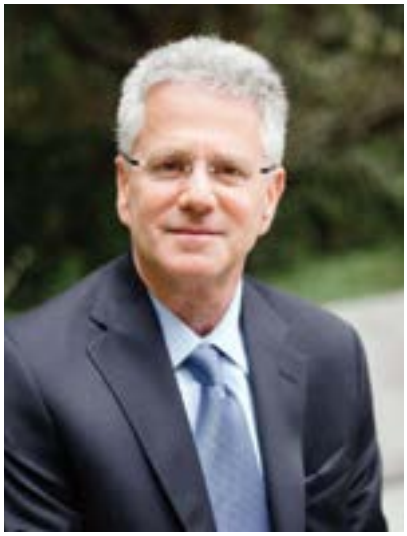
BRAIN & BEHAVIOR RESEARCH FOUNDATION

2022 Young Investigators

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

RESEARCH
19 35 years 87
FOR CURES



"BBRF Young Investigators represent a new generation of researchers who will pioneer breakthroughs in mental health research. We are excited to be able to support the work of these young scientists, who will apply powerful new technologies and insights to finding better treatments, cures, and methods of prevention for mental illness."

September 2022

We are pleased to present to you the 2022 Brain & Behavior Research Foundation Young Investigator Grantees. 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 opportunities and supports basic, translational, and clinical researchers.

This year, the Foundation's Scientific Council, led by Dr. Herbert Pardes and comprised of 177 world-renowned scientists with expertise in every area of brain research, reviewed more than 630 applications and selected the 150 meritorious research projects summarized in the pages that follow.

The 2022 Young Investigators are focused on a broad range of psychiatric illnesses, including depression, schizophrenia, and PTSD. Nearly two dozen grantees will perform innovative research on addiction, including the epidemics of opioid- and alcohol-use disorders, which appear to have intensified during the pandemic. As rates of suicide in the U.S. continue to increase, seven grantees are creatively addressing new and better ways of predicting who among us is at greatest risk of suicide, and on ways of preventing or reducing suicidal behavior.

It is also notable that a dozen of the 2022 projects involve brain stimulation, including approaches that are both invasive and non-invasive, and new applications which are rapid-acting. Several seek to better understand how transcranial magnetic stimulation (TMS) changes neural cells and circuits to achieve therapeutic effects.

Some 2022 Young Investigators are performing pioneering studies of new and as yet unproven methods of brain stimulation. Several are working with t-FUS (focused transcranial ultrasound stimulation), which delivers acoustic energy to targets of interest deep in the brain. This potentially could be a non-invasive alternative to deep-brain stimulation.

These projects represent 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.

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 $440 million in 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

OUR SCIENTIFIC COUNCIL

177 Scientific Council Members (24 Emeritus)
49 Members of the National Academy of Medicine
39 Chairs of Psychiatry & Neuroscience Departments
16 National Institutes of Health Chiefs & Directors
7 Members of the National Academy of Sciences
3 Recipients of the National Medal of Science
2 Directors of the National Institute of Mental Health
1 Nobel Prize Winner

PRESIDENT
Herbert Pardes, M.D.

VICE PRESIDENT EMERITUS
Floyd E. Bloom, M.D.

Ted Abel, Ph.D.
Anissa Abi-Dargham, M.D.
Nii A. Addy, Ph.D.
Susanne E. Ahmari, M.D., Ph.D.
Schahram Akbarian, M.D., Ph.D.
Susan G. Amara, Ph.D.
Stewart A. Anderson, M.D.
Nancy C. Andreasen, M.D., Ph.D.
Victoria Arango, Ph.D.
Amy F.T. Arnsten, Ph.D.
Gary S. Aston-Jones, Ph.D.
Randy P. Auerbach, Ph.D.
Jay M. Baraban, M.D., Ph.D.
Deanna M. Barch, Ph.D.
Samuel H. Barondes, M.D.
Carrie E. Bearden, Ph.D.
Francine M. Benes, M.D., Ph.D.
Karen F. Berman, M.D.
Wade H. Berrettini, M.D., Ph.D.
Randy D. Blakely, Ph.D.
Pierre Blier, M.D., Ph.D.
Hilary P. Blumberg, M.D.
Vadim Bolshakov, Ph.D.
Antonello Bonci, M.D.
Kathleen T. Brady, M.D., Ph.D.
Kristen J. Brennand, Ph.D.
Robert W. Buchanan, M.D.
Peter F. Buckley, M.D.
Edward T. Bullmore, Ph.D.
William E. Bunney, Jr., M.D.
Joseph D. Buxbaum, Ph.D.
William Byerley, M.D.
Tyrone D. Cannon, Ph.D.
William Carlezon, Ph.D.
William T. Carpenter, Jr., M.D.
Cameron S. Carter, M.D.
Peter Jeffrey Conn, Ph.D.
Edwin H. Cook, Jr., M.D.
Richard Coppola, D.Sc.
Christopher W. Cowan, Ph.D.
Joseph T. Coyle, M.D.
Jacqueline N. Crawley, Ph.D.
Z. Jeff Daskalakis, M.D., Ph.D.
Karl Deisseroth, M.D., Ph.D.
J. Raymond DePaulo, Jr., M.D.
Robert Desimone, Ph.D.
Ariel Y. Deutch, Ph.D.
Ralph DiLeone, Ph.D.
Lisa Beth Dixon, M.D., M.P.H.
Wayne C. Drevets, M.D.
Kafui Dzirasa, M.D., Ph.D.
Guoping Feng, Ph.D.
Robert L. Findling, M.D., MBA
Stan B. Floresco, Ph.D.
Judith M. Ford, Ph.D.
Alan Frazer, Ph.D.
Robert Freedman, M.D.
Aurelio Galli, Ph.D.
Mark S. George, M.D.
Elliot S. Gershon, M.D.
Mark A. Geyer, Ph.D.
Jay N. Giedd, M.D.
Jay A. Gingrich, M.D., Ph.D.
James M. Gold, Ph.D.
David Goldman, M.D.
Joshua A. Gordon, M.D., Ph.D.
Elizabeth Gould, Ph.D.
Anthony A. Grace, Ph.D.
Raquel E. Gur, M.D., Ph.D.
Suzanne N. Haber, Ph.D.
Philip D. Harvey, Ph.D.
Stephan Heckers, M.D.
René Hen, Ph.D.
Takao K. Hensch, Ph.D.
Robert M.A. Hirschfeld, M.D.
Elliot Hong, M.D.
Yasmin L. Hurd, Ph.D.
Robert B. Innis, M.D., Ph.D.
Jonathan A. Javitch, M.D., Ph.D.
Daniel C. Javitt, M.D., Ph.D.
Dilip V. Jeste, M.D.
René S. Kahn, M.D., Ph.D.
Ned H. Kalin, M.D.
Peter W. Kalivas, Ph.D.
Eric R. Kandel, M.D.
Richard S.E. Keefe, Ph.D.
Martin B. Keller, M.D.
John R. Kelsoe, M.D.
Kenneth S. Kendler, M.D.
James L. Kennedy, M.D.
Robert M. Kessler, M.D.
Mary-Claire King, Ph.D.
John H. Krystal, M.D.
Amanda J. Law, Ph.D.
James F. Leckman, M.D., Ph.D.
Francis S. Lee, M.D., Ph.D.
Ellen Leibenluft, M.D.
Robert H. Lenox, M.D.
Pat R. Levitt, Ph.D.
David A. Lewis, M.D.
Jeffrey A. Lieberman, M.D.
Kelvin Lim, M.D.
Sarah Hollingsworth Lisanby, M.D.
Joan L. Luby, M.D.
Irwin Lucki, Ph.D.
Gary Lynch, Ph.D.
Robert C. Malenka, M.D., Ph.D.
Anil K. Malhotra, M.D.
Husseini K. Manji, M.D., F.R.C.P.C.
J. John Mann, M.D.
John S. March, M.D., M.P.H.
Stephen Maren, Ph.D.
Daniel H. Mathalon, Ph.D., M.D.
Helen S. Mayberg, M.D.
Carla A. Mazefsky, Ph.D.
Colleen A. McClung, Ph.D.
Ronald McKay, Ph.D.
James H. Meador-Woodruff, M.D.
Herbert Y. Meltzer, M.D.
Kathleen R. Merikangas, Ph.D.
Richard J. Miller, Ph.D.
Guo-Li Ming, M.D., Ph.D.
Karoly Mirnics, M.D., Ph.D.
Bita Moghaddam, Ph.D.
Lisa M. Monteggia, Ph.D.
Charles B. Nemeroff, M.D., Ph.D.
Eric J. Nestler, M.D., Ph.D.
Andrew A. Nierenberg, M.D.
Patricio O'Donnell, M.D., Ph.D.
Dost Ongur, M.D., Ph.D.
Maria A. Oquendo, M.D., Ph.D.
Godfrey D. Pearlson, M.D., Ph.D.
Peter Penzes, Ph.D.
Mary L. Phillips, M.D., M.D. (CANTAB)
Marina R. Picciotto, Ph.D.
Daniel S. Pine, M.D.
Robert M. Post, M.D.
James B. Potash, M.D., M.P.H.
Susan Powell, Ph.D.
Pasko Rakic, M.D., Ph.D.
Judith L. Rapoport, M.D.
Perry F. Renshaw, M.D., Ph.D., M.B.A.
Kerry J. Ressler, M.D., Ph.D.
Victoria B. Risbrough, Ph.D.
Carolyn B. Robinowitz, M.D.
Carolyn Rodriguez, M.D., Ph.D.
Bryan L. Roth, M.D., Ph.D.
Laura M. Rowland, Ph.D.
Scott Russo, Ph.D.
Gerard Sanacora, M.D., Ph.D.
Akira Sawa, M.D., Ph.D.
Alan F. Schatzberg, M.D.
Nina R. Schooler, Ph.D.
Robert Schwarcz, Ph.D.
Yvette I. Sheline, M.D.
David A. Silbersweig, M.D.
Vikaas S. Sohal, M.D., Ph.D.
Matthew W. State, M.D., Ph.D.
Murray B. Stein, M.D., M.P.H., F.R.C.F.C.
Stephen M. Strakowski, M.D.
Carol A. Tamminga, M.D.
Laurence H. Tecott, M.D., Ph.D.
Flora M. Vaccarino, M.D.
Rita J. Valentino, Ph.D.
Jeremy M. Veenstra-VanderWeele, M.D.
Susan M. Voglmaier, M.D., Ph.D.
Aristotle N. Voineskos, M.D., Ph.D.
Nora D. Volkow, M.D.
Karen Dineen Wagner, M.D., Ph.D.
Daniel R. Weinberger, M.D.
Myrna M. Weissman, Ph.D.
Jared W. Young, Ph.D.
L. Trevor Young, M.D., Ph.D., F.R.C.P.C., F.C.A.H.S.
Carlos A. Zarate, Jr., M.D.
Jon-Kar Zubieta, M.D., Ph.D.

MEMBERS EMERITUS
George K. Aghajanian, M.D.
Huda Akil, Ph.D.
Jack D. Barchas, M.D.
BJ Casey, Ph.D.
Dennis S. Charney, M.D.
Bruce M. Cohen, M.D., Ph.D.
Fred H. Gage, Ph.D.
Fritz A. Henn, M.D., Ph.D.
Steven E. Hyman, M.D.
Samuel J. Keith, M.D.
Kenneth K. Kidd, Ph.D.
Rachel G. Klein, Ph.D.
Steven M. Paul, M.D.
Steven G. Potkin, M.D.
John L.R. Rubenstein, M.D., Ph.D.
Bernardo Sabatini, M.D., Ph.D.
Solomon H. Snyder, M.D.
John S. Strauss, M.D.
John A. Talbott, M.D.
Ming T. Tsuang, M.D., Ph.D., D.Sc.
Kay M. Tye, Ph.D.
Jim van Os, M.D., Ph.D., MRCPsych
Mark von Zastrow, M.D., Ph.D.
Marina E. Wolf, Ph.D.

SUMMARY OF 2022 YOUNG INVESTIGATOR GRANTS BY ILLNESS*

23 **ADDICTION / SUBSTANCE-USE DISORDERS** (pp. 7–11)	9 **ADHD** (pp. 11–12)	27 **ANXIETY DISORDERS** (pp. 12–17)	12 **AUTISM SPECTRUM DISORDER** (pp. 17–19)
11 **BIOLOGY OF THE BRAIN** (pp. 9–21)	8 **BIPOLAR DISORDER** (pp. 21–22)	2 **BORDERLINE PERSONALITY DISORDER** (pp. 22–23)	45 **DEPRESSION** (pp. 23-30)
7 **EATING DISORDERS** (pp. 30–31)	9 **OBSESSIVE-COMPULSIVE DISORDER (OCD)** (pp. 32–33)	7 **OTHER DISORDERS** (pp. 33–34)	2 **PERSONALITY-DISORDERS (GENERAL)** (p. 34)
15 **PTSD** (pp. 35–37)	8 **PSYCHOSIS** (pp. 37–38)	34 **SCHIZOPHRENIA** (pp. 38–44)	7 **SUICIDE PREVENTION** (pp. 44–45)

*These statistics reflect the fact that many projects are relevant in more than one category; in the pages that follow, grantee project descriptions appear under each relevant category.

CO-CHAIRS OF THE YOUNG INVESTIGATOR GRANT SELECTION COMMITTEE

Judy M. Ford, Ph.D.

Professor, Department of Psychiatry
University of California, San Francisco

2003 Independent Investigator

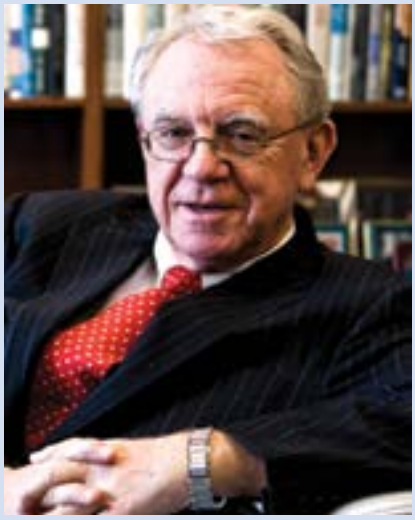
BBRF Scientific Council Member

Suzanne N. Haber, Ph.D.

Professor, Department of Pharmacology and Physiology
University of Rochester School of Medicine and Dentistry

2011 Distinguished Investigator

BBRF Scientific Council Member



"BBRF Young Investigator grants have led to groundbreaking research that has improved the lives of people living with mental illness. These early-career scientists are making significant strides in basic research, early intervention, and diagnostic tools, new technologies, and next-generation therapies that will offer the best hope for advances in treatments for psychiatric illnesses."

Herbert Pardes, M.D.

President of the BBRF Scientific Council
Executive Vice Chairman of the Board of Trustees
NewYork-Presbyterian Hospital

SINCE 1987

AWARDED
6,400
GRANTS

FUNDED
$440M
GRANTS

THE 2022 YOUNG INVESTIGATOR GRANTEES

The Foundation is pleased to announce over $10.2 million in 150 new two-year grant awards to support the work of promising young scientists with innovative ideas in mental health research.

632
YOUNG INVESTIGATOR APPLICATIONS

150
YOUNG INVESTIGATOR GRANTS AWARDED

$10.2
MILLION AWARDED IN YOUNG INVESTIGATOR GRANTS

RESEARCH CATEGORIES

Basic Research (102 Grants)
To understand what happens in the brain to cause mental illness

Next-Generation Therapies (37 Grants)
To reduce symptoms of mental illness and ultimately cure and prevent brain and behavior disorders

Diagnostic Tools/Early Intervention (22 Grants)
To recognize early signs of mental illness and treat as early as possible

New Technologies (10 Grants)
To advance or create new ways of studying and understanding the brain

About 68 percent of the projects funded are **basic research**, the wellspring of innovation in brain research, as in all sciences.

About 25 percent of the 2022 grants fund projects that specifically aim to develop **next-generation therapies.**

About 15 percent of the projects funded are **diagnostic tools/early intervention** that aim to prevent brain and behavior disorders.

About 7 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.

Seventy-three percent of grantees are from the United States (110 grantees). Twenty-seven percent of grantees come from 14 other countries (40 grantees): Australia, Austria, Canada, France, Germany, Ireland, Israel, Mexico, Portugal, The Netherlands, Spain, Sweden, Switzerland, and Turkey.

THE 2022 BBRF YOUNG INVESTIGATOR GRANTEES

ADDICTION / SUBSTANCE-USE DISORDERS

Aditi Banerjee, Ph.D., Harvard Medical School, seeks to characterize the principles of dopamine release in striatum. Generally, such release is evoked by action potentials and triggered by proteins called calcium sensors, which trigger either synchronous or asynchronous release. This project seeks to visualize synchronous and asynchronous dopamine release in brain slices using dopamine sensor imaging and determine the individual contributions of synchronous vs. asynchronous release in maintaining dopamine levels and function. Identifying key molecular mechanisms ensuring temporal dynamics of dopamine release and signaling is important since dopamine signaling is impaired in a wide range of disorders, including addiction.

Basic Research

Inbal Ben-Ami Bartal, Ph.D., Abarbanel Mental Health Center Tel Aviv University, Israel, is interested in molecular mechanisms involved in the brain's reward and motivation systems, particularly in the nucleus accumbens (NAc), and is seeking to study whether social reward may override reward afforded by various addictive substances. This project will elucidate the neural activation specifically associated with pro-social reward, potentially shedding light on new strategies for treating patients with substance use disorder and enhancing individual wellbeing. Working with rodent models, the investigator will test the idea that daily sustained helping behavior is more effective in preventing relapse than social interaction.

Next-Generation Therapies

Sujan Chandra Das, Ph.D., University of California, Irvine, proceeds from research that has identified the nucleus accumbens, a critical ventral striatal brain region, as a modulator of alcohol drinking. This project will use a variety of technologies to answer these questions: Does alcohol differentially affect each cell population within the nucleus accumbens? If a particular cell population is affected by alcohol use disorder (AUD), what are the genes and protein alterations within those affected cell populations? This is the first study of cell specificity of human nucleus accumbens from individuals who died with AUD, as confirmed by autopsy. A cell-type-specific molecular signature may identify therapeutic targets for reversal of some features of AUD.

Basic Research

Matthew P. Gardner, Ph.D., Concordia University, will take a 'bottom-up' approach to substance use. This entails characterization of brain circuits believed to be involved in substance use disorders (SUDs) during normal function and in response to drugs, or following drug exposure. He will focus on how the neural systems underlying rational choice in rodents operate under drug-naïve and previous drug-exposure conditions. He seeks to understand whether prior drug use disrupts the processes in the orbitofrontal cortex (OFC) important for making rational decisions when confronted with new situations. To do this, he will record from the OFC in rats while they perform an economic decision-making task during presentation of food pairs that the subject has seen many times before or has never encountered. Prior work showed that the OFC is only required during these latter types of situations. This work has the potential to shed light on how neural systems underlying decision-making are modified following previous drug use.

Basic Research

Ahmed N. Hassan, M.D., Centre for Addiction and Mental Health, University of Toronto, Canada, hopes to identify the interaction between specific genes and significant environmental distress that contributes to the risk of alcohol consumption and development of alcohol use disorder (AUD). This could help in early identification and in providing interventions for prevention. Dr. Hassan cites studies finding that racial discrimination is associated with poor mental and physical health, including binge drinking. The hypothesis in this project is that revealing clues may lie in genetics. It will analyze an existing genomic dataset which consists of 22,848 samples, capturing 295,218 single-letter DNA variations (SNPs), genotyped for all individuals. Dr. Hassan will use sophisticated study design to ensure balanced observed covariates between two groups of individuals with and without racial discrimination.

Diagnostic Tools/Early Intervention

Basic Research

Max Emanuel Joffe, Ph.D., University of Pittsburgh, suggests that understanding how ethanol affects prefrontal cortex (PFC) circuit function is essential to better understand the etiology of alcohol use disorder (AUD) and to guide the development of new medications. He seeks to manipulate alcohol memories by modulating prefrontal cortex parvalbumin interneurons. This project aims to build a better understanding of how inhibitory fast-spiking interneurons expressing parvalbumin (PV-INs) contribute to persistent

alcohol memories and to discover new druggable targets expressed by these cells. PV-INs are indispensable for coordinating PFC circuit function, and PFC PV-INs display specialized transcriptomes and proteomes relative to other interneuron subtypes, to pyramidal cells, and to glia. Thus, Dr. Joffe says, there is great potential to target PV-INs for the development of next-generation pharmacological interventions.

Basic Research
Next-Generation Therapies

Kari A. Johnson, Ph.D., Uniformed Services University of the Health Sciences, proceeds from recent studies showing that global deletion of the gene encoding metabotropic glutamate receptor 2 (mGlu2), a critical presynaptic regulator of glutamate transmission in the CNS, increases vulnerability to excessive consumption of drugs including alcohol, cocaine, and heroin. Novel pharmacological agents that enhance mGlu2 activity reduce drug use in preclinical models and are currently in clinical development to treat substance use disorders. However, the mechanisms by which mGlu2 bidirectionally regulates drug consumption are not well understood. Using a transgenic mouse model that allows conditional deletion of mGlu2 from defined neuron populations, this project seeks to delineate how mGlu2 regulation of discrete brain circuits contributes to high-risk patterns of drug use.

Basic Research

Thang M. Le, Ph.D., Yale University, recently demonstrated a mutually reinforcing relationship between negative affect, avoidance response, and problem drinking. This relationship is associated with diminished modulation of the prefrontal cortex and enhanced recruitment of the pain circuit during punishment avoidance. The lab also reported that pain and reward circuits exert antagonistic influences on alcohol misuse. Building on these findings, this project seeks to investigate dysfunctional pain reactivity and cognitive control during avoidance learning as a principal mechanism of the comorbidity, by collecting fMRI, arousal, and behavioral data in individuals diagnosed with AUD, with and without depression comorbidity. The goal is to identify biopsychological markers to advance understanding of alcohol use disorder/depression phenotypes, improve diagnosis, and develop novel treatments.

Basic Research

Emilia M. Lefevre, Ph.D., University of Minnesota, wants to characterize the molecular underpinnings of opioid addiction, a step toward identifying targets for therapeutic intervention. She seeks to identify patterns of opioid-evoked gene expression changes and characterize these transcriptional adaptations within the nucleus accumbens with sub-region and cell-type specificity. She will leverage advances in single-cell and spatial RNA sequencing to conduct a comprehensive transcriptomic profile of the nucleus accumbens in a mouse model of fentanyl self-administration. In these datasets, she aims to identify patterns of opioid-evoked genes and expects that these patterns will diverge across cell-types and sub-regions. The results may further our understanding of the molecular mechanisms of opioid addiction and provide novel genetic targets for potential therapeutic intervention.

Basic Research

Snigdha Mukerjee, Ph.D., Vanderbilt University, is inspired by research on flavor perception and ingestive behavior suggesting that low sensitivity to the chemosensory feedback of ethanol is associated with preference for spirits with high ethanol, as well as with genetic association studies implicating receptors involved in oral chemesthesis (the sensitivity of mucosal surfaces to environmental chemicals) in risk for alcohol use disorder (AUD). People carrying variations in the TRPV1 gene have a reduced chemesthetic perception of ethanol, making it a key target of this project. Rodent models will be used to identify molecular targets and receptors in the peripheral cluster of sensory neurons within the trigeminal ganglion (TG) that relay sensory information to the brain, and to establish the coding rules used by the TG neurons to detect ethanol exposure in the mouth. This work can lead to future studies aimed at manipulating oral chemesthetic sensation and manipulating ethanol preference in individual animals.

Basic Research

Lyonna F. Parise, Ph.D., Icahn School of Medicine at Mount Sinai, studies the relationship between stress, mood disorders, and substance abuse. She has shown that chronic exposure to alcohol increases the expression of peripheral neutrophils, leading to breakdown of the blood-brain barrier in reward regions such as the nucleus accumbens, and facilitating the infiltration of pro-inflammatory factors into the brain, leading to stress susceptibility. This work has identified a neutrophil-released protease that is increased after alcohol exposure that can target tight junction proteins. To determine the precise function of neutrophil elastase (NE) in alcohol-induced mood alterations, she will utilize a transgenic mouse model in which NE is inactive. Mice will be exposed to a binge-drinking alcohol paradigm, a chronic stressor, and then to various antidepressant treatments, including traditional (fluoxetine) and novel (ketamine) antidepressants, as well as a commercially available NE inhibitor. Changes in tight junction protein expression, BBB permeability, and the levels of peripheral inflammatory markers will be analyzed.

Basic Research

Rachel Rabin, Ph.D., Douglas Mental Health University Institute, Canada, suggests a better understanding of how tobacco use affects the brain may help scientists develop new medications to treat people with tobacco use disorder (TUD). She focuses on the endocannabinoid (eCB) system, i.e., naturally circulating endocannabinoids and their enzymes, such as anandamide, which is degraded by the enzyme fatty acid amide hydrolase (FAAH). This neuroimaging study aims to determine, for the first time, whether FAAH levels in the brain differ between individuals with TUD and healthy volunteers. She predicts that brain FAAH levels will be higher in individuals with TUD compared to healthy volunteers. If results indicate that eCB system dysregulation plays a role in TUD, medications that decrease FAAH levels may be an effective target for the development of novel tobacco use treatments.

Next-Generation Therapies

David J. Reiner, Ph.D., National Institute on Drug Abuse (NIDA/NIH), in past research has shown that the piriform cortex (Pir), an olfaction-related region not previously studied in drug relapse, plays a critical role in relapse to the potent opioid fentanyl after food choice-induced abstinence. This project will use an animal model to study the role of Pir connectivity in fentanyl relapse at the circuit and cellular/molecular levels. The aim is to identify the role of neuronal inputs to Pir in fentanyl relapse by first identifying inputs to Pir activated during fentanyl relapse and then inhibiting the activity of these inputs to study how this changes fentanyl relapse-related behavior. The project also aims to determine connectomic and transcriptomic changes in Pir neuronal outputs after fentanyl relapse using high-throughput mapping of single neurons by sequencing barcoded RNA.

Basic Research

Zhenhao Shi, Ph.D., University of Pennsylvania School of Medicine, seeks to elucidate the impact of social adversity factors, including low socioeconomic status (SES) and low social support, on brain functioning and treatment outcome in patients with opioid use disorder (OUD). Prior research has demonstrated heightened aversion to financial risk and oversensitivity to social rejection in low-SES and low-social-support individuals. fMRI imaging has shown that financial risk and social rejection activate the anterior cingulate cortex (ACC) and anterior insular cortex (AIC). This project will include 84 OUD patients in early treatment and 52 matched controls. SES and social support will be assessed by structured interviews. Neural correlates of risk aversion and rejection sensitivity will be measured by fMRI risk-taking and social rejection paradigms. The primary outcome for OUD patients will be relapse to opioid use during the 24-week follow-up. The hope is to identify key neural circuits as novel targets and guide the development of new interventions to ameliorate the neurocognitive deficits induced by low SES and low social support.

Basic Research

Benjamin M. Siemsen, Ph.D., University of Maryland, Baltimore, seeks to understand the neural mechanisms underlying pathological reward-seeking behaviors following perinatal exposure to opioids. In his animal model of perinatal opioid exposure, he has preliminary RNA-sequencing data indicating that in the medial prefrontal cortex (mPFC), particularly the prelimbic subdivision, perinatal fentanyl exposure engages transcriptional adaptations linked to enhanced neuroinflammatory signaling. The consequences of such augmented neuroinflammatory signaling on subsequent natural (i.e. sucrose) and opioid (i.e. heroin) self-administration and seeking behavior are unknown. This project seeks to understand the impact of perinatal fentanyl exposure on a) self-administration and seeking for natural rewards and opioids, and b) the transcriptional adaptations, specifically in microglia isolated from the prelimbic cortex, that occur following self-administration of natural rewards or opioids in young adulthood following perinatal fentanyl exposure.

Basic Research

Hua Tang, Ph.D., National Institute of Mental Health (NIMH/NIH), notes that we survive in changing environments by making beneficial choices and avoiding harmful choices. Dr. Tang studies reinforcement learning (RL), the behavioral process of learning to associate stimuli or responses with gaining and losing positive reinforcers. Dysfunction of RL contributes substantially to disorders including addiction, obsessive-compulsive disorder, schizophrenia, and anxiety. This study, conducted in non-human primates, will test the theory that computations underlying learning to associate visual stimuli with gains vs. losses of secondary reinforcers are the result of neural processing across a ventral frontal-striatal circuit. It will target a series of core questions and thereby provide a new perspective on the neural circuit mechanisms of appetitive and aversive learning, and help us understand the mechanisms of psychiatric disorders that follow from dysfunction in reinforcement learning in both positive and negative directions.

Basic Research

Victor M. Tang, M.D., Centre for Addiction and Mental Health, University of Toronto, Canada, says cannabis use disorder (CUD) is being increasingly recognized as a serious public health problem. Current estimates suggest over 200 million users worldwide, 10%-18% of whom report daily use with 30% of these individuals developing CUD. He proposes the potential efficacy of rTMS (non-invasive brain stimula-

tion) to treat CUD through modulation of brain regions involved in cannabis craving, in particular the prefrontal cortex and insula. This grant will support a pilot clinical trial evaluating the feasibility of this approach. Patients with CUD will be offered 3 weeks of daily treatment with a novel rTMS coil at either high-frequency or low-frequency stimulation to see which parameter is optimal. The team will use fMRI to perform a comprehensive assessment of rTMS effects on cannabis craving, cognitive performance, and changes in network connectivity.

Next-Generation Therapies

Sarah A. Thomas, Ph.D., Bradley Hospital, Brown University, seeks to know more about how teen cannabis use (CU) disrupts circuits mediating cognitive flexibility (adaptation to changing rewards and punishments), reward motivation (the amount of goal-directed behavior to earn rewards), and how the brain is connected at rest (resting state functional connectivity [RSFC]). The hypothesis is that CU in the context of teen brain development results in fronto-striatal circuitry alterations and impaired cognitive flexibility and reward motivation that will vary as a function of cannabis exposure and depression. The team will: (1) identify the brain/behavior mechanisms of cognitive flexibility and RSFC associated with co-occurring CU and depression using fMRI; (2) define behavioral alterations in reward motivation associated with co-occurring CU and depression; (3) use a computational psychiatry model to identify how latent decision-making components vary for CU teens according to the presence of depression.

Basic Research

Jason M. Tucciarone, M.D., Ph.D., Stanford University, notes opioids exert their rewarding and addictive effects through action at the mu-opioid receptor (MOR), present in a peculiar neuroanatomic organization referred to as "patch" or "striosome," with dense regional expression situated in a network of islands throughout dorsal striatum and nucleus accumbens. The region outside of these islands is referred to as matrix. Dr. Tucciarone believes the neuroanatomy of "patch" vs "matrix," and the cell types contained within each compartment, opens a new way to look at the functional organization of the nucleus accumbens in motivated behavior and addiction. Recently, mouse genetics revealed two separate populations of direct pathway medium spiny neurons housed within MOR-positive patch networks; one encodes positive valence and positive reinforcement, the other encodes negative valence and negative reinforcement, challenging the traditional dogma of the direct pathway. This project seeks to define a role for these cell populations in preclinical models of opioid abuse.

Basic Research

Mark Wagner, Ph.D., National Institutes of Health (NIH), suggests that learning to anticipate reward-related behavioral outcomes could be a key cerebellar contribution to brain function. Compulsive reward-seeking is viewed as one of the central components of certain forms of addiction. He seeks to determine if the cerebellum develops representations and neural dynamics for the prediction and anticipation of behaviors that yield dopamine reward. His team will conduct experiments in animals, monitoring learned changes in the ensemble dynamics of cerebellar granule cells during operant behavior and the subsequent delivery of the dopamine reward. These and other experiments aim to reveal learned representations of a compulsive reward-seeking behavior, as well as cerebellar signals related to the anticipation of the dopamine reward. The project may also reveal how the cerebellum processes compulsive reward-seeking behaviors, opening pathways to new cerebellar addiction research.

Basic Research

Kevin S. Weiner, Ph.D., University of California, Berkeley, notes the human cerebral cortex contains neuroanatomical structures and shallow indentations known as tertiary sulci (TS) which develop during gestation through the post-birth period and whose role is unknown in mental health outcomes. He will examine the relationship between TS morphology in orbitofrontal cortex (OFC) and emotion-related impulsivity (ERI) in a transdiagnostic sample. ERI is defined by frequent loss of control during strong emotion states and is a robust predictor of internalizing disorders (e.g., depression), externalizing disorders (e.g., substance abuse), aggression, and suicidality. The hypothesis is that tertiary, but not primary or secondary, sulcal morphology in OFC will be related to ERI. Findings have the potential to shift the focus from morphological analyses of primary brain structures in different syndromes and diseases to tertiary brain structures which emerge in the third trimester.

Basic Research

Genevieve J. Yang, M.D., Ph.D., Icahn School of Medicine at Mount Sinai, suggests that a dual diagnosis of opioid use disorder (OUD) and ADHD represents a potentially neurobiologically distinct subgroup requiring specialized consideration for treatment. She will use real-time fMRI neurofeedback (rt-fMRI NF), a form of noninvasive brain stimulation that allows subjects to gain volitional control over activity in precisely defined brain regions, to noninvasively manipulate function of the ventral striatum (the location of the nucleus accumbens or NAc) in dually-diagnosed patients. The aim is to reduce NAc drug-cue reactivity, which could improve clinical outcomes such as emotional regulation of craving, which may generalize to abstinence and treatment adherence. It is also possible that the degree of reduction

of drug (relative to non-drug) cue reactivity may relate to ADHD symptom improvement.

Next-Generation Therapies

New Technologies

Farhana Yasmin, Ph.D., Northwestern University, proceeds from the suggestion that high-potency cannabinoids can cause adverse mental health outcomes such as anxiety disorders and psychotic episodes. This project will test the hypothesis that high-potency cannabinoid-induced plasticity in afferent input strength from dorsal midline thalamus (dMT) to defined neuronal populations in the central amygdala (CeA) has pathophysiological consequences. Dr. Yasmin will utilize a combination of viral and genetic tools, along with ex vivo optogenetics. These investigations could elucidate distinct synaptic mechanisms by which cannabinoids reorganize circuits that lead to pathological behavioral manifestations of cannabis overuse.

Basic Research

ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

Samuel William Centanni, Ph.D., Wake Forest University, seeks to uncover molecular mechanisms driving stress-induced hyperactivity, a factor in a range of affective disorders. The team will use multiple methods to define unique genetic signatures of insula-to-BNST neurons and determine the direct impact of stress on active ribosomal translation in this subpopulation. This approach could identify new pharmacological targets that minimize the damaging dysregulated activity caused by stress, while not impacting the regular function of surrounding non-stressed cells.

Basic Research

Xiaomo Chen, Ph.D., University of California, Davis, notes that our gap in understanding the underlying neural mechanisms of attention means we have an incomplete understanding of the pathophysiology of attention disorders like ADHD. This research focuses on how the brain voluntarily controls the focus of attention based on internal goals (voluntary attention). Dr. Chen will apply a newly developed large-scale recording technique to simultaneously record neuronal activity in medial frontal cortex and dorsolateral prefrontal cortex to identify frontal circuits that mediate voluntary attention. This will allow the team to record activity from thousands of neurons simultaneously across cortical layers and brain regions to study the circuit organization and dynamics underlying attention. The aim is to inform non-invasive therapeutic approaches such as neurofeedback and brain stimulation to alter specific functional states of the medial frontal cortex circuitry to enhance voluntary control of attention.

Basic Research

Sarah M. Clark, Ph.D., University of Maryland, Baltimore, notes that immune dysfunction has been reported across a range of psychiatric disorders such as schizophrenia and bipolar disorder, as well as neurodevelopmental disorders including autism and ADHD. Her research suggests impaired adaptive immunity may contribute to divergent social behaviors reported in these disorders, having shown that T cells promote stress-induced learning and fear responsivity, as well as adolescent social behavior when there is no threat. This project seeks to delineate the role of T cells in the postnatal development of the BNST and the downstream effects on adolescent social behavior. To accomplish this, she will employ a cell-depletion model in neonatal rats to reduce the CD4+ T cell population during their early postnatal development.

Basic Research

Ahmed Eltokhi, Ph.D., University of Washington, asks whether there is common pathophysiology at the circuit level that could be targeted for therapeutic interventions across disorders. He is focusing on voltage-gated sodium (Nav) channels, which are among the most frequent targets of disruptive genetic mutations associated with disorders such as schizophrenia, autism, bipolar disorder, and attention-deficit hyperactivity disorder. The objective of this study is to determine how gating pore current can give rise to psychiatric-like phenotypic outcomes on the cellular and behavioral levels. Such knowledge could enable unraveling the underlying mechanisms by which the Nav channels can contribute to the cellular and systems dysfunction in schizophrenia and autism and perhaps pave the way for establishing new therapeutic targets.

Basic Research

Aaron Kucyi, Ph.D., Northeastern University, notes that mind-wandering is particularly pervasive in adults with ADHD who often no longer experience hyperactivity in terms of increased motility (as in childhood ADHD) but instead as a feeling of mental restlessness. Yet no ADHD treatments have been designed to target and modulate the patterns of brain activity from which spontaneous, uncontrollable, internal experiences arise. Using fMRI, Dr. Kucyi has discovered a neural marker of mind-wandering based on a specific pattern of coordination between widely distributed parts of the brain and demonstrated it is hyper-expressed in adults with ADHD. This project is a proof-of- principle study in 30 adults to test whether the marker can be targeted and controlled with a new method called closed-loop connectomic

neuromodulation. This would be a step toward a treatment specifically addressing mind-wandering/mental restlessness in adults with ADHD.

Next-Generation Therapies
New Technologies

Kristina Lanko, Ph.D., Erasmus Medical Center, University Medical Center Rotterdam, Netherlands, notes the finding that in many neurodevelopmental disorders, more males are affected than females and that males have more severe symptoms. This skew is prominent to varying degrees in autism, ADHD, and schizophrenia. She proposes a new approach to understand the mechanisms behind sex-linked differences, taking the recently identified SETD1B disorder as an example. This illness is characterized by developmental delay and epilepsy as well as ASD, hyperactivity, sleep disturbance, anxiety, and aggression. Behavioral changes are more frequent in males than in females. This project aims to understand the reasons for these behavioral differences at the place of their origin—the cell. Stem-cell technology will be used to grow cultures of cells from affected males and females, which will be developed as neural cells to form brain organoids. Gene expression and other studies could provide insights into fundamental differences between organoids derived from male and female cell-donors.

Basic Research

Violeta G. Lopez-Huerta, Ph.D., National Autonomous University of Mexico, is studying the thalamus, a group of subcortical nuclei whose operations range from sensory relay to attention control, arousal, and motor and sensory integration. Thalamic functional diversity requires complex inhibition. The thalamic reticular nucleus (TRN) is the only structure that inhibits all thalamic nuclei. Studies suggest TRN dysfunction may underlie some behavioral deficits in disorders including schizophrenia, autism, and ADHD. This project seeks to characterize how TRN subpopulations differentially exert inhibition onto discrete thalamic nuclei; determine if there is refinement of subcircuit configurations during postnatal stages; and how perturbation of inhibition with CRISPR gene editing in vivo could alter thalamic circuitry development. Studies on normal and pathological development of TRN and thalamic GABAergic circuits are crucial to gain knowledge of the circuit-level etiology of core symptoms in brain disorders.

Basic Research

Jessica Taubert, Ph.D., University of Queensland, Australia, wants to know if dogs can help children recover social function in ADHD. She will use fMRI to map the neural signature of gaze following, the cornerstone of social cognition and communication, in children ages 8-12. She will directly compare functional brain activity between children with a primary diagnosis of ADHD and controls, expecting to find less activation in response to gaze cues in the children with ADHD. Next, she will use fMRI to investigate the plasticity of the underlying brain mechanisms in typically developing children by testing the novel hypothesis that increased social contact with dogs at home (i.e., dog ownership) predicts an increased neural response to the gaze direction cues in dog faces. Finally, she will explore the possibility that dog ownership increases brain activity in response to gaze cues in children with ADHD. The hypothesis is that dog ownership will not only predict increased sensitivity to gaze cues in dog faces but also increased sensitivity to gaze cues in human faces.

Next-Generation Therapies

Genevieve J. Yang, M.D., Ph.D., Icahn School of Medicine at Mount Sinai, suggests that a dual diagnosis of opioid use disorder (OUD) and ADHD represents a potentially neurobiologically distinct subgroup requiring specialized consideration for treatment. She will use real-time fMRI neurofeedback (rt-fMRI NF), a form of noninvasive brain stimulation that allows subjects to gain volitional control over activity in precisely defined brain regions, to noninvasively manipulate function of the ventral striatum (the location of the nucleus accumbens or NAc) in dually-diagnosed patients. The aim is to reduce NAc drug-cue reactivity, which could improve clinical outcomes such as emotional regulation of craving, which may generalize to abstinence and treatment adherence. It is also possible that the degree of reduction of drug (relative to non-drug) cue reactivity may relate to ADHD symptom improvement.

Next-Generation Therapies
New Technologies

ANXIETY DISORDERS

Ryan T. Ash, M.D., Ph.D., Stanford University, seeks to advance transcranial ultrasound stimulation (TUS), an emerging technology that may enable noninvasive neuromodulation of deep-brain areas like the amygdala. Recent research has demonstrated that TUS can produce enduring but reversible changes in neural circuit activity in deep-brain areas, as well as meaningful changes in cognitive function and behavior, at safe ultrasound intensities. This grant will support the foundational development and optimization of human neuroscience tools to target TUS to the amygdala for the purpose of enhancing the extinction of associative fear memories.

New Technologies

Jessica Lynn Bolton, Ph.D., Georgia State University, studies how early-life experiences, especially adversity, modulate brain circuits. This project will focus on microglia, a type of brain cell that is known to influence synapses in sensory systems and other circuits, and look at the interactions of microglia and neurons in a stress-responsive brain region called the amygdala. It will also study whether manipulating microglia early in life prevents the development of depression-like behavior in adolescence due to early-life adversity.
Basic Research

Stefano Brigidi, Ph.D., University of Utah, is studying how brain cells encode and process information for learning. This project follows up on preliminary data demonstrating that learning switches on unique sets of genes across different sets of hippocampal pyramidal neurons, which helps determine how excitable individual neurons are to subsequent experiences. Dr. Brigidi seeks to identify unique patterns of gene expression that encode experiences among single neurons in support of learning and behavioral flexibility. Results could be relevant to disorders including PTSD which arise from traumatic experience and are characterized by learning and memory dysfunction.
Basic Research

Samuel William Centanni, Ph.D., Wake Forest University, seeks to uncover molecular mechanisms driving stress-induced hyperactivity, a factor in a range of affective disorders. The team will use multiple methods to define unique genetic signatures of insula-to-BNST neurons and determine the direct impact of stress on active ribosomal translation in this subpopulation. This approach could identify new pharmacological targets that minimize the damaging dysregulated activity caused by stress, while not impacting the regular function of surrounding non-stressed cells.
Basic Research

Joseph M. Cichon, M.D., Ph.D., University of Pennsylvania, notes that the mechanisms initiating and sustaining plasticity associated with rapid antidepressant action remain unclear. In a rodent model of chronic stress, he will test the hypothesis that changes in neuronal activity imposed acutely by nitrous oxide (NO2) automatically give rise to sustained plasticity through activity-dependent mechanisms. This notion is based on work on activity-dependent plasticity in the cortex and his own research suggesting that nitrous oxide specifically and directly activates layer-5 cortical neurons which mediate cortico-cortical connectivity. The project lays groundwork for understanding the mechanisms through which acute pharmacologic interventions can lead to sustained therapeutic benefits in psychiatric illnesses.
Basic Research

Romain M. Durand, Ph.D., Icahn School of Medicine at Mount Sinai, is studying neuroimmune mechanisms underlying reward deficits in depression. A healthy blood-brain barrier (BBB) tightly controls interactions between peripheral circulation and the brain, whereas in major depression and animal models of chronic social defeat stress (CSDS), there is disruption of the BBB, leading to increased permeability and peripheral cytokine infiltration. Dr. Durand will measure serum concentrations of a panel of peripheral cytokines/chemokines (e.g., IL-6) as well as their infiltration in the NAc in CSDS mice and will correlate these inflammatory biomarkers with reward sensitivity. The research also seeks to determine if cytokine neutralization of IL-6 or other cytokines using monoclonal antibodies is sufficient to rescue reward sensitivity deficits following stress exposures.
Basic Research

Carlos Fernandez-Pena Acuna, Ph.D., St. Jude Children's Research Hospital, seeks to characterize the role of C1 and A1 neurons—an intermingled group of catecholamine neurons located in the rostral ventrolateral medulla (RVLM)—in promoting anxiety. His preliminary data suggest that optogenetic stimulation of C1 neurons, but not A1, promotes anxiety-like behaviors in mice, and that stimulation of C1 neurons alone is aversive in a real-time place preference. This suggests C1 neurons are part of a novel circuit that promotes anxiety in mice. He proposes to perform molecular and electrophysiological experiments that will help to elucidate the organization and function of this circuit, which could support the discovery of more selective treatment strategies.
Basic Research

Jakob Hartmann, Ph.D., McLean Hospital, Harvard University, will investigate sex-specific gene networks in a brain area called the BNST that modulate susceptibility and resilience to chronic stress; he will do so by combining state-of-the-art single-cell transcriptomics in animal models with causal chemogenetic tools. Despite playing important roles in the stress response and emotional and social behaviors, the BNST has been largely overlooked with respect to its possible sex-specific dysregulation in mood and anxiety disorders. Providing a more detailed understanding of the sexually dimorphic neuronal heterogeneity and transcriptional specificity within the BNST following chronic social defeat stress (CSDS) in rodents will make possible the further dissection of its function in the context of psychiatric disorders.
Basic Research

Daniel A. Jercog, Ph.D., INSERM, France, seeks to discover the circuitry and computations underlying maladaptive fear generalization, specifically, amygdala-prefrontal interactions during stress-induced fear generalization. He notes that predictions based on past experience can be detrimental if,

for example, threatening situations are generalized as safe, or safe situations are generalized as threatening. This is the case in individuals with anxiety and trauma-related disorders, who often fear stimuli and situations that are safe or barely similar to the original trauma situation. This project aims to identify the underlying altered neurophysiological signals that correlate with fear generalization. It aims to counteract the effect of these altered signals by using pathway and pattern-specific optogenetic stimulation approaches.

Basic Research

Erin Kang, Ph.D., Montclair State University, notes that cognitive flexibility is the ability to effectively and flexibly adapt thinking and attention between tasks. It appears to play an integral role in core autism symptoms and impacts quality of life throughout the lifespan, and is also a relevant mechanism for co-occurring anxiety. This project studies the relationship between parent- and self-reported anxiety symptoms and behavioral and neuroscientific differences in cognitive flexibility, as measured via questionnaires, behavioral tasks, and electroencephalography (EEG), to look at brain activity related to cognitive flexibility. Findings will inform understanding of the neural basis of cognitive inflexibility and help us better understand links between the brain and behavioral presentations of flexible thinking and core autism spectrum disorder and anxiety symptoms in autistic youth.

Basic Research

Sabine Krabbe, Ph.D., Deutsches Zentrum für Neurodegenerative Erkrankungen, Germany, notes that the basolateral amygdala (BLA) has been shown to control fear learning and anxiety behavior, yet consists of diverse neural cell types whose functional roles are poorly understood. Dr. Krabbe seeks to show that dopamine can modify BLA activity and control anxiety by orchestrating neural ensembles of diverse cell types during exploratory behavior. To investigate the role of dopamine in anxiety encoding in amygdala microcircuits, she will map dopamine receptor expression in the highly diverse BLA cell types. This will address whether dopamine preferentially modulates defined subtypes of local interneurons and/or projection neurons in distinct anatomical BLA subregions. Experiments in freely-moving mice will visualize dopamine release during anxiety behavior, revealing time points during specific exploratory or defensive states when dopamine can modulate neural activity within amygdala microcircuits. Deep-brain imaging and optogenetics will permit analysis of how neural encoding of anxiety states in BLA circuits is affected by reduced dopamine release. These experiments promise to show how activity patterns of specific cell types are altered by acute impairment of dopamine neurotransmission.

Basic Research

Shibin Li, Ph.D. Stanford University, recently characterized hypothalamic circuitry underlying stress-induced insomnia/hyperarousal. Dr. Li found that corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus of hypothalamus (PVN) directly innervate wake-promoting hypocretin (Hcrt) neurons in the lateral hypothalamus (LH). Genetic ablation of HcrtLH neurons or CRISPR-Cas9-mediated disruption of the crh gene in CRHPVN neurons was found to compromise arousal level upon optogenetic stimulation of CRHPVN→HcrtLH circuitry or restraint stress exposure. Dr. Li will conduct experiments seeking to determine if optogenetic activation of the AVPPVN→LepRbLH→HcrtLH pathway will counteract the activity of CRHPVN→HcrtLH circuitry, ameliorating hyperarousal/insomnia induced by stress exposure.

Basic Research

Indira Mendez-David, Ph.D., Paris-Saclay Univeristy, France, conducts research in support of developing new fast-acting anxiolytics (anti-anxiety agents). Her team has found that 1) activating the serotonin 4 (5- HT4R) receptors and 2) targeting the projections of the medial prefrontal cortex (mPFC) in the dorsal raphe nucleus (DRN) may constitute a new way to treat anxiety with a fast onset of action. At this point, though, the contribution to fast anxiolytic effects of 5-HT4R located on mPFC-raphe projections is unknown. This project, conducted in rodents, seeks to confirm the necessity of cortical 5-HT4R activation for fast anxiolytic-like effects using a tissue-specific knockout approach; link fast anxiolytic activity to neurochemical changes in the DRN; and optogenetically stimulate or silence cortical projections to the DRN to evaluate neurochemical and anxiolytic-behavioral consequences.

Basic Research

Next-Generation Therapies

Saptarnab Naskar, Ph.D., Northwestern University, studies mechanisms underlying the way stress impacts the brain. Dr. Naskar notes that projections from the prelimbic area (PL) of PFC to periaqueductal grey (PAG), ventral tegmental area (VTa), and nucleus accumbens (NAc) form an important output triad influencing various aspects of approach and consumption of reward; and that 2-arachidonoylglycerol (2-AG), a widely circulating endocannabinoid (eCB), is strongly implicated in stress induced alteration in the activity of PFC neuronal sub-populations in a circuit-specific manner. The team will utilize a combination of ethologically relevant quantitative behavioral approaches, in-vivo single cell calcium imaging in freely behaving animals, and pharmacology to ask, ultimately, if stress-induced deficits in reward evaluation and procurement can be reversed by selectively modulating 2-AG levels.

Basic Research

Nancy Padilla-Coreano, Ph.D., University of Florida, notes that for social animals, including humans, to thrive, they must show social competence and adjust behavior based on social history (e.g. social rank or degree of familiarity) and context. Social motivation is a critical component of social competence that is necessary for health and survival, and is impaired in depression, anxiety and autism. Her past work has shown that the medial prefrontal cortex (mPFC) encodes social rank and that mPFC input to the lateral hypothalamus (LH) regulates social behavior between familiar mice, suggesting a role for the mPFC-LH circuit in social history. This project seeks to learn more about familiarity and social rank, and to resolve the issue of subjective human quantification of social behaviors by using novel machine-learning tools. The central hypothesis is that dopaminergic modulation of mPFC and LH changes across social history states to enable social motivational differences.

Basic Research

Lyonna F. Parise, Ph.D., Icahn School of Medicine at Mount Sinai, studies the relationship between stress, mood disorders, and substance abuse. She has shown that chronic exposure to alcohol increases the expression of peripheral neutrophils, leading to breakdown of the blood-brain barrier in reward regions such as the nucleus accumbens, and facilitating the infiltration of pro-inflammatory factors into the brain, leading to stress susceptibility. This work has identified a neutrophil-released protease that is increased after alcohol exposure that can target tight junction proteins. To determine the precise function of neutrophil elastase (NE) in alcohol-induced mood alterations, she will utilize a transgenic mouse model in which NE is inactive. Mice will be exposed to a binge-drinking alcohol paradigm, a chronic stressor, and then to various antidepressant treatments, including traditional (fluoxetine) and novel (ketamine) antidepressants, as well as a commercially available NE inhibitor. Changes in tight junction protein expression, BBB permeability, and the levels of peripheral inflammatory markers will be analyzed.

Basic Research

Zachary T. Pennington, Ph.D., Icahn School of Medicine at Mount Sinai, has used whole-brain activity mapping in mice to examine how an acute, severe stressor is able to augment subsequent neural and behavioral responses to a novel stressor a week later. This revealed hyperactivation of the anterior hypothalamic nucleus (AHN) in severely stressed animals, which represents a novel target for treatment intervention. This project seeks to uncover the contribution of the AHN to the sensitization of fear and anxiety by prior severe stress, and to assess whether a subpopulation of cells within the AHN might be targeted to attenuate stress responses.

Basic Research

Jose Rodriguez-Romaguera, Ph.D., University of North Carolina at Chapel Hill, notes that dysregulation of the neural circuitry responsible for encoding arousal responses is thought to contribute to disturbed motivated behavior, a characteristic of social anxiety disorders. Rapid changes in arousal responses can be tracked by recording certain physiological metrics (such as pupil size), yet little is known about the neural circuits that regulate these rapid arousal responses. He recently discovered that neurons expressing the prepronociceptin gene in the BNST (BNSTPnoc neurons) encode for the arousal responses that occur rapidly upon exposure to motivationally salient stimuli such as predator and food odors. These neurons project to the medial amygdala (MeA) and the medial preoptic area (mPOA), regions that regulate aspects of social motivation. This project studies how BNSTPnoc neurons projecting to MeA or mPOA regulate social arousal responses. The hypothesis is that unique populations of BNSTPnoc neurons will selectively encode arousal responses to social stimuli in a stimulus-specific manner.

Basic Research

Stefanie Russman Block, Ph.D., University of Michigan, seeks to improve the effectiveness of emotion regulation strategies for those with anxiety using real-time fMRI neurofeedback, a novel technology that allows individuals to control their own brain activity. In this project, participants with anxiety will practice reinterpreting the meaning of negative images, a common emotion regulation strategy taught in therapy, while receiving feedback about brain activity in the dorsomedial prefrontal cortex, a brain region involved in emotion regulation. This work will help us understand the neural circuity of emotion regulation and lay the groundwork to test if psychotherapy outcomes can be enhanced using neurofeedback.

Next-Generation Therapies

New Technologies

Anna Schroeder, Ph.D., University of Freiburg, Germany, proceeds from evidence that the zona incerta (ZI), a small subthalamic nucleus composed mostly of inhibitory neurons, can impact the way we feel. Deep brain stimulation of this structure resulted in reductions in reported fear and anxiety by patients, as well as changes in mood. This project seeks to prove the hypothesis that the ZI actively encodes and modulates emotional states. Dr. Schroeder posits that ZI subpopulations differentially respond to, and also regulate, distinct emotions, thereby allowing this brain region to convert emotional information into targeted behavioral strategies such as specific defensive reactions. To flesh this out, she will utilize state-of-the-art technologies to map circuits at the level of molecularly-defined subtypes, probe synaptic connections, manipulate neuronal activity in mouse

models, characterize functional responses, and robustly assess behavioral outcomes.

Basic Research

Sheila R. Shanmugan, M.D., Ph.D., University of Pennsylvania, proceeds from the hypothesis that variation in the functional topography of personalized default mode networks (DFM) in part underlie sex differences in internalizing symptoms (seen in mood disorders including anxiety and depression). Since these symptoms typically emerge in childhood and adolescence, the hypothesis will be evaluated in the cohort for the NIH's ABCD study of youths, n = 11,572. Dr. Shanmugan will evaluate whether the topography of personalized default mode networks underlie sex differences in current internalizing psychopathology, and will use baseline variation in functional topography to predict the longitudinal course of internalizing psychopathology. The project could establish that sex differences in personalized functional networks underly sex differences in internalizing psychopathology.

Basic Research

Thomas Steinkellner, Ph.D., Medical University of Vienna, Austria, recently discovered a neuronal circuit that connects a key brain region known to be perturbed in mood and anxiety disorders with a small brain area that is involved in the processing of environmental information including visual and auditory cues. This small brain region uses two types of neurotransmitters to communicate with other cells, both of which are well known to play a role in depression, fear, and anxiety. He will test the individual contributions of these two neurotransmitters within this circuit using sophisticated cell-type-specific mouse genetic tools. He will focus on behaviors relevant to mood disorders to determine whether this novel dual transmitter circuit could be a new target for the development of future antidepressant medications.

Basic Research

Michelle E. Stepan, Ph.D., University of Pittsburgh School of Medicine, notes that slow-wave sleep is a biomarker of sleep disturbance that is reduced in depression, anxiety, and other mood disorders. Slow-wave activity normally promotes neural plasticity via synaptic downscaling, which renews information processing capacity and cognitive control processes. This, in turn, is important for downregulating negative affect to aversive stimuli. Acoustic stimulation involves playing brief sub-arousal tones during slow-wave sleep to enhance slow-wave activity without disturbing sleep. It can reliably enhance slow-wave activity, particularly in young adults, and improve cognitive processes. This project will use a commercial headband device to test acoustic stimulation in young adults (ages 18–25) with elevated anxiety/depression symptoms and will assess acute (1 night) and extended (14 nights) effects on sleep, cognitive control, and emotional reactivity to aversive stimuli.

Next-Generation Therapies

Alex Tang, Ph.D., University of Western Australia, suggests that to improve the efficacy of rTMS (a non-invasive brain stimulation treatment often used in depression), a greater understanding of how it changes brain cells and whether these changes are affected by key biological factors such as age and sex is needed. To avoid the difficulty and danger of studying this directly in people, Dr. Tang will use brain samples donated from neurosurgery patients. He will investigate genes and biological functions that are altered after rTMS. He hopes to uncover why the effects of rTMS varies between patients, which could inform efforts to develop a more targeted and efficient use of rTMS to treat a wide range of mental health disorders.

Next-Generation Therapies

Hua Tang, Ph.D., National Institute of Mental Health (NIMH/NIH), notes that we survive in changing environments by making beneficial choices and avoiding harmful choices. Dr. Tang studies reinforcement learning (RL), the behavioral process of learning to associate stimuli or responses with gaining and losing positive reinforcers. Dysfunction of RL contributes substantially to disorders including addiction, obsessive-compulsive disorder, schizophrenia, and anxiety. This study, conducted in non-human primates, will test the theory that computations underlying learning to associate visual stimuli with gains vs. losses of secondary reinforcers are the result of neural processing across a ventral frontal-striatal circuit. It will target a series of core questions and thereby provide a new perspective on the neural circuit mechanisms of appetitive and aversive learning, and help us understand the mechanisms of psychiatric disorders that follow from dysfunction in reinforcement learning in both positive and negative directions.

Basic Research

Sarah M. Tashjian, Ph.D., California Institute of Technology, notes Pavlovian extinction is a valuable model for phobia-related anxieties because extinction involves disaggregating a threatening outcome from a distinct stimulus. But she says this is a limited basis for fully understanding and treating more prevalent and problematic anxiety disorders such as generalized anxiety and social anxiety, which often involve less discrete threats and fears. This project aims to elucidate computational and neural systems of safety decisions to identify how and to what extent safety processing contributes to anxiety during development. She will specify a computational model of safety acquisition decisions during

development and then pair a safety task in adolescents with fMRI to identify neural systems that are uniquely associated with safety computations and overlap with reward and threat processing. The aim is to differentiate systems that support maladaptive coping strategies such as avoidance from adaptive coping strategies such as flexible safety acquisition.
Basic Research

Xinzhu Yu, Ph.D., University of Illinois, seeks to better understand neurobiological mechanisms by which anxiety is regulated and how they become dysregulated in disease. Evidence has suggested that altered synaptic plasticity in the prefrontal cortex (PFC) underlies stress-induced anxiety. However, factors modulating this process remain inadequately understood. Astrocytes, the most abundant class of glial cells in the brain, modulate synaptic function via dynamic intracellular Ca2+ signals. Emerging evidence suggests that genetically manipulating astrocyte Ca2+ signaling leads to synaptic changes resulting in psychiatric phenotypes in mice. This project seeks to discover how prefrontal cortex astrocyte Ca2+ signaling contributes to synaptic plasticity associated with anxiety and stress resilience, using a systematic approach with innovative genetic tools, Ca2+ imaging, electrophysiology and behavioral assays. The central hypothesis is that PFC astrocyte Ca2+ signaling alterations contribute to anxiety-like behavior by structurally and functionally altering synaptic plasticity.
Basic Research

AUTISM SPECTRUM DISORDER (ASD)

Sarah M. Clark, Ph.D., University of Maryland, Baltimore, notes that immune dysfunction has been reported across a range of psychiatric disorders such as schizophrenia and bipolar disorder, as well as neurodevelopmental disorders including autism and ADHD. Her research suggests impaired adaptive immunity may contribute to divergent social behaviors reported in these disorders, having shown that T cells promote stress-induced learning and fear responsivity, as well as adolescent social behavior when there is no threat. This project seeks to delineate the role of T cells in the postnatal development of the BNST and the downstream effects on adolescent social behavior. To accomplish this, she will employ a cell-depletion model in neonatal rats to reduce the CD4+ T cell population during their early postnatal development.
Basic Research

Ahmed Eltokhi, Ph.D., University of Washington, asks whether there is common pathophysiology at the circuit level that could be targeted for therapeutic interventions across disorders. He is focusing on voltage-gated sodium (Nav) channels, which are among the most frequent targets of disruptive genetic mutations associated with disorders such as schizophrenia, autism, bipolar disorder, and attention-deficit hyperactivity disorder. The objective of this study is to determine how gating pore current can give rise to psychiatric-like phenotypic outcomes on the cellular and behavioral levels. Such knowledge could enable unraveling the underlying mechanisms by which the Nav channels can contribute to the cellular and systems dysfunction in schizophrenia and autism and perhaps pave the way for establishing new therapeutic targets.
Basic Research

Erin Kang, Ph.D., Montclair State University, notes that cognitive flexibility is the ability to effectively and flexibly adapt thinking and attention between tasks. It appears to play an integral role in core autism symptoms and impacts quality of life throughout the lifespan, and is also a relevant mechanism for co-occurring anxiety. This project studies the relationship between parent- and self-reported anxiety symptoms and behavioral and neuroscientific differences in cognitive flexibility, as measured via questionnaires, behavioral tasks, and electroencephalography (EEG), to look at brain activity related to cognitive flexibility. Findings will inform understanding of the neural basis of cognitive inflexibility and help us better understand links between the brain and behavioral presentations of flexible thinking and core autism spectrum disorder and anxiety symptoms in autistic youth.
Basic Research

Saskia B.J. Koch, Ph.D., Radboud University, Netherlands, aims to identify clinically relevant biomarkers of communicative problems in autism and social anxiety. The project will capitalize on two recent developments: 1) the availability of two multi-task neuroimaging datasets directly mapping communicative deficits in the same autistic and socially anxious participants (52 with autism, 52 socially anxious, and 52 controls), and 2) methodological advances in data-driven technologies allowing the integration of these two neuroimaging datasets. Participants will perform several communication tasks that tap into their ability to engage in dynamically unfolding interactions. Brain activity during these tasks will be measured with MRI in one study, and EEG in a second. By integrating the datasets in one state-of-the-art overarching data analysis, new biomarkers of communication deficits may be identified.
Diagnostic Tools/Early Intervention

Kristina Lanko, Ph.D., Erasmus Medical Center, University Medical Center Rotterdam, Netherlands, notes the finding that in many neurodevelopmental disorders, more males are affected than females and that males have more severe symptoms. This skew is prominent to varying degrees in autism, ADHD, and schizophrenia. She proposes a new approach to understand the mechanisms behind sex-linked differences, taking the recently identified SETD1B disorder as an example. This illness is characterized by developmental delay and epilepsy as well as ASD, hyperactivity, sleep disturbance, anxiety, and aggression. Behavioral changes are more frequent in males than in females. This project aims to understand the reasons for these behavioral differences at the place of their origin—the cell. Stem-cell technology will be used to grow cultures of cells from affected males and females, which will be developed as neural cells to form brain organoids. Gene expression and other studies could provide insights into fundamental differences between organoids derived from male and female cell-donors.

Basic Research

Violeta G. Lopez-Huerta, Ph.D., National Autonomous University of Mexico, is studying the thalamus, a group of subcortical nuclei whose operations range from sensory relay to attention control, arousal, and motor and sensory integration. Thalamic functional diversity requires complex inhibition. The thalamic reticular nucleus (TRN) is the only structure that inhibits all thalamic nuclei. Studies suggest TRN dysfunction may underlie some behavioral deficits in disorders including schizophrenia, autism, and ADHD. This project seeks to characterize how TRN subpopulations differentially exert inhibition onto discrete thalamic nuclei; determine if there is refinement of subcircuit configurations during postnatal stages; and how perturbation of inhibition with CRISPR gene editing in vivo could alter thalamic circuitry development. Studies on normal and pathological development of TRN and thalamic GABAergic circuits are crucial to gain knowledge of the circuit-level etiology of core symptoms in brain disorders.

Basic Research

Adele Mossa, Ph.D., Icahn School of Medicine at Mount Sinai, hopes to unravel the cellular and molecular functions of the autism risk gene DDX3X during neuronal development. DDX3X mutations are a leading cause of DDX3X syndrome, a co- morbid neurodevelopmental disorder mainly affecting females and associated with ADHD, autism spectrum disorder, anxiety disorders, intellectual disability, and sensory processing abnormalities. Using a mouse model for DDX3X syndrome, Dr. Mossa will modulate female neurons and male neurons lacking Ddx3x and examine morphogenesis, synaptogenesis and mRNA translation. By tagging and tracking mRNAs in neurons, she will address how sex differences shape the neuronal proteome. The hope is that this work will lead to a better understanding of the mechanisms underlying neurodevelopmental disorders, especially in females, and pinpoint targets to develop new therapies.

Basic Research

Aya Osman, Ph.D., Icahn School of Medicine at Mount Sinai, is interested in the role of the early microbiome as a contributory factor in autism spectrum disorder (ASD). The microbiome communicates with the brain in multiple ways, one of which is through the production of neuroactive metabolites such as short-chain fatty acids (SCFAs). Peripherally, these metabolites can influence gut wall integrity and gut immune profile. Dr. Osman uses a Shank3 deletion mouse model that lacks all functional isoforms of Shank3 (Shank3KO) to study gene-environment interactions. Shank3KO mice display social deficits in concert with baseline changes in microbiome composition, metagenomic and metabolic profile, and reduced levels of the SCFA acetate. Dr. Osman seeks to elicudate the role of gut-derived metabolites in regulating neuroimmune and epigenetic interactions, by fully understanding how acetate modulates social behavior in Shank3 mice.

Basic Research

Nancy Padilla-Coreano, Ph.D., University of Florida, notes that for social animals, including humans, to thrive, they must show social competence and adjust behavior based on social history (e.g. social rank or degree of familiarity) and context. Social motivation is a critical component of social competence that is necessary for health and survival, and is impaired in depression, anxiety and autism. Her past work has shown that the medial prefrontal cortex (mPFC) encodes social rank and that mPFC input to the lateral hypothalamus (LH) regulates social behavior between familiar mice, suggesting a role for the mPFC-LH circuit in social history. This project seeks to learn more about familiarity and social rank, and to resolve the issue of subjective human quantification of social behaviors by using novel machine-learning tools. The central hypothesis is that dopaminergic modulation of mPFC and LH changes across social history states to enable social motivational differences.

Basic Research

Nisha Raj, Ph.D., Emory University, is using a comparative network approach to identify defects in proteostasis across patient-derived organoid models of Fragile X syndrome (FXS) and other neuropsychiatric disorders. The aim is to profile the nascent and steady-state proteome during early human brain development using 3D cortical organoids generated from patient-derived induced pluripotent stem cells (iPSC).

By employing this approach across multiple iPSC lines from individuals with different neuropsychiatric disorders, the team will build human brain-specific protein networks that could reveal modules with strong associations to pathological and clinical phenotypes. Identification of cellular and molecular drivers of symptoms of FXS and other related disorders could provide insight on novel diagnostic biomarkers or therapeutic targets.

Basic Research

Jeff L. Waugh, M.D., Ph.D., University of Texas Southwestern Medical Center at Dallas, wants to investigate the striatum to better understand its relation to OCD and other disorders including tic disorders and autism. He notes striatal projection neurons are segregated into competing tissue compartments, the matrix and striosomes. The ratio of projections is critical for normal function: selective matrix activation results in uncontrolled, excessive movements; hyperactivation of striosomes induces repetitive, stereotyped movements. His team has identified pairs of subjects (disorder vs. healthy control) with OCD, autism, and tic disorders who have archived brain MRI data, allowing assessment of the tissue composition in each disorder. They hypothesize that in OCD, the volume and structural connectivity of the striosome compartment will be increased relative to the matrix compartment. More broadly, Dr. Waugh believes tipping the striatal balance toward striosomes may underlie obsessions and compulsive behaviors in neurodevelopmental disorders.

Basic Research

Xingjian Zhang, Ph.D., University of California, Los Angeles, will study interbrain synchrony of neuronal subpopulations in autism spectrum disorder (ASD) mouse models to obtain a more complete picture of neural processes during social activities. This project will 1) investigate the interbrain synchrony of medial prefrontal cortex GABAergic inhibitory neurons and glutamatergic excitatory neurons and compare the structures of their representations of animals' social behaviors; and (2) investigate the interbrain synchrony of Shank3B mutant mice and test the effects of upregulating GABAergic neurons on restoring social behaviors and interbrain synchrony. This could provide a novel perspective for understanding the neural basis of deficiencies in socialization widely seen in autism among other disorders.

Basic Research

BIOLOGY OF THE BRAIN

These projects focus on how the brain works

CELLULAR MATURATION

Fernando C. Alsina, Ph.D., Duke University, will study how cytoskeleton dynamics and RNA metabolism are integrated during neuronal maturation and dysregulated in neurological disorders. He will focus on an indispensable multiprotein complex recently discovered to dually bind and regulate mRNA and microtubules. He seeks to identify mechanisms by which this complex dictates axonal and dendrite growth. This could shed light on how dual regulation of microtubules and RNA metabolism is essential for neuronal maturation.

Basic Research

EMOTION REGULATION/AGGRESSION

Macià Buades-Rotger, Ph.D., University of Barcelona, Spain, is studying the role of estrogen and progesterone in emotion regulation and aggression. She notes that humans possess an innate tendency to approach reward signals and avoid punishment signals (congruent approach-avoidance behavior). In contrast, individuals usually show difficulties in tasks requiring the opposite behavior, namely, approaching threatening stimuli and avoiding positive ones. In a projected cohort of 150 cisgender women aged 20–35 with a regular menstrual cycle, she will test whether low estrogen and high progesterone is linked with impairments in the control of approach-avoidance tendencies, and whether this effect is in turn associated with higher reactive aggression and mood disturbances.

Basic Research

IMMUNITY & BRAIN DEVELOPMENT

Maria Ester Coutinho, M.D., Ph.D., University of Coimbra, Portugal, notes that exposure to maternal infections, toxins, or immune molecules has been linked with increased risk of adverse neurodevelopmental and mental health outcomes in offspring, including autism spectrum disorder (ASD), schizophrenia, and depression. Maternal Immunoglobulin-G (mIgG) antibodies are of particular relevance, and this project investigates whether mIgG antibodies, beyond their immunological role, are also crucially important for normal brain development and how they affect neurodevelopmental processes. This could help reveal how the maternal immune system affects the offspring's neurodevelopment.

Basic Research

OXYGENATION & BRAIN DEVELOPMENT

Laura R. Fenlon, Ph.D., University of Queensland, Australia, observes that we don't know the ultimate effects of premature birth on the brain, and to what extent early high oxygen exposure contributes to problems with brain development. She will use a mouse model of premature birth to study the effects of birth timing on the development of the neocortex, a brain area heavily involved in learning and memory, social interaction, and sensorimotor functions, and involved in many neurodevelopmental disorders. She will perform a comprehensive comparison of the organization of brain cells, as well as their connectivity and gene expression in the neocortex of premature and full-term offspring, then test the influence of changes in oxygenation of the premature brain as a fundamental contributor to altered development of the neocortex.

Basic Research

TRANSDIAGNOTIC MARKERS

Antonia N. Kaczkurkin, Ph.D., Vanderbilt University, is interested in the degree to which fluctuations in brain activity repeat similar patterns over time. This repetition in activity can be quantified mathematically by the Hurst exponent and is thought to index a critical state where the brain can more easily transition to other brain states. Higher Hurst exponent values are associated with better cognitive functioning and lower levels of mental health symptoms, making this measure a potentially useful transdiagnostic biomarker of psychopathology. Using a sample of over 11,000 youth with multiple timepoints of neuroimaging, cognitive, and psychopathology data collected as part of the NIMH's ABCD Study, this project will use a longitudinal design to 1) examine the Hurst exponent as a predictor of future psychopathology symptoms and cognitive performance, and 2) investigate lower gestational age at birth as a potential risk factor for atypical ability to transition between brain states.

Diagnostic Tools/Early Intervention

MARKERS OF MEMORY IMPAIRMENT

Darrin J. Lee, M.D., Ph.D., University of Southern California, seeks to identify electrophysiological and cerebral blood volume (CBV) markers involved in learning and memory and to utilize deep-brain stimulation (DBS) to reduce memory deficits. Data from his lab demonstrates that DBS of the medial septal nucleus can improve spatial working memory in a model of NMDA receptor hypofunction. To understand the effects of NMDA receptor antagonism Dr. Lee will test administration of MK-801, a drug, on neural circuit electrophysiology, cerebral blood flow, and behavior using simultaneous network electrophysiology and functional ultrasound imaging recordings. The aim is to better understand how DBS modulates these measures. This could improve understanding of electrophysiological and cerebrovascular aspects of impaired brain function due to systemic and regionally specific glutamate hypofunction and serve as a catalyst for research centered on therapeutic neuromodulation.

Basic Research

RESPONSE INHIBITION

Aqilah M. McCane, Ph.D., Oregon Health and Science University, will investigate the neural mechanisms of response inhibition, a behavior related to clinical expression of impulsivity. Dr. McCane hypothesizes that response inhibition is encoded differently in adolescents and adults by specific cortico-striatal networks. To test this, the team will record neural activity in the brains of adolescents and adults during a response inhibition task during which they will perform a battery of computational analyses to enhance understanding of how the orbitofrontal cortex and dorsomedial striatum compute impulsive responding in adults versus adolescents. They also seek to determine the causal role of cell-specific populations on expression of response inhibition. These experiments are aimed to causally delineate computational and cell-specific mechanisms of impulsivity in adolescents.

Basic Research

CHROMATIN REGULATORS

Hume Akahori Stroud, Ph.D., University of Texas Southwestern Medical Center at Dallas, notes that chromatin, which packages DNA within the cell nucleus, plays a key role in gene regulation. The mammalian brain undergoes dramatic changes in chromatin composition such that levels of DNA methylation and methyl-DNA-binding protein, MECP2, increase through development. Mutations in methyl-regulators or MECP2 lead to a variety of neurological disorders. Dr. Stroud seeks a comprehensive understanding of the molecular mechanisms of MECP2 recruitment to DNA and how MECP2 controls gene transcription. In this project the hope is to elucidate the formation of a previously undescribed form of MECP2 targeting to the genome. Understanding how MECP2 functions in normal cells may contribute to understanding how its disruption leads to neurological disorders, and could inform therapeutic strategies to help alleviate the illnesses.

Basic Research

IMPULSIVITY & REWARD

Karly M. Turner, Ph.D., University of New South Wales, Australia, seeks to identify how dopamine release differs between low- and high-impulsive individuals when they make the decision to act and how they respond to rewards. She will examine real-time changes in dopamine release in

rats when they wait, act, and receive reward information. Overall, this project seeks to provide knowledge about learning-related dopamine signals in impulsive individuals, and how the baseline-dependent effects of stimulant medication influence dopamine and behavior. This new knowledge can build a deeper understanding of the biological basis for impulse control deficits and may help to elucidate how changes in natural and medication-induced dopamine dynamics alter impulsivity in conditions such as ADHD.

Basic Research

MATERNAL MICROBIOME & DEVELOPMENT

Denise M. Werchan, Ph.D., New York University, notes the mother is the primary regulator of the developing child's microbiome, beginning before birth and continuing throughout the first few postnatal years—a sensitive period for brain development—through breastmilk, skin, and oral transmission. Yet it is unclear (1) whether maternal regulation of the developing child's microbiome has a subsequent impact on brain and behavioral development, and (2) whether alterations in the maternal microbiome is a biological mechanism linking perinatal psychopathology with altered neurodevelopment. This project tests the hypothesis that the maternal microbiome is a causal mechanism in the intergenerational transmission of risk for mental health disorders through developmental shaping of the child's microbiome. Dr. Werchan will conduct a prospective longitudinal study, considering the role of maternal breastmilk as an important regulator of the developing child's microbiome, and seeking to learn whether variations in maternal postnatal nutrition and diet can act as risk or protective factors for child neurobehavioral outcomes.

Basic Research

ULTRASONIC NEUROMODULATION

Sangjin Yoo, Ph.D., California Institute of Technology, works with ultrasonic neuromodulation (UNM), a new technology being developed for its potential to provide non-invasive control of neural activity in deep-brain regions with millimeter spatial precision. This project follows upon Dr. Yoo's prior findings, seeking biophysical understanding of UNM as predicate for predicting and designing optimal stimulation parameters and long-term safety in a human application. This project seeks a complete mechanistic understanding of UNM, and to use this to optimize UNM parameters and develop a "sonogenetic" approach to target its activity to specific neuronal populations. Sonogenetics utilizes ultrasound to noninvasively manipulate and control cells genetically engineered with ultrasound-responsive proteins; it can be applied to manipulate cellular functions.

New Technologies

Next-Generation Therapies

BIPOLAR DISORDER

Ahmed Eltokhi, Ph.D., University of Washington, asks whether there is common pathophysiology at the circuit level that could be targeted for therapeutic interventions across disorders. He is focusing on voltage-gated sodium (Nav) channels, which are among the most frequent targets of disruptive genetic mutations associated with disorders such as schizophrenia, autism, bipolar disorder, and attention-deficit hyperactivity disorder. The objective of this study is to determine how gating pore current can give rise to psychiatric-like phenotypic outcomes on the cellular and behavioral levels. Such knowledge could enable unraveling the underlying mechanisms by which the Nav channels can contribute to the cellular and systems dysfunction in schizophrenia and autism and perhaps pave the way for establishing new therapeutic targets.

Basic Research

Judit García-González, Ph.D., Icahn School of Medicine at Mount Sinai, notes the clinical heterogeneity of bipolar disorder, with patients diagnosed with type I or type II, depending on symptom duration and severity. The most effective treatment combination typically is identified in each patient by trial and error. This suggests the value of identifying reliable genetic biomarkers that stratify patients into more homogeneous subgroups with similar etiologies which can inform treatment decisions. This project will calculate polygenic risk scores (PRS) summarizing the joint effect of common genetic risk variants for >39,000 bipolar disorder patients collected by the Psychiatrics Genomics Consortium (PGC). The aim is to see if PRS at pathway and cell-type resolution can better differentiate BD I vs BD II patients compared to existing PRS and to cluster individuals into subgroups with similar genetic risk profiles. Such research is a pathway to optimized treatments.

Diagnostic Tools/Early Intervention

Inge R. Holtman, Ph.D., University Medical Center, Groningen, Netherlands, co-founded the Netherlands Neurogenetics Database to integrate extensive clinical and neuropathological summaries with genotype information from donors to the Netherlands Brain Bank. This led to identification of 90 cross-disorder neurological and psychiatric signs and symptoms, including 20 symptoms specific for psychiatric symptoms such as hallucinations, psychosis, mania, and depressed mood. Using machine-learning natural language processing models, they have scored the manifestation of these symptoms on clinical records, providing detailed information on disease trajectories. This project seeks to add an additional layer of information by performing gene-expression profiling on brain tissue from donors

who were diagnosed with schizophrenia, bipolar disorder, and major depression. This step should further clarify the relationship between clinical symptoms, DSM-diagnosis, and genetic susceptibility.

Diagnostic Tools/Early Intervention

Rebekah S. Huber, Ph.D., University of Utah, is studying sleep disturbance and suicide risk in adolescents with bipolar disorder (BD). She notes that fine-grained real-time assessment of suicidal ideation (SI) over short periods of time may reveal distinct phenotypes related to future suicide behaviors. Sleep disturbances including insomnia, hypersomnia, short and long sleep duration, and nightmares have been linked to risk for suicide. Moreover, sleep disturbance is associated with decreased attention and inhibition and may be related to difficulty controlling thoughts of suicide. This project will investigate functional connectivity associated with SI and cognitive control in 30 adolescents with BD and a history of recent suicide attempt and will implement objective ambulatory sleep assessment (actigraphy) in combination with real-time assessment of SI and cognitive control using ecological momentary assessment (EMA).

Basic Research

Diagnostic Tools/Early Intervention

Anouar Khayachi, Ph.D., McGill University, Canada, is motivated by the need for new clinical treatment and management strategies to help patients with bipolar disorder (BD), who often must try various regimens to find one that is at least partly effective. To address this, the project will study the content of extracellular vesicles (EVs) secreted from stem cell-derived neurons in healthy individuals, BD lithium responders, and non-responders, in search of responsiveness markers. Follow-up is aimed at identifying biomarkers to monitor disease state and develop a diagnostic test against which to predict patient responsiveness to therapy. Results could help speed up treatment choice, and thereby accelerate recovery and reduce years of suffering in many patients, in addition to cutting costs.

Next-Generation Therapies

Diagnostic Tools/Early Intervention

Camila Nayane D.C. Lima, Ph.D., University of Texas Health Science Center at Houston, will investigate the biological underpinnings of accelerated aging and their hallmarks in bipolar disorder (BD). She will analyze gene expression changes in peripheral blood of patients with BD and healthy controls characterized for aging using a predictor of lifespan called "GrimAge." Neuroimaging will be used to estimate "brain age" and develop a marker comparing predicted brain age and chronological age. The study will also test the association between biological aging measures in blood and in the brain, which could inform epidemiological studies with BD and other clinical populations.

Diagnostic Tools/Early Intervention

Sarah H. Sperry, Ph.D., University of Michigan, has in past work established that intra-individual dynamics in emotion, behavior, and cognition, assessed over short timescales (weeks), are strong predictors of symptom severity and even predict the development of bipolar disorder (BD) in those at risk. Distinct patterns of longitudinal fluctuations in mood are associated with different clinical presentations. This study, inspired by the goals of precision medicine, will use time-series approaches and dynamic structural equation modeling to identify intraindividual trajectories of mood and how these dynamics predict meaningful clinical outcomes. These methods allow examination of whether patients with BD can be stratified by their patterns of intraindividual dynamics, potentially reflecting more data-driven characterizations of BD.

Diagnostic Tools/Early Intervention

BORDERLINE PERSONALITY DISORDER

Sarah Kathryn Fineberg, M.D., Ph.D., Yale University, is studying problems that people with borderline personality disorder (BPD) have in making and updating their beliefs about other people. She proposes that these problems in social learning may contribute to symptoms. This project will test if social learning problems get better as people recover from BPD. Dr. Fineberg will use computer games to measure social learning in people with BPD, expecting that social learning in people with remitted or recovered BPD will be improved compared to people with current BPD. She will also measure social learning during social stress, expecting that people with recovered BPD will be more resilient under social stress than people with current BPD or remitted BPD. The hope is that these experiments about social learning will help reveal what is getting in the way of stable relationships for people with BPD.

Basic Research

Jenna M. Traynor, Ph.D., McLean Hospital, Harvard University, says that we have a poor understanding of which individuals with personality disorders require generalist v. specialist levels of care to experience a reduction in suicidal thinking. She will test whether new diagnostic tools can be used prognostically to predict reductions in suicidal thinking, compared to more traditional ways of measuring personality-disorder symptoms. Data from 100 suicidal patients beginning treatment in a partial hospitalization program will be used to study these associations. If alternative diagnostic

tools can provide more precise measurements of symptom severity from mild to extreme impairment, this research may identify thresholds of personality disorder impairment associated with improvements following partial hospitalization, leading to a better understanding of which patients benefit most from short-term partial hospitalization (i.e., generalist treatment), and which require more specialist personality disorder treatments that are typically longer term.

Diagnostic Tools/Early Intervention

DEPRESSION

Jessica Lynn Bolton, Ph.D., Georgia State University, studies how early-life experiences, especially adversity, modulate brain circuits. This project will focus on microglia, a type of brain cell that is known to influence synapses in sensory systems and other circuits, and look at the interactions of microglia and neurons in a stress-responsive brain region called the amygdala. It will also study whether manipulating microglia early in life prevents the development of depression-like behavior in adolescence due to early-life adversity.

Basic Research

Davide Balos Cappon, Ph.D., Harvard Medical School, Harvard University, is trying to develop non-invasive neuromodulation therapies for major depressive disorder (MDD) paired with dementia (MDD+D). One aim of this project is to determine the feasibility of the simultaneous administration of tDCS and tACS, two forms of neurostimulation, in a form administered in the participant's home (HB-tES) utilizing a remotely monitored caregiver-led technique that has been found to be safe and effective. He will determine whether the intervention improves depression and memory symptoms and associated disability. A second aim is to determine whether any observed improvements in depression and memory are related to the amount of electrical field generated in symptom-specific targeted brain circuits.

Next-Generation Therapies

Samuel William Centanni, Ph.D., Wake Forest University, seeks to uncover molecular mechanisms driving stress-induced hyperactivity, a factor in a range of affective disorders. The team will use multiple methods to define unique genetic signatures of insula-to-BNST neurons and determine the direct impact of stress on active ribosomal translation in this subpopulation. This approach could identify new pharmacological targets that minimize the damaging dysregulated activity caused by stress, while not impacting the regular function of surrounding non-stressed cells.

Basic Research

Kenny L. Chan, Ph.D., Icahn School of Medicine at Mount Sinai, notes evidence suggesting a correlation between major depressive disorder and inflammation. He seeks to identify brain-to-gut neural circuits that trigger gut inflammation and increase gut permeability during stress. To investigate potential targets, he can deliver a virus that carries a fluorescent protein from the intestine to the gut, as well as use whole-brain imaging to generate a comprehensive map of stress-activated brain regions that innervate the large intestine. The aim is to directly activate or inhibit specific cells in these regions to evaluate their contribution to gut inflammation and permeability. This research could inform development of novel therapeutics that target neurons or immune cells in the gut.

Next-Generation Therapies

Jun Chen, Ph.D., University of California, Los Angeles, notes that sleep disturbance is a core symptom of depression, which often precedes depressive episodes and can persist during remission. Diagnostic tools for sleep disturbance, e.g., polysomnography, need to be conducted overnight by clinicians in health facilities. Sleep trackers, e.g., wristband sensors and under-bed sensors, are often expensive and inaccurate. This project will test a smart bedsheet for depression pre-diagnosis as a way of recognizing early sleep disturbance signs. It is based on the concept that biomechanical activities during sleep, (e.g., body movements, ballistic forces generated by the heart, and breathing activities) will deform the smart bedsheet and induce current signals. The project will assess the concept in a pilot study.

Diagnostic Tools/Early Intervention

New Technologies

Tina Chou, Ph.D., Massachusetts General Hospital, Harvard University, is interested in the default mode network (DMN), which is active during negative self-referential thoughts in people with major depression. Interventions such as psilocybin that change activity in posterior default mode network regions (e.g., the posterior cingulate cortex, or PCC), can change how people think about themselves. This project will test transcranial focused ultrasound (tFUS), a novel form of non-invasive brain stimulation that can deliver acoustic energy anywhere in the brain. Targeting the PCC, the aim will be to reduce negative self-thinking in depressed individuals. The team will adopt a personalized approach, targeting specific areas within the PCC that are specifically involved when an individual is engaging in negative self-thinking.

Next-Generation Therapies

New Technologies

Joseph M. Cichon, M.D., Ph.D., University of Pennsylvania, notes that the mechanisms initiating and sustaining plasticity associated with rapid antidepressant action remain unclear. In a rodent model of chronic stress, he will test the hypothesis that changes in neuronal activity imposed acutely by nitrous

oxide (NO2) automatically give rise to sustained plasticity through activity-dependent mechanisms. This notion is based on work on activity-dependent plasticity in the cortex and his own research suggesting that nitrous oxide specifically and directly activates layer-5 cortical neurons which mediate cortico-cortical connectivity. The project lays groundwork for understanding the mechanisms through which acute pharmacologic interventions can lead to sustained therapeutic benefits in psychiatric illnesses.

Basic Research

Ana Paula Costa, Ph.D., Weill Cornell Medical College, observes that lipidomics is increasingly recognized as a potent approach for investigating disease-induced lipid metabolism changes associated with major depression (MDD). The goal of this project is to study the role that lipid pathway dysregulation plays in MDD. Using members of a 3-generation cohort who have been subjects in the study of depression cohort of families, Dr. Costa will first conduct lipidomic studies, using plasma and saliva, for the identification of lipid pathway metabolites associated with risk for MDD. The project will also use iPSCs to test whether the dysregulation of lipid metabolic pathways is cell-type specific and to identify the sufficiency and necessity of functional targets in lipid metabolism using genetic knock-down and overexpression. This has the potential to identify biomarkers for early disease susceptibility and therapeutic targets in lipid metabolism.

Diagnostic Tools/Early Intervention

Adam J. Culbreth, Ph.D., University of Maryland, proceeds from evidence that abnormal effort-cost decision-making (ECDM)—calculations performed to weigh the "cost vs. benefits" of actions—may contribute to motivational deficits in schizophrenia and major depression. Such calculations are critical for goal-directed behavior. He seeks to clarify whether motivational deficits are driven by reduced sensitivity to rewards or heightened sensitivity to efforts associated with actions. This project will use experimental tasks and associated computational modeling approaches to quantify the relative contributions of effort and reward sensitivity to effort-cost decision-making in people with major depressive disorder and healthy controls.

Basic Research

Romain M. Durand, Ph.D., Icahn School of Medicine at Mount Sinai, is studying neuroimmune mechanisms underlying reward deficits in depression. A healthy blood-brain barrier (BBB) tightly controls interactions between peripheral circulation and the brain, whereas in major depression and animal models of chronic social defeat stress (CSDS), there is disruption of the BBB, leading to increased permeability and peripheral cytokine infiltration. Dr. Durand will measure serum concentrations of a panel of peripheral cytokines/chemokines (e.g., IL-6) as well as their infiltration in the NAc in CSDS mice and will correlate these inflammatory biomarkers with reward sensitivity. The research also seeks to determine if cytokine neutralization of IL-6 or other cytokines using monoclonal antibodies is sufficient to rescue reward sensitivity deficits following stress exposures.

Basic Research

Immanuel Elbau, M.D., Ph.D., Weill Cornell Medical College, will work with a new deep brain stimulation protocol that involves implanting 10 bilateral electrodes with 160 stimulation contacts spanning numerous corticolimbic circuits. Patients undergo a 10-day inpatient monitoring interval to evaluate responses to an array of focal stimulations and to establish relationships between stimulation characteristics and clinical response. In this project, Dr. Elbau will probe network-specific behavioral responses by using repeated multi-echo resting-state fMRI imaging acquired prior to electrode implantation in three patients. The goal is to precisely map stimulation-evoked behavioral responses to distinct functional networks. Specifically, the aim is to predict behavioral responses from network stimulation and determine whether network-specific stimulation evokes behavioral responses that are similar across individuals.

Next-Generation Therapies

Joline M. Fan, M.D., University of California, San Francisco, is investigating the strong link between sleep-wake activity ("arousal level") and mood. To map the circuitry of arousal within mood networks in patients with mood disorders, Dr. Fan will leverage an ongoing clinical trial in patients with treatment-resistant depression, implanting intracranial electrodes within the corticolimbic mood network to systematically assess the acute response to focal electrical stimulation. She will test the hypothesis that there is an extension of classical subcortical arousal pathways that are distributed into and overlapping with corticolimbic mood networks, explaining the co-modulation of arousal and mood. The research is a step toward enabling precision targeting of corticolimbic sites for personalized deep brain stimulation tailored to individual patients with treatment-resistant mood disorders.

Basic Research

Itay Hadas, Ph.D., University of California, San Diego, has developed a set of neurophysiological markers of cortical circuit activity and connectivity in depression. These markers are able to differentiate between healthy controls and depressed patients. Importantly, the markers were normalized to healthy control levels after efficacious rTMS brain stimulation treatment, but did not change after placebo treatment, making them a potentially prognostic marker of treatment response.

This project aims to validate these markers in association with diffusion tensor imaging (DTI) anatomical connectivity metrics as well as functional magnetic resonance imaging (fMRI) markers, and associate these complementary measures with treatment-resistant depression improvement with rTMS.
Diagnostic Tools/Early Intervention

Jakob Hartmann, Ph.D., McLean Hospital, Harvard University, will investigate sex-specific gene networks in a brain area called the BNST that modulate susceptibility and resilience to chronic stress; he will do so by combining state-of-the-art single-cell transcriptomics in animal models with causal chemogenetic tools. Despite playing important roles in the stress response and emotional and social behaviors, the BNST has been largely overlooked with respect to its possible sex-specific dysregulation in mood and anxiety disorders. Providing a more detailed understanding of the sexually dimorphic neuronal heterogeneity and transcriptional specificity within the BNST following chronic social defeat stress (CSDS) in rodents will make possible the further dissection of its function in the context of psychiatric disorders.
Basic Research

Frederick L. Hitti, M.D., Ph.D., University of Texas Southwestern Medical Center at Dallas, is studying the role of the lateral habenula (LHb) in treatment-resistant depression. While several brain regions have been implicated in depression, the LHb is an attractive target because it is activated by reward omission and punishment, and it is connected to other brain areas that control serotonin and dopamine release. Moreover, it is hyperactive in depression, and inhibition of the LHb has been shown to reverse stress-induced social withdrawal and despair in rodents. Using a rodent model of treatment-resistant depression, Dr. Hitti will test whether hyperactivity of the LHb mediates treatment-resistance, and if inhibition of the LHb will ameliorate stress-induced social withdrawal and despair.
Basic Research
Next-Generation Therapies

Inge R. Holtman, Ph.D., University Medical Center, Groningen, Netherlands, co-founded the Netherlands Neurogenetics Database to integrate extensive clinical and neuropathological summaries with genotype information from donors to the Netherlands Brain Bank. This led to identification of 90 cross-disorder neurological and psychiatric signs and symptoms, including 20 symptoms specific for psychiatric symptoms such as hallucinations, psychosis, mania, and depressed mood. Using machine-learning natural language processing models, they have scored the manifestation of these symptoms on clinical records, providing detailed information on disease trajectories. This project seeks to add an additional layer of information by performing gene-expression profiling on brain tissue from donors who were diagnosed with schizophrenia, bipolar disorder, and major depression. This step should further clarify the relationship between clinical symptoms, DSM-diagnosis, and genetic susceptibility.
Diagnostic Tools/Early Intervention

Caroline P. Hoyniak, Ph.D., Washington University, St. Louis, notes that given the costs of depression in early childhood and across the lifespan, it is critical to identify children who are at risk as soon as possible. In adults, sleep and circadian rhythm disturbances have shown promise as biomarkers, but virtually no research has explored such markers in early-childhood depression. This project will explore how disturbances in circadian rhythm contribute to the emergence and maintenance of depression and sleep/wake disturbances in young children. It is expected that blunted daily profiles of melatonin, cortisol, or both, and evidence of poor circadian rhythmicity, will be associated with heightened depression symptomology. The study should inform whether bright light therapy or melatonin-based medications, which have been useful for normalizing endogenous melatonin and cortisol rhythms, may be a useful adjunct to treatments for early-childhood depression.

Diagnostic Tools/Early Intervention
Next-Generation Therapies

Kyle D. Ketchesin, Ph.D., University of Pittsburgh, notes that people with major depression (MDD) show disrupted circadian rhythms in gene expression in the nucleus accumbens (NAc), which consists of a variety of transcriptionally distinct cell types with differential roles in depression. The role of rhythms in these cell types has not been investigated. D1 and D2 medium spiny neurons (MSNs) are prominent in the NAc and recent studies have identified opposing roles for these in depressive-like behavior. Notably, molecular clock dysfunction in D1 MSNs, but not D2 MSNs, regulates vulnerability to helpless behavior in mice, suggesting that circadian rhythms in D1 MSNs may play a key role in depression. This project will measure cell type-specific rhythms in the human brain central to understanding the cell type-specific mechanisms underlying circadian dysfunction in MDD. This could establish circadian rhythm changes in D1 MSNs as a novel therapeutic target.
Basic Research
Next-Generation Therapies

Daniel C. Kopala-Sibley, Ph.D., University of Calgary, Canada, seeks to determine whether altered brain structure and function are an antecedent or outcome of depression onset by using a prospective cohort of adolescents at high familial risk. The cohort will consist of 215 adolescents (67% female)

aged 12 to 14 with at least one parent with a history of major depression (MDD) but who themselves have not experienced diagnosable levels of depression. The research will determine whether neuroimaging abnormalities associated with depression predate the illness, and therefore might predict onset, or are residual 'scars' of depression. This could improve the early identification of youth at risk for depression and help guide psychosocial and neurobiological prevention efforts, including use of prophylactic familial and adolescent psychosocial interventions to prevent the first lifetime episodes of MDD.

Diagnostic Tools/Early Intervention

Thang M. Le, Ph.D., Yale University, recently demonstrated a mutually reinforcing relationship between negative affect, avoidance response, and problem drinking. This relationship is associated with diminished modulation of the prefrontal cortex and enhanced recruitment of the pain circuit during punishment avoidance. The lab also reported that pain and reward circuits exert antagonistic influences on alcohol misuse. Building on these findings, this project seeks to investigate dysfunctional pain reactivity and cognitive control during avoidance learning as a principal mechanism of the comorbidity, by collecting fMRI, arousal, and behavioral data in individuals diagnosed with AUD, with and without depression comorbidity. The goal is to identify biopsychological markers to advance understanding of alcohol use disorder/depression phenotypes, improve diagnosis, and develop novel treatments.

Basic Research

Stephanie L. Leal, Ph.D, Rice University, will examine the impact of antidepressants on emotional memory and underlying neural mechanisms of depression. Depression is associated with general memory impairment as well as a negativity bias. One potential mechanism of negativity bias could be hippocampal pattern separation, a process in which similar experiences are remembered as distinct, allowing individuals to recall negative details. She will examine the effect of antidepressants on emotional memory in depression using a sensitive emotional mnemonic discrimination task. Then she seeks to establish the effect of antidepressants on amygdala and hippocampal activity during emotional pattern separation in depression. Finally, she seeks, during emotional pattern separation in depression, to determine the effect of antidepressants on connectivity in the medial temporal lobe (MTL). This could lead to more targeted interventions directed at specific emotional biases and their underlying neural mechanisms in depression.

Basic Research

Shibin Li, Ph.D. Stanford University, recently characterized hypothalamic circuitry underlying stress-induced insomnia/hyperarousal. Dr. Li found that corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus of hypothalamus (PVN) directly innervate wake-promoting hypocretin (Hcrt) neurons in the lateral hypothalamus (LH). Genetic ablation of HcrtLH neurons or CRISPR-Cas9-mediated disruption of the crh gene in CRHPVN neurons was found to compromise arousal level upon optogenetic stimulation of CRHPVN→HcrtLH circuitry or restraint stress exposure. Dr. Li will conduct experiments seeking to determine if optogenetic activation of the AVPPVN→LepRbLH→HcrtLH pathway will counteract the activity of CRHPVN→HcrtLH circuitry, ameliorating hyperarousal/insomnia induced by stress exposure.

Basic Research

Dong Liu, Ph.D., Columbia University, is working to further develop focused ultrasound (FUS), a form of neuromodulation targeting deep subcortical regions of the brain. This project builds on Dr. Liu's recent finding that a 2-minute application of FUS can alter functional connectivity for hours in non-human primates. It will target the dorsal striatum in non-human primates and analyze the impacts with fMRI to determine: 1) whether the effect of FUS is limited to brain structures of the target region or within the cortico-striatal circuits; 2) whether the brain shows different activation patterns before and after FUS neuromodulation. This will test the potential for developing FUS neuromodulation as a non-invasive alternative for patients with treatment-resistant schizophrenia. If successful, the approach can be extended to other psychiatric disorders, such as depression and obsessive-compulsive disorder, for which deep brain stimulation is a possible treatment.

New Technologies

Next-Generation Therapies

Hermany Munguba, Ph.D., Weill Cornell Medical College, seeks to better understand the mechanisms underlying fast-acting antidepressants, especially at the circuit level. He notes converging evidence indicating that specific classes of prefrontal cortex (PFC) cells are fundamental to the function of fast-acting antidepressants. His broad hypotheses are: (1) modulation of distinct neuron types in the PFC can bi-directionally control mood; (2) stress-sensitive somastostatin-expressing neurons are fundamental to the control of mood; (3) mapping neuromodulatory receptors within the PFC will reveal novel cell-type-specific antidepressant targets. The project thus will test a microcircuit model of antidepressant neuromodulatory signaling and use it to identify uniquely expressed, multiplexable pharmacological targets capable of alleviating depression-associated behavioral impairments.

Basic Research

Corina Nagy, Ph.D., Douglas Mental Health University Institute, Canada, seeks to uncover the molecular features underlying sex-specific cellular phenotypes and networks to discern how susceptibility and development of major depression (MDD) differ between sexes. This project will examine individual brain cells from people with a history of MDD and matched controls to disentangle the contribution of cells and their networks, within and across brain regions, to given depressive traits. This resolution will allow Dr. Nagy to define sex- and disease-specific molecular and cellular networks that can provide more precise information for intervention and therapeutics. Identifying disrupted molecular and cellular networks may bring us one step closer to identifying causal biological changes associated with MDD.

Basic Research

Saptarnab Naskar, Ph.D., Northwestern University, studies mechanisms underlying the way stress impacts the brain. Dr. Naskar notes that projections from the prelimbic area (PL) of PFC to periaqueductal grey (PAG), ventral tegmental area (VTa), and nucleus accumbens (NAc) form an important output triad influencing various aspects of approach and consumption of reward; and that 2-arachidonoylglycerol (2-AG), a widely circulating endocannabinoid (eCB), is strongly implicated in stress induced alteration in the activity of PFC neuronal sub-populations in a circuit-specific manner. The team will utilize a combination of ethologically relevant quantitative behavioral approaches, in-vivo single cell calcium imaging in freely behaving animals, and pharmacology to ask, ultimately, if stress-induced deficits in reward evaluation and procurement can be reversed by selectively modulating 2-AG levels.

Basic Research

Sean M. Nestor, M.D., Ph.D., Sunnybrook Health Sciences Centre, University of Toronto, Canada, notes that people with ultra-treatment-resistant depression (UTRD) do not respond to several first-line and second-line antidepressants, psychotherapy, and brain stimulation therapies including ECT. The biology underpinning UTRD is poorly understood. This pilot study aims to acquire cross-sectional iTBS (intermittent theta-burst stimulation) fMRI for 28 adults with mild treatment-resistant depression (TRD) referred for TMS antidepressant treatment, and another 28 adults with UTRD referred for neurosurgical treatment of depression. The goal is to determine the most influential DLFPC (dorsolateral prefrontal cortex) brain activity relationships associated with iTBS that differentiate TRD and UTRD. Some participants will receive an accelerated 5-day iTBS protocol that will individually target the DLPFC mood circuit. This will enable assessment of whether pre-treatment iTBS-induced changes to brain function can identify/predict a subset of persons with TRD/UTRD that respond to clinical treatment with iTBS.

Next-Generation Therapies

Nancy Padilla-Coreano, Ph.D., University of Florida, notes that for social animals, including humans, to thrive, they must show social competence and adjust behavior based on social history (e.g. social rank or degree of familiarity) and context. Social motivation is a critical component of social competence that is necessary for health and survival, and is impaired in depression, anxiety and autism. Her past work has shown that the medial prefrontal cortex (mPFC) encodes social rank and that mPFC input to the lateral hypothalamus (LH) regulates social behavior between familiar mice, suggesting a role for the mPFC-LH circuit in social history. This project seeks to learn more about familiarity and social rank, and to resolve the issue of subjective human quantification of social behaviors by using novel machine-learning tools. The central hypothesis is that dopaminergic modulation of mPFC and LH changes across social history states to enable social motivational differences.

Basic Research

Lyonna F. Parise, Ph.D., Icahn School of Medicine at Mount Sinai, studies the relationship between stress, mood disorders, and substance abuse. She has shown that chronic exposure to alcohol increases the expression of peripheral neutrophils, leading to breakdown of the blood-brain barrier in reward regions such as the nucleus accumbens, and facilitating the infiltration of pro-inflammatory factors into the brain, leading to stress susceptibility. This work has identified a neutrophil-released protease that is increased after alcohol exposure that can target tight junction proteins. To determine the precise function of neutrophil elastase (NE) in alcohol-induced mood alterations, she will utilize a transgenic mouse model in which NE is inactive. Mice will be exposed to a binge-drinking alcohol paradigm, a chronic stressor, and then to various antidepressant treatments, including traditional (fluoxetine) and novel (ketamine) antidepressants, as well as a commercially available NE inhibitor. Changes in tight junction protein expression, BBB permeability, and the levels of peripheral inflammatory markers will be analyzed.

Basic Research

Zachary T. Pennington, Ph.D., Icahn School of Medicine at Mount Sinai, has used whole-brain activity mapping in mice to examine how an acute, severe stressor is able to augment subsequent neural and behavioral responses to a novel stressor a week later. This revealed hyperactivation of the anterior hypothalamic nucleus (AHN) in severely stressed animals, which represents a novel target for treatment intervention. This project seeks to uncover the contribution of the AHN to the sensitization of fear and anxiety by prior severe stress, and to assess whether a subpopulation of cells within the AHN might be targeted to attenuate stress responses.

Basic Research

Dominique Piber, M.D., Charité – Universitätsmedizin Berlin, Freie Universitat Berlin, Germany, proceeds from evidence suggesting the association between major depression (MDD) and obesity might be mediated by a dysregulation of immune-metabolic pathways in T cells, particularly CD4+ T cells. This project is an ancillary study to an ongoing clinical trial (simvastatin add-on to escitalopram in patients with comorbid obesity and major depression.) This study will examine whether 12-week treatment with simvastatin mitigates dysregulation of CD4+ T cell immunometabolism in comorbid MDD and obesity. Dr. Piber will evaluate CD4+ T cell immunometabolism and MDD severity at baseline, week 4, and week 12 in a trial subsample (n=40 in the statin group, n=40 in the placebo group). The goals are to determine if simvastatin mitigates dysregulation of CD4+ T cell immunometabolism and whether reduced levels of mitochondrial CPT1a and mitochondrial superoxide will be associated with clinical improvement of MDD.

Next-Generation Therapies

Stefanie Russman Block, Ph.D., University of Michigan, seeks to improve the effectiveness of emotion regulation strategies for those with anxiety using real-time fMRI neurofeedback, a novel technology that allows individuals to control their own brain activity. In this project, participants with anxiety will practice reinterpreting the meaning of negative images, a common emotion regulation strategy taught in therapy, while receiving feedback about brain activity in the dorsomedial prefrontal cortex, a brain region involved in emotion regulation. This work will help us understand the neural circuity of emotion regulation and lay the groundwork to test if psychotherapy outcomes can be enhanced using neurofeedback.

Next-Generation Therapies

New Technologies

Sheila R. Shanmugan, M.D., Ph.D., University of Pennsylvania, proceeds from the hypothesis that variation in the functional topography of personalized default mode networks (DFM) in part underlie sex differences in internalizing symptoms (seen in mood disorders including anxiety and depression). Since these symptoms typically emerge in childhood and adolescence, the hypothesis will be evaluated in the cohort for the NIH's ABCD study of youths, n = 11,572. Dr. Shanmugan will evaluate whether the topography of personalized default mode networks underlie sex differences in current internalizing psychopathology, and will use baseline variation in functional topography to predict the longitudinal course of internalizing psychopathology. The project could establish that sex differences in personalized functional networks underly sex differences in internalizing psychopathology.

Basic Research

Thomas Steinkellner, Ph.D., Medical University of Vienna, Austria, recently discovered a neuronal circuit that connects a key brain region known to be perturbed in mood and anxiety disorders with a small brain area that is involved in the processing of environmental information including visual and auditory cues. This small brain region uses two types of neurotransmitters to communicate with other cells, both of which are well known to play a role in depression, fear, and anxiety. He will test the individual contributions of these two neurotransmitters within this circuit using sophisticated cell-type-specific mouse genetic tools. He will focus on behaviors relevant to mood disorders to determine whether this novel dual transmitter circuit could be a new target for the development of future antidepressant medications.

Basic Research

Michelle E. Stepan, Ph.D., University of Pittsburgh School of Medicine, notes that slow-wave sleep is a biomarker of sleep disturbance that is reduced in depression, anxiety, and other mood disorders. Slow-wave activity normally promotes neural plasticity via synaptic downscaling, which renews information processing capacity and cognitive control processes. This, in turn, is important for downregulating negative affect to aversive stimuli. Acoustic stimulation involves playing brief sub-arousal tones during slow-wave sleep to enhance slow-wave activity without disturbing sleep. It can reliably enhance slow-wave activity, particularly in young adults, and improve cognitive processes. This project will use a commercial headband device to test acoustic stimulation in young adults (ages 18–25) with elevated anxiety/depression symptoms and will assess acute (1 night) and extended (14 nights) effects on sleep, cognitive control, and emotional reactivity to aversive stimuli.

Next-Generation Therapies

Yue Sun, Ph.D., Stanford University, focuses on depression in the context of Parkinson's disease (PD). It is one of the most prevalent non-motor symptoms in PD, affecting 35% of patients. Depression can occur before the onset of motor symptoms, indicating that it may be part of the PD pathology rather than a consequence of motor dysfunction. Dr. Sun seeks to uncover mechanisms underlying the early development of depression in PD. Dopamine neurons in the ventral tegmental area (VTA) are lost in PD, and given other evidence linking the VTA to depression, Dr. Sun hypothesizes that dopamine signaling in the VTA is disturbed in early-stage PD and contributes to the development of depression. This mechanistic thesis will be investigated in experiments conducted in mouse models of depression-like behaviors.

Basic Research

Alex Tang, Ph.D., University of Western Australia, suggests that to improve the efficacy of rTMS (a non-invasive brain stimulation treatment often used in depression), a greater understanding of how it changes brain cells and whether these changes are affected by key biological factors such as age and sex is needed. To avoid the difficulty and danger of studying this directly in people, Dr. Tang will use brain samples donated from neurosurgery patients. He will investigate genes and biological functions that are altered after rTMS. He hopes to uncover why the effects of rTMS varies between patients, which could inform efforts to develop a more targeted and efficient use of rTMS to treat a wide range of mental health disorders.

Next-Generation Therapies

Tuan Leng Tay, Ph.D., Boston University, will address glial dynamics (e.g., gliosis, release of inflammatory and neurotrophic cytokines) to the efficacy of deep brain stimulation (DBS) in major depression (MDD). The presence of proinflammatory microglial states, which exacerbate disease, have been reported in MDD patients and animal models. This suggests that any additional chronic glial reactivity resulting from electrode implantation could add to disease burden. Conversely, sustained glial reactivity and inflammation could lead to neuronal death and detrimental tissue scarring. Thus, addressing the spatial and temporal contexts of glial responses at the interface of the brain and the foreign device through this project could explain some of the inconsistencies in the efficacy of DBS in MDD. Experiments to shed light on the process will be conducted in transgenic reporter mouse models. The hope is to reveal the extent of glia-mediated tissue damage or recovery caused by neural devices and open new avenues to improve the efficacy of DBS in MDD, potentially through additional drug targeting of glia at the appropriate treatment stage.

Next-Generation Therapies

Joseph J. Taylor, M.D., Ph.D., Brigham and Women's Hospital, Harvard University, is working with accelerated intermittent theta burst stimulation (iTBS), a novel transcranial magnetic stimulation (TMS) protocol that involves multiple daily treatments, and specifically, a protocol called Stanford Neuromodulation Therapy (SNT), which has only been tested at a single site in a small number of patients and so far never without neuronavigation and individualized targeting based on resting state functional connectivity, neither of which are widely available. This study aims to explore these issues. In this pilot trial, patients with treatment-resistant depression (n=40) will be randomized to one of two active treatment arms, one with and one without individualized targeting. The ultimate aim is to provide a real-world estimate of the clinical value of individualized targeting, a costly and complex difference from traditional TMS that may limit development and scalability of SNT.

Next-Generation Therapies

Sarah A. Thomas, Ph.D., Bradley Hospital, Brown University, seeks to know more about how teen cannabis use (CU) disrupts circuits mediating cognitive flexibility (adaptation to changing rewards and punishments), reward motivation (the amount of goal-directed behavior to earn rewards), and how the brain is connected at rest (resting state functional connectivity [RSFC]). The hypothesis is that CU in the context of teen brain development results in fronto-striatal circuitry alterations and impaired cognitive flexibility and reward motivation that will vary as a function of cannabis exposure and depression. The team will: (1) identify the brain/behavior mechanisms of cognitive flexibility and RSFC associated with co-occurring CU and depression using fMRI; (2) define behavioral alterations in reward motivation associated with co-occurring CU and depression; (3) use a computational psychiatry model to identify how latent decision-making components vary for CU teens according to the presence of depression.

Basic Research

Nicholas T. Trapp, M.D., University of Iowa, notes that researchers don't yet understand exactly what TMS stimulation does to underlying brain networks or structures connected to the stimulation site. He will apply experimental brain stimulation in patients who have intracranial electrodes implanted for clinical reasons, to compare what happens intracranially with what noninvasive connectivity measures would predict based on brain imaging. The team will use a machine-learning approach to predict the propagation patterns of brain stimulation. They then intend to test this artificial intelligence approach to better understand the information most crucial for accurate prediction of TMS propagation. Finally, they seek to refine and calibrate their algorithm to generate the machine-learning algorithm which provides the best predictive capabilities, which could then serve as a tool for future researchers aiming to target brain stimulation based on neuroimaging connectivity.

Next-Generation Therapies

Akina Umemoto, Ph.D., Columbia University, notes that alterations in reward processing have long been implicated in major depression (MDD), and that research has called attention to the importance of characterizing different stages of reward processing in MDD, particularly reward anticipation and consummatory processes (i.e., initial reward responsiveness) across different units of analysis. Although research has shown that MDD is associated with both anticipatory and consummatory reward functioning, the role of neurotransmitters in modu-

lating these processes, as well as the interrelationship of these processes, is not well understood. This project seeks to provide key insights regarding the role of noradrenergic functioning during reward anticipation on dopaminergic functioning following reward receipt as well as prospectively assessed, real-world outcomes in adolescents with depression. The hope is that this will help pinpoint novel neuromodulatory clinical targets that can improve treatment outcomes in major depression.
Basic Research

Manuel Valero Garcia, Ph.D., New York University, will dissect functional changes in the hippocampus-accumbens connections of normal mice and mice modeling major depression (MDD) by using dual hippocampal and ventral striatum recordings. A fundamental physiological element of the hippocampo-ventral striatum dialogue is the reactivation of striatal cells during sharp-wave ripples (SPW-r), hippocampal periods of highly coordinated activity. SPW-r propagate to many cortical and subcortical structures; abnormal SPW-r have been observed in several psychiatric disorders, including chronic stress and MDD. He will attempt to reverse the behavioral and physiological changes observed in MDD mice with SPW-r-triggered reactivation of nucleus accumbens cells via optogenetic stimulation. The hypothesis is that SPW-r optogenetically-assisted reactivation of ventral striatum will reverse excitability changes of nucleus accumbens neurons observed in MMD, protecting or ameliorating physiological and behavioral long-term effects of the disorder.
Basic Research

Akila S. Weerasekera, Ph.D., Massachusetts General Hospital, Harvard University, is testing transcranial photobiomodulation (t-PBM) therapy—the use of low-power lasers to stimulate the brain. This non-invasive modality improves the metabolic capacity of neurons via increased oxygen consumption and ATP production. He seeks evidence of the optimal dose irradiance of t-PBM and its dose-dependent neurometabolic impact in MDD. Proton magnetic resonance spectroscopy will be used to evaluate the dose-dependent neurometabolic effects of t-PBM in major depression (MDD) patients. Study outcomes could be relevant to future decisions on the development of t-PBM as an effective treatment modality in MDD.
Next-Generation Therapies
Diagnostic Tools/Early Intervention

Kevin S. Weiner, Ph.D., University of California, Berkeley, notes the human cerebral cortex contains neuroanatomical structures and shallow indentations known as tertiary sulci (TS) which develop during gestation through the post-birth period and whose role is unknown in mental health outcomes. He will examine the relationship between TS morphology in orbitofrontal cortex (OFC) and emotion-related impulsivity (ERI) in a transdiagnostic sample. ERI is defined by frequent loss of control during strong emotion states and is a robust predictor of internalizing disorders (e.g., depression), externalizing disorders (e.g., substance abuse), aggression, and suicidality. The hypothesis is that tertiary, but not primary or secondary, sulcal morphology in OFC will be related to ERI. Findings have the potential to shift the focus from morphological analyses of primary brain structures in different syndromes and diseases to tertiary brain structures which emerge in the third trimester.
Basic Research

EATING DISORDERS

Sofia Beas Parodi, Ph.D., University of Alabama at Birmingham, notes the prevalence and potential lethality of eating disorders. She will use innovative methods to record and manipulate the activity of specific neurons during food-seeking and food consumption. Of particular interest is the paraventricular nucleus of the thalamus (PVT), a brain region that integrates bottom-up homeostatic signals with top-down cortical information. Two distinct subpopulations of neurons that differ in their genetic identity, connectional features, and functionality are focal points of the research, Type1PVT and Type2PVT neurons, involved in the encoding of engagement in food-seeking behavior. Understanding the neural circuits that mediate food-seeking could provide insight enabling development of novel treatments for those suffering from eating disorders.
Basic Research

Lauren Breithaupt, Ph.D., Massachusetts General Hospital, Harvard University, seeks to elucidate the interaction between immune and metabolic markers in females with anorexia nervosa. Recent genomic research encourages the reconceptualization of anorexia nervosa as both a psychiatric and metabolic disorder. Dr. Breithaupt's research in epidemiology, proteomics, and neuroimaging has provided evidence for the role of inflammation in the acute stages of anorexia nervosa. This project aims to examine the interaction between inflammation and metabolism in individuals with anorexia nervosa. The central hypothesis is that weight loss drives inflammation, and that energetically favorable brain networks may persist despite the energy-deficient state. To test this, she will investigate the contribution of immune and metabolic plasma makers on dynamic energetic fluctuations in anorexia nervosa and healthy controls.
Basic Research

Marie A. Labouesse, Ph.D., ETH Zurich, Switzerland, proceeds from fMRI data indicating connectivity between the nucleus accumbens (reward region) and the hypothalamus (metabolic region) is altered in patients with eating disorders. She seeks to model fMRI findings using neural circuit approaches in mice to determine whether alterations in nucleus accumbens-to-hypothalamus connectivity could causally induce feeding behavior abnormalities. She also hopes to identify mechanisms that could drive the appearance of altered connectivity across childhood and adolescence, periods of maximal risk for eating disorder onset. Experiments will test the prediction that the postnatal accumbens shell drives optimal development of connectivity patterns between reward and metabolic centers, a phenotype altered in patients with eating disorders.

Basic Research

Fernando Midea Cuccovia V. Reis, Ph.D., University of California Los Angeles, notes recent studies in mice that have shown the lateral periaqueductal gray matter (lPAG) to be the downstream region of a wide distributed network that regulates feeding-related behaviors. He hypothesizes this midbrain region integrates survival circuits that evolved to support binging on high-caloric food whenever these sources of energy were available. To elucidate the role of lPAG in neural circuits involved in controlling compulsive behavior, this project will examine how the lPAG-Vgat (vesicular GABA transporter) neuronal population contributes to factors involved in actions toward palatable reward (sucrose) despite negative aversive consequences. The goal is to show how the lPAG encodes simultaneously aversive and rewarding states and how it is important for the development of compulsive-related behaviors, a symptom present in millions of patients suffering from eating disorders.

Basic Research

Alejandro Ramirez, M.D., Ph.D., Columbia University, will study the circuits and mechanisms by which sensory cues drive feeding behavior in the absence of hunger. Understanding how sensory cues promote feeding in circumstances when homeostatic signals limit consumption is critical for understanding eating disorders. Dr. Ramirez will train mice to associate specific sensory cues with rewarding foods, and later use the cue to increase food consumption, then use various molecular biology methods to test the hypothesis that amygdala-related circuits drive cue-induced feeding behaviors via the lateral hypothalamus, and can drive feeding during the absence of hunger. Understanding the neural mechanisms whereby sensory cues can drive feeding behavior in the absence of physiologic need will help identify the mechanisms and circuits that underlie binge-eating disorder, anorexia-nervosa, and a number of related symptoms that cut across mental illness.

Basic Research

Chen Ran, Ph.D., Harvard Medical School, notes that while the causes of eating disorders are far from clear, interoception, the ability of the brain to sense the inner body, has been strongly implicated. The nucleus of the solitary tract (NTS) in the brainstem is a major interoceptive hub in the brain. As the sensory nucleus of the vagus nerve, the NTS closely monitors the composition and quantity of ingested food, as well as visceral malfunction and distress. In the NTS, vagal inputs from the body interact with top-down feedback from the cortex and limbic system, and the integrated signals are then distributed to higher-order brain structures to orchestrate sensations of appetite and stress, eating decisions, and maintaining energy homeostasis. Dysregulation of body-to-brain signaling in the NTS could generate aberrant feeding signals. Dr. Ran seeks to understand how gastrointestinal information, after being processed in the NTS, further ascends in the brain to generate food reward and control eating behavior. He will also investigate how visceral information processing goes awry under pathological conditions.

Basic Research

Rachel Amy Ross, M.D., Ph.D., Albert Einstein College of Medicine, notes that in anorexia nervosa (AN) there can be a tendency to perceive otherwise rewarding caloric input as a threat, which may be relevant to the capacity to override the hunger drive. She wants to understand how brain and body work together to coordinate such behavior, in health and illness. Dr. Ross will address this by studying a novel population of feeding-related neurons in the medial prefrontal cortex. She has previously shown these neurons are involved in body weight regulation and food intake. The goal of this project is to measure the changes in the neuron activity in the hungry state that occur when an animal is engaging in a risky decision-making task that incorporates a choice to get food in the setting of a stressful threat, and to connect these feeding-related cortical neurons to specific, molecularly identifiable inputs from brain regions involved in fear/threat response behavior. The result could be a mechanistic understanding of how the brain integrates hunger state with other environmental inputs and guides hunger-related behavior change.

Basic Research

OBSESSIVE-COMPULSIVE DISORDER (OCD)

Samuel William Centanni, Ph.D., Wake Forest University, seeks to uncover molecular mechanisms driving stress-induced hyperactivity, a factor in a range of affective disorders. The team will use multiple methods to define unique genetic signatures of insula-to-BNST neurons and determine the direct impact of stress on active ribosomal translation in this subpopulation. This approach could identify new pharmacological targets that minimize the damaging dysregulated activity caused by stress, while not impacting the regular function of surrounding non-stressed cells.

Basic Research

Iakovos Lazaridis, Ph.D., Massachusetts Institute of Technology, notes that the basal ganglia (BG), at times referred to as the 'OCD circuit', are the brain's control center for establishing action priorities and selection of appropriate actions. Dysfunction of BG circuitry could contribute to the compulsive selection of the same action with the inability to adapt the behavioral output. This project will investigate the contribution of two BG circuits to the transition from goal-directed to habitual to compulsive actions—a parallel set of direct and indirect pathways, complementary and parallel. These include the striosomal direct (Sd) and indirect (Si) pathways, originating in discrete areas of the basal ganglia called striosomes, considered to be highly relevant for habit formation. This project will explore Sd/Si pathways as potentially key nodes in BG modulation of action, and perhaps the transition into habit formation and compulsive behavior.

Basic Research

Nan Li, Ph.D., University of Texas Southwestern Medical Center at Dallas, recognizes the importance of brain cells called astrocytes in various neurological disorders. This project focuses on investigating the brain-wide activity and impacts of astrocytes in healthy mice and mice that model obsessive-compulsive disorder (OCD). The strategy is to combine whole-brain fMRI with advanced genetic tools to characterize the spatiotemporal dynamics of astrocyte activity. The aim is to address how neurons and astrocytes work collectively in the brain, especially in OCD-related behaviors. The resulting understanding of astrocyte activity and its impact on the cellular and circuit-level brain function could facilitate astrocyte-specific treatments for OCD and related neuropsychiatric disorders.

Basic Research

Dong Liu, Ph.D., Columbia University, is working to further develop focused ultrasound (FUS), a form of neuromodulation targeting deep subcortical regions of the brain. This project builds on Dr. Liu's recent finding that a 2-minute application of FUS can alter functional connectivity for hours in non-human primates. It will target the dorsal striatum in non-human primates and analyze the impacts with fMRI to determine: 1) whether the effect of FUS is limited to brain structures of the target region or within the cortico-striatal circuits; 2) whether the brain shows different activation patterns before and after FUS neuromodulation. This will test the potential for developing FUS neuromodulation as a non-invasive alternative for patients with treatment-resistant schizophrenia. If successful, the approach can be extended to other psychiatric disorders, such as depression and obsessive-compulsive disorder, for which deep brain stimulation is a possible treatment.

New Technologies

Next-Generation Therapies

Alex Tang, Ph.D., University of Western Australia, suggests that to improve the efficacy of rTMS (a non-invasive brain stimulation treatment often used in depression), a greater understanding of how it changes brain cells and whether these changes are affected by key biological factors such as age and sex is needed. To avoid the difficulty and danger of studying this directly in people, Dr. Tang will use brain samples donated from neurosurgery patients. He will investigate genes and biological functions that are altered after rTMS. He hopes to uncover why the effects of rTMS varies between patients, which could inform efforts to develop a more targeted and efficient use of rTMS to treat a wide range of mental health disorders.

Next-Generation Therapies

Hua Tang, Ph.D., National Institute of Mental Health (NIMH/NIH), notes that we survive in changing environments by making beneficial choices and avoiding harmful choices. Dr. Tang studies reinforcement learning (RL), the behavioral process of learning to associate stimuli or responses with gaining and losing positive reinforcers. Dysfunction of RL contributes substantially to disorders including addiction, obsessive-compulsive disorder, schizophrenia, and anxiety. This study, conducted in non-human primates, will test the theory that computations underlying learning to associate visual stimuli with gains vs. losses of secondary reinforcers are the result of neural processing across a ventral frontal-striatal circuit. It will target a series of core questions and thereby provide a new perspective on the neural circuit mechanisms of appetitive and aversive learning, and help us understand the mechanisms of psychiatric disorders that follow from dysfunction in reinforcement learning in both positive and negative directions.

Basic Research

Nicholas T. Trapp, M.D., University of Iowa, notes that researchers don't yet understand exactly what TMS stimulation does to underlying brain networks or structures connected to the stimulation site. He will apply experimental brain stimulation in patients who have intracranial electrodes implanted for clinical reasons, to compare what happens intracranially with what non-invasive connectivity measures would predict based on brain imaging. The team will use a machine-learning approach to predict the propagation patterns of brain stimulation. They then intend to test this artificial intelligence approach to better understand the information most crucial for accurate prediction of TMS propagation. Finally, they seek to refine and calibrate their algorithm to generate the machine-learning algorithm which provides the best predictive capabilities, which could then serve as a tool for future researchers aiming to target brain stimulation based on neuroimaging connectivity.
Next-Generation Therapies

Jeff L. Waugh, M.D., Ph.D., University of Texas Southwestern Medical Center at Dallas, wants to investigate the striatum to better understand its relation to OCD and other disorders including tic disorders and autism. He notes striatal projection neurons are segregated into competing tissue compartments, the matrix and striosomes. The ratio of projections is critical for normal function: selective matrix activation results in uncontrolled, excessive movements; hyperactivation of striosomes induces repetitive, stereotyped movements. His team has identified pairs of subjects (disorder vs. healthy control) with OCD, autism, and tic disorders who have archived brain MRI data, allowing assessment of the tissue composition in each disorder. They hypothesize that in OCD, the volume and structural connectivity of the striosome compartment will be increased relative to the matrix compartment. More broadly, Dr. Waugh believes tipping the striatal balance toward striosomes may underlie obsessions and compulsive behaviors in neurodevelopmental disorders.
Basic Research

Brian Zaboski, Ph.D., Yale University, notes OCD is successfully treated with SSRI medications in 40%-50% of cases. Little is known about what factors predict non-response. He is investigating correlates and predictors of SSRI response using high-resolution resting-state fMRI. Parallel analysis using EEG provides limited spatial resolution but superb temporal resolution. Fusion of fMRI and EEG data holds great promise for refined mapping of brain network architecture, and potentially for more sensitive prediction of treatment response. He hopes to fuse EEG and parcellated fMRI data using sophisticated convolutional neural networks. The team will collect time-locked resting-state fMRI and EEG at baseline and after 18 weeks of treatment with the SSRI fluoxetine in 20 adults with OCD and 20 controls. They will examine changes following treatment and identify changes that correlate with symptom improvement; and examine baseline EEG/fMRI data to identify predictors of response.
Diagnostic Tools/Early Intervention

OTHER DISORDERS

EPILEPSY

Allison M. Ahrens, Ph.D., Boston University, notes that some inhibitory GABA neurons suppress seizures and others paradoxically cause increases in excitation that promote them. She seeks to discover how genetic diversity in GABA neurons relates to functional activity, knowledge that could reveal new pathways for restoring inhibitory control in epilepsy patients. She will use cutting-edge technologies to determine which GABA neuronal subtypes play the most prominent roles in the initiation, propagation, maintenance, and termination of seizures.
Basic Research

CONDUCT DISORDER

Gregor Kohls, Ph.D., Technical University of Dresden, Germany, studies whether girls and boys with conduct disorder (CD) differ in their behavioral and brain capacities to learn from punishment. CD is one of the most common but least understood mental disorders in youth, especially in girls. Youth with CD show severe antisocial and aggressive behaviors. Mechanisms underlying these behaviors are unclear but may be expressed differently in boys and girls. One proposed mechanism is punishment insensitivity, the inability to learn to avoid behavioral choices that lead to punishment rather than reward. The project includes comprehensive clinical assessments of CD problems as well as learning through reward and punishment from a large cohort of girls and boys with and without CD. The team expects that subject-level modeling of task performance will reveal differences between girls and boys with CD, particularly in their behavioral and brain capacities to learn from punishment.
Basic Research

TOURETTE SYNDROME

Iakovos Lazaridis, Ph.D., Massachusetts Institute of Technology, notes that the basal ganglia (BG), at times referred to as the 'OCD circuit', are the brain's control center for establishing action priorities and selection of appropriate actions. Dysfunction of BG circuitry could contribute to the compulsive selection of the same action with the inability to adapt the behavioral output. This project will investigate the contribution of two BG circuits to the transition from goal-directed to habitual to compulsive actions—a parallel

set of direct and indirect pathways, complementary and parallel. These include the striosomal direct (Sd) and indirect (Si) pathways, originating in discrete areas of the basal ganglia called striosomes, considered to be highly relevant for habit formation. This project will explore Sd/Si pathways as potentially key nodes in BG modulation of action, and perhaps the transition into habit formation and compulsive behavior.
Basic Research

TOURETTE SYNDROME

Jeff L. Waugh, M.D., Ph.D., University of Texas Southwestern Medical Center at Dallas, wants to investigate the striatum to better understand its relation to OCD and other disorders including tic disorders and autism. He notes striatal projection neurons are segregated into competing tissue compartments, the matrix and striosomes. The ratio of projections is critical for normal function: selective matrix activation results in uncontrolled, excessive movements; hyperactivation of striosomes induces repetitive, stereotyped movements. His team has identified pairs of subjects (disorder vs. healthy control) with OCD, autism, and tic disorders who have archived brain MRI data, allowing assessment of the tissue composition in each disorder. They hypothesize that in OCD, the volume and structural connectivity of the striosome compartment will be increased relative to the matrix compartment. More broadly, Dr. Waugh believes tipping the striatal balance toward striosomes may underlie obsessions and compulsive behaviors in neurodevelopmental disorders.
Basic Research

FRAGILE X

Nisha Raj, Ph.D., Emory University, is using a comparative network approach to identify defects in proteostasis across patient-derived organoid models of Fragile X syndrome (FXS) and other neuropsychiatric disorders. The aim is to profile the nascent and steady-state proteome during early human brain development using 3D cortical organoids generated from patient-derived induced pluripotent stem cells (iPSC). By employing this approach across multiple iPSC lines from individuals with different neuropsychiatric disorders, the team will build human brain-specific protein networks that could reveal modules with strong associations to pathological and clinical phenotypes. Identification of cellular and molecular drivers of symptoms of FXS and other related disorders could provide insight on novel diagnostic biomarkers or therapeutic targets.
Basic Research

SEVERE MENTAL ILLNESS

Jie Song, Ph.D. Karolinksa Insititue, Sweden, seeks to leverage data from five Swedish genetic studies (N = 32,000) combined within a trans-Nordic collaboration framework (Sweden, Denmark and Norway) to systematically investigate the heterogeneity of severe mental illness (SMI) using multiple cognitive-related traits and cognitive genomics. The key hypothesis is that trans-diagnostic subgroups of SMI can be identified by adding information on cognitive-related traits, and that these subgroups could be more homogenous in clinical outcomes and could be predicted by SMI and cognitive genetic loading. The first aim is to dissect SMI heterogeneity by incorporating cognitive-related traits using trans-Nordic population register data. The second aim is to predict the subgroup membership established from Aim 1 by incorporating SMI and cognitive genetics in large genotyped Nordic cohorts.
Basic Research

PARKINSON'S DISEASE

Yue Sun, Ph.D., Stanford University, focuses on depression in the context of Parkinson's disease (PD). It is one of the most prevalent non-motor symptoms in PD, affecting 35% of patients. Depression can occur before the onset of motor symptoms, indicating that it may be part of the PD pathology rather than a consequence of motor dysfunction. Dr. Sun seeks to uncover mechanisms underlying the early development of depression in PD. Dopamine neurons in the ventral tegmental area (VTA) are lost in PD, and given other evidence linking the VTA to depression, Dr. Sun hypothesizes that dopamine signaling in the VTA is disturbed in early-stage PD and contributes to the development of depression. This mechanistic thesis will be investigated in experiments conducted in mouse models of depression-like behaviors.
Basic Research

PERSONALITY DISORDERS (General)

Jenna M. Traynor, Ph.D., McLean Hospital, Harvard University, says that we have a poor understanding of which individuals with personality disorders require generalist v. specialist levels of care to experience a reduction in suicidal thinking. She will test whether new diagnostic tools can be used prognostically to predict reductions in suicidal thinking, compared to more traditional ways of measuring personality-disorder symptoms. Data from 100 suicidal patients beginning treatment in a partial hospitalization program will be used to study these associations. If alternative diagnostic tools can provide more precise measurements of symptom severity from mild to extreme impairment, this research may identify thresholds of personality disorder impairment associated with improvements following partial hospitalization, leading to a better understanding of which patients benefit most from short-term partial hospitalization (i.e., generalist treatment), and which require more specialist personality disorder treatments that are typically longer term.
Diagnostic Tools/Early Intervention

POST-TRAUMATIC STRESS DISORDER (PTSD)

Ryan T. Ash, M.D., Ph.D., Stanford University, seeks to advance transcranial ultrasound stimulation (TUS), an emerging technology that may enable noninvasive neuromodulation of deep-brain areas like the amygdala. Recent research has demonstrated that TUS can produce enduring but reversible changes in neural circuit activity in deep-brain areas, as well as meaningful changes in cognitive function and behavior, at safe ultrasound intensities. This grant will support the foundational development and optimization of human neuroscience tools to target TUS to the amygdala for the purpose of enhancing the extinction of associative fear memories.

New Technologies

Jessica Lynn Bolton, Ph.D., Georgia State University, studies how early-life experiences, especially adversity, modulate brain circuits. This project will focus on microglia, a type of brain cell that is known to influence synapses in sensory systems and other circuits, and look at the interactions of microglia and neurons in a stress-responsive brain region called the amygdala. It will also study whether manipulating microglia early in life prevents the development of depression-like behavior in adolescence due to early-life adversity.

Basic Research

Stefano Brigidi, Ph.D., University of Utah, is studying how brain cells encode and process information for learning. This project follows up on preliminary data demonstrating that learning switches on unique sets of genes across different sets of hippocampal pyramidal neurons, which helps determine how excitable individual neurons are to subsequent experiences. Dr. Brigidi seeks to identify unique patterns of gene expression that encode experiences among single neurons in support of learning and behavioral flexibility. Results could be relevant to disorders including PTSD which arise from traumatic experience and are characterized by learning and memory dysfunction.

Basic Research

Samuel William Centanni, Ph.D., Wake Forest University, seeks to uncover molecular mechanisms driving stress-induced hyperactivity, a factor in a range of affective disorders. The team will use multiple methods to define unique genetic signatures of insula-to-BNST neurons and determine the direct impact of stress on active ribosomal translation in this subpopulation. This approach could identify new pharmacological targets that minimize the damaging dysregulated activity caused by stress, while not impacting the regular function of surrounding non-stressed cells.

Basic Research

Kirstie A. Cummings, Ph.D., University of Alabama at Birmingham, following from evidence that morphine exerts a protective effect during the development of PTSD and can mitigate symptoms, will study mechanisms by which prefrontal morphine-activated neurons called SST-INs exert inhibitory control over fear behavior. The goal is to reveal an attractive new potential therapeutic target. She will use miniature head-mounted microscopes to reveal the in vivo activity dynamics of fear- and morphine-activated SST-INs in freely behaving mice. This should reveal with single-cell resolution how these functionally opposed ensembles interact with one another in real time and how these interactions evolve during fear memory acquisition and expression, and how this is impacted by morphine administration. She will also determine the circuit plasticity mechanisms of these antagonistic interactions.

Basic Research

Next-Generation Therapies

Daniel A. Jercog, Ph.D., INSERM, France, seeks to discover the circuitry and computations underlying maladaptive fear generalization, specifically, amygdala-prefrontal interactions during stress-induced fear generalization. He notes that predictions based on past experience can be detrimental if, for example, threatening situations are generalized as safe, or safe situations are generalized as threatening. This is the case in individuals with anxiety and trauma-related disorders, who often fear stimuli and situations that are safe or barely similar to the original trauma situation. This project aims to identify the underlying altered neurophysiological signals that correlate with fear generalization. It aims to counteract the effect of these altered signals by using pathway and pattern-specific optogenetic stimulation approaches.

Basic Research

Shibin Li, Ph.D. Stanford University, recently characterized hypothalamic circuitry underlying stress-induced insomnia/hyperarousal. Dr. Li found that corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus of hypothalamus (PVN) directly innervate wake-promoting hypocretin (Hcrt) neurons in the lateral hypothalamus (LH). Genetic ablation of HcrtLH neurons or CRISPR-Cas9-mediated disruption of the crh gene in CRHPVN neurons was found to compromise arousal level upon optogenetic stimulation of CRHPVN→HcrtLH circuitry or restraint stress exposure. Dr. Li will conduct experiments seeking to determine if optogenetic activation of the AVPPVN→LepRbLH→HcrtLH pathway will counteract

the activity of CRHPVN→HcrtLH circuitry, ameliorating hyperarousal/insomnia induced by stress exposure.
Basic Research

Saptarnab Naskar, Ph.D., Northwestern University, studies mechanisms underlying the way stress impacts the brain. Dr. Naskar notes that projections from the prelimbic area (PL) of PFC to periaqueductal grey (PAG), ventral tegmental area (VTa), and nucleus accumbens (NAc) form an important output triad influencing various aspects of approach and consumption of reward; and that 2-arachidonoylglycerol (2-AG), a widely circulating endocannabinoid (eCB), is strongly implicated in stress induced alteration in the activity of PFC neuronal sub-populations in a circuit-specific manner. The team will utilize a combination of ethologically relevant quantitative behavioral approaches, in-vivo single cell calcium imaging in freely behaving animals, and pharmacology to ask, ultimately, if stress-induced deficits in reward evaluation and procurement can be reversed by selectively modulating 2-AG levels.
Basic Research

Zachary T. Pennington, Ph.D., Icahn School of Medicine at Mount Sinai, has used whole-brain activity mapping in mice to examine how an acute, severe stressor is able to augment subsequent neural and behavioral responses to a novel stressor a week later. This revealed hyperactivation of the anterior hypothalamic nucleus (AHN) in severely stressed animals, which represents a novel target for treatment intervention. This project seeks to uncover the contribution of the AHN to the sensitization of fear and anxiety by prior severe stress, and to assess whether a subpopulation of cells within the AHN might be targeted to attenuate stress responses.
Basic Research

Stefanie Russman Block, Ph.D., University of Michigan, seeks to improve the effectiveness of emotion regulation strategies for those with anxiety using real-time fMRI neurofeedback, a novel technology that allows individuals to control their own brain activity. In this project, participants with anxiety will practice reinterpreting the meaning of negative images, a common emotion regulation strategy taught in therapy, while receiving feedback about brain activity in the dorsomedial prefrontal cortex, a brain region involved in emotion regulation. This work will help us understand the neural circuity of emotion regulation and lay the groundwork to test if psychotherapy outcomes can be enhanced using neurofeedback.
Next-Generation Therapies
New Technologies

Anna Schroeder, Ph.D., University of Freiburg, Germany, proceeds from evidence that the zona incerta (ZI), a small subthalamic nucleus composed mostly of inhibitory neurons, can impact the way we feel. Deep brain stimulation of this structure resulted in reductions in reported fear and anxiety by patients, as well as changes in mood. This project seeks to prove the hypothesis that the ZI actively encodes and modulates emotional states. Dr. Schroeder posits that ZI subpopulations differentially respond to, and also regulate, distinct emotions, thereby allowing this brain region to convert emotional information into targeted behavioral strategies such as specific defensive reactions. To flesh this out, she will utilize state-of-the-art technologies to map circuits at the level of molecularly-defined subtypes, probe synaptic connections, manipulate neuronal activity in mouse models, characterize functional responses, and robustly assess behavioral outcomes.
Basic Research

Alex Tang, Ph.D., University of Western Australia, suggests that to improve the efficacy of rTMS (a non-invasive brain stimulation treatment often used in depression), a greater understanding of how it changes brain cells and whether these changes are affected by key biological factors such as age and sex is needed. To avoid the difficulty and danger of studying this directly in people, Dr. Tang will use brain samples donated from neurosurgery patients. He will investigate genes and biological functions that are altered after rTMS. He hopes to uncover why the effects of rTMS varies between patients, which could inform efforts to develop a more targeted and efficient use of rTMS to treat a wide range of mental health disorders.
Next-Generation Therapies

Sarah M. Tashjian, Ph.D., California Institute of Technology, notes Pavlovian extinction is a valuable model for phobia-related anxieties because extinction involves disaggregating a threatening outcome from a distinct stimulus. But she says this is a limited basis for fully understanding and treating more prevalent and problematic anxiety disorders such as generalized anxiety and social anxiety, which often involve less discrete threats and fears. This project aims to elucidate computational and neural systems of safety decisions to identify how and to what extent safety processing contributes to anxiety during development. She will specify a computational model of safety acquisition decisions during development and then pair a safety task in adolescents with fMRI to identify neural systems that are uniquely associated with safety computations and overlap with reward and threat processing. The aim is to differentiate systems that support maladaptive coping strategies such as avoidance from adaptive coping strategies such as flexible safety acquisition.
Basic Research

Nicholas T. Trapp, M.D., University of Iowa, notes that researchers don't yet understand exactly what TMS stimulation does to underlying brain networks or structures connected to the stimulation site. He will apply experimental brain stimulation in patients who have intracranial electrodes implanted for clinical reasons, to compare what happens intracranially with what noninvasive connectivity measures would predict based on brain imaging. The team will use a machine-learning approach to predict the propagation patterns of brain stimulation. They then intend to test this artificial intelligence approach to better understand the information most crucial for accurate prediction of TMS propagation. Finally, they seek to refine and calibrate their algorithm to generate the machine-learning algorithm which provides the best predictive capabilities, which could then serve as a tool for future researchers aiming to target brain stimulation based on neuroimaging connectivity.

Next-Generation Therapies

Hein Johan Floris van Marle, M.D., Ph.D., Amsterdam University Medical Centers, Netherlands, notes studies in healthy individuals showing that sleep can be deepened and memory storage can be boosted by EEG-guided acoustic stimulation. He will test if it is possible to deepen sleep in PTSD patients. This is a proof-of-concept study to test whether the effectiveness of exposure-based treatment in PTSD can be increased by deepening post-treatment sleep. He predicts that deepening sleep using acoustic stimulation during each night of an existing 5-day treatment program for PTSD will strengthen the consolidation of therapeutic memories and generally restore disturbed deep sleep, resulting in an augmented treatment effect. He will use a state-of- the-art, closed-loop stimulation set-up, in which real-time analysis of sleep EEG, measured by ambulatory headband, informs the precise timing of the acoustic stimulation.

Next-Generation Therapies

New Technologies

PSYCHOSIS

Marieke J. H. Begemann, Ph.D., University Medical Center Groningen, Netherlands, will use this grant to support a subproject to be implemented within a larger Dutch trial, called HAMLETT, in which 512 first-episode psychosis patients are randomized to either continue their antipsychotic medication or gradually reduce their dose/discontinue. The subproject aims to determine whether antipsychotic medication results in additional reduction in brain volume. If so, it will have major consequences for prescribing these drugs, as a decrease of brain volume over time in schizophrenia is associated with poor outcome. The working hypothesis is that antipsychotics do not have a negative effect on total brain volume when controlling for confounding factors, including disease severity and hospitalization.

Next-Generation Therapies

Kara Dempster, M.D., Nova Scotia Health Authority, Canada, notes there are no objective tests to help doctors determine who will improve with traditional antipsychotic medications, and who will require clozapine. Dr. Dempster aims to obtain objective brain findings to guide treatment decisions. Glutamate in the anterior cingulate cortex (ACC) has been found to be elevated in individuals experiencing a first episode of psychosis (FEP) who continue to suffer from psychotic symptoms despite taking antipsychotic medicines. This project will measure glutamate in the ACC using magnetic resonance spectroscopy (MRS) in minimally treated individuals with FEP and investigate whether elevated glutamate at the onset of illness is associated with treatment resistance after 6 months. This could help identify patients who may benefit from clozapine treatment at the earliest opportunity.

Next-Generation Therapies

Ilvana Dzafic, Ph.D., University of Melbourne, Australia, proceeds from evidence that glutamate may be altered in early schizophrenia, and perhaps even before someone is diagnosed with a psychotic disorder. By measuring glutamate alterations, Dr. Dzafic hopes to be able to predict who is at risk to develop a psychotic disorder. Greater knowledge of glutamate's role might also lead to the development of preventive treatments. This project will test whether using electroencephalography, or EEG, which measures brain waves that are known to be related to glutamate, can help predict risk of developing a psychotic disorder.

Basic Research

Roselinde (Roos) M.C.A. Pot-Kolder, Ph.D., University of Melbourne Australia, is working with virtual reality (VR) as means of potentially treating impairments in social functioning in young people with psychotic disorders. The aim is to help patients overcome paranoid anxiety and develop social skills that can generalize from VR to the real world. Research until now has been focused on adults. She wants to further the evolution of VR intervention to address age-appropriate critical targets in the recent onset of psychosis. She also seeks to make VR therapy suitable for treating both paranoid ideation and hallucinations. Many people with a psychotic disorder suffer from both in social situations, and this challenge should be addressed in therapy. VR social environments will be created for and with young adults with recent-onset psychosis. A trial will test whether the therapy is effective for improving social functioning in young people with recent-onset psychosis.

Next-Generation Therapies

Alejandro G. Szmulewicz, M.D., Chan School of Public Health, Harvard University, is studying the comparative effectiveness and safety of strategies for the management of early psychosis. The need is clear. Long-term outcomes for patients living with psychotic disorders can be devastating; 8 years after a first episode of psychosis (FEP), 60-70% of patients are still unemployed. Dr. Szmulewicz has been creating an international consortium of observational cohorts of individuals with FEP, the FEP-CAUSAL Collaboration, whose goal is to evaluate the comparative effectiveness and safety of treatment strategies. By pooling high-quality data from several cohorts, the collaboration will introduce explicit emulation of target trials to observational analyses in psychiatry. The plan is to design a target trial emulation to find if anticonvulsants possess safe antipsychotic dose-sparing effects. FEP-CAUSAL can also be a platform to conduct other target trial emulations on important topics in FEP in the future.

Next-Generation Therapies

Sunny Xiaojing Tang, M.D., Feinstein Institute for Medical Research/Northwell Health, seeks to meet the need for sensitive, objective biomarkers of psychosis illness trajectory. Recent advances in computational methods allow for automated extraction of rich, clinically-relevant data from speech. This project seeks to develop longitudinal biomarkers for psychosis that provide biologically relevant information in a quantitative, cost-effective, and scalable way. The aims are to: 1) characterize relationships between quantitative speech biomarkers and longitudinal changes in psychosis symptoms; 2) use quantitative speech biomarkers to predict treatment trajectories among hospitalized patients with schizophrenia spectrum disorders (n=80) admitted to an acute psychiatric hospitalization. Speech samples will be recorded in four weekly follow-up visits. Quantitative speech features will be used to model longitudinal changes in positive psychosis symptoms and predict future treatment trajectory.

Diagnostic Tools/Early Intervention

Umit H. Yesilkaya, M.D., Bakirköy Prof. Mazhar Osman Training and Research Hospital, Turkey, observes that sleep supports memory consolidation, which stabilizes, integrates, and enhances recently encoded salient memories. This is achieved by the activity of sleep spindles, neuronal oscillations that originate in thalamus, in concert with hippocampal ripples and cortical slow waves (CSW). Sleep spindle activity is reduced in schizophrenia, a deficit associated with impaired sleep-dependent memory consolidation. This project will examine memory consolidation and its underlying neurobiology in first-episode psychosis patients and individuals at high risk for schizophrenia. It will entail investigation of sleep-dependent motor procedural memory consolidation in medication-naïve first-episode schizophrenia patients and first-degree relatives and controls. The team will also study the association of sleep spindle activity, spindle-CSW coordination, and thalamus structure with memory consolidation. This framework may provide a basis for novel early interventions that target this critical cognitive deficit.

Basic Research

Tingting Zhou, Ph.D., Massachusetts Institute of Technology, notes studies on schizophrenia and psychosis patients suggesting that delusions are caused by impaired belief updating in dynamic environments. Dr. Zhou has been focusing on studying delusions by modeling belief updating in mice with schizophrenia high-risk mutations. The hypothesis underlying this project is that medial dorsal thalamus (MD)-prefrontal cortex (PFC) circuit alterations mediate belief updating deficits in mice with schizophrenia-associated mutations. Testing this hypothesis will involve characterizing the MD-PFC circuit impairment in Grin2aY700X+/- mice with ex-vivo electrophysiology. The team will investigate how the altered circuits mediate neuronal encoding of belief updating rate and uncertainty with in vivo electrophysiology recording in mutant animals. Dr. Zhou will try to rescue the performance of mutant mice by restoring the neural connectivity of MD and PFC, using optogenetic tools and test whether this rescue approach can be generalized to other mouse models bearing different schizophrenia-associated mutations.

Basic Research

SCHIZOPHRENIA

Aurina Arnatkeviciute, Ph.D., Monash University, Australia, will leverage genotyping and diffusion-weighted imaging data from the UK Biobank dataset (N = 43 800) to comprehensively investigate the genetics of brain connectivity and determine the genetic mechanisms giving rise to altered connectivity patterns in schizophrenia. Data will be used to generate mathematical models of connectome development that could indicate how specific sets of genes might give rise to the altered connectivity patterns. The project thus seeks to provide a direct link between molecular function and large-scale brain organization in schizophrenia.

Basic Research

Marieke J. H. Begemann, Ph.D., University Medical Center Groningen, Netherlands, will use this grant to support a subproject to be implemented within a larger Dutch trial, called HAMLETT, in which 512 first-episode psychosis patients are randomized to either continue their antipsychotic medication or gradually reduce their dose/discontinue. The

subproject aims to determine whether antipsychotic medication results in additional reduction in brain volume. If so, it will have major consequences for prescribing these drugs, as a decrease of brain volume over time in schizophrenia is associated with poor outcome. The working hypothesis is that antipsychotics do not have a negative effect on total brain volume when controlling for confounding factors, including disease severity and hospitalization.

Next-Generation Therapies

Anya Bershad, M.D., Ph.D., University of California, Los Angeles, notes that one potential target for pharmacologic treatment of impaired social motivation in schizophrenia is the opioid system. Deficits in social motivation are an important negative symptom in schizophrenia and are a major cause of disability and suffering for many patients. In a double-blind, cross-over, placebo-controlled study, Dr. Bershad will test the effects of a low dose of buprenorphine (0.2mg) on validated measures of approach and avoidance motivation in 40 patients with schizophrenia who have significant negative symptoms. The hypothesis is that buprenorphine will enhance patients' valuation of social reward and reduce their affective responses to social rejection.

Next-Generation Therapies

Sean P. Carruthers, Ph.D., Swinburne University of Technology, Australia, will combine daily assessments of suicide ideation and objective and self-reported sleep features to investigate the temporal relationship between sleep disturbances and suicide in individuals living with chronic schizophrenia. The outcomes could enhance clinical care and inform novel interventions aimed at easing both suicide risk and daily disease burden.

Diagnostic Tools/Early Intervention

Jingyuan Chen, Ph.D., Massachusetts General Hospital, Harvard University, is intrigued by the hypothesis that disrupted memory consolidation in sleep may play an important role in impairing cognition in schizophrenia. This is supported by observations that sleep spindles, a thalamocortical oscillation that advances memory consolidation in sleep, are diminished in schizophrenia. A key challenge in testing this hypothesis is the lack of a method to track sleep-dependent memory consolidation in humans. In this research, Dr. Chen is developing non-invasive methods to elucidate how reduced sleep spindles disrupt memory consolidation, perhaps causing cognitive deficits in schizophrenia.

Basic Research

Sarah M. Clark, Ph.D., University of Maryland, Baltimore, notes that immune dysfunction has been reported across a range of psychiatric disorders such as schizophrenia and bipolar disorder, as well as neurodevelopmental disorders including autism and ADHD. Her research suggests impaired adaptive immunity may contribute to divergent social behaviors reported in these disorders, having shown that T cells promote stress-induced learning and fear responsivity, as well as adolescent social behavior when there is no threat. This project seeks to delineate the role of T cells in the postnatal development of the BNST and the downstream effects on adolescent social behavior. To accomplish this, she will employ a cell-depletion model in neonatal rats to reduce the CD4+ T cell population during their early postnatal development.

Basic Research

Adam J. Culbreth, Ph.D., University of Maryland, proceeds from evidence that abnormal effort-cost decision-making (ECDM)—calculations performed to weigh the "cost vs. benefits" of actions—may contribute to motivational deficits in schizophrenia and major depression. Such calculations are critical for goal-directed behavior. He seeks to clarify whether motivational deficits are driven by reduced sensitivity to rewards or heightened sensitivity to efforts associated with actions. This project will use experimental tasks and associated computational modeling approaches to quantify the relative contributions of effort and reward sensitivity to effort-cost decision-making in people with major depressive disorder and healthy controls.

Basic Research

Kara Dempster, M.D., Nova Scotia Health Authority, Canada, notes there are no objective tests to help doctors determine who will improve with traditional antipsychotic medications, and who will require clozapine. Dr. Dempster aims to obtain objective brain findings to guide treatment decisions. Glutamate in the anterior cingulate cortex (ACC) has been found to be elevated in individuals experiencing a first episode of psychosis (FEP) who continue to suffer from psychotic symptoms despite taking antipsychotic medicines. This project will measure glutamate in the ACC using magnetic resonance spectroscopy (MRS) in minimally treated individuals with FEP and investigate whether elevated glutamate at the onset of illness is associated with treatment resistance after 6 months. This could help identify patients who may benefit from clozapine treatment at the earliest opportunity.

Next-Generation Therapies

Shalini Dogra, Ph.D., Vanderbilt University, notes that some symptoms of schizophrenia are associated with dysregulation of excitatory synaptic transmission in the nucleus accumbens (NAc), and that recent clinical trials have revealed

beneficial effects of NAc deep brain stimulation in patients. Dr. Dogra's preliminary findings show that administration of subchronic phencyclidine increases excitatory neurotransmission in the NAc, although the circuitry mediating these effects is unclear. This project will test newly developed highly selective negative allosteric modulators of the mGlu3 receptor in rodents. The aim is to provide preliminary evidence that mGlu3 receptor activation induces robust long-term depression of excitatory neurotransmission in the NAc. This should help elucidate the therapeutic potential of mGlu3 receptor agonists/potentiators in providing relief from negative symptoms of schizophrenia.

Next-Generation Therapies

Ilvana Dzafic, Ph.D., University of Melbourne, Australia, proceeds from evidence that glutamate may be altered in early schizophrenia, and perhaps even before someone is diagnosed with a psychotic disorder. By measuring glutamate alterations, Dr. Dzafic hopes to be able to predict who is at risk to develop a psychotic disorder. Greater knowledge of glutamate's role might also lead to the development of preventive treatments. This project will test whether using electroencephalography, or EEG, which measures brain waves that are known to be related to glutamate, can help predict risk of developing a psychotic disorder.

Basic Research

Ahmed Eltokhi, Ph.D., University of Washington, asks whether there is common pathophysiology at the circuit level that could be targeted for therapeutic interventions across disorders. He is focusing on voltage-gated sodium (Nav) channels, which are among the most frequent targets of disruptive genetic mutations associated with disorders such as schizophrenia, autism, bipolar disorder, and attention-deficit hyperactivity disorder. The objective of this study is to determine how gating pore current can give rise to psychiatric-like phenotypic outcomes on the cellular and behavioral levels. Such knowledge could enable unraveling the underlying mechanisms by which the Nav channels can contribute to the cellular and systems dysfunction in schizophrenia and autism and perhaps pave the way for establishing new therapeutic targets.

Basic Research

Chris Greene, Ph.D., Trinity College, Dublin, Ireland, is interested in one of the strongest genetic risk factors for schizophrenia, called DiGeorge Syndrome, which is caused by a deletion on one copy of chromosome 22 resulting in the loss of one copy of as many as 40 genes. He recently discovered a cerebrovascular clue: that the gene claudin-5, important in the blood-brain barrier (BBB), is linked with the development of several symptoms of schizophrenia. Claudin-5 is one of the deleted genes in DiGeorge Syndrome. This project will focus on determining if reintroduction of claudin-5 in a mouse model of the syndrome will attenuate the schizophrenia phenotype. It will also explore transcriptome changes occurring at the BBB in model mice to identify pathways and processes perturbed in this condition.

Basic Research

Jia Guo, Ph.D., Columbia University, seeks to identify biomarkers for schizophrenia, using genetically modified mice to define a brain-wide imaging phenotype associated with altered glutamate metabolism. The hypothesis is that schizophrenia is associated with hippocampal hyperactivity, increased glutamate, and atrophy, and that these measures can be tempered by inhibition of glutaminase (GLS), a glutamate precursor and potential therapeutic target. Dr. Guo's experiments could establish imaging biomarkers based on glutamate metabolism and he will test their potential to report on schizophrenia risk and progression in mice, with direct relevance to clinical phenotypes and pharmacotherapy.

Basic Research

Diagnostic Tools/Early Intervention

Inge R. Holtman, Ph.D., University Medical Center, Groningen, Netherlands, co-founded the Netherlands Neurogenetics Database to integrate extensive clinical and neuropathological summaries with genotype information from donors to the Netherlands Brain Bank. This led to identification of 90 cross-disorder neurological and psychiatric signs and symptoms, including 20 symptoms specific for psychiatric symptoms such as hallucinations, psychosis, mania, and depressed mood. Using machine-learning natural language processing models, they have scored the manifestation of these symptoms on clinical records, providing detailed information on disease trajectories. This project seeks to add an additional layer of information by performing gene-expression profiling on brain tissue from donors who were diagnosed with schizophrenia, bipolar disorder, and major depression. This step should further clarify the relationship between clinical symptoms, DSM-diagnosis, and genetic susceptibility.

Diagnostic Tools/Early Intervention

Kiyohito Iigaya, Ph.D., Columbia University, notes that in the context of schizophrenia, anhedonia, or the inability to experience pleasure, can lead to social isolation or even suicide. The brain mechanisms underlying anhedonia remain largely unknown, and standard antipsychotic drugs used to treat schizophrenia have little effect on this symptom. Dr. Iigaya has developed a computational framework that quantitatively describes the temporal dynamics of reward anticipation, validated in healthy volunteers. This project will apply

the framework to schizophrenia patients with anhedonia and elucidate the neural dynamics underlying diminished anticipatory pleasure, using his mathematical models of anticipation combined with functional magnetic resonance imaging (fMRI) decision-making experiments. The hypothesis is that the hippocampus, rarely associated with negative symptoms, plays a pivotal role in impaired anticipatory computation.

Basic Research

Agnieszka Kalinowski, M.D., Ph.D., Stanford University, notes that variation in the number of copies of the C4A gene, a risk factor for schizophrenia, may affect the expression of genes coding for synapses. Dr. Kalinowski will test this hypothesis using genetically engineered brain organoids with and without exposure to an immune molecule, interferon gamma, that determines whether or not the C4A gene is expressed. Gene expression and imaging of synapses in brain organoids will be performed at two early developmental time points. She will use a novel imaging technique to obtain details about multiple synaptic types and proteins associated with regulating synapses, and will ask: how human synaptic gene expression and synaptic constitution are altered by exposure to early-life exposures to an immune molecule that is elevated during infection and stress; and probe whether the changes seen in synapses in brain organoids resemble those found in postmortem brain samples.

Basic Research

David B. Kastner, M.D., Ph.D., University of California, San Francisco, studies prepulse inhibition (PPI) of the acoustic startle response, a commonly used behavioral paradigm to validate animal models of schizophrenia. PPI measures the way the startle reflex in response to a loud sound decreases when that loud sound is preceded by a softer sound, or "prepulse," which attenuates the subsequent startle response. He has developed a novel method for measuring PPI which models the full range of the startle response function across startle pulse intensities and determines how this startle response function changes with a prepulse. He will apply the method to two different rat models of schizophrenia and measure PPI in human subjects and adapt the methodology to provide equivalent information for humans. The project also seeks to determine how antipsychotic medications change PPI in rat models of schizophrenia, which could shed light on how they help to change behavior.

Basic Research

Linda Katona, Ph.D., University College Cork, Ireland, studies how radical changes in the gut microbiome can impair brain structure and function impacting social memory, with particular attention to schizophrenia. Recent research shows that information from our gut gets transferred to our brain through the vagus nerve. We don't know how this vagal information gets processed in the brain. Dr. Katona's research seeks to answer (sex/gender-dependently): (1) Do gut microbes influence our social interactions? (2) How does our gut microbiome (through the vagus nerve) interfere with how well we remember? (3) What new social memory-improving therapies can be established based on gut microbiome-brain interactions? She will map out and exploit one specific brain pathway likely to control the gut bacteria's influence on our social memory.

