

2016

# Young Investigator Grant Program

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## SUMMARY OF 2016 YOUNG INVESTIGATOR GRANTS BY ILLNESS

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Addiction	10
ADHD	6
Anxiety	3
Autism Spectrum Disorder	31
Bipolar Disorder	5
Depression	38
Eating Disorder	3
Mental Illness General	20
Mental Illness Multiple	43
OCD	2
Psychosis	3
PTSD	6
Suicide Prevention	1
Schizophrenia	25
Other	
Parkinson's	1
Fragile X	1

## RESEARCH CATEGORIES

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Basic Research	152
Next Generation Therapies	23
New Technologies	13
Diagnostic Technologies / Early Intervention	10

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## ABOUT THE YOUNG INVESTIGATOR GRANT PROGRAM

Initiated in 1987 the NARSAD Young Investigator Grants help researchers launch careers in neuroscience and psychiatric research and gather pilot data to apply for larger federal and university grants.

The Foundation's Young Investigator Grant provides support for the most promising young scientists conducting neurobiological research. This program is intended to facilitate innovative research opportunities and supports basic science, as well as translational and/or clinical investigators. All research must be relevant to our understanding, treatment and prevention of serious brain and behavior disorders such as schizophrenia, mood disorders, anxiety disorders or child and adolescent mental illnesses.

## HOW THE YOUNG INVESTIGATOR GRANT PROGRAM IS UNIQUE

- Research projects to be funded are selected by the best in the field: our world-renowned Scientific Council comprised of leading researchers across disciplines in brain and behavior research make all grant recommendations.
- Only innovative, cutting-edge projects get funded.
- Two-year awards up to \$70,000, or \$35,000 per year, are provided to enable promising investigators to either extend research fellowship training or begin careers as independent research faculty.
- The grants have proven to be catalytic—our survey shows they have led to subsequent grant funding on average 11–19 times the original grant amount.

### SINCE 1987

- Awarded 4,086 YI Grants
- \$244 Million Funded
- Resulting In More Than \$2.4 Billion in Subsequent Research Funding

## THE 2016 YOUNG INVESTIGATOR GRANTEES

The Foundation is pleased to announce \$13.7 million in 198 new two-year grant awards to support the work of promising young scientists with innovative ideas in mental health research. The grants for 2016 address outstanding research questions across diagnostic categories, from schizophrenia and depression to anxiety, PTSD, autism spectrum disorder, ADHD, addiction and bipolar disorder, among others.

About 75 percent of the projects funded are basic research, the wellspring of innovation in brain research as in all sciences.

Covering a broad spectrum of brain and behavior disorders, these NARSAD Young Investigator Grants function as catalysts to get new ideas off the ground that may not otherwise be supported.

On the following pages you will find our 2016 Grantees and their area of research listed under these categories:

**Basic Research** to understand what happens in the brain to cause mental illness

**New Technologies** to advance or create new ways of studying and understanding the brain

**Next Generation Therapies** to reduce symptoms of mental illness and ultimately cure and prevent brain and behavior disorders

- About 18 percent of the 2016 grants fund projects that specifically aim to develop next-generation therapies.
- About seven percent fund the development of new technologies that will power both basic research and new developments in the clinic.
- About 80 percent of grantees are from the United States. The remaining grantees come from 15 other nations including: Africa, Australia, Brazil, Canada, China, France, Germany, Ireland, Italy, Japan, the Netherlands, Portugal, Sweden, Switzerland, the UK.

We are very grateful to all of our donors for making these important awards possible.

### IN 2016

- 761 Applications
- 198 Grants Awarded
- \$13.7 Million Funded

# 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

Co-Chair of the Young Investigator Grant Selection Committee  
and Foundation Scientific Council Member

*"Over my long career, I have seen how a Young Investigator award has launched the career of so many young scientists, committed to the belief that they can contribute to our understanding and treatment of mental illness. I am humbled and honored to now be part of choosing the best of the best."*



*"NARSAD Young Investigator Grants have led to groundbreaking and important new research that has improved the lives of people living with mental illness, through enhanced treatments and therapies, and a better understanding of the causes of mental illness. These early career scientists are making great strides in basic research, new technologies, next generation therapies and early intervention techniques. This is the kind of out of the box research that will offer the best hope for change."*

## HERBERT PARDES, M.D.

President of the Scientific Council

Executive Vice Chairman of the Board of Trustees, NewYork-Presbyterian Hospital



## Suzanne N. Haber, Ph.D.

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

2011 Distinguished Investigator

Co-Chair of the Young Investigator Grant Selection Committee  
and Foundation Scientific Council Member

*"It is a privilege to play this role in providing the highly coveted Young Investigator's award that helps to kick-start their careers at a critical time."*



*"NARSAD Young Investigator Grants enable early career scientists to garner pilot data for innovative ideas before they have 'proof of concept' for their work. After our initial funding, these scientists usually go on to receive additional funding from other sources at an average of 11 to 19 times their original NARSAD Grant. Our grants offer the first critical backing of their work."*

**JEFFREY BORENSTEIN, M.D.**

President & CEO

# BASIC RESEARCH

## ADDICTION

**Pinar Ayata, Ph.D.**, Icahn School of Medicine at Mount Sinai, will examine the role of microglia—brain cells that support neuronal activity—in cocaine addiction. Microglia affect brain circuits by eliminating weak neuronal connections and releasing chemicals to boost neuronal growth. Dr. Ayata believes that cocaine use stimulates microglia and related genes to alter the stability of neuronal connections. Testing this hypothesis in mice, Dr. Ayata will also look for behavioral effects of any altered connections and examine the molecular and behavioral effects of deleting dopamine receptors in microglia.

**Paul Leon Brown, Ph.D.**, University of Maryland, will investigate sex differences in the brain that may explain why men are more prone to lifelong substance abuse and women more rapid in the transition from drug use to addiction, as well as more vulnerable to relapse. Dr. Brown will conduct electrophysiological tests to measure the effects of altered estrogen receptor activity in a deep brain structure, the lateral habenula, that tracks negative experiences. His team predicts that estrogen in this brain region alters the release of dopamine, a pleasure-causing chemical crucial for addiction, in ways that dampen the negative experiences of drug use.

**Maged Harraz, Ph.D.**, Johns Hopkins University, hopes to identify new therapeutic targets for cocaine addiction by studying how cocaine affects neurons. Dr. Harraz seeks to explore whether autophagy, a process through which cells normally recycle damaged components, is involved in the stimulant effect of cocaine. Encouraged by previous results suggesting that blocking autophagy in mice blocks the cocaine's stimulant effects, Dr. Harraz hopes to find new avenues for treating cocaine addiction.

**Anna B. Konova, Ph.D.**, New York University, will conduct a study to help identify behavioral, neural, and circuit-level biomarkers of the craving state, which is a major impediment to recovery from opioid addiction. Using functional magnetic resonance imaging (fMRI) to study the brains of opioid-addicted patients, she will test the hypothesis that specific, quantifiable changes in the brain's valuation system during craving influence the subjective valuation of opioids. Dr. Konova hopes that this research will inform the development of more targeted interventions to combat craving.

**Vivek Kumar, Ph.D.**, The Jackson Laboratory, hopes to further understanding of the genetic susceptibility to addiction by exploring the role of a gene called *Cyfp2*, which regulates responses to cocaine. *Cyfp2* is also a component of two distinct complexes that regulate the structure of neurons. Dr. Kumar aims to find *Cyfp2*'s precise location of action within the brain and examine how its activity changes in the context of cocaine addiction.

**Yao-Ying Ma, M.D., Ph.D.**, State University of New York in Binghamton, will investigate the neurological changes that result from prenatal alcohol exposure (PAE). PAE is a known risk factor for brain disorders, including drug addiction, but little is known how it affects the developing brain. Dr. Ma will focus on how proteins on nerve cells called AMPA receptors are altered by PAE and how these changes may increase the risk of addiction and other mental illness.

**Mary-Louise Risher, Ph.D.**, Duke University Medical Center, wants to know more about the fate of astrocytes, or helper cells, in the brain during alcohol abuse. Astrocytes can become 'reactive' in response to injury and disease, resulting in the release of signaling molecules and subsequent remodeling of neuronal circuitry. Among these signaling molecules are members of the thrombospondin family of matricellular proteins, which are known to induce synapse formation via the voltage-gated calcium channel subunit,  $\alpha 2\delta-1$ . How these synaptogenic proteins are affected by ethanol and whether they are involved in the remodeling of circuits after alcohol abuse is the aim of this project, which will investigate the role of  $\alpha 2\delta-1$  in drinking behavior and in addiction-related reward processes in male and female mice.

**Dorothy Jean Yamamoto, Ph.D.**, University of Colorado, Denver, notes that alcohol is rapidly metabolized to acetate, which accumulates in the brain. In humans, a moderate dose of alcohol decreases brain glucose metabolism while increasing acetate uptake. Heavy drinkers have higher brain acetate levels, uptake and metabolism than normal controls. Withdrawal symptoms during early sobriety may be related to decreasing acetate levels. There have been no studies addressing the fundamental effects of acetate versus alcohol on brain function and behavior. Dr. Yamamoto and colleagues will perform a functional magnetic resonance (fMRI) scanning study that will compare the effects of acetate alone vