BRAIN & BEHAVIOR RESEARCH FOUNDATION

2021 Young Investigators

BRAIN & BEHAVIOR
RESEARCH FOUNDATION
Awarding **NARSAD** Grants

"Breakthroughs in science cannot be predicted. Sometimes researchers start with one idea but are led in a different direction by their results or the results of other scientists. BBRF Young Investigators represent the next generation of scientists who we expect will make great strides in basic research, new technologies, next-generation therapies and early intervention techniques. This is the kind of out-of-the-box research that will offer the best hope for improved treatments, cures, and methods of prevention for our loved ones."

October 2021

We are pleased to present the 2021 Young Investigator grantees of the Brain & Behavior Foundation. This extraordinary group of scientists represents a broad range of the best ideas in innovative brain research.

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.

This year, the Foundation's Scientific Council, led by Dr. Herbert Pardes and comprised of 176 world-renowned scientists with expertise in every area of brain research, reviewed more than 780 applications and selected the 150 meritorious research projects summarized in the pages that follow.

Many of our Young Investigator grantees are pursuing basic research projects. Others are specifically focusing on novel ideas for therapies, diagnostic tools, and new technologies. These research projects will provide future insights and advances that will help move the fields of psychiatry and neuroscience forward.

Since BBRF's inception, the selection of Young Investigator Grantees has been based upon our Scientific Council members' assessment of projects that represent "the best science possible."

A number of this year's projects focus on early development of the brain, beginning in the fetal period and extending into the months and years following birth. This critical time of rapid brain growth is also the period during which many researchers seek to trace abnormalities thought to underlie many brain and behavior disorders. How does early brain development impact the emerging ability to recognize and meaningfully engage with other individuals? How do certain stressful experiences at the dawn of life impact connectivity in brain areas involved in regulating social interaction? These are just a few of the "developmental" questions being pursued by 2021 Young Investigators.

Some grantees are addressing very timely issues. One project, for instance, seeks to discover whether major depression is associated with impaired response to COVID-19 vaccines. Another grantee project seeks to assess how racial discrimination may heighten risk of future depression in adolescent African-American girls with mothers who have been clinically depressed. Another project assesses the impact of stress upon refugees and victims of war trauma.

A few other intriguing 2021 Young Investigator projects include: probing a possible relationship between "screen time" and emotional and cognitive problems in adolescents; the possible role of dietary supplements to improve the health of women with the eating disorder anorexia nervosa who are pregnant; testing a biofeedback-based therapy to treat PTSD in young people; testing a smartphone app which collects data that could help prevent suicidal behaviors.

BBRF is a collaboration between our donors and scientists. A grant awarded to a Young Investigator not only funds an innovative research project, but is also an investment in the career of a promising young scientist. We are proud to report that since 1987 we have provided more than $430 million in more than 6,200 research grants to more than 5,100 scientists globally. **100% of every dollar donated for research is invested in our research grants.** Our operating expenses are covered by separate foundation grants.

With your support we can continue to fund scientists on the path to discovery for better treatments, cures, and methods of prevention for psychiatric illness so that more people can live full, happy, and productive lives.

Sincerely,

Jeffrey Borenstein, M.D.
President & CEO

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"For more than 30 years BBRF has focused on funding visionary young investigators who see opportunities in forging new paths. By supporting ground-breaking work BBRF helps set the trajectory of brain research and builds momentum toward discoveries that we expect will yield advances in neuroscience. These grants enable outstanding scientists to pursue bold new ideas to answer important questions or help identify potentially game-changing targets for treatment. The awards function as seed funding for new directions which would otherwise be highly unlikely."

Herbert Pardes, M.D.

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SINCE 1987

AWARDED
6,200+
GRANTS

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GRANTS

THE 2021 YOUNG INVESTIGATOR GRANTEES

The Foundation is pleased to announce over $10.3 million in 150 new two-year grant awards to support the work of promising young scientists with innovative ideas in mental health research.

788
YOUNG INVESTIGATOR APPLICATIONS

150
YOUNG INVESTIGATOR GRANTS AWARDED

$10.3
MILLION AWARDED IN YOUNG INVESTIGATOR GRANTS

RESEARCH CATEGORIES

Basic Research (109 Grants)
To understand what happens in the brain to cause mental illness

Next-Generation Therapies (30 Grants)
To reduce symptoms of mental illness and ultimately cure and prevent brain and behavior disorders

Diagnostic Tools/Early Intervention (24 Grants)
To recognize early signs of mental illness and treat as early as possible

New Technologies (15 Grants)
To advance or create new ways of studying and understanding the brain

About 73 percent of the projects funded are **basic research**, the wellspring of innovation in brain research, as in all sciences.

About 20 percent of the 2021 grants fund projects that specifically aim to develop **next-generation therapies.**

About 16 percent of the projects funded are **diagnostic tools/early intervention** that aim to prevent brain and behavior disorders.

About 10 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 percent of grantees are from the United States (120 grantees). Twenty percent of grantees come from 13 other countries (30 grantees): Australia, Austria, Canada, Denmark, France, Germany, Israel, Italy, Portugal, Republic of China (Taiwan), Switzerland, The Netherlands, United Kingdom.

INVENTORY OF PROJECTS: 2021 GRANTEES

(sorted by category; some projects are relevant in multiple categories)

ADDICTION / SUBSTANCE-USE DISORDERS

ATTENTION-DEFICIT HYPERACTIVITY DINSORDER (ADHD)

ANXIETY DISORDERS

AUTISM SPECTRUM DISORDER (ASD)

BIPOLAR DISORDER

BORDERLINE PERSONALITY DISORDER

DEPRESSION

EATING DISORDERS

OBSESSIVE-COMPULSIVE DISORDER (OCD)

PSYCHOSIS

POST-TRAUMATIC STRESS DISORDER (PTSD)

SCHIZOPHRENIA

SUICIDE PREVENTION

BIOLOGY OF THE BRAIN

These projects focus on how the brain works.

OTHER DISORDERS

Epilepsy

Fragile X syndrome

Gender Dysphoria

Tourette syndrome

THE 2021 BBRF YOUNG INVESTIGATOR GRANTEES
(in alphabetical order)

Mohsin Saeed Ahmed, M.D., Ph.D., Research Foundation for Mental Hygiene, Inc./Nathan Kline Institute, will use techniques for functionally imaging the activity of large populations of brain cells, along with simultaneous, targeted manipulations of defined elements in these populations, to gain deeper biological insights and uncover causal relationships between brain circuit activity and fear memory behaviors. The research seeks to identify brain circuit activity mechanisms underlying memories that link events in time, with the long-term goal of identifying potential clinical targets for the treatment and prevention of psychopathology caused by the dysregulation of cognition, fear, and/or traumatic memories.

Basic Research

Ivan Alekseichuk, Ph.D., University of Minnesota, will apply traveling-wave transcranial alternating current stimulation (tACS) in schizophrenia patients, in a double-blinded, placebo-controlled, randomized trial, to test its applicability as a therapeutic to improve cognitive performance. The stimulation will focus on the frontoparietal network, which plays a crucial role in cognitive function. Individual computational models will be prepared for each study participant using structural MRI to optimize and personalize the stimulation. The result could be a novel methodology for alleviating cognitive impairment and improving the quality of life in people with schizophrenia.

Next-Generation Therapies

New Technologies

Neal D. Amin, M.D., Ph.D., Stanford University, hopes to build upon recent advances in human induced pluripotent stem cell (hiPS) technology that has enabled the generation of patient-derived neural cells within self-organizing 3D cell cultures called organoids. This project concerns human brain assembloid preparations obtained by fusing organoids resembling distinct brain regions—in this case, assembloids that model spatial patterning of neural progenitors and neural connectivity across midline brain structures. These will be used to investigate normal and pathological midline development and phenotypes and mechanisms of 22q11.2 deletion syndrome, a genetic syndrome which is a risk factor for psychosis and associated with defects in midline brain structures and connectivity.

New Technologies

Basic Research

Liza Ashbrook, M.D., University of California, San Francisco, is studying the possible genetic basis of resilience in individuals who need less than 6.5 hours of sleep per night (familial natural short sleepers, or FNSS). Identifying those with FNSS has led to the discovery of multiple genes associated with the trait: DEC2, GRM1, ADRB1 and NPSR1. Dr. Ashbrook will test the hypothesis that resilience is associated with FNSS by examining resilience in a cohort of FNSS individuals and unaffected family members. A related mouse model might provide a unique angle to study the neurobiology of resilience, supporting the goal of providing insight into ways of boosting resilience and reducing the risk of PTSD and depression following repeated stressors.

Basic Research

Anita Ellen Autry, Ph.D., Albert Einstein College of Medicine, studies neurobiological mechanisms underlying postpartum depression (PPD). She will follow up on her past discovery that urocortin-3 expressing neurons in the perifornical area of the hypothalamus (PeFAUcn3) are involved in infant-directed behavior, and are sensitive to stress. Focusing on neurons expressing corticotrophin releasing factor receptor 2 (CRFR-2), which in the posterior amygdala is essential for social and mood-related behaviors, the team aims to determine the role of CRFR-2 expressing neurons in the posterior amygdala in parenting and mood-related behaviors by recording and manipulating CRFR-2 expressing neurons in male and female mice during social and mood-related behaviors.

Basic Research

Estefania Pereira Cardoso Azevedo, Ph.D., The Rockefeller University, has identified a specific population of neurotensin (NT)-expressing neurons in the lateral septum (LSNT), a brain area involved in emotional regulation, that are selectively activated by acute stress and suppress eating via projections to the hypothalamus. Over 70% of LSNT neurons co-express a receptor, GLP1R, suggesting a possible mechanism involved in the regulation of LSNT activity and behavior in response to stress. The team now seeks to identify the cell type-specific circuit involved in GLP-1R signaling and stress integration in the lateral septum by LSNT neurons and determine the requirement of GLP-1 signaling in LSNT neurons for stress integration, using acute and chronic stress mouse models. This could contribute to understanding maladaptive eating behaviors and other behaviors regulated by stress such as anxiety and motivation.

Basic Research

Nicholas L. Balderston, Ph.D., University of Pennsylvania, has discovered that neuromodulation with TMS brain stimulation in the frontoparietal attention network (FPN) can causally modulate levels of anxiety in a healthy volunteer anxiety model (unpredictable threat). This forms the basis for the current work, which seeks to examine the role of the FPN in the expression and regulation of anxiety by measuring the changes in brain activity induced by FPN stimulation. By combining threat, fMRI, TMS, and psychophysiology, this study could generate evidence for a causal role of FPN imbalance in anxiety regulation, with evidence of target engagement through simultaneous TMS/fMRI. Such data could lay the groundwork for a clinical trial examining the effect of FPN stimulation on anxiety in generalized anxiety disorder (GAD), which could become a novel evidence-based TMS treatment for GAD.

Next-Generation Therapies

Pia Baldinger-Melich, M.D., Ph.D., Medical University of Vienna, Austria, is exploring the concept that an interaction of various factors related to neuronal plasticity contributes to the antidepressant effects of ECT. To learn about ECT's mechanism of action, the team will deliver 8 ECT treatments over 4 weeks to 30 ECT-qualifying patients. MRI will assess neuroanatomical (gray and white matter) and neurochemical changes induced by the treatment. Cerebrospinal fluid and blood samples will be gathered before and after the ECT course to measure markers of neurogenesis, neurodegeneration, neuroinflammation and genetic markers potentially influenced by the treatment. Machine-learning will be used to identify predictive markers of ECT response out of the gathered data. Results could help establish individualized ECT for major depression patients by delineating predictors of ECT response.

Next-Generation Therapies

Marjolein E.A. Barendse, Ph.D., University of Oregon, suggests that by unraveling developmental differences in potential bidirectional associations between connectivity and depression, knowledge will be gained relevant for the timing of prevention and intervention efforts. The team aims to (1) establish whether associations between brain connectivity and depressive symptoms in adolescent girls are unidirectional or bidirectional, and (2) determine to what extent the directionality and strength of associations between connectivity and depressive symptoms is dependent on age or pubertal stage. They will use an ongoing study collecting 4 time points of depressive symptoms, brain white matter imaging, and functional MRI from 174 adolescent girls. The hypothesis is that determining brain developmental risk factors in this sensitive developmental period can help identify targets for treatment.

Basic Research

Daniel S. Barron, M.D., Ph.D., Brigham and Women's Hospital and Harvard University, notes that because the interaction of depression, anxiety, and pain remains unclear, treatments targeting the brain circuits that give rise to these phenomena can't be developed with precision. The aim is to help bridge the divide between an individual patient's experience and relevant neurobiology. The team will use data from the U.K. Biobank with the aim of demonstrating that a person's report of depression and anxiety can be summarized as a quantitative depression-anxiety phenotype. In this way they aim to measure how an individual's pain changes as a function of their depression-anxiety phenotype. Second, they aim to define brain circuits that predict individual differences in depression-anxiety and pain phenotypes. This could inform future analyses of neuromodulatory treatments, both circuit-based (e.g., brain stimulation) and pharmacological.

Basic Research

Nicole M. Benson, M.D., McLean Hospital, notes that 2.6-20.8 per 100,000 persons per year experience their first episode of mania (FEM) or new-onset bipolar disorder. Determining the timing of onset of bipolar disorder is challenging given the nature of the disease. A method for identifying new-onset patients would provide an opportunity to start interventions earlier than has historically been feasible. This project will use multiple large, linked datasets, including clinically detailed electronic health records, to develop and validate prediction models to identify and define the early phenotype of patients with FEM and early bipolar disorder. It will also examine patterns of subsequent care received by subjects predicted to have FEM.

Diagnostic Tools/Early Intervention

Antoine Besnard, Ph.D., Institute of Functional Genomics, Université de Montpellier, France, notes that alleviating avoidance symptoms is a prerequisite to improving outcomes in exposure therapy for PTSD. But active avoidance and its neural correlates remain poorly understood. This project will investigate whether the hippocampus and its downstream partner the lateral septum prevent persistent place avoidance by inhibiting the activity of the ventral striatum. It is hoped the findings can guide functional brain imaging studies in order to optimize treatment response in patients suffering from PTSD, including deep-brain stimulation protocols and brain-machine interfaces, to curb excessive avoidance behavior in PTSD.

Basic Research

Diagnostic Tools/Early Intervention

Aparna Bhaduri, Ph.D., University of California, Los Angeles, is interested in autism and other neurodevelopmental and neuropsychiatric disorders which begin to develop during early stages of brain development. The team will use

organoids to learn more, hoping to test which internal signaling pathways will create a more uniform prefrontal cortex organoid, as well as whether outside cues can be used to refine this entity. The experiments will help the team describe how the prefrontal cortex arises, and in the process, better understand where along that developmental trajectory the development of brains in which autism occurs might be different. Additionally, they hope to improve the cortical organoid model to be more relevant for other studies of area-specific disorders.

Basic Research

New Technologies

Wenjie Bian, Ph.D., Stanford University, will investigate the contribution of specific sleep components in shaping social behavior and whether increasing a particular component (sleep improvement, SI) can ameliorate social deficits in a relevant mouse model previously developed. The team has identified dopamine (DA) neurons in the ventral tegmental area (VTA) as a key player and found that the social novelty-dependent activation of these neurons is impaired and their projection profile is altered in animals with social deficits. The new experiments will delve into the circuit mechanisms underlying the developmental role of sleep and focus on the VTA-DA neurons and their projections in two major output targets, the nucleus accumbens (NAc) and prefrontal cortex (PFC).

Basic Research

Ana-Clara Bobadilla, Ph.D., University of Wyoming, notes that the opioid epidemic has included the use of opiates in combination with other types of drugs, i.e., polysubstance use. This project will explore the hypothesis that neurobiological mechanisms underlying drug-seeking in polysubstance use rely on segregated networks of neurons in the nucleus accumbens core which undergo selective plasticity. Specifically, the team seeks to discover whether different classes of drugs of abuse operate in similar or distinct ways at the ensemble level. The team will 1) develop a mouse model of polysubstance use and relapse; 2) establish how reward-specific neuronal networks relate to each other within the same brain region; 3) determine if structural synaptic plasticity is reward-specific.

Basic Research

Kerem Böge, Ph.D., Charité University Medicine Berlin and Freie Universität Berlin, Germany, is exploring how improvements in negative symptoms and empathy can be made in schizophrenia patients through mindfulness-based group therapy (MBGT). In tests, it has enhanced oxytocin (OXT) associated with heightened empathy, pro-social behavior, and reductions in negative affect. This proof-of-concept randomized study involving 60 participants seeks to (1) examine the effect of MBGT on OXT levels in blood serum and saliva as well as empathic cognitions and behavior; (2) explore whether polygenic risk scores (PRS) for cognitive empathy and self-reported empathy can predict empathy levels; (3) investigate whether empathy and genetic variations in OXT receptors can predict MBGT outcomes and OXT levels in blood and saliva.

Next-Generation Therapies

Kelsey A. Bonfils, Ph.D., University of Southern Mississippi, notes that up to 80% of people with schizophrenia spectrum disorders experience significant sleep disturbance, which is linked to heightened symptoms, suicide risk, reduced well-being, and impaired functioning. This project explores the relationship between sleep disturbance and social cognition. The team will examine the complex daily associations of sleep disturbance and social cognition and behavior using a combination of actigraphy and ecological momentary assessment (EMA) methods in 25 people diagnosed with schizophrenia spectrum disorders and 25 healthy control participants. They expect people with schizophrenia-spectrum disorders will experience greater sleep disturbance than healthy control participants as well as lower social cognitive abilities and greater social isolation; also, that sleep disturbance will be linked to reduced and/or unsatisfactory social interactions and behavior the following day.

Basic Research

Gabriel D. Bosse, Ph.D., University of Utah, who studies opioid use disorder (OUD), notes that traditional animal models are sometimes not optimal for drug discovery efforts and that zebrafish represent a novel, tractable alternative to existing mammalian models. The lab previously generated a novel opioid self-administration assay using adult zebrafish, which made possible the discovery that an inhibitor of the proton exchanger NHE1 reduces opioid intake without affecting locomotion or feeding behavior. NHE1 is an important regulator of intracellular pH at the presynaptic cleft. This project seeks in part to elucidate the role of pH homeostasis in opioid addiction, by measuring the impact of long-term opioid exposure on intracellular pH regulation and on expression of NHE1 and other pH regulators. The work could help explain the role of neuronal pH homeostasis in opioid use disorders and could lead to the development of novel therapeutics.

Basic Research

Chloe C. Boyle, Ph.D., University of California, Los Angeles, wants to identify mechanisms that contribute to heightened vulnerability to depression in younger females. One candidate mechanism is elevated inflammation, and past work in the lab has shown that an acute inflammatory challenge with low-dose endotoxin reduces response to monetary

reward cues in reward-related brain regions in female, but not male, adults. It is not known if female vulnerability to inflammation-induced reward deficits persists across the lifespan. The team will conduct a double-blind, placebo-controlled, inflammatory challenge with endotoxin in premenopausal and postmenopausal women to evaluate whether younger females are more vulnerable to endotoxin-induced reward deficits but equally likely to exhibit activation of a response that includes up-regulation of proinflammatory genes in circulating immune cells, relative to older females.

Basic Research

Katharine K. Brewster, M.D., Research Foundation for Mental Hygiene, Inc./Nathan Kline Institute, studies age-related hearing loss (HL), which has been associated with cognitive decline, dementia, and major depressive disorder (MDD). She notes that HL is the largest potentially modifiable risk factor for cognitive decline, accounts for as many as 8% of new dementia cases, and triples risk for MDD, itself a potent risk factor for cognitive decline. The project will comprehensively assess older adults with HL to examine the brain, emotional, social, and cognitive mechanisms by which HL is linked to affective dysregulation and MDD. Data from this pilot study could provide vital mechanistic information to inform future research aimed at identifying novel therapeutic targets for MDD and cognitive dysfunction.

Basic Research

Isaac Cervantes-Sandoval, Ph.D., Georgetown University, notes that anxiety and PTSD are associated with problems in generalization. The team will take advantage of new insights into the genetic and circuit mechanisms regulating forgetting in fruit flies to test the hypothesis that forgetting is required for fear generalization. The project involves behaviorally dissecting the nature of a generalized memory. This could help reveal whether long-term aversive memories are generalized as appetitive memories; whether generalized memories are exclusively long-term memories; whether memory generalization is protein synthesis-dependent; and a host of other research questions. The project will make use of in vivo calcium imaging to determine synaptic changes that occur during generalization, and the impact upon these changes of bidirectional modulation of forgetting.

Basic Research

Lucas M. Cheadle, Ph.D., Cold Spring Harbor Laboratory, is interested in mechanisms underlying synapse elimination. Interactions between the immune system and the nervous system are increasingly thought to regulate synapse elimination in the healthy brain and to contribute to neurodevelopmental and psychiatric disorders such as schizophrenia. Dr. Cheadle has discovered a novel role for signaling between the cytokine TWEAK and its receptor Fn14 in synapse elimination. He found that microglia express TWEAK during postnatal development, and that microglia-derived TWEAK binds Fn14 at synapses to promote their elimination. The current project will test the hypothesis that TWEAK-Fn14 signaling between microglia and neurons contributes to the inappropriate removal of mature synapses in mice subjected to maternal immune activation, a mouse model that recapitulates key features of schizophrenia.

Basic Research

Pao-Huan Chen, M.D., Taipei Medical University, Republic of China, notes that cardiac function is impaired in young adults with bipolar disorder, independent of conventional cardiovascular risk factors. This project seeks to discover peripheral biomarkers to inform the pathogenesis of cardiac dysfunction specific to patients with bipolar disorder. 90 participants <40 years of age will be enrolled, with the hope of finding a miRNA signature that distinguishes bipolar disorder patients and controls. The study will also investigate whether there are overlapping miRNAs and related target genes and pathways that are associated with bipolar disorder and pre-clinical cardiac dysfunction. The aim is to open a window to investigate pathophysiological mechanisms underlying the development of premature cardiovascular disease in bipolar disorder.

Diagnostic Tools/Early Intervention

Shuo Chen, Ph.D., New York University, notes that patients with autism often have a lower novelty-seeking trait, believed to be rooted in a difference in how the brain orients to novel, changing sensory stimuli. Environmental enrichment has aided the treatment of autism by enhancing cognition and facilitating neurodevelopment. Despite its importance, little is known about which brain regions and what neural circuits are responsible for novelty processing. This work focuses on an understudied region in the hypothalamus, the supramammillary nucleus (SuM), which may be a novelty hub in the brain. The team will use their newly developed near-infrared (NIR) upconversion optogenetics technology to optogenetically stimulate the SuM neurons. When applied to an autism mouse model, the hope is that NIR SuM stimulation will enhance novelty signaling and alleviate autism symptoms.

Basic Research

New Technologies

Lois W. Choi-Kain, M.D., McLean Hospital, notes various problems in connecting individuals with borderline personality disorder (BPD) with treatments that can help them. She suggests that a vast majority of individuals can access existing psychoeducational videos about BPD and self-assessments online. The effects of using these free publicly

available resources have never been studied. This project aims to design a suite of online videos for psychoeducation in addition to a reliable protocol for digital phenotyping of self-reported symptoms, neuropsychological performance, and vocal variation; and to test the effects of these online resources as a potential clinical prescription that requires low-effort and little additional training for treating clinicians for wider dissemination.

Diagnostic Tools/Early Intervention
Next-Generation Therapies

Changuk Chung, Ph.D., University of California, San Diego, is studying focal cortical dysplasia (FCD) and hemimegalencephaly (HME), pediatric brain disorders involving cortical malformation that are frequently accompanied by intractable epilepsy. FCD also shows comorbid neuropsychiatric disabilities including autism, intellectual disability, depression, anxiety, ADHD, bipolar disorder, psychosis, and personality disorders. Dr. Chung hypothesizes that there are novel genes other than already recognized mTOR signaling genes which are involved in the etiology of FCD. This project seeks to discover them, and to associate clinical information with genotypes to dissect subtypes of FCD.

Basic Research

Jonathan A. Coleman, Ph.D., University of Pittsburgh, notes that 4% of people will develop a seizure disorder, making epilepsy one of the most common neurological disorders. Neuropsychiatric drugs which target transport proteins are important therapeutics. Synaptic vesicles (SVs) store neurotransmitters that are released into the synapse and the contents of SVs are organized by a system of transport proteins. Recent studies have suggested an involvement of SV2A in schizophrenia and Alzheimer's and Parkinson's diseases. Thus far however, it has not been possible to determine the structure of SV2A. The aim of this project is to elucidate the molecular function, architecture, and high-affinity drug binding sites of SV2A by determining single particle cryo-EM structures.

Basic Research

Jonathan R. Coleman, Ph.D., King's College London, UK, notes a general problem regarding DNA variations: many DNA regions associated with mental disorders contain many variants, but only a few of these variants are likely to have a biological effect that increases the risk of developing mental disorders. This project seeks to increase our understanding of how variants that are associated with mental disorders act in the brain. The approach is to combine data from studies of variants associated with mental disorders and studies examining brain cells in order to gain insights into how the action of variants in the brain increases a person's risk for developing a mental disorder.

Basic Research

Guusje Collin, M.D., Ph.D., Radboud University, The Netherlands, notes the paucity of early intervention options for youth with mental health symptoms in the mild or subthreshold range. As a result, intervention is often postponed until more serious mental problems arise, wasting crucial opportunities for early intervention. This project utilizes insight on brain and behavioral trajectories of mental illness to develop a neurobiologically informed early intervention for at-risk youth. Given that internalizing problems are a common precursor of mental illness development and that associated neural circuits including the default mode network are sensitive to mindfulness-based intervention, the team will test a mindfulness-based fMRI neurofeedback. Using this method, they will train at-risk youth to modulate their own brain activity with the aim of alleviating early complaints and, ultimately, attenuating progression into serious mental illness.

Diagnostic Tools/Early Intervention
Next-Generation Therapies

Nuria Daviu Abant, Ph.D., University of Calgary, Canada, has shown that corticotropin-releasing hormone (CRH) cells in the paraventricular nucleus of the hypothalamus (PVN) encode stress controllability and control future behaviors. CRH neurons control the balance between active and passive coping strategies, which can perhaps be shifted simply by altering the activity of CRH neurons using optogenetic manipulations. This project, using laboratory mice, will test whether the changes in the activity of CRH neurons caused by uncontrollable stress, which results in a passive coping strategy, can be reversed to an active coping strategy by exposing individuals to controllable stress.

Basic Research
Next-Generation Therapies

Mickaël Degoulet, Ph.D., Aix-Marseille University/CNRS, France, notes that identifying vulnerable individuals before they transition to more harmful patterns of drug use is a key challenge for addiction research. He has shown that some rats display an abnormal increase in low-frequency oscillations of the subthalamic nucleus (STN) during loss of control over cocaine intake. When exposed to negative consequences of cocaine seeking (a mild foot-shock), these animals exhibit a compulsive trait, as they keep seeking cocaine despite the punishment. This predictive biomarker of compulsivity could potentially allow the early detection of vulnerable individuals and thus is further investigated in this project using recording electrodes implanted within the STN to monitor local field potentials, while cortical activity of the prefrontal or motor areas will be recorded with electrocorticographic measures.

Diagnostic Tools/Early Intervention

Javier Diaz Alonso, Ph.D., University of California, Irvine, is studying the GluA1 gene, associated with schizophrenia. GluA1 knock-out mice display severe deficits in synaptic plasticity and altered cognitive function. This project tests a new knock-in mouse model in which the GluA1 cytoplasmic tail is truncated (ΔCTD GluA1). Surprisingly, no major deficits in hippocampal synaptic transmission and plasticity were found in these mice. However, they display some of the behavioral phenotypes caused by GluA1 genetic ablation. The project will explore the synaptic mechanisms, brain regions, and neural circuits where the GluA1 CTD contributes to schizophrenia-related behavioral phenotypes. It is hoped that this will expand our understanding of basic principles governing excitatory synaptic transmission and plasticity and reveal the neurobiological substrate of some of the behavioral traits characterizing schizophrenia.

Basic Research

Jennifer Jane Donegan, Ph.D., Dell Medical School, University of Texas at Austin, seeks to extend results obtained in healthy animals to determine if targeting specific microcircuits can alleviate discrete behavioral deficits associated with schizophrenia in rodents exposed to maternal immune activation (MIA), a known risk factor for schizophrenia. The circuits connect the ventral hippocampus (vHipp) and the nucleus accumbens (NAc), manipulation of which in rodents has improved behavioral correlates of positive symptoms. The research aims to determine if the structure and function of vHipp microcircuits is altered by MIA. It will then test the hypothesis that manipulating specific vHipp microcircuits will alleviate discrete schizophrenia-like behavioral deficits in the MIA model, and identify potential molecular candidates for targeting these circuits.

Basic Research

Stephanie Dooves, Ph.D., Vrije Universiteit Amsterdam, The Netherlands, will combine stem cell-culture techniques with measurements of neuronal electrical activity and in-depth analysis of neuronal connections to develop a system to study human brain communication in psychiatric disorders. She will compare neuronal communication from patients with a genetic form of autism with controls. The experiments will include measurements in patient-derived cells of brain networks with and without treatment with drugs that are known to improve neuronal activity, to test how communication parameters are changed.

Basic Research

Xiaoming Du, Ph.D., University of Maryland, is studying non-invasive brain stimulation in individuals with schizophrenia spectrum disorders. Dr. Du will recruit patients with refractory auditory hallucination (AH) symptoms and randomize them to receive either rTMS over left dorsomedial prefrontal cortex (dmPFC), inhibitory rTMS over left dmPFC or left temporoparietal junction (TPJ). The inhibitory rTMS over TPJ and dmPFC will work as active controls to demonstrate whether a new strategy of rTMS over dmPFC is superior to the existing rTMS treatment at TPJ and/or other rTMS approaches over dmPFC in terms of improving AH. This project aims to address a gap in the field by applying rTMS to prefrontal cortex for AH treatment. Results of the investigation may suggest a better rTMS treatment strategy for auditory hallucinations in patients with schizophrenia.

Next-Generation Therapies

Dominic B. Dwyer, Ph.D., Ludwig Maximillian University, Germany, will address the problem of "missing heritability"—as yet unaccounted for genetic liability—in early psychosis by focusing on epigenetic processes influenced by the environment and which can regulate how genes are expressed. Epigenetic regulation can be measured using blood-derived DNA methylation, which the team will calculate from existing DNA samples in a large consortium project called PRONIA. They seek to determine if an abnormal methylomic signature can be found in the "clinical deficit" subgroup they have previously identified. A second phase involves using a larger sample of PRONIA cases to discover new epigenetic subgroups. Advanced statistical methods will be used to join the clinical, brain, and epigenetic subgroup levels and search for a "multilevel deficit" subgroup.

Basic Research

Amanda L. Elliott, M.D., Ph.D., Massachusetts General Hospital and Harvard University, will use a large genetic dataset to address the question of cardiometabolic disease risk in schizophrenia. The team will assess the relationship between genetic risk for schizophrenia and the age of onset of diabetes to determine any relation with antipsychotic medication use, a known risk for diabetes in this population. They will also interrogate the population for genetic variants associated with the metabolic response to starting an antipsychotic medication after a schizophrenia diagnosis. And they will use a 10-year pooled cardiovascular risk equation, adapting it to include antipsychotic medication use data and polygenic risk for disease, to see if this improves prediction of cardiovascular disease in schizophrenia.

Diagnostic Tools/Early Intervention

Ian Thomas Ellwood, Ph.D., Cornell University, has developed a way to record neural activity in PFC-amygdala neurons while monitoring PFC dopamine, via a virtual reality environment under a two-photon microscope that permits simultaneous imaging of neural activity and PFC dopamine as mice virtually navigate on a spherical treadmill. To study

anxiety, the team developed a task in which mice run through a virtual bright open area to a dark sheltered area to get a water reward. They seek to measure how the concentration of dopamine and neural activity in the PFC-amygdala projection are correlated at different levels of environmental threat. They will also stimulate or silence the dopamine system to see how this affects neural activity and induces or suppresses anxious behavior. The aim is to reveal the role that PFC dopamine plays in either increasing or decreasing PFC inhibition of the amygdala. This could facilitate development of new approaches to treat anxiety through selective manipulation of the prefrontal dopamine system.

Basic Research

New Technologies

Ben B. Engelhard, Ph.D., Technion-Israel Institute of Technology, Israel, will address the following questions: What are the functional and anatomical characteristics of dopamine neurons active during the presentation of social stimuli? What are the differences in the activity of VTA dopamine neurons between wild-type and and autism spectrum disorder (ASD)-model mice during the presentation of social stimuli? Can social impairments in ASD-model mice be rescued by the activation of specific functional subpopulations of VTA dopamine neurons? Success in this study will further an understanding of how dopamine dysfunction contributes to social deficits in ASD and could guide the development of novel targeted therapeutics for ASD.

Basic Research

Angela Fang, Ph.D., University of Washington, will test the effect of intranasal oxytocin and matching placebo on brain mechanisms underlying vicarious extinction learning. 25 adults with social anxiety disorder and 25 healthy control participants will perform a task that involves three phases: (1) a standard social fear acquisition procedure, followed by (2) a vicarious extinction and (3) fear reinstatement test procedure while being scanned. Participants will receive oxytocin or placebo prior to the extinction phase. Results could determine if social safety learning improves fear regulation in social anxiety disorder, and whether oxytocin enhances this effect. The goal is to advance novel therapeutic strategies for patients with anxiety disorders by leveraging pharmacology to target social learning processes.

Next-Generation Therapies

Shannon Farris, Ph.D., Virginia Polytechnic Institute and State University, notes that Fragile X syndrome, the most common form of inherited intellectual disability, accounts for as much as 5% of autism cases. It is caused by the loss of the fragile X mental retardation protein (FMRP), a ubiquitous RNA binding protein that regulates 4% of the brain transcriptome. FMRP associates with target RNAs in particles, called fragile x granules, that restrict RNA translation until specific cues are encountered. This FMRP-mediated translational regulation is required for synaptic modifications underlying learning and memory. The aim of this research is to learn how FMRP associates with its hundreds of target RNAs in intact neural circuits. The team will use multiplexed, super resolution imaging to simultaneously investigate 12 FMRP granule components and their learning-induced remodeling in intact neuronal circuits.

Basic Research

New Technologies

Julien Ferent, Ph.D., INSERM, France, notes that organization of the cortex takes place during the development of the embryonic brain in a series of precise biological events (generation of cells, positioning of these cells, connection of these cells). Neurodevelopmental disorders, including autism spectrum disorder and ADHD, arise when one or several of these steps are disrupted. In cell differentiation in the early brain, cells change their behavior in response to molecules present in their environment, among these, morphogens. This research will investigate how neural progenitors modulate their responses to morphogens, to induce required behaviors for the formation of the brain architecture. The work will involve comparing mouse and human brain development using human embryos and organoids.

Basic Research

Joana Ferreira, Ph.D., Center for Neuroscience and Cell Biology, Portugal, will study the interaction between two major synaptic players, the GluN2B subunit of N-methyl-D-aspartate type receptors (NMDARs) and the presynaptic molecule Neurexin2. Given their crucial role in brain development and synaptic plasticity, this interaction is thought to have a major impact in neurotransmission. Both proteins have been highly associated with neuropsychiatric disorders including schizophrenia. The molecular complex GluN2B-Neurexin2 will be thoroughly investigated in this project using a combination of biochemical, confocal, and state-of-the-art super-resolution imaging and electrophysiology techniques. Consequences of interfering with this interaction for synaptic physiology and animal behavior will be comprehensively examined.

Basic Research

Anna J. Finley, Ph.D., University of Wisconsin, notes that individuals who show an abnormally slow recovery from emotional upsets combined with blunted initial reactivity to and reduced subsequent savoring of positive events may be at a higher risk for anxiety and depression, particularly after experiencing stress. By parsing patterns of neural activity

during emotional states, it is possible to predict the strength of emotional states experienced while viewing emotional images, as well as probe individual differences in the amount of emotional "spill-over" when processing unrelated neutral stimuli. The team will utilize data from 242 individuals to test neural signatures of positive and negative emotions. The signatures will be applied to a third sample of 42 participants with neuroimaging data collected shortly before the COVID-19 pandemic to identify individuals most at-risk of adverse mental health impacts.

Diagnostic Tools/Early Intervention

Bart N. Ford, Ph.D., Laureate Institute for Brain Research, will recruit up to 200 volunteers with major depressive disorder (MDD) and non-depressed comparison controls. Psychological assessments and blood draws will be taken before and 45 days after SARS-CoV-2 vaccination. To determine if major depression is associated with impaired vaccine response, robust immunological techniques will be used to quantify the immune response, including the rise in circulating antibodies, T-cell responsiveness, and the formation of memory B-cells. The second aim is to determine individual differences that can be used to predict vaccine response within the MDD group. Baseline measurements of circulating inflammation-related cytokine concentrations and detailed T-cell profiles will be tested as predictors of vaccine response. If, as hypothesized, MDD subjects who demonstrate these immune abnormalities have attenuated vaccine responses, the study could identify immune biomarkers for MDD-related functional immune impairments.

Diagnostic Tools/Early Intervention

Akira Fushiki, Ph.D., Columbia University, studies dopamine neurons, which respond transiently to unexpected rewards and reward-predicting stimuli, conveying a reward prediction error that can drive circuit plasticity and guide behaviors toward positive outcomes. Hypothesizing that there are different dopamine subtypes, with different molecular and cellular properties and different anatomical inputs which subserve different functions, Dr. Fushiki will conduct anatomical and functional characterization of different classes of genetically identified midbrain dopamine neurons and determine if they do in fact subserve different behavioral functions. This could yield new knowledge about the source of heterogeneity of dopamine responses.

Basic Research

Xiaojing Gao, Ph.D., Stanford University, is investigating ways of regulating gene quantity in individual neurons, a potential enabling step in gene therapy. The team will use molecular circuits, biomolecules engineered to regulate each other and realize novel functions, and, in this case, to maintain the expression of a therapeutic gene at a predefined level despite the randomness of vector-based delivery. The biomolecular circuits created could offer a novel solution to a major challenge for treating rare illnesses caused by absence of one or more gene copies in cells, and also demonstrate that molecular circuits hold the promise of achieving single cell-level quantitative consistency suitable for manipulating neural circuits and treating neurogenetic diseases.

Basic Research

Next-Generation Therapies

New Technologies

Yudong Gao, Ph.D., Duke University, notes that many schizophrenia risk genes are associated with the synapse. Uncovering the proteomic interactors of synaptic targets may shed light on mechanisms responsible for synaptic dysregulation in the illness. Dr. Gao will use innovative tools of genome editing and proximity proteomics to resolve these interactions, via fusing a biotin ligase enzyme to endogenously expressed schizophrenia targets and uncovering surrounding biotinylated proteins using quantitative mass-spectrometry. He will also try to identify synaptic dysfunctions following sequential disruption of selected schizophrenia genes, thereby informing the polygenic etiology of the illness.

Basic Research

New Technologies

Neta Gazit Shimoni, Ph.D., University of California, Berkeley, seeks fundamental insights into the role of the brain's reward system for hedonic feeding and obesity. The project aims to identify hedonic feeding-related brain circuits involved in feeding motivation and obesity progression that can be modulated by changes in food abundance. The latter goal is motivated by the team's discovery of a novel brain circuit potentially involved in hedonic feeding which can be bi-directionally modulated by the abundance of calorie-rich food. Having found that the neuropeptide neurotensin (NTS) is involved in this regulation, the team will examine the possibility that a high-fat diet induces long-term changes in NTS tone in reward-related circuits.

Basic Research

Next-Generation Therapies

Akhgar Ghassabian, M.D., Ph.D., New York University School of Medicine, studies gender dysphoria, which refers to the emotional distress that gender-diverse children and others experience. The project seeks to 1) determine structural and function brain correlates of gender incongruence in young adolescents using multi-modal brain MRI; 2) examine the role of prenatal exposure to phthalates, a group of endocrine-disrupting chemicals, on brain development and gender incongruence in adolescents. The hypothesis is that prenatal

phthalate exposures influence brain regions with differential development between boys and girls and subsequently contribute to the development of gender dysphoria. Progress in providing care to youth with gender dysphoria has been hampered by our poor understanding of the etiology.
Basic Research

Erin M. Gibson, Ph.D., Stanford University, notes that myelin, the material that protectively coats neuronal axons, facilitates communication between neurons. The project seeks to add to our understanding of brain development by appreciating how myelin-forming precursor cells called oligodendrocytes are regulated. One mechanism known to be exquisitely interconnected with the cell cycle is the circadian, or 24-hour, clock. Most neuropsychiatric disorders, including autism, present with both circadian and myelin deficiencies. The team posits that circadian disruption of myelin-forming cells during development may lay the foundation for a broad range of neuropsychiatric disorders. They seek a comprehensive understanding of the interplay between circadian modulation and oligodendrocyte precursor cell maintenance and myelination.
Basic Research

Ariel Gilad, Ph.D., Hebrew University, Israel, notes that individual differences between mice are quite important when studying social interactions in mouse models of human illness. This project will attempt to bridge our gap in understanding such differences by applying a novel multi-fiber method to measure the brain-wide networks of two mice engaging in freely moving and natural social interactions. This method makes it possible to record neuronal activity from 24 recording sites brain-wide, including social-related areas such as the prefrontal cortex, amygdala, hippocampus, and thalamus. The expectation is that brain-wide social networks will differ across mice and strongly relate to social parameters such as social rank and individual personality. These results would be relevant to research on social networks in mouse models of autism and schizophrenia.
Basic Research
New Technologies

Anubhuti Goel, Ph.D., University of California, Riverside, wants to understand neural mechanisms that contribute to sensory discrimination in the presence of distractors. Hypersensitivity can contribute to the socialization problems encountered, for instance, in individuals with ASD or Fragile X syndrome, who may perceive normal stimuli as overwhelming, or may be unable to tune out irrelevant stimuli. The team has designed a novel sensory distractor task in a mouse model of Fragile X. Using microscopy, they seek to identify circuit mechanisms in the brain that contribute to hypersensitivity. Preliminary work has called to their attention top-down input from prefrontal cortex and subcortical cholinergic input, which strongly influence sensory processing and arousal by improving the selectivity and reliability of neuronal responses in the primary visual cortex. The distractor task in mice is expected to enable delineation of the contribution of subcortical and prefrontal inputs to stimulus selectivity and thus could bolster current mechanistic understanding of distractibility.
Basic Research

Elizabeth V. Goldfarb, Ph.D., Yale University, studies the neurocognitive origins of PTSD symptoms like avoiding trauma reminders, inflexible intrusive thoughts, and high co-occurrence of substance use disorders. She proposes these symptoms are associated with a bias toward forming inflexible, habitual associations between stimuli and responses, a learning process that requires the dorsal striatum. This project aims to quantify the contributions of striatal function and habit memory to PTSD resilience and symptom severity. The team will compare patients with PTSD to trauma-exposed controls, enabling them to identify dimensions of habit and striatal engagement associated with PTSD risk or resilience (rather than simply resulting from prior stressor exposure). They will also examine associations between habit and striatal engagement with PTSD symptom severity, focusing on symptoms related to avoidance, intrusive thoughts, indelible memories, and comorbid substance use. This may provide new markers of risk for developing PTSD.
Basic Research

Melanie J. Grubisha, M.D., Ph.D., University of Pittsburgh, is following up on postmortem findings in schizophrenia indicating reductions in dendritic length and complexity in cortical pyramidal cells, a unique and potentially specific targetable pathology. Normally, dendrite structure appears stable during adolescence and adulthood due to a dynamic balance of opposing growth and retraction pathways. The team has shown that OMGp, a ligand for Nogo receptor 1 (NGR1), activates a signaling pathway that shifts this balance leading to dendritic regression, a pathway requiring the active domain of KAL9. This project will more deeply characterize the signaling pathway responsible for OMGp-mediated dendritic regression, using a mouse model. The work could provide insight into how normal adolescent development, marked by naturally increasing OMGp/NGR1/KAL9 activity, intersects with genetic risk for schizophrenia.
Basic Research

Lindsay R. Halladay, Ph.D., Santa Clara University, is using mouse maternal separation with early weaning (MSEW) to model early-life adversity, which robustly reduces social

interaction and increases anxiety-like behavior, recapitulating effects of childhood abuse and neglect. Following up on past work which evidenced a central regulatory role for the anterior bed nucleus of the stria terminalis (aBNST) in MSEW-induced social deficits, this project takes the critical next step of explicating cell-type and projection-specific aBNST mechanisms governing MSEW-induced social deficits. The goal is to identify potential therapeutic targets for individuals suffering the debilitating consequences of exposure to early-life adversity.

Basic Research

Holly K. Hamilton, Ph.D., University of California, San Francisco, hypothesizes that the psychedelic hallucinogen psilocybin's reported antidepressant effects depend on two interacting mechanisms: neural plasticity and cognitive flexibility. This randomized, placebo-controlled clinical trial of psilocybin in depression patients seeks to: 1) determine psilocybin's effects on neural plasticity using a novel electroencephalography (EEG)-based paradigm; 2) investigate psilocybin's effects on cognitive flexibility using a well-established measure adapted for EEG; and 3) explore relationships between psilocybin-induced changes in neural plasticity and cognitive flexibility. The team will also examine if changes in neural plasticity and cognitive flexibility predict changes in depression symptoms and improvements in daily functioning following psilocybin therapy. This project could contribute to the development of psilocybin therapy.

Basic Research

Next-Generation Therapies

Jordan Hamm, Ph.D., Georgia State University, notes that aberrations in predictive information processing undermine how individuals with schizophrenia perceive and relate to a changing environment. To study such abnormalities, researchers have employed auditory or visual "oddball" paradigms to quantify a difference in evoked brain responses to a) "redundant" (i.e., predictable) stimuli and b) "deviant" stimuli (i.e., oddballs). Augmented neural responses to deviants reflect a form of sensory "prediction error," an effect that is reduced in people with schizophrenia. Dr. Hamm has discovered that deviance detection is limited to a distinct ensemble of sensory cortical neurons, a subpopulation of pyramidal cells in layer 2/3 of primary sensory cortex. This project seeks to learn more about the function of these neuronal "deviance detectors," research which could provide clues for developing new treatments aimed specifically at treating perceptual processing dysfunction in schizophrenia.

Basic Research

Katia M. Harle, Ph.D., University of California, San Diego, seeks to develop a computational training protocol aimed at reducing anhedonia and improving existing interventions for psychiatric conditions characterized by reward processing deficits. 50 treatment-seeking adults with major depressive disorder (MDD) or general anxiety disorder (GAD), and with moderate to high anhedonia, will be recruited. The team will: 1) test the usefulness of a computational cognitive training task in boosting reward sensitivity and reducing anhedonia; 2) delineate the neurocomputational mechanisms of change associated with such intervention. The objective is to train the brain to obtain rewards and boost positive mood among depressed and anxious individuals.

Next-Generation Therapies

Nathaniel G. Harnett, Ph.D., McLean Hospital, seeks to identify brain structure/biochemistry relationships that contribute to PTSD susceptibility in the early aftermath of trauma. Recently trauma-exposed individuals will be recruited from emergency departments within the greater Boston area. Dr. Harnett will leverage whole-brain proton magnetic resonance spectroscopy (H1-MRS) to derive brain-wide neurometabolite profiles (e.g., glutamate/glutamine, N-Acetyl-Aspartate, choline and creatine) related to traumatic stress symptoms in the early aftermath of trauma. A second goal is to combine whole-brain structural and H1-MRS brain data into multivariate structure-neurometabolite profiles associated with acute and later PTSD symptoms. The completion of these aims could significantly advance our understanding of the neurobiological basis of PTSD.

Basic Research

Moritz Herle, Ph.D., King's College London, UK, is motivated by research suggesting that eating disorders and their early-onset symptoms show significant heritability, as well as evidence that eating disorders are marked by divergent weight trajectories already present in childhood. This study combines genetic, behavioral, and metabolic data in childhood to identify bio-behavioral risk factors. It will leverage data from the Gemini Twin cohort, a birth cohort of over 2,000 U.K. families with twins born in 2008. The team will use hypothesis-free prediction modelling including multiple polygenic scores as well as the longitudinally measured phenotypes during childhood to identity potential bio-behavioral risk factors associated with eating disorder symptoms in adolescence. The study aims to carry these identified risk factors forward to elucidate complex underlying bio-behavioral mechanisms.

Basic Research

Rasmus Herlo, Ph.D., Columbia University, notes evidence of distorted patterns of cortical activity as a common causal denominator for behaviors seen in schizophrenia. These distortions could represent a unifying downstream convergence point for distinct genetic risk factors, implying

that a restoration of organized circuit activity could reverse schizophrenia behaviors. The team will take advantage of two advanced optical technologies, photolytically caged compounds and holographic photo-stimulation, to release neuromodulators at strategic time-points during a clinically relevant task, where mouse-model subjects use visual cues to guide their choices. The task has demonstrated high translatability between schizophrenia mouse models and human patients. If the strategy succeeds to restore both cortical circuit dynamics and behavioral performance in the schizophrenia models, it could serve a guideline for new therapeutic interventions.

Basic Research

New Technologies

Stephanie L. Hickey, Ph.D., Michigan State University, will explore brain region- and age-specific treatments for schizophrenia. She proposes to: 1) use thousands of publicly available RNA-seq data sets to build networks of brain region- and developmental stage-specific functionally related genes; and 2) use these context-aware networks along with high confidence differentially expressed genes to predict brain region- and age-specific druggable targets. Using the millions of RNA-sequencing samples from thousands of experiments and expert-curated gold-standard examples of functionally related gene-gene pairs in the cortex and hippocampus at 13 different developmental stages, she will train machine-learning models to predict the probability that each pair of genes is functionally related in the context of interest. She will then build a network for every region-stage combination in which every gene is a node in the network and the connection between each pair of nodes is weighted by the predicted probability of their interaction.

Basic Research

Kuangfu Hsiao, Ph.D., The Rockefeller University, focuses on an auditory perceptual network, the corticothalamic pathway, dysfunction of which has been linked to autism spectrum disorder (ASD) in human brain imaging studies. One common symptom of ASD is auditory over-sensitivity. It is not yet clear how corticothalamic pathway disfunction found in some autism patients disrupts auditory processes. Dr. Hsiao seeks to learn more about these defects by studying neural activity patterns and biochemical signals in the corticothalamic pathway. To accomplish this, collections of simultaneously recorded neural activity and biochemical signals from important brain areas related to auditory processing will be documented and analyzed from in mouse models for ASD.

Basic Research

Rafiq Huda, Ph.D., Rutgers University, seeks to define novel cortical mechanisms of aberrant interoceptive processing that contribute to compulsive alcohol use. The aim is to lay the groundwork for developing novel neural circuit-based therapies for alcohol use disorder (AUD). The project will test the hypothesis that binge-drinking recruits specific subtypes of anterior cingulate cortex (ACC) interneurons, resulting in hyper-representation of arousal that plays a causal role in transition from binge to compulsive drinking. By longitudinally tracking the activity of identified ACC interneuron and excitatory neuron circuits over weeks, the team will establish how arousal activity of these cells during binge drinking relates to subsequent compulsive alcohol use. Manipulating the activity of these cells during binge drinking could establish their causal role.

Basic Research

John B. Issa, M.D., Ph.D., Northwestern University, is studying interval timing, which is timing on the order of seconds to minutes, that is often disrupted in patients with psychiatric disorders such as depression. Can we understand something about the disease pathology by better understanding interval timing? This question necessitates first answering where a sense of time is generated in the brain. One possibility is that we have a single clock that continuously ticks off time. But this model stands at odds with experiments that have found neurons in multiple brain regions that encode timing information. The team has developed an interval timing task that mice can perform reliably in virtual reality, allowing use of an upright microscope to image the brain during behavior. To overcome the limitation of conventional imaging approaches that achieve only a single focal plane, Dr. Issa has developed a multifocus microscope and novel surgical preparation.

Basic Research

New Technologies

Heather M. Joseph, M.D., University of Pittsburgh, will build upon research examining school-aged children and adolescents with ADHD. She proposes to longitudinally assess preschool-aged children at high and low risk for ADHD to examine functional neural connectivity between brain regions responsible for sustained attention, which is altered in children with ADHD. The project will enroll 58 children, half at high risk (at least one parent with ADHD) and half at low risk for ADHD (both parents without ADHD). All children will be examined with functional near infrared spectroscopy (fNIRS). Assessments will occur at ages 4 and 5 to examine changes in attention and brain activity at the transition to school. The project will test (1) whether preschool-aged children at high risk for ADHD have lower brain connectivity between the prefrontal cortex and the dorsal attention network at "rest" and elevated connectivity

during periods of attention compared to low-risk children; and (2) whether connectivity in these brain regions predicts attention 1 year later, at school entry.

Basic Research

Diagnostic Tools/Early Intervention

Garrett A. Kaas, Ph.D., Vanderbilt University, seeks to explore novel therapeutic targets (genes/proteins) associated with bipolar disorder (BD). A number of genes in patients have been found to exhibit altered DNA cytosine methylation (m5dC) patterns, suggesting disrupted epigenetic mechanisms. Also, mood-stabilizing drugs have been repeatedly shown to alter m5dC patterns. In line with these findings, expression levels of the m5dC regulatory enzyme Ten Eleven Translocation 1 (TET1) have been reported to be significantly elevated in BD postmortem brains. Dr. Kaas will use hydroxymethylated RNA immunoprecipitation sequencing (hMeRIP-seq) to generate an unbiased, transcriptome-wide map of hm5C-marked RNAs in the mouse brain; and will test the hypothesis that TET1S bidirectionally regulates the stability of mRNAs important for neuronal physiology.

Basic Research

Iliana Irini Karipidis, Ph.D., Stanford University, will systematically investigate sex differences in pubertal brain patterns involved in reward processing in a study of transgender youth. By comparing these youths with cisgender peers, it may be possible to identify specific patterns of brain activity directly linked to pubertal sex hormones. Better understanding the role of sex hormones in brain mechanisms of reward may provide crucial knowledge regarding treatment and prevention of depression in teenagers. This research will also have a direct impact on our understanding of transgender health, the promotion of well-being in sexual and gender minority youth, and may have the potential to integrate evidence about sex differences into clinical practice of child and adolescent psychiatry.

Basic Research

Brian C. Kavanaugh, Psy.D., Brown University, notes that the dorsolateral prefrontal cortex (DLPFC) is the structural foundation of working memory (WM), and that the interaction between slow and fast brain waves ("theta/gamma coupling" or TGC) is a neural, functional foundation of WM. For this reason, the DLPFC and TGC are potential brain-based targets for the modulation of WM with brain stimulation. The project will investigate whether non-invasive intermittent theta burst stimulation (iTBS) can lead to a lasting modulation of WM-related neural oscillations (e.g., TGC). In a crossover, double-blind design, a sample of 12 adolescents (13-17 years old) with WM deficits across the spectrum of psychopathology will complete a 2-week course of active iTBS and a two-week course of placebo treatment to their left DLPFC (based on brain MRI).

Next-Generation Therapies

Michael D. Kendig, Ph.D., University of Sydney, Australia, notes that foods commonly eaten during binges are high in saturated fat and sugar and low in nutrients. High intake of such foods is associated with cognitive impairment in adolescence, and with dysregulated composition of the gut microbiota. Long-term effects of binge-like consumption of foods high in fat and sugar remain to be fully elucidated, as is the importance of the gut microbiota in these changes. To explore these questions, Dr. Kendig will expose adolescent rats to a palatable "cafeteria-style" diet for 4 weeks, with access provided either continuously or in binges of 1 or 3 days. Measures of cognitive function, gut microbiota composition and adiposity will be collected. The team will study effects of adolescent binge eating on these markers. They will also assess whether adolescent binge eating leads to lasting changes by testing after a period of reversal to food.

Basic Research

Dalia Khalil, Ph.D., Wayne State University, notes that children may appraise the threat and stress level in the environment through the lens of their parents' reactions and experiences. The purpose of this study is to: 1) examine differences between refugee families and immigrant families in terms of shortened telomere length (TL)—a measure of genes that reflects stress experienced over the lifespan. Behavioral outcomes in children will also be studied, to parse the impact of war trauma from the stress of migration; and 2) examine the parent-child relationship as a possible moderator between psychological symptoms and behavioral outcomes. The cohort consists of Middle Eastern immigrant families and Syrian refugee families. The project involves analysis of 70 children from each group with their parents. New data to be collected consist of buccal swab samples to measure TL from both parents and children, quality of the parent-child relationship, and child behavioral problems.

Basic Research

Mudasir A. Khanday, Ph.D., Beth Israel Deaconess Medical Center, is investigating the specific brain areas and mechanisms responsible for the sleep-wake disturbances in response to stress. The bed nucleus of the stria terminalis (BNST) is a key brain region involved in stress and emotional regulation and robustly projects to major wake-promoting regions including locus coeruleus (LC) and parabrachial nucleus (PB). Both LC and PB may act as a general alarm to induce arousal in response to various stressors. This project tests the hypothesis that BNST neurons activated by stress (corticotrophin-releasing hormone [CRH]-containing

neurons) may specifically target the LC and the PB to cause stress-induced changes in sleep-wake patterns.

Basic Research

Ji-Woon Kim, Ph.D., Vanderbilt University, is studying how ketamine can produce sustained antidepressant effects. In recent work, the team demonstrated such effects are mediated by a transcription-dependent mechanism: BDNF-dependent phosphorylation at S421 of methyl-CpG-binding protein (MeCP2), a transcriptional regulator, which is required for ketamine's longer-term antidepressant action and synaptic changes. But it remains unclear how BDNF regulates MeCP2 phosphorylation, which is required for the sustained effects of ketamine. In this project Dr. Kim will investigate the intermediate molecular mechanism between BDNF and phospho-MeCP2 changes underlying ketamine-mediated sustained antidepressant action and synaptic changes, hoping to provide insight into the molecular mechanism underlying the sustained antidepressant effects of ketamine.

Next-Generation Therapies

Basic Research

Christina K. Kim, Ph.D., Stanford University, observes that the prefrontal cortex (PFC) plays a key role in regulating reward-seeking behavior, particularly in response to punishment or risk. Yet it remains unclear whether there are specific proteomic markers in PFC neurons that specifically encode punishment during reward-seeking. Knowing which molecular markers are enriched in these neurons could reveal cellular substrates for targeting these cells in novel therapeutics to treat neuropsychiatric diseases. This project aims to apply a newly developed technology, FLiCRE, to molecularly probe neurons in the PFC that are responsive to punishment and that regulate reward-seeking in the face of risk. More broadly, the ability to functionally tag, manipulate, and molecularly probe behaviorally-relevant populations of neurons is a potentially transformative technology.

New Technologies

Basic Research

Tina D. Kristensen, Ph.D., Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Denmark, notes that psychosis is associated with cerebral white matter (WM) changes and cognitive impairments, but no prognostic biomarkers or specific predictors for psychotic development have been identified. This project will use a novel method called fixel-based analysis (FBA) to extract structural measures such as fibre density (FD) and fibre-bundle cross-section (FC), thereby offering refined insight to specific WM fibre integration. The team will apply FBA to investigate the longitudinal interplay between structural and functional brain connectivity, psychopathology, and cognition in a cohort of 347 individuals at ultra-high risk for psychosis (UHR) and antipsychotic-naïve patients with first-episode psychosis (FEP) without current or lifetime substance abuse or dependency.

Basic Research

Sara Liane Kroll, Ph.D., University of Zurich Brain Research Institute, Switzerland, notes that the endogenous cannabinoid anandamide (AEA) plays a key role in the regulation of stress response and may act as an emotional buffer with protective effects on stress-related behavior. Endocannabinoid plasma levels might give important information about dysfunctional stress responses, which are likely drivers of stress-induced craving and relapse in drug addiction. This project seeks to establish the influence of the endocannabinoid system on cocaine and opioid addiction, testing if endocannabinoid transmission is altered in chronic cocaine and opioid users, leading to inadequate stress response resulting in increased craving and drug relapse. Plasma samples of 183 cocaine and opioid users and 168 healthy controls will be used to address these questions.

Basic Research

Karina A. Kruth, Ph.D., University of Iowa, studies a small family of proteins called MICALs which have been shown to trigger actin destabilization and collapse in the presence of oxidative stress, which is elevated in patients with bipolar disorder (BD). Actin networks are necessary in neurons not only for dendritic spines, but also for cellular energy production and proper trafficking of neurotransmitters between cells. The hypothesis in the project is that elevated oxidative stress in BD leads to MICAL-mediated destabilization of actin networks in neurons, resulting in dendritic spine collapse and disruption to cellular energetics. Dr. Kruth will investigate the role of MICALs in neurons from BD patient-derived induced pluripotent stem cells to better understand how oxidative stress leads to neural dysfunction, which may in turn help identify new drug targets for the treatment of BD.

Basic Research

Matthew A. Lalli, Ph.D., Icahn School of Medicine at Mount Sinai, wants to help discern the function of autism risk genes and their mutations in the context of brain development. Studying each of these genes separately in animal or cell models is a daunting if not impossible task, he points out. He seeks to develop a method to study the function of many disease associated genes simultaneously. His team's method combines CRISPR/Cas9, single-cell RNA-sequencing, and human induced pluripotent stem cells (iPSCs) to identify the functional signatures of many disease genes in parallel. They will apply this new technology to understand how 50

large-effect ASD risk genes affect gene expression and neuronal differentiation in human iPSC derived neural progenitors and differentiated neurons.

New Technologies

Basic Research

Marco Lanzilotto, Ph.D., University of Turin, Italy, is studying social, communicative, and behavioral deficits that affect working and daily life conditions for those with developmental disabilities such as ASD. In relevant regions of the primate brain, he seeks to understand the neuronal mechanisms underlying facial mimicry, which enable a person to reproduce another's facial expressions and thus converge emotionally. The project, in macaques, focuses on two clinically relevant brain regions implicated in emotion processing: the amygdala and anterior cingulate cortex. The team will simultaneously record single neuron activity from both areas and will reversibly inactivate each of them. The objective is to understand how these areas cooperate and coordinate to synchronize an individual's facial expressions with those observed in others.

Basic Research

Long Li, Ph.D., Icahn School of Medicine at Mount Sinai, studies the relationship between stress-induced social reward deficits and susceptibility to depression and its underlying mechanisms. Dr. Li notes that although women are nearly twice as vulnerable to depression as men, studies investigating social reward processing dysfunctions in females are still limited. To more broadly test the impact of chronic social defeat stress (CSDS) on social behavior in mice, the team will use a battery of tests to tap into different aspects of threat detection, social avoidance, and social preference behaviors in both males and females. Having identified in past work that neurotensin neurons in the lateral septum (LSNT) showed hyperactivity compared to control and resilient mice in both sexes, and that inhibiting LSNT neurons rescued social reward in susceptible mice in both sexes, Dr. Li's team will continue studying LSNT neurons in their depression model by identifying their cell-type specific upstream and downstream regions and their functions in social reward deficit.

Basic Research

Qingyun Li, Ph.D., Washington University School of Medicine, notes that one of the most extensively studied environmental factors strongly linked with schizophrenia and autism is called maternal immune activation (MIA), in which the mothers of the affected individuals are exposed to viral, bacterial, or fungal infections causing activation of their immune system during the first or second trimester of pregnancy. A major unanswered question is what cells in the fetus MIA may directly affect to induce disease phenotypes. This project will test the hypothesis that MIA may directly activate microglia, immune cells in the mother's blood circulation which later enter the embryo and may generate dysregulated microglia, resulting in disruption of normal brain development and function. The project contemplates genetically removing these maternal immune cells to investigate whether loss of this presumable target of MIA alleviates disease pathology in mouse models.

Basic Research

Zhen Li, Ph.D., Children's National Hospital, notes research showing that removing one copy of CHD7 from the genome will lead to detrimental effects on organ development. Little is known about the pathological mechanism and the effect of deleterious CHD7 mutation at the molecular level, especially in the context of neurodevelopment. Past work by Dr. Li suggests CHD7 is expressed at a higher level in a particular neural progenitor cell population in the developing mouse brain. It is possible that the symptoms associated with impaired brain development in ASD and other neurodevelopmental disorders are caused primarily by defects in specific cells, rather than the whole brain tissue. Dr. Li will explore the hypothesis that the particular population of progenitor cells identified in his previous study is more affected by CHD7 deficiency than other cells. This will be investigated using a mouse model system and transgenics technology.

Basic Research

João Paulo Lima Santos, M.D., University of Pittsburgh, notes that greater screen time and insufficient sleep have been associated with reduced white matter integrity; but it remains largely unknown how these associations affect brain development and clinical problems such as anxiety and depression. This project uses diffusion magnetic resonance imaging (dMRI) and unprocessed neuroimaging data of 1,000 participants from the Adolescent Brain Cognitive Development (ABCD) study to identify the effects of screen time and sleep on brain development. Clinical, sociodemographic, behavioral, pubertal, and neuroimaging data for this study have been made available for baseline (ages 9-10 years) and the first 2-year follow-up (ages 11-12 years). The hypothesis is that brain tracts demonstrating more changes over time will be susceptible to the negative effects of excessive screen time and insufficient sleep, particularly in regions close to the gray-white matter interface, and, as a consequence, participants who show these associations will present more emotional and cognitive problems.

Basic Research

Jeffrey Lopez-Rojas, Ph.D., Columbia University, notes studies pointing to the importance of the dorsal region of the CA2 region of the hippocampus for the encoding, consolidation, and recall of social memories. To serve this function, the

hippocampus relies on a variety of external inputs. Dr. Lopez-Rojas is interested in the role of the entorhinal cortex, which provides the primary source of multimodal sensory input from neocortex to hippocampus. This project will test the hypothesis that a dysregulation of communication between the lateral entorhinal cortex (LEC) and dorsal CA2 is at the core of the social impairment observed in schizophrenia. The team will record neuronal activity from these regions under control and disease conditions in a mouse model of the 22q11.2 microdeletion, one of the strongest known genetic risk factors for schizophrenia.

Basic Research

Nathan J. Marchant, Ph.D., Amsterdam University Medical Centers, The Netherlands, seeks to describe neurobiological processes by which the brain controls the decision to either seek nicotine or to refrain from nicotine seeking under threat of punishment. He proposes that the balance of activity between the left and right anterior insula cortex (aINS) is a critical determinate of approach or avoidance of nicotine seeking and taking. He will use chemogenetics to test the extent to which nicotine seeking is lateralized in the rodent brain and will attempt to unravel the mechanisms by which the two hemispheres communicate with each other to regulate approach or avoidance of the nicotine-taking response during self-administration and punishment. Findings could have implications for understanding the brain control of relapse, and may provide novel targeting strategies in humans using transcranial modulation of brain activity. They also have the potential to pave the way for future research into the mechanisms underlying lateralization of brain control over behavior.

Basic Research

Bianca J. Marlin, Ph.D., Columbia University, is studying the possibility that parental stress can be inherited, via epigenetic mechanisms (which can modify the expression of genes). Her past work has demonstrated that odors in the environment of a mouse that are associated with aversive consequences result in compensatory alterations in the olfactory system of their offspring. This project seeks to understand the transfer of information inherent in neurons of the parent, through the gamete, to neurons of their offspring. Implicit is the notion that the experience of our parents, and even our grandparents, can affect our brain and behavior. Elucidating the mechanisms through which learning and emotion in one generation are transmitted not culturally, but rather biologically through DNA, could have profound implications in societal health and mental well-being.

Basic Research)

Marilena Marraudino, Ph.D., University of Turin, Italy, will investigate the possible consequences of the use of soy as a nutritional substitute in diets poor in macronutrients, during pregnancy, on the mother and offspring. Using an anorexia nervosa animal model and testing different diets low in macronutrients and/or genistein (GEN)—a phytoestrogen that can disrupt the endocrine system that is enriched in vegetarians and vegans—two questions will be addressed: can soy, rich in GEN, generate strong repercussions at the neuroendocrine level, in mothers with eating disorders (who already have strong hormonal alterations due to both dietary and stressful states)? And can exposure to a high level of phytoestrogens, with their properties of endocrine disruption, have effects on the already altered intrauterine environment of mothers with eating disorders? More broadly, does soy have potential value as a nutritional supplement in mothers with anorexia nervosa?

Basic Research

Jesse Marshall, Ph.D., Harvard University, has recently developed DANNCE, a new tool for 3D behavioral tracking that allows his team to track the precise 3D kinematics of rodents over development. They will use it in rodent models to study repetitive motor behaviors seen in ASD, ADHD and other disorders which are thought to be modeled by disruptions in the frequency and patterning of self-grooming behaviors. In both humans and rodents, these aberrant behaviors are thought to be driven by changes in the excitability and connectivity in cortico-striatal circuits during developmental windows. This project will employ DANNCE with the hope of learning more about how and when molecular and structural deficits in these neural circuits lead to alterations in a few behaviors. Are these behaviors driven by a select "focus" of hyperexcitable cells? Or do these behaviors become overrepresented in the brain, making them more likely to be selected?

Basic Research

New Technologies

Rhiannon V. McNeill, Ph.D., University Hospital Würzburg, Germany, is interested in single-letter DNA variations called SNPs in a gene called ADGRL3, which have been found to increase the risk of developing of ADHD. Research in mice has shown that this gene is important for certain brain cells to grow and communicate properly. How the SNPs affecting the gene might be involved in ADHD remains unclear, as there is a lack of research using human samples. This project will study the question using induced pluripotent stem cell technology and skin cells donated by individuals with and without ADHD, performing multiple tests on the cultured cells to determine the effect of SNPs in the ADGRL3 gene.

Basic Research

Robert G. Mealer, M.D., Ph.D., Massachusetts General Hospital and Harvard University, is interested in complement C4 protein and multiple enzymes involved in the addition of carbohydrates to proteins through glycosylation. Recent studies have highlighted the role of complement in brain development and genetic risk for schizophrenia, with the schizophrenia-associated C4A allele causing increased microglia synaptic pruning. This project will analyze C4 glycosylation in the brain during development and measure isoform-specific variation in C4A and C4B glycosylation. Dr. Mealer hypothesizes that C4 glycosylation in the brain will change during development, and that glycosylation of the schizophrenia-associated C4A protein will differ from C4B. This could be a basis for future studies determining the functional implications of differential complement glycosylation and microglia phagocytosis relating to risk for schizophrenia. Since many glycosylation abnormalities can be reversed through targeted supplementation, there is potential for developing novel therapeutic targets based on genetic associations for schizophrenia.

Basic Research

Susanna Molas Casacuberta, Ph.D., University of Massachusetts Medical School, notes that identifying the neuronal circuits and mechanisms underlying innate defensive behaviors and how they are disrupted in anxiety disorders—i.e., when they are expressed in the absence of real threats—is fundamental for the design of improved therapeutic strategies for anxiety. She seeks to determine if inhibitory GABAergic neurons in the interpeduncular nucleus (IPN) of the midbrain that project to the laterodorsal tegmental nucleus (LDTg) modulate threat processing and anxiety-like behavior and whether this circuitry is disrupted in anxiety disorders. To do so, she will use a multidisciplinary research strategy that includes viral circuit analysis, fiber photometry combined with biosensors/optogenetics and mouse behavior.

Basic Research

Carla Nasca, Ph.D., The Rockefeller University, wants to probe the possible role of mitochondrial mechanisms in the therapeutic action of rTMS non-invasive brain stimulation treatments for depression, with reference to four postulated biotypes of major depressive disorder identified in a recent study by BBRF grantee Conor Liston M.D. and colleagues. In each of the four biotypes, Dr. Nasca seeks to determine the role of mitochondrial mechanisms in epigenetic regulation of brain plasticity. The study leverages an existing NIMH-funded clinical rTMS trial involving 202 subjects scanned before and after a conventional 6-week course of rTMS. To test the specificity of the results for rTMS, they will be compared with the results of parallel studies of the antidepressant ketamine. This work could help determine the utility of targeting a mitochondrial signaling pathway to enhance responses to rTMS therapy in some patients.

Next-Generation Therapies

Joshua R. Oltmanns, Ph.D., Stony Brook University, notes initial studies showing that artificial intelligence (AI)-based scoring of PTSD using natural language can detect PTSD. However, current methods have relied mostly on social media samples as opposed to clinical interviews, have been trained on PTSD proxies rather than validated PTSD measures, and have been limited to small samples (≤ 300). This study will address these problems by developing AI markers for PTSD from language in clinical interviews with 3,000 World Trade Center (WTC) responders oversampled for clinician-rated PTSD. The tools that emerge may facilitate screening and care by providing objective PTSD markers and informing prognosis and monitoring of treatment response, while simultaneously reducing—or ultimately eliminating—assessment time demands.

Diagnostic Tools/Early Intervention

Cynthia Ortinau, M.D., St. Louis College of Pharmacy and Washington University in St. Louis, seeks to delineate risk factors that influence psychological distress in mothers and partners, and determine the impact of depression, anxiety, and stress on fetal brain development and childhood neurodevelopmental outcome, which is critical for improving the clinical care of congenital heart disease (CHD). CHD is the most common birth defect and often requires cardiac surgery in the first year of life. This proposal will leverage an ongoing prospective longitudinal study of families who receive a prenatal diagnosis of CHD to identify the frequency and patterns of parental psychological distress. The project aims to gain insights to improve psychological and neurodevelopmental care for CHD families by informing the design of interventional studies aimed at reducing parental psychological distress after a prenatal diagnosis of CHD.

Diagnostic Tools/Early Intervention

Clare E. Palmer, Ph.D., University of California, San Diego, studies neurodevelopmental pathways underlying the emergence of psychiatric disorders in early adolescence. This project will use a data-driven approach to test for heterogeneity in the pattern of neurodevelopment across the brain that is specifically associated with general psychopathology. The team will draw on data from the Adolescent Brain and Cognitive Development (ABCD) Study, which includes longitudinal, multimodal neuroimaging, genetics and behavioral data from 11,880 youth at 9–11 and 11-13 years old. One aim is to determine if there is a single, common maturational profile associated with disorders across the full sample, or, as they hypothesize, multiple groups of subjects with differing spatial patterns of associations indicative of the presence of

multiple mechanistic pathways underlying disorders. If the latter is true, they hope to specify external factors such as environmental adversity and genetic risk for psychopathology that discriminate between individuals in different groups.
Basic Research

Eric M. Parise, Ph.D., Icahn School of Medicine at Mount Sinai, is studying the extracellular matrix (ECM) of the brain, which provides structural support and is intimately involved in regulating synaptic plasticity and remodeling. He hypothesizes that alterations to this complex network of proteins surrounding neurons and glial cells regulates morphological processes that may be involved in major depressive disorder (MDD). This project will characterize ECM-specific changes in gene expression within the nucleus accumbens (NAc) and prefrontal cortex (PFC) of male and female MDD patients that also occur in mice exposed to chronic stress. He will then seek to determine the causal contribution of identified ECM targets to stress-response via direct manipulation in the NAc and PFC. After confirming cell-type-specificity for these targets, he will develop viral vectors capable of overexpressing or knocking down identified ECM-related targets selectively in the appropriate cell type and deliver them directly into the NAc or PFC to then assess for changes in behavioral reactivity to stress.
Basic Research

Beatriz Penalver Bernabe, Ph.D., University of Illinois at Chicago, notes that the use of portable technology to detect perinatal mood disorders is very limited and has not yet been integrated with microbial assessments. In this project, she aims to use portable device-enabled monthly measurements of brain activity and cognition to enhance an ongoing study of perinatal depression (PND) and gut microbiota. This project will enroll 140 pregnant women in the add-on study to establish 1) the association of portable EEG signals and cognitive scores with PND and 2) the connections between brain activity, cognitive tests, and microbial features, using dynamic machine learning approaches, which together could be sensitive PND predictors. This approach could serve to develop novel tools to predict the risk of PND.
Diagnostic Tools/Early Intervention

Amy Peters, Ph.D., Massachusetts General Hospital and Harvard University, notes evidence of possible involvement of cerebral small vessel disease in cognitive function in bipolar disorder. Preventative efforts are currently hampered by a limited ability to diagnose and monitor microvascular disease in a clinical setting. This project seeks to visualize normal and disease-affected small vessels at the microscopic level using non-invasive imaging of retinal small vessels via Optical Coherence Tomography. If successful, this work could produce novel tools for large-scale screening, diagnosis, and monitoring of small vessel disease and its impact on cognition. Indeed, retinal imaging could potentially revolutionize clinical approaches to identifying risk of small vessel disease and subsequent cognitive decline in bipolar disorder, by removing the costs, logistical challenges, and expertise requirements associated with MRI imaging.
Diagnostic Tools/Early Intervention
New Technologies

Sara Pinto dos Santos Matias, Ph.D., Harvard University, studies how the brain represents probabilistic events and makes decisions. This project will use Distributional Reinforcement Learning (DRL), a new framework developed in the context of reinforcement learning (RL), which provides a novel way to address this issue. DRL algorithms allow an agent to learn the entire distribution over rewards, instead of only the mean expected reward, as in traditional RL, by considering multiple value predictors and corresponding reward prediction error (RPE) channels. Using computational and optogenetic techniques, this project could shed light on how dopaminergic activity modulates the evaluation animals make of probabilistic outcomes and how such predictions can bias behaviors, and open new quantitative avenues to study the neural substrates of depression, such as anhedonia, or in addiction, insensitivity to harmful outcomes.
Basic Research

Giovanna Punzi, M.D., Lieber Institute for Brain Development, Johns Hopkins University, will build on earlier findings to determine whether suicide by violent means is associated with an alteration of microglial purinergic signaling in the context of mitochondrial metabolic activation in neurons. Dr. Punzi will perform single-nuclei RNAseq in brain tissue from patients who died by violent suicide, and from controls. The working hypothesis is that greater differences in gene transcription might emerge at the single-cell level. In this way, the research may be able to identify cell-specific transcripts associated with suicide by violent means in neurons, microglia, and other cell types. The results could have a significant positive impact as they will help identify critical pathways associated with suicide, and could inform the development of targeted prevention and treatments.
Basic Research

Ryan H. Purcell, Ph.D., Emory University School of Medicine, notes genetic risk factors for schizophrenia are concentrated in genes that are highly expressed in neurons, suggesting that the underlying biology of schizophrenia is likely driven by neuronal development and function. Until recently, live human neurons have been impervious to direct

investigation. Dr. Purcell's team has collected cell samples reflecting specific genetic variations associated with schizophrenia which, via stem cell technology, can be coaxed to become nearly any cell type in the human body, including functional neurons. This project will facilitate further development of this toolset, enabling the team to test the hypothesis that the biology of 22q11.2 deletion and 3q29 deletion converge at molecular, cellular, or circuitry-based levels, and may therefore reveal common mechanisms for schizophrenia risk with therapeutic implications.

Basic Research

Tara Raam, Ph.D., University of California, Los Angeles, notes that social relationships represent the context in which many psychiatric disorders emerge, and that the development of psychiatric and neurodevelopmental disorders such as anxiety, depression, and autism can lead to deficits in social behaviors. But the neural circuits mediating social interactions remain poorly understood. This project aims to (1) longitudinally measure the activity of dorsomedial prefrontal cortex (dmPFC) neurons that project to ventral tegmental area (VTA) or nucleus accumbens (NAc) using calcium imaging and (2) optogenetically manipulate dmPFC projections to VTA or NAc to understand how these projections represent and regulate social reward seeking. These tools will facilitate access to mPFC-NAc and mPFC-VTA projections with high spatiotemporal resolution. This research could lead to a more incisive understanding of the neural basis for social reward deficits in a variety of psychiatric disorders.

Basic Research

Juan F. Ramirez-Villegas, Ph.D., Institute of Science and Technology, Austria, is interested in the hypothesis that respiration coordinates network dynamics across different brain subsystems, with impacts on emotion and cognition. This project seeks to advance our understanding of how volitional respiration in humans modulates arousal, and how maladaptive autonomic responses impact mnemonic function in anxiety disorders. The project thus seeks system-level mechanistic insights into the interplay between respiratory control, arousal, and mnemonic function. Physiological markers and target mechanisms that are uncovered could advance the use of non-pharmacological intervention strategies to restore brain function.

Basic Research

Ryan Rampersaud, M.D., Ph.D., University of California, San Francisco, studies alterations in gut microbiota composition (termed "dysbiosis") leading to altered signaling along the route of communication between the gut and the brain (termed the gut-microbiota-brain axis). He believes this represents a novel modifiable target associated with major depressive disorder (MDD). This project aims to determine how changes in the metabolic capacity of the gut microbiome to generate aromatic amino acid metabolites contributes to the pathophysiology of MDD. It will use stool and blood samples from a well characterized cohort of unmedicated MDD subjects along with healthy controls and samples from these same unmedicated subjects after 8 weeks of antidepressant treatment. The hope is to identify changes in microbial-encoded metabolic pathways associated with MDD and SSRI treatment, revealing novel pathways implicated in the pathogenesis of disease.

Basic Research

Siyuan Rao, Ph.D., University of Massachusetts Medical School, is working with mouse models in which restoration of a mutant version of a gene called SHANK3, implicated in autism, could result in correction of certain pathologies. What is the neural cellular mechanism at work in restoring SHANK3 expression and rescuing autism-like phenotypes in mice? This project aims at (1) validating long-term optical recording on mouse anterior cingulate cortex (ACC) in the context of ASD-related behavioral assays; (2) dissecting cell type-specific neural activity during the restoration of SHANK3 in ACC; and (3) optogenetic and pharmacological intervention on targeted ACC neurons during the rescue of autism-like phenotypes in SHANK3 mutant mice. The outcome of this project will facilitate the understanding of the causal relationships between gene expression, cellular activity, and behavioral output in ASD studies.

Basic Research

Sebastian Reinartz, Ph.D., University of Basel, Switzerland, notes that the sensation of time on a scale from milliseconds to seconds is necessary for learning and behavior. In psychophysical studies with schizophrenia patients, behavioral measures suggest that an overestimation of perceived durations correlates with the severity of positive symptoms. As no dedicated sensory system exists, time perception has an intimate connection to the experience of sensory features of the event. This project seeks to uncover neuronal computations and circuit dynamics underlying the perception of time using the mouse auditory system. Results potentially could be useful for psychophysical studies in humans to develop preliminary diagnostic routines.

Basic Research

William Renthal, M.D., Ph.D., Brigham and Women's Hospital and Harvard University, is working on the problem of selectively targeting epigenomically modified neurons involved in drug-seeking behavior without also affecting nearby cells in unrelated circuits. This project tests an innovative approach to label cells that drive opioid-seeking behavior

based on their unique epigenomic profile. Advantages of Dr. Renthal's approach include the ability to label cells involved in drug-seeking behavior without need for transgenic mice or precisely timed conditioned stimuli. By using evolutionarily conserved gene regulatory elements to drive viral expression, this approach has the potential to translate to patients with refractory opioid use disorder.

Basic Research

Emily Julia Ricketts, Ph.D., University of California, Los Angeles, notes that disturbance in the sleep-wake cycle is prevalent in individuals with Tourette disorder (TD), with insomnia and sleep disturbance associated with tic severity. Frontal cerebral thermal therapy (i.e., forehead cooling) provides one potentially useful intervention, designed to treat insomnia and hyperarousal by targeting underlying neurobiology. This project will examine the preliminary effects of frontal cerebral thermal therapy on insomnia as evidenced by objectively measured sleep-onset latency, and wake-after-sleep onset in 25 adults with TD and co-occurring insomnia disorder. Findings have implications for utility of nonpharmacological interventions tailored to the underlying neurobiology of insomnia to treat hyperarousal in TD.

Next-Generation Therapies

Nathaniel S. Rieger, Ph.D., Boston College, notes that corticotropin-releasing factor (CRF) is important in orchestrating the stress response and plays a role in evaluating the valence of environmental cues and altering behavior in response to these cues. CRF type 1 receptors (CRF1) are present in the insula and Dr. Rieger has shown that in males but not females, CRF increases insular excitation leading to augmented social behavior. This project seeks to: 1) describe changes in CRF receptor distribution in the insula of males and females exposed to prenatal infection; and 2) to rescue social affective preference formation by direct activation of the insula. The hypothesis is that CRF1-positive cells will be reduced in the insula of males and increased in the insula of females exposed to maternal immune activation, compared to control animals. It is also hypothesized that direct stimulation of the insula will rescue social affective preference formation in males exposed to maternal immune activation.

Basic Research

Maria Rogdaki, M.D., Ph.D., King's College London, UK, recently found that that individuals with 22q11.2 deletion—a genetic syndrome associated strongly with psychosis and schizophrenia—have increased capacity for dopamine production in the striatum compared to healthy controls and individuals with 22q11.2 duplication. It remains unclear what causes this increased dopamine production at the molecular level. This project will investigate the mechanisms underlying dopamine dysfunction by using artificially grown miniature organs resembling the brain, called organoids. These are created by stem cells from individuals with 22q11.2 deletion and controls who took part in Dr. Rogdaki's prior work. She will use these to test a novel drug in its ability to decrease the capacity for dopamine production in brain cells that produce dopamine in brain organoids.

Basic Research

Next-Generation Therapies

Marit F.L. Ruitenberg, Ph.D., Leiden University, The Netherlands, seeks to tailor treatment for different depression subtypes, which could lead to higher success rates of treatment, improved psychological and financial well-being of patients and their support system, and fewer people succumbing to depression. The project is predicated on the notion that sensorimotor measures affected in depression (e.g., muscle strength, balance, motor learning) are ideal for the identification of subtypes as they are easy to use, quick to administer, and inexpensive to determine. In addition to developing models based on performance across a wide range of sensorimotor tasks to detect depression subtypes, the team will also try to identify which specific sensorimotor functions are predictive of treatment outcome.

Diagnostic Tools/Early Intervention

Justin D. Russell, Ph.D., University of Wisconsin-Madison, cites emerging evidence implicating disruption of a key neural circuit in pediatric PTSD involving the ventromedial prefrontal cortex and amygdala (vmPFC-AMYG). Deficiency in this circuit is a potent predictor of difficulty regulating emotion and arousal during times of stress. This study uses a neuroscience-informed approach to evaluate a novel biofeedback treatment that targets self-regulation. Biofeedback teaches individuals to recognize bodily sensations indicative of high arousal and then use that knowledge to control the arousal. Yet, this approach typically requires attention and engagement from the individual, which can be difficult for youths. To this end, the study implements biofeedback training using a virtual reality video game, DEEP VR, which uses respiratory biofeedback to guide players through a vivid, underwater adventure.

Next-Generation Therapies

Shai Sabbah, Ph.D., Hebrew University of Jerusalem, Israel, investigates the possibility of enhanced antidepressant efficacy when antidepressants are supplemented with light therapy. This points to the possibility of targeting mood-modulating, light-sensitive networks. This project will map mechanisms underlying the operation of such networks and their responses to light. The work follows from two important recent discoveries: the existence of specialized retinal cells that encode

environmental light intensity, and a newly-identified light sensitivity in a brain region connected to mood-regulating areas, innervated by retinal cells. Advanced techniques for recording neural cells' activity in conjunction with light manipulation and a highly specific localized genetic silencing of brain areas of interest will be used in conjunction with antidepressants in mice.

Next-Generation Therapies

Richard C. Sando, Ph.D., Vanderbilt University, notes that neural circuit function requires the specific, stereotyped establishment of diverse synaptic connections. This project concerns adhesion class G-protein-coupled receptors (GPCRs) called latrophilins (Lphns) and follows evidence that Lphn3 variants are strongly associated with ADHD. To probe their possible mechanistic role in synapses and neural circuits underlying ADHD-related behaviors, Dr. Sando will use Lphn3 knock-out mice to analyze the behavioral consequences of Lphn3 deletion from specific striatal and neuromodulatory cell populations known to be involved with ADHD-related behaviors. He will focus on behavioral paradigms of hyperactivity, attention and focus, anxiety, and reward learning. This will provide novel insights into how defined synapse subtypes and synaptic circuits are altered in ADHD-related mouse models.

Basic Research

Simon Thomas Schafer, Ph.D., Salk Institute for Biological Studies, is developing a methodological framework to elucidate autism spectrum disorder, asking: which neuronal cell types in the developing cortex are particularly vulnerable to ASD pathology? And, how do changes during early development lead to ASD pathology at later stages? Building upon a novel personalized induced pluripotent stem cell model he devised for a group of ASD subjects with macrocephaly, he will probe human organoid models from different subgroups of ASD patients with defined clinical endophenotypes to interrogate the cortical cell types that are particularly vulnerable to changes associated with ASD. He will then assess what consequences such early emerging changes have for later stages of brain development.

Basic Research

Pamela L. Scorza Bianchotti, Ph.D., Columbia University, will test epigenetic aging as a novel biological pathway for how mothers' childhood trauma is transmitted to their offspring, increasing risk for mental disorders. Her team will examine epigenetic aging in umbilical cord blood samples from over 250 newborns, whose mothers have reported on their own childhood trauma during the second trimester of pregnancy. Cord blood samples were collected when the babies were born, and infant cognitive development was measured when babies were four months old. The team will analyze DNA methylation and calculate epigenetic aging in the infant umbilical cord blood samples, then statistically analyze whether mothers' childhood trauma is associated with epigenetic aging in their infants, and whether epigenetic aging is associated with less optimal cognitive development.

Diagnostic Tools/Early Intervention

Johanna Seitz-Holland, M.D., Ph.D., Brigham and Women's Hospital and Harvard University, is studying aging of the brain in psychosis. This project focuses on the senescence-associated secretory phenotype (SASP) as a potentially clinically feasible early biomarker for accelerated aging in psychosis. The SASP comprises multiple proteins expressed by cells that no longer replicate and are involved in cell-cycle control, communication, and the immune-inflammatory response. The accumulation of SASP with age is linked to metabolic dysregulation, tissue deterioration (including the brain), and fragility. The central hypotheses are: 1) even young (age 16-35 years) patients with early psychosis display an increased SASP, which is associated with structural impairments of the brain; and 2) the SASP mediates the association between physical health-related factors (e.g., metabolic dysregulation, medication) and brain health in psychosis. A group of 40 patients and 30 controls will provide the data for the study.

Diagnostic Tools/Early Intervention

Nicolas B. Senese, Ph.D., University of Illinois at Chicago, proceeds from recent data suggest Gαq-coupled receptors, such as 5-HT2A (a serotonin receptor), primarily regulate cellular signaling from membrane subdomains known as lipid rafts. Although lipid rafts have been linked to antidepressant efficacy, the effects of the psychedelic psilocybin on lipid raft signaling have never been studied. Preliminary data show that psilocin (the active metabolite of psilocybin) reduces lipid raft localization of Gαq. Among other objectives, this study seeks to determine the extent of 5-HT2A receptor desensitization between raft and non-raft domains, and compare these processes between brain-derived (neuronal SK-N-SH and glial C6) and peripheral (kidney HEK-293) cell lines. The hope is that this information will be useful for researchers trying to develop novel antidepressants based on psilocybin's mechanism of action.

Next-Generation Therapies

Basic Research

Melissa J. Sharpe, Ph.D., University of California, Los Angeles, asks: how might positively valenced experience change the brain's fear circuit, and could this protect against the pathological fear responses that characterize anxiety disorders like PTSD? Specifically, this project will explore whether

past experience with reward learning shifts the encoding of fear memories toward the lateral hypothalamus and away from the traditional amygdala fear circuit; and whether reward learning, and the recruitment of lateral hypothalamus to encode fear memories, protects against the development of pathological fear. Dr. Sharpe will employ cell-type specific optogenetics and calcium imaging using fiber photometry in the context of a rodent model of PTSD.

Basic Research

Ikuko Smith, Ph.D., University of California, Santa Barbara, notes that a single cortical neuron has tens of thousands of excitatory synaptic inputs arriving onto small specialized protrusions on the dendrites called dendritic spines. These synaptic inputs provide noisy and unreliable electrical signals. It is up to the dendrites to cut through the cacophony, recognize and respond reliably to certain patterns. Dr. Smith will employ in vivo two-photon calcium imaging with genetically encoded calcium sensors, GCaMP8, and direct dendritic patch-clamp recordings to examine the changes in synaptic functions in cortical neurons of a well-established mouse model of tauopathy. This mouse overexpresses mutant human tau protein and exhibits progressive dendritic spine loss in sensory cortical neurons beginning around 5 months of age. The goal is to probe beyond structural changes to the functional principles of dendritic pathogenesis, which is present in a wide variety of brain and behavior disorders.

Basic Research

Sofia Soares, Ph.D., Harvard Medical School, is studying the dynamics within the cortex underlying learning and cognitive flexibility. This project probes how neocortical circuits change and interact during abstract visual-to-motor learning to promote flexible cognitive behavior. The main goal is to identify how novel activity patterns emerge and are maintained, both within and across multiple neocortical areas during learning. To achieve this goal, Dr. Soares, among other experiments, will train mice in a new virtual reality navigation task that isolates a period in which learning of abstract visual-to-motor associations must be flexibly integrated with previous knowledge. She will simultaneously image the activity of thousands of neurons spanning six neocortical areas while tracking the same neurons for more than one month within a period before, during and after mice learn this task. She will also investigate how communication between single neurons of the same vs. different neocortical areas develops and changes during learning.

Basic Research

Vaughn R. Steele, Ph.D., Yale University School of Medicine, seeks to develop novel interventions to help curb the opioid crisis. The open question in opioid use disorder (OUD), Dr. Steele says, is whether reduced craving and drug use are related to changes in underlying mechanisms related to dampening craving or increases in executive control to stop drug use. He proposes that assessing neuroplasticity via imaging and determining its relationship to behavioral measures of craving and executive control after an acute session of excitatory and inhibitory rTMS non-invasive brain stimulation could uncover these effects. The critical question addressed in this project is which rTMS type (excitatory vs inhibitory) applied to l-dlPFC modulates executive control and craving. The study will be conducted in a cohort of 30 patients.

Next-Generation Therapies

Tamara J. Sussman, Ph.D., Research Foundation for Mental Hygiene, Inc., is studying the ways in which adverse childhood experiences (ACEs) impact the brain's decision-making capacity, with special reference to risk for substance use disorder (SUD). She builds on 20 years of longitudinal assessments of ACEs in substance use in the Boricua Youth Study to examine the impact of ACEs on cognitive control in youth before the initiation of substance use, while accounting for familial SUD risk, such as parental substance use. She will add a reinforcement learning (RL) task to this study, allowing determination of whether ACEs lead to changes in strategic approaches to task performance vs. decrements in cognitive control. She hopes that modeling subject-level task performance will reveal which components of decision making are altered by ACEs, thus supporting development of novel approaches of prevention, e.g., cognitive remediation therapies for ACE-impacted aspects of decision making.

Basic Research

Patrick R. Sweeney, Ph.D., University of Illinois at Urbana-Champaign, seeks to develop a preventive therapy for stress-induced anorexia, anxiety, and anhedonia. Of specific interest is the melanocortin-3-receptor (MC3R), which is highly expressed in hypothalamic agouti-related peptide (AgRP) neurons, This project builds on the team's successful MC3R knockout mice which show enhanced anorexia in response to social isolation and restraint stress, and increased anxiety-related behavior. Preliminary data indicate that pharmacological activation of MC3R both increases feeding and reduces anxiety in an AgRP neuron-dependent manner. The team will administer MC3R agonists as a pharmacological strategy for preventing stress induced anorexia and anxiety-related behavior in the mice.

Next-Generation Therapies

Kristin L. Szuhany, Ph.D., New York University, is studying the role of exercise in the consolidation of fear extinction learning in adults with high anxiety sensitivity (AS). Mechanisms

underlying exercise's effect on fear extinction consolidation to guide optimal translation to practice are not well understood in anxiety patients with high AS. To better understand a variety of proposed mechanisms and their potential effects, the team will isolate the impact of exercise without cognitive behavioral therapy (CBT). This study will investigate exercise's effects on extinction learning consolidation in anxious adults with high AS, and examine potential mechanistic pathways including expectancy, affect, and stress-response markers. 50 adults with high AS and a primary anxiety disorder will participate. The team will measure mechanistic factors, including expected negative consequences of exercise (e.g., fainting), affect during exercise, and changes pre/post exercise in neuroendocrine markers and their effects on extinction recall.

Next-Generation Therapies

Keerthi Thirtamara Rajamani, Ph.D., Icahn School of Medicine at Mount Sinai, is studying oxytocin (OXT) in the context of brain disorders with social behavior deficits including schizophrenia and autism spectrum disorder (ASD). To learn more about neurocircuitry driving different forms of social behavior including social recognition, the team will (1) determine the role of PVN-OXT neurons (located in the hypothalamus) in acquisition vs. consolidation of long-term social recognition memory; (2) characterize neural responses in the supramammillary nucleus (SuM)—a brain structure in the posterior hypothalamus implicated in social recognition—during social interaction in wild type and Shank3-deficient rats; (3) examine if activation of PVN-OXT neurons and/or the PVN-OXT to SuM projections can reverse the long-term social recognition memory deficits in Shank3-deficient rats.

Basic Research

Brandy N. Tiernan, Ph.D., Western Carolina University, studies borderline personality disorder (BPD), in which patients have trouble regulating their emotions, suppressing impulses, and often have tumultuous and unstable interpersonal relationships. Cognitive control involves both intrapersonal and interpersonal monitoring and is important for relationships and social functioning. Dr. Tiernan will use the Dual Mechanisms of Control framework to examine how people with high BPD features use proactive control (e.g., resist interference) and reactive control (e.g., response efficiency) after a performing a social stressor task that triggers feelings of rejection. She hypothesizes that participants with "high BPD features" will have diminished ability to focus on goal-directed activity and that social stress will disrupt proactive and reactive control. Examining the neural mechanisms behind control-related deficits and features of emotion dysregulation could lead to discovering techniques to modify inflexible ways of thinking and promote cooperative behavior and functioning.

Basic Research

Max Tischfield, Ph.D., Rutgers University, is studying cognitive and sensory processing and attentional control deficits using animal models for Tourette syndrome (TS) with comorbid ADHD, with the ultimate goal of elucidating circuit mechanisms underlying hyperactivity, attentional impairments, and impulsivity in TS/ADHD. TS is hypothesized to result from functional imbalances in cortico-basal ganglia-thalamocortical (CBGTC) circuits that regulate sensorimotor processing and cognitive control. The team hypothesizes that the gene CELSR3 has novel circuit functions necessary to regulate both top-down and bottom-up control of sensory processing and attentional control. The hypothesis will be tested in a novel animal model. The experiments will position the team to use novel genetic models for TS/ADHD that have been engineered to express human mutations in CELSR3. These approaches could help build novel frameworks to elucidate circuit mechanisms that underlie hyperactivity, attentional impairments, and impulsivity in TS/ADHD.

Basic Research

Alejandro M. Trujillo, Ph.D., Icahn School of Medicine at Mount Sinai, is interested in tandem repeats (TRs), stretches of DNA comprised of two or more contiguous copies of a sequence of nucleotides arranged in head-to-tail pattern, e.g., CAG-CAG-CAG, that in some cases can undergo expansions, i.e. gain of copies. In addition to occurring in several neurological diseases, studies have shown that rare expansions of short tandem repeats (STRs) and common copy number variation of variable number of tandem repeats (VNTRs) may be linked to risk for schizophrenia. This project will screen for novel TR Expansions (TREs) and systematically genotype VNTR copy numbers in schizophrenia patients. It will investigate the hypothesis that common polymorphic copy number variation of VNTRs can act as a risk factor for schizophrenia, using datasets containing genome sequence information from thousands of patients and parents and controls.

Diagnostic Tools/Early Intervention

Blair Uniacke, M.D., Research Foundation for Mental Hygiene, Inc./Nathan Kline Institute, seeks to understand the role of dopamine in the development and persistence of pathological dietary restriction in anorexia nervosa (AN). This study will use neuromelanin-sensitive magnetic resonance imaging (NM-MRI), a high-resolution neuroimaging technique which provides a measure of dopamine neuron function in the midbrain, to examine dopamine function within the substantia nigra in adolescents with AN (n=40) and age-matched healthy volunteers (n=40). It will test the potential clinical utility of NM-MRI as a novel and noninvasive biomarker that can used safely in pediatric and adult

populations with AN. It will also will test a novel model of illness which proposes that reduced midbrain dopamine function in AN interferes with model-based learning and results in reliance on model-free learning and a heightened vulnerability to the development of persistent maladaptive eating behavior.

Basic Research

Diagnostic Tools/Early Intervention

Anna Robinson Van Meter, Ph.D., Feinstein Institute for Medical Research/Northwell Health, seeks to test "digital phenotyping" using data collected through smartphones to offer objective measurement of factors associated with near-term suicide risk in youth, possibly enabling short-term prediction. BiAffect collects metadata from the smartphone keyboard about the nature of patients' typing behavior, but not what is typed, to protect sensitive patient data. BiAffect variables map onto cognitive and affective domains associated with suicide, allowing for passive, objective assessment of risk with minimal burden. Adolescents aged 14-18 (40 with bipolar disorder, 40 with major depressive disorder) will have BiAffect installed on their phones to determine the effectiveness of the technology. Statistical learning techniques will produce predictive models for suicidal thoughts or behaviors.

Diagnostic Tools/Early Intervention

Sanne J.H. van Rooij, Ph.D., Emory University School of Medicine, cites studies showing positive effects on reducing PTSD symptoms of 1Hz TMS, a non-invasive brain stimulation therapy, focused on the right dorsolateral prefrontal cortex (rDLPFC). But the underlying mechanisms are unclear and there is no method to select the best TMS target for an individual patient. This study aims to individualize TMS treatment targets for PTSD and assess their stability and treatment efficacy. Patients will be randomized to 2 weeks of active (N=30) or placebo (N=30) TMS treatment. MRI scans and clinical measures will be collected before and after treatment. The goal is to define the rDLPFC area most strongly functionally connected with right amygdala. Using TMS neuronavigation, this region will be reliably targeted with 20 twice-daily TMS sessions over 10 consecutive weekdays.

Next-Generation Therapies

Youna Vandaele, Ph.D., University of Lausanne, Switzerland, is studying the "habit theory" in substance use disorder (SUD), which suggests that transition to SUD could emerge from the progressive dominance of drug habits over goal-directed behaviors, a process mediated by a shift in dopaminergic signaling from the mesolimbic to the nigrostriatal pathway. Yet drug addicts typically face a multitude of choices between drug and nondrug alternatives. It is thus critical to establish whether and how drug habits persist in real-world scenarios to promote compulsive drug use and SUD. Dr. Vandaele's preliminary findings show that cue-induced habitual learning is associated with dynamic changes in mesolimbic dopamine signaling. This leads to the hypothesis that dopamine signaling at the time of reward delivery promotes habits. This project will directly test this hypothesis and develop a new animal model of dopamine-induced habit in a choice setting.

Basic Research

Michael L. Wallace, Ph.D., Boston University, is studying the synaptic and cellular actions of serotonin in a brain area implicated in depression, the lateral habenula (LHb). It is a major target of serotonin neurons and known to be involved in evaluating outcomes of recently performed actions, with strong influence over regions involved in reward processing such as dopamine neurons. This project seeks to define and describe the specific circuit elements within the LHb modulated by serotonin. The team will target genetically defined neuron-types in the LHb and record their responses following serotonin application. This could reveal how LHb output is modulated by serotonin and how decreased serotonin level in depression affects LHb function. Additionally, synaptic input to the LHb from three different brain regions will be explored.

Basic Research

Meiyan Wang, Ph.D., Salk Institute for Biological Studies, will study inflammation-associated pathological changes in the brain to better understand how deregulation of immune processes increases risk for neuropsychiatric disorders. Dr. Wang will use technologies that enable generation of 3D brain organoids from human pluripotent stem cells. She has established a platform to study human astrocytes, a type of glial cell that mediates inflammatory signals in the brain. She aims to examine the morphological, molecular, and functional changes of human astrocytes under inflammatory conditions and to investigate how these changes could affect neuronal function. Such knowledge could reveal new molecular and cellular targets for developing therapeutic interventions for neuropsychiatric disorders.

Basic Research

Yun Wang, M.D., Ph.D., Research Foundation for Mental Hygiene, Inc./Nathan Kline Institute, seeks to elucidate the mechanism underlying the association between prenatal SSRI exposure and social behavior deficits in offspring. The study will draw upon a birth cohort in Sherbrooke, Canada, initially enrolling pregnant women with (n=250) and without (n=125) a depressive disorder (ages 18-35) during the first trimester of

pregnancy, and assess the course of their depressive symptoms and medication usage over gestation. A subsample (n=60) will have scans at birth to improve the measurement of myelin contents; an eye-tracking paradigm will be added to measure visual attention to social cues at 12 months. Given studies showing that prenatal SSRI exposure adversely affects offspring brain myelination, the team hypothesizes that in utero SSRI exposure will be associated with decreased myelination.
Basic Research

Cory R. Weissman, M.D., University of California, San Diego, has generated evidence that improvement in suicidality symptoms with brain stimulation treatment is correlated with changes in cortical inhibition. A prospective clinical trial to confirm the effectiveness of bilateral brain stimulation on suicidality, while exploring cortical inhibition, is urgently needed, Dr. Weissman says. The team will recruit 80 patients diagnosed with treatment-resistant depression and struggling with suicidality. Objectives are first to confirm the therapeutic effects of bilateral theta burst stimulation (TBS) as a treatment for suicidality in this patient population compared to placebo. A second is to confirm the therapeutic effects of this configuration of TBS on overall depression, and on the suicidality-related outcomes of suicide attempts and completions. Third, the team will explore biological targets of bilateral TBS using an emerging, powerful tool to measure cortical inhibition: combined transcranial magnetic stimulation and electroencephalography (TMS-EEG).
Next-Generation Therapies

Elizabeth A. West, Ph.D., Rowan University, notes that a history of substance use disorder (SUD) leads to heightened prefrontal cortex activation to drug-associated stimuli, which correlates with feelings of craving before cocaine use. It also leads to reduced prefrontal brain activity when viewing cues linked to non-drug rewards. Dr. West has reported a similar phenomenon in rats in which the prelimbic cortex (PrL) shows increased activation to drug cues but dampened activation to reward predictive cues (non-drug). This project will link differential neural firing within the PrL and infralimbic cortex (IL) to drug reward cues and nondrug reward cues with GABAergic interneuron activity. A cell-type specific viral construct will be used to measure calcium dynamics in this specific population with cellular resolution in awake and behaving rats. This could help delineate microcircuit-level mechanisms underlying craving and loss of desire for natural rewards, which could help optimize treatment for SUD.
Basic Research

Melinda Westlund Schreiner, Ph.D., University of Utah, aims to learn about neurobiological characteristics associated with self-injurious thoughts and behaviors (SITBs) and will examine mechanisms of action of a promising intervention targeting rumination in reducing SITBs and subsequent hospitalizations. Rumination has been closely associated with SITBs and can interfere with treatment progress. The hypothesis is that rumination will be associated with specific neural connectivity patterns and that targeting rumination via a specific intervention will reduce SITBs. The project will add a sample of adolescents with SITBs and a recent hospitalization to an existing NIH-funded study of rumination-focused cognitive behavioral therapy (RFCBT) for adolescents with remitted major depressive disorder. Participants will receive 10-14 sessions of RFCBT. They will also complete pre- and post-intervention neuroimaging.
Next-Generation Therapies

Shawniqua Williams Roberson, M.D., Vanderbilt University Medical Center, notes that of the 4 million+ annual ICU admissions in the U.S., 27%-40% of survivors suffer new or worsening anxiety, depression, impaired cognition and/or post-traumatic stress symptoms—psychological manifestations of Post-Intensive Care Syndrome (PICS). This project aims to generate pilot data to support a study validating EEG as an early diagnostic tool for post-ICU anxiety, depression, and PTSD. Major depression, generalized anxiety disorder, and post-traumatic stress disorder are all associated with changes in brain functional connectivity and oscillatory patterns measurable by electroencephalography (EEG). This research asks whether neurofeedback training, a form of EEG-based biofeedback that allows individuals to improve their brain activity patterns, can decrease symptom severity in anxiety, depression, and post-traumatic stress symptoms associated with PICS.
Next-Generation Therapies
Diagnostic Tools/Early Intervention

Miles Wischnewski, Ph.D., University of Minnesota, will conduct an experiment in which rTMS efficacy for obsessive-compulsive disorder is optimized by customizing brain stimulation parameters to each person's brain oscillation "fingerprint." Recently, the team developed a "closed-loop" rTMS system that reads out brain oscillation phase in real-time to adjust stimulation. That is, electroencephalography recordings are used to determine an individual's personal brain oscillation fingerprint and rTMS is delivered to the exact rhythm of that brain oscillation. Thus, rTMS is personalized and time-specific, related to the beta oscillation phase (~20 Hz). Since frontal cortex beta oscillations are associated with affective and cognitive symptoms in OCD, personalized rTMS is hypothesized to improve these functions. In this study, participants in the experimental group will receive a personalized rTMS session, which will be compared to results in two control groups.
Next-Generation Therapies

Justin M. Wolter, Ph.D., University of North Carolina at Chapel Hill, aims to establish a resource to systematically identify genetic interactions between high-risk autism genes and common genetic variation. This project will build upon work in which Dr. Wolter established a cell culture-based approach to conduct genome wide association studies in primary neural progenitor cells. Here, he will establish a pilot library of genetically diverse induced pluripotent stem cell (iPSC) lines stratified by autism risk scores. This library will be used to test a novel pooled cell culture system, which can rapidly and efficiently quantify cellular phenotypes in up to 100 distinct cell lines cultured together in a single experiment. This system will be used to identify how common genetic variation and baseline autism risk affects neural progenitor proliferation in the context of PTEN haploinsufficiency, a genetic aberration which causes autism with macrocephaly.

Basic Research

Mary L. Woody, Ph.D., University of Pittsburgh, notes that racial stress and trauma (RST), the significant fear and distress that can caused by exposure to racial discrimination and bias, is linked to the initial development of depression among black youth, particularly early adolescent black girls. Yet it is often neglected in models seeking to understand causes of depression. This project posits that black early adolescent girls, compared to their white peers, will be more likely to exhibit attentional vigilance for threat of racial harm, which will impair goal-directed attention, be associated with higher levels of RST, and heighten risk for future increases in depressive symptoms. Dr. Woody will test these hypotheses using steady-state visual evoked potentials (SSVEPs) derived from participant brain waves (via EEG) to provide a brain-based index of attentional vigilance for threat stimuli relevant to racial discrimination and gauge the extent to which it impairs attention to a primary cognitive task. Participants will be recruited from an ongoing longitudinal study of 90 adolescent girls with increased risk for depression due to clinical depression in their mothers.

Diagnostic Tools/Early Intervention

Frances Xia, Ph.D., University of California, San Francisco, will explore the neuronal and circuit mechanisms underlying changes in ventral hippocampal-amygdala interactions in a depressed population. By performing large-population neural recordings in ventral hippocampus and amygdala simultaneously, Dr. Xia will identify patterns of activity in two regions that track with mood and examine how they are altered in those susceptible to depression. He will identify specific projections and circuits that underpin ventral hippocampal-amygdala interactions to generate mood-related behavior. And he will test how specific cell types and pathways can be manipulated to enhance stress resilience. The findings could provide insight into mechanisms by which depression alters the processing of emotional information.

Basic Research

Junhua Yang, Ph.D., Johns Hopkins University School of Medicine, notes repeated use of cocaine can cause long-term changes in the brain's dopamine (DA) system. Recent studies indicate that disinhibition of ventral tegmental area (VTA) DA neurons via inhibition of local VTA GABA neurons represents a key mechanism in drugs of abuse. Swell1-dependent Volume-Regulated Anion Channel (VRAC), a major player in cell volume regulation, has been shown to be permeable to neurotransmitters, including GABA. How drug use drives inhibitory transmission and whether VTA astrocytes play a role in this process remain largely unknown. This project seeks to determine the role of the astrocytic Swell1 channel in tonic GABA release and the potential impact of this tonic GABA on cocaine addiction.

Basic Research

Kazunari Yoshida, M.D., Ph.D., Centre for Addiction and Mental Health, University of Toronto, Canada, seeks to develop a tool that will identify individuals taking antipsychotic medicines who are at risk of developing weight gain. The advent of novel technologies allowing researchers to estimate the effects of multiple genetic risk variants (i.e., polygenic risk scores, PRS), provides a means of investigating the overlap of the genetic liability to antipsychotic-induced weight gain (AIWG) and antipsychotic efficacy. This project seeks to discover: (1) Are there overlapping genetic factors for AIWG and antipsychotic efficacy? (2) Is there a correlation between PRSs for AIWG, antipsychotic efficacy, and related metabolic outcomes (e.g., diabetes and hyperlipidemia)? (3) Can AIWG and antipsychotic efficacy be predicted using state-of-the-art machine learning algorithms integrating clinical and genetic factors? (4) Is there a causal relationship between AIWG and treatment response? A large, well-characterized sample of individuals with schizophrenia prospectively assessed for AIWG and antipsychotic efficacy will be used for the study.

Diagnostic Tools/Early Intervention

Peng Zhong, Ph.D., SRI International, studies dysfunction of sleep-control circuits in depression. Sleep problems occur in ~90% of patients with major depressive disorder, suggesting that the two conditions share biological features, yet the neural mechanisms underlying the association between sleep and depression are poorly understood. The hypothesis in

this project is that rapid eye movement (REM) sleep-control melanin-concentrating hormone (MCH) neurons become dysfunctional in depression. Using chronic mild unpredictable stress as a mouse model of depression, the team seeks to determine if chronic stress causes sleep disturbance and whether it affects the firing patterns of REM-active MCH neurons across sleep-wake cycles.

Basic Research

Yang Zhou, Ph.D., McGill University, Canada, notes that among hundreds of genes contributing to autism risk, CHD8 has emerged as a leading candidate. It encodes a protein that is a master regulator of epigenetic modification of DNA. This project seeks to boost understanding of astrocyte-specific-roles of CHD8 in postnatal brain development and behavioral function. During the first 3 weeks of postnatal development, the number of astrocytes expands many-fold; appropriate proliferation, differentiation and function are crucial to the regulation of neural development. This project seeks to identify astrocyte-specific transcriptional signatures mediated by the CHD8 gene. This could reveal the role of CHD8 in the proliferation and maturation of astrocytes in the postnatal brain. It could help reveal how CHD8 contributes to astrocyte-mediated synaptic development and animal behavior. Outcomes could contribute to the identification of molecular mechanisms underlying neurodevelopmental disorders resulting from CHD8 mutation.

Basic Research

Anna Zilverstand, Ph.D., University of Minnesota, seeks to develop a dynamic medical tool to track real-life risk of early drinking. She will investigate risk factors underlying early initiation of alcohol use during childhood. Early age of alcohol initiation predicts later heavy drinking, alcohol-related problems, and risk for persistent substance dependence in adulthood. She proposes that risk factors predictive of and causally linked to initiation of alcohol use may vary by age. The project will employ machine learning to investigate complex factors underlying risk of early drinking at different ages (e.g., 10, 11, 12 years old). Based on the premises that environmental factors dominate early in life when the child is more dependent, and that developmental changes during early adolescence initiate a period of increasing independence, the team expects to find that predictive models of risk of early drinking will need to be age-dependent to dynamically track risk with increasing age. The hypothesis will be tested using the NIH's Adolescent Brain Cognitive Development (ABCD) study dataset.

Diagnostic Tools/Early Intervention

Institutions of 2021 Young Investigators, at the time of grant award

Aix-Marseille University/CNRS, France

Albert Einstein College of Medicine

Amsterdam University Medical Centers, The Netherlands

Beth Israel Deaconess Medical Center

Boston College

Boston University

Brigham and Women's Hospital (3)

Brown University

Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Denmark

Center for Neuroscience and Cell Biology, Portugal

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

Charité University Medicine Berlin and Freie Universitat Berlin, Germany

Children's National Hospital

Cold Spring Harbor Laboratory

Columbia University (5)

Cornell University

Dell Medical School, University of Texas at Austin

Duke University

Emory University School of Medicine (2)

Feinstein Institute for Medical Research/Northwell Health

Georgetown University

Georgia State University

Harvard University (8)

Harvard Medical School

Hebrew University, Israel (2)

Icahn School of Medicine at Mount Sinai (5)

INSERM, France

Institute of Functional Genomics, Université de Montpellier, France

Institute of Science and Technology, Austria

Johns Hopkins University School of Medicine

King's College London, UK (3)

Laureate Institute for Brain Research

Leiden University, The Netherlands

Lieber Institute for Brain Development, Johns Hopkins University

Ludwig Maximillian University, Germany

Massachusetts General Hospital (3)

McGill University, Canada

McLean Hospital (3)

Medical University of Vienna, Austria

Michigan State University

New York University (2)

New York University School of Medicine

Northwestern University

Radboud University, The Netherlands

Rutgers University (2)

Research Foundation for Mental Hygiene, Inc./ Nathan Kline Institute (5)

Rowan University

St. Louis College of Pharmacy and Washington University in St. Louis

Salk Institute for Biological Studies (2)

Santa Clara University

SRI International

Stanford University (6)

Stony Brook University

Taipei Medical University, Republic of China

Technion-Israel Institute of Technology, Israel

The Rockefeller University (3)

University Hospital Würzburg, Germany

University of Basel, Switzerland

University of Calgary, Canada

University of California, Berkeley

University of California, Irvine

University of California, Los Angeles (5)

University of California, Riverside

University of California, San Diego (4)

University of California, San Francisco (4)

University of California, Santa Barbara

University of Illinois at Chicago (2)

University of Illinois at Urbana-Champaign

University of Iowa

University of Lausanne, Switzerland

University of Maryland

University of Massachusetts Medical School (2)

University of Minnesota 3

University of North Carolina at Chapel Hill

University of Oregon

University of Pennsylvania

University of Pittsburgh (5)

University of Southern Mississippi

University of Sydney, Australia

University of Turin, Italy (2)

University of Utah (2)

University of Washington

University of Wisconsin

University of Wisconsin-Madison

University of Wyoming

University of Zurich Brain Research Institute, Switzerland

Vanderbilt University (3)

Vanderbilt University Medical Center

Virginia Polytechnic Institute and State University

Vrije Universiteit Amsterdam, The Netherlands

Wayne State University

Washington University School of Medicine

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As of August 2021

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