Basic Research

Kristina Lanko, Ph.D., Erasmus Medical Center, University Medical Center Rotterdam, Netherlands, notes the finding that in many neurodevelopmental disorders, more males are affected than females and that males have more severe symptoms. This skew is prominent to varying degrees in autism, ADHD, and schizophrenia. She proposes a new approach to understand the mechanisms behind sex-linked differences, taking the recently identified SETD1B disorder as an example. This illness is characterized by developmental delay and epilepsy as well as ASD, hyperactivity, sleep disturbance, anxiety, and aggression. Behavioral changes are more frequent in males than in females. This project aims to understand the reasons for these behavioral differences at the place of their origin—the cell. Stem-cell technology will be used to grow cultures of cells from affected males and females, which will be developed as neural cells to form brain organoids. Gene expression and other studies could provide insights into fundamental differences between organoids derived from male and female cell-donors.

Basic Research

Dong Liu, Ph.D., Columbia University, is working to further develop focused ultrasound (FUS), a form of neuromodulation targeting deep subcortical regions of the brain. This project builds on Dr. Liu's recent finding that a 2-minute application of FUS can alter functional connectivity for hours in non-human primates. It will target the dorsal striatum in non-human primates and analyze the impacts with fMRI to determine: 1) whether the effect of FUS is limited to brain structures of the target region or within the cortico-striatal circuits; 2) whether the brain shows different activation patterns before and after FUS neuromodulation. This will test the potential for developing FUS neuromodulation as a non-invasive alternative for patients with treatment-resistant schizophrenia. If successful, the approach can be extended to other psychiatric disorders, such as depression and obsessive-compulsive disorder, for which deep brain stimulation is a possible treatment.

New Technologies

Next-Generation Therapies

Violeta G. Lopez-Huerta, Ph.D., National Autonomous University of Mexico, is studying the thalamus, a group of subcortical nuclei whose operations range from sensory relay to attention control, arousal, and motor and sensory integration. Thalamic functional diversity requires complex inhibition. The thalamic reticular nucleus (TRN) is the only structure that inhibits all thalamic nuclei. Studies suggest TRN dysfunction may underlie some behavioral deficits in disorders including schizophrenia, autism, and ADHD. This project seeks to characterize how TRN subpopulations differentially exert inhibition onto discrete thalamic nuclei; determine if there is refinement of subcircuit configurations during postnatal stages; and how perturbation of inhibition with CRISPR gene editing in vivo could alter thalamic circuitry development. Studies on normal and pathological development of TRN and thalamic GABAergic circuits are crucial to gain knowledge of the circuit-level etiology of core symptoms in brain disorders.

Basic Research

Tina Fabia Notter, Ph.D., University of Zurich, Switzerland, hopes to better explain cognitive symptoms of schizophrenia associated with specific neurophysiological abnormalities. This project seeks to provide a comprehensive set of mechanistic, preclinical data to help unravel intricate interactions between abnormal glial cell activity, neurochemical imbalances, and cognitive deficits pertaining to schizophrenia and related disorders. Dr. Notter will use a chemogenetic mouse model that allows for a selective manipulation of astrocytes, a class of specialized glial cells known to be altered in schizophrenia, in the prefrontal cortex of freely behaving animals. Emphasis will be placed on the role of kynurenic acid (KYNA), a brain metabolite produced by astrocytes that blocks synaptic signaling at excitatory synapses. The overall aim is to test the hypothesis that KYNA is a critical molecular mediator underlying the disruption of schizophrenia-associated cognitive functions after selective activation of prefrontal astrocytes.

Basic Research

Aarron J. Phensy, Ph.D., University of California, San Francisco, notes that disruptions to communication between the prefrontal cortex (PFC) and mediodorsal nucleus of the thalamus (MD) are believed to contribute to cognitive deficits in schizophrenia. The reciprocal connections between these regions require precisely tuned neuronal activity to coordinate appropriate behavior. One way these networks achieve this precision is through synchronization of neurons into rhythmic activity known as neural oscillations. His lab has previously shown that in the PFC, cross-hemispheric synchronization of neural oscillations in the gamma frequency (Xh-γSynchrony) is necessary for mice to shift between goal-oriented strategies. This project, following findings that Xh-γSynchrony peaks in neurons that project from the PFC to the MD (PFC-MD neurons) as mice shift strategies, seeks to determine if synchrony in PFC-MD neurons has a causal role in strategy shifts or arises consequentially.

Basic Research

Roselinde (Roos) M.C.A. Pot-Kolder, Ph.D., University of Melbourne Australia, is working with virtual reality (VR) as means of potentially treating impairments in social functioning in young people with psychotic disorders. The aim is to help patients overcome paranoid anxiety and develop social skills that can generalize from VR to the real world. Research until now has been focused on adults. She wants to further the evolution of VR intervention to address age-appropriate critical targets in the recent onset of psychosis. She also seeks to make VR therapy suitable for treating both paranoid ideation and hallucinations. Many people with a psychotic disorder suffer from both in social situations, and this challenge should be addressed in therapy. VR social environments will be created for and with young adults with recent-onset psychosis. A trial will test whether the therapy is effective for improving social functioning in young people with recent-onset psychosis.

Next-Generation Therapies

Seung-Eon Roh, Ph.D., Johns Hopkins University, notes that reduced cognitive flexibility has long been associated with schizophrenia. The control of excitation/inhibition (E/I) balance by parvalbumin interneurons (PV-INs) in the prefrontal cortex (PFC) plays a critical role in cognitive flexibility and related psychiatric pathophysiology. Building on the team's recent observation that expression of the gene NPTX2 is reduced in cerebrospinal fluid (CSF) of recent-onset schizophrenia patients and is correlated with cognitive performance, this project seeks to discover whether NPTX2 loss of function is a unifying feature of schizophrenia that underlies heightened vulnerability to stress and impaired adaptive control of PV-INs.

Basic Research

Audrey Sederberg, Ph.D., University of Minnesota, will use advanced data analytic methods and in silico mechanistic modeling to uncover how internally generated dynamics in cortical activity arise from synaptic interactions in cortical populations. The sequences of states that unfold in prefrontal cortical areas capture the evolution of information in the brain over time, and activity states and transitions between states reflect synaptic interactions between neurons. It isn't clear what the basis of these dynamics is, nor how disruption of synaptic interactions distorts the evolution of neural states over time, but Dr. Sederberg believes that answering these

questions may hold the key to understanding schizophrenia. Using a published dataset including neuronal ensemble recording in monkey PFC acquired during a cognitive task, she will analyze the evolution of state dynamics in primate PFC during a task requiring working memory and cognitive control. From this, she will develop network models capable of performing the cognitive task. The model framework may predict how disruption of mechanisms or circuits leads to a network-level breakdown in information processing.

Basic Research

Zhixiong Sun, Ph.D., Columbia University, seeks to decipher molecular and cellular effects of SETD1A deficiency in schizophrenia. SETD1A is rare risk gene Dr. Sun first identified that is robustly associated with schizophrenia; mutaitions in the gene confer a large increase in disease liability, and provide a starting point for disease modeling and for translating a ubiquitous molecular process such as chromatin modification into mechanistic and disease-specific insights. The aim is to use 2D and 3D human culture models to establish causal relationships between molecular effects and cellular malfunctions of SETD1A mutations, undertaking rescue of schizophrenia-relevant phenotypes via genetic restoration or drugs.

Basic Research

Alejandro G. Szmulewicz, M.D., Chan School of Public Health, Harvard University, is studying the comparative effectiveness and safety of strategies for the management of early psychosis. The need is clear. Long-term outcomes for patients living with psychotic disorders can be devastating; 8 years after a first episode of psychosis (FEP), 60-70% of patients are still unemployed. Dr. Szmulewicz has been creating an international consortium of observational cohorts of individuals with FEP, the FEP-CAUSAL Collaboration, whose goal is to evaluate the comparative effectiveness and safety of treatment strategies. By pooling high-quality data from several cohorts, the collaboration will introduce explicit emulation of target trials to observational analyses in psychiatry. The plan is to design a target trial emulation to find if anticonvulsants possess safe antipsychotic dose-sparing effects. FEP-CAUSAL can also be a platform to conduct other target trial emulations on important topics in FEP in the future.

Next-Generation Therapies

Hua Tang, Ph.D., National Institute of Mental Health (NIMH/NIH), notes that we survive in changing environments by making beneficial choices and avoiding harmful choices. Dr. Tang studies reinforcement learning (RL), the behavioral process of learning to associate stimuli or responses with gaining and losing positive reinforcers. Dysfunction of RL contributes substantially to disorders including addiction, obsessive-compulsive disorder, schizophrenia, and anxiety. This study, conducted in non-human primates, will test the theory that computations underlying learning to associate visual stimuli with gains vs. losses of secondary reinforcers are the result of neural processing across a ventral frontal-striatal circuit. It will target a series of core questions and thereby provide a new perspective on the neural circuit mechanisms of appetitive and aversive learning, and help us understand the mechanisms of psychiatric disorders that follow from dysfunction in reinforcement learning in both positive and negative directions.

Basic Research

Sunny Xiaojing Tang, M.D., Feinstein Institute for Medical Research/Northwell Health, seeks to meet the need for sensitive, objective biomarkers of psychosis illness trajectory. Recent advances in computational methods allow for automated extraction of rich, clinically-relevant data from speech. This project seeks to develop longitudinal biomarkers for psychosis that provide biologically relevant information in a quantitative, cost-effective, and scalable way. The aims are to: 1) characterize relationships between quantitative speech biomarkers and longitudinal changes in psychosis symptoms; 2) use quantitative speech biomarkers to predict treatment trajectories among hospitalized patients with schizophrenia spectrum disorders (n=80) admitted to an acute psychiatric hospitalization. Speech samples will be recorded in four weekly follow-up visits. Quantitative speech features will be used to model longitudinal changes in positive psychosis symptoms and predict future treatment trajectory.

Diagnostic Tools/Early Intervention

Fumihiko Ueno, M.D., Centre for Addiction and Mental Health, University of Toronto, Canada, studies the response to clozapine in patients with treatment-resistant schizophrenia. Neuromelanin (NM)-sensitive MRI (NM-MRI) has emerged as a non-invasive approach to indirectly measure dopamine function in pathways associated with the pathophysiology of schizophrenia. NM is a metabolite of dopamine and can be found in the substantia nigra (SN), which contains the majority of dopamine neurons. No study has focused on differences in SN-NM levels between patients with ultra-treatment-resistant schizophrenia (URS) and those with non-URS. This study will measure NM signals in the SN in patients with TRS using NM-MRI, and compare longitudinal changes in SN-NM levels before and after clozapine treatment between the URS and non-URS groups. It will be the first study to prospectively assess treatment-responsiveness to clozapine in patients with treatment resistance.

Basic Research

Next-Generation Therapies

Milene Vandal, Ph.D., University of Calgary, Canada, proceeds from evidence suggesting that impaired cerebrovascular function is present at an early stage of schizophrenia and is associated with symptoms, including cognitive dysfunction. Reduction in the expression of reelin glycoprotein is observed in the brain, CSF, and plasma of patients suffering from schizophrenia. Dr. Vandal's data suggest a novel physiological role for reelin in the regulation of cerebral blood flow. As the protein is reduced in schizophrenia patients, the theory is that reelin depletion contributes to cognitive dysfunction via altered cerebral blood flow. To test the hypothesis, this project will use awake two-photon microscopy to study brain vascular function in mice with reelin depleted. Using a genetic approach, Dr. Vandal will investigate the mechanisms underlying reelin's action on the cerebrovasculature. Finally, a gene therapy approach will be used to study the behavioral consequences of rescuing this pathway in a mouse model of schizophrenia.

Basic Research

Umit H. Yesilkaya, M.D., Bakirköy Prof. Mazhar Osman Training and Research Hospital, Turkey, observes that sleep supports memory consolidation, which stabilizes, integrates, and enhances recently encoded salient memories. This is achieved by the activity of sleep spindles, neuronal oscillations that originate in thalamus, in concert with hippocampal ripples and cortical slow waves (CSW). Sleep spindle activity is reduced in schizophrenia, a deficit associated with impaired sleep-dependent memory consolidation. This project will examine memory consolidation and its underlying neurobiology in first-episode psychosis patients and individuals at high risk for schizophrenia. It will entail investigation of sleep-dependent motor procedural memory consolidation in medication-naïve first-episode schizophrenia patients and first-degree relatives and controls. The team will also study the association of sleep spindle activity, spindle-CSW coordination, and thalamus structure with memory consolidation. This framework may provide a basis for novel early interventions that target this critical cognitive deficit.

Basic Research

Tingting Zhou, Ph.D., Massachusetts Institute of Technology, notes studies on schizophrenia and psychosis patients suggesting that delusions are caused by impaired belief updating in dynamic environments. Dr. Zhou has been focusing on studying delusions by modeling belief updating in mice with schizophrenia high-risk mutations. The hypothesis underlying this project is that medial dorsal thalamus (MD)-prefrontal cortex (PFC) circuit alterations mediate belief updating deficits in mice with schizophrenia-associated mutations. Testing this hypothesis will involve characterizing the MD-PFC circuit impairment in Grin2aY700X+/- mice with ex-vivo electrophysiology. The team will investigate how the altered circuits mediate neuronal encoding of belief updating rate and uncertainty with in vivo electrophysiology recording in mutant animals. Dr. Zhou will try to rescue the performance of mutant mice by restoring the neural connectivity of MD and PFC, using optogenetic tools and test whether this rescue approach can be generalized to other mouse models bearing different schizophrenia-associated mutations.

Basic Research

SUICIDE PREVENTION

Sean P. Carruthers, Ph.D., Swinburne University of Technology, Australia, will combine daily assessments of suicide ideation and objective and self-reported sleep features to investigate the temporal relationship between sleep disturbances and suicide in individuals living with chronic schizophrenia. The outcomes could enhance clinical care and inform novel interventions aimed at easing both suicide risk and daily disease burden.

Diagnostic Tools/Early Intervention

Rebekah S. Huber, Ph.D., University of Utah, is studying sleep disturbance and suicide risk in adolescents with bipolar disorder (BD). She notes that fine-grained real-time assessment of suicidal ideation (SI) over short periods of time may reveal distinct phenotypes related to future suicide behaviors. Sleep disturbances including insomnia, hypersomnia, short and long sleep duration, and nightmares have been linked to risk for suicide. Moreover, sleep disturbance is associated with decreased attention and inhibition and may be related to difficulty controlling thoughts of suicide. This project will investigate functional connectivity associated with SI and cognitive control in 30 adolescents with BD and a history of recent suicide attempt and will implement objective ambulatory sleep assessment (actigraphy) in combination with real-time assessment of SI and cognitive control using ecological momentary assessment (EMA).

Basic Research

Diagnostic Tools/Early Intervention

Autumn Joy Kujawa, Ph.D., Vanderbilt University, seeks to address the critical need for identification of biomarkers of past and future suicidal behaviors (SB) in high-risk youth. Is there a way to objectively assess the role of alterations in reward valuation (i.e., preference for smaller immediate rather than larger delayed rewards) and threat processing (i.e., reduced fear of threats of bodily harm)? This project will use cutting-edge EEG technology to provide an innovative test of alterations in brain function in youth with a history of

SB. 90 adolescents in acute psychiatric treatment for recent suicidal ideation (SI) and/or SB will be recruited; they are deemed at high risk for SB following discharge. The aim is to provide unique insights into alterations in brain function underlying adolescent SB and examine the utility of economical and accessible neural measures derived from EEG for predicting SB, which might be translated to the clinic.

Diagnostic Tools/Early Intervention

Gonzalo Martinez-Ales, M.D., Ph.D., Harvard University, notes that about 35% of persons who attempt suicide eventually engage in self-harm again, and that risk of re-attempt and of death by suicide peaks during the first weeks following a suicide attempt. Accordingly, the period after an attempt is a critical window of opportunity for prevention. Using electronic health records of 67,000 Veterans Administration patients discharged following hospitalization due to nonfatal suicide attempt between 2010-2016, the team will emulate a set of target trials examining initiation of antidepressants for individuals discharged following admission due to suicidal ideation or suicide attempt and diagnosed with a disorder potentially treatable with antidepressants. The team will analyze the comparative effectiveness of commonly prescribed antidepressants in head-to-head comparisons and examine specific antidepressants and consider a strategy where antidepressant initiation is temporarily postponed to better understand the effect of immediate vs. delayed antidepressant initiation.

Diagnostic Tools/Early Intervention

Eric T. Monson, M.D., Ph.D., University of Utah, suggests better predictive measures for suicidal behavior could be developed by focusing on differences within specific groups of individuals who have died by suicide. This project leverages the Utah Suicide Genetic Research Study, encompassing over 10,000 individuals who have died by suicide and are linked to the Utah Population Database, providing a wealth of clinical information. Over half of these individuals also have genotyping data to allow genetic assessment. The project is particularly focused on the evaluation of individuals with a history of trauma exposure who died by suicide as compared with individuals who died by suicide with no prior documented trauma exposure. Following the identification of trauma-exposed and non-trauma suicide groups, evaluation of clinical, genetic, and demographic factors will take place between these groups and versus control subjects. These analyses can help to define unique and shared environmental as well as genetic risk factors for suicide death, potentially offering targets for future studies and providing information that could be used to improve screening practices.

Diagnostic Tools/Early Intervention

Jenna M. Traynor, Ph.D., McLean Hospital, Harvard University, says that we have a poor understanding of which individuals with personality disorders require generalist v. specialist levels of care to experience a reduction in suicidal thinking. She will test whether new diagnostic tools can be used prognostically to predict reductions in suicidal thinking, compared to more traditional ways of measuring personality-disorder symptoms. Data from 100 suicidal patients beginning treatment in a partial hospitalization program will be used to study these associations. If alternative diagnostic tools can provide more precise measurements of symptom severity from mild to extreme impairment, this research may identify thresholds of personality disorder impairment associated with improvements following partial hospitalization, leading to a better understanding of which patients benefit most from short-term partial hospitalization (i.e., generalist treatment), and which require more specialist personality disorder treatments that are typically longer term.

Diagnostic Tools/Early Intervention

Kevin S. Weiner, Ph.D., University of California, Berkeley, notes the human cerebral cortex contains neuroanatomical structures and shallow indentations known as tertiary sulci (TS) which develop during gestation through the post-birth period and whose role is unknown in mental health outcomes. He will examine the relationship between TS morphology in orbitofrontal cortex (OFC) and emotion-related impulsivity (ERI) in a transdiagnostic sample. ERI is defined by frequent loss of control during strong emotion states and is a robust predictor of internalizing disorders (e.g., depression), externalizing disorders (e.g., substance abuse), aggression, and suicidality. The hypothesis is that tertiary, but not primary or secondary, sulcal morphology in OFC will be related to ERI. Findings have the potential to shift the focus from morphological analyses of primary brain structures in different syndromes and diseases to tertiary brain structures which emerge in the third trimester.

Basic Research

Institutions of 2022 Young Investigators, at the time of grant award

Abarbanel Mental Health Center Tel Aviv University, Israel

Albert Einstein College of Medicine

Amsterdam University Medical Centers, Netherlands

Bakirköy Prof. Mazhar Osman Training and Research Hospital, Turkey

Boston University (2)

Bradley Hospital, Brown University

Brigham and Women's Hospital

California Institute of Technology (2)

Centre for Addiction and Mental Health, University of Toronto, Canada (3)

Chan School of Public Health, Harvard University

Charité – Universitätsmedizin Berlin, Germany

Freie Universitat Berlin, Germany

Columbia University (6)

Concordia University

Deutsches Zentrum für Neurodegenerative Erkrankungen, Germany

Douglas Mental Health University Institute, Canada (2)

Duke University

Emory University

ETH Zurich, Switzerland

Erasmus Medical Center, University Medical Center Rotterdam, Netherlands

Feinstein Institute for Medical Research/Northwell Health

Georgia State University

Harvard Medical School (3)

Harvard University (9)

Icahn School of Medicine at Mount Sinai (8)

INSERM, France

Johns Hopkins University

Karolinksa Insititue, Sweden

McGill University, Canada

McLean Hospital (2)

Massachusetts General Hospital (4)

Massachusetts Institute of Technology (2)

Medical University of Vienna, Austria

Monash University, Australia

Montclair State University

National Autonomous University of Mexico

National Institute of Mental Health (NIMH/NIH)

National Institute on Drug Abuse (NIDA/NIH)

National Institutes of Health (NIH)

New York University (2)

Northeastern University

Northwestern University (2)

Nova Scotia Health Authority, Canada

Oregon Health and Science University

Paris-Saclay Univeristy, France

Radboud University, Netherlands

Rice University

St. Jude Children's Research Hospital

Stanford University (5)

Sunnybrook Health Sciences Centre, University of Toronto, Canada,

Swinburne University of Technology, Australia

Technical University of Dresden, Germany

Trinity College, Dublin, Ireland

Uniformed Services University of the Health Sciences

University of Alabama at Birmingham (2)

University of Barcelona, Spain

University of Calgary, Canada (2)

University of California, Berkeley

University of California, Los Angeles (4)

University of California, Davis

University of California, Irvine

University of California, San Diego

University of California, San Francisco (3)

University College Cork, Ireland

University of Coimbra, Portugal

University of Florida

University of Freiburg, Germany

University of Illinois

University of Iowa

University of Maryland

University of Maryland, Baltimore (2)

University Medical Center Groningen, Netherlands (2)

University of Melbourne, Australia (2)

University of Michigan (2)

University of Minnesota (2)

University of New South Wales, Australia

University of North Carolina at Chapel Hill

University of Pennsylvania (2)

University of Pennsylvania School of Medicine

University of Pittsburgh (2)

University of Pittsburgh School of Medicine

University of Queensland, Australia (2)

University of Southern California

University of Texas Health Science Center at Houston

University of Texas Southwestern Medical Center at Dallas (4)

University of Utah (3)

University of Washington

University of Western Australia

University of Zurich, Switzerland

Vanderbilt University (4)

Wake Forest University

Washington University, St. Louis

Weill Cornell Medical College (3)

Yale University (3)

BY THE NUMBERS SINCE 1987

As of August 2022

AWARDED TO SCIENTISTS

$440 MILLION

GRANTS

6,400

GRANTEES

5,100+

UNIVERSITIES & MEDICAL CENTERS

587

COUNTRIES, INCLUDING THE U.S.

37

177 ACTIVE SCIENTIFIC COUNCIL MEMBERS (AND 24 EMERITUS MEMBERS)

The all-volunteer BBRF Scientific Council is composed of leading experts across disciplines in brain & behavior research who review grant applications and recommend the most promising ideas to fund.

The group includes:

- **49** Members of the National Academy of Medicine
- **39** Chairs of Psychiatry & Neuroscience Departments
- **16** National Institutes of Health Chiefs & Directors
- **7** Members of the National Academy of Sciences
- **3** Recipients of the National Medal of Science
- **2** Directors of the National Institute of Mental Health
- **1** Nobel Prize Winner

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

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

747 Third Avenue, 33rd Floor,
New York, NY 10017

646.681.4888 | 800.829.8289
info@bbrfoundation.org
bbrfoundation.org

Research for Recovery

Publication Credits

Writers
Lauren Duran
Peter Tarr, Ph.D.

Editors
Lauren Duran
Peter Tarr, Ph.D.

Design
Gene Smith

100% OF EVERY DOLLAR DONATED FOR RESEARCH GOES TO RESEARCH

Our operating expenses are covered by separate foundation grants.
Sign up for eNews at **bbrfoundation.org/signup**.
Find BBRFoundation on: