project will test whether administration of EVs isolated from adolescents with SB to mice will induce behavioral and molecular changes in brain circuits relevant to SB. The team will isolate and characterize plasma EVs from 30 adolescents (ages 12–17 years) with SB and 30 age- and sex-matched controls. To investigate the functional role of dysregulated miRNAs, isolated EVs will be used to develop a preclinical mouse model.

Basic Research

Reza Rahimian, Ph.D., McGill University, Canada, notes there is a life-course association between childhood adversity and elevated peripheral inflammatory markers in adulthood, suggesting inflammation as a possible mediator linking adverse experiences in early life to psychopathology in adulthood. The choroid plexus (CP), a highly vascularized tissue that produces cerebrospinal fluid, is an interface between peripheral and central immune responses that participates in regulating neurogenesis, inflammatory signals, and plasticity. It is among the least studied structures in psychiatric conditions, particularly in depression. This project investigates the cellular and molecular profiles of the CP of the lateral ventricle in postmortem samples from age- and sex-matched depressed suicide victims with and without a history of childhood abuse, and psychiatrically healthy controls (3 groups; n=32 per group, with at least 50% of subjects female). The goal is to expand what is known about depression pathology in suicide subjects who were exposed to severe childhood adversity.

Basic Research

Institutions of the 2025 Young Investigators, at the time of grant award

Aarhus University, Denmark

Adelphi University

Baylor College of Medicine (2)

Boys Town National Research Hospital

The Broad Institute of MIT

Butler Hospital

Centre for Addiction and Mental Health, University of Toronto, Canada

Centre National de la Recherche Scientifique, France

Charité - University Medicine Berlin, Germany

Children's National Medical Center

Chinese Academy of Sciences, People's Republic of China

Columbia University (3)

Cornell University

Creedmoor Psychiatric Center

Dell Medical School, University of Texas at Austin

Drexel University

Emory Clinic

Emory University

ESPCI Paris, France

Feinstein Institute for Medical Research/Northwell Health

Fundacio Institut Mar d'Investigacions Mediques, Spain

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Massachusetts Institute of Technology

Mayo Clinic, Jacksonville

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McLean Hospital (2)

McMaster University, Canada

Medical University of South Carolina

Montana State University

National Institute of Mental Health (NIMH/NIH) (2)

New York University (4)

New York University Medical Center

New York University School of Medicine (2)

Northwestern University (4)

Ocean State Research Institute, Inc.

Orygen, Australia

Princeton University

Psychiatric Center Ballerup, Mental Health Services of the Capital Region of Denmark

Research Foundation for Mental Hygiene, Inc./NKI (3)

Research Foundation for Mental Hygiene, Inc./NYSPI (2)

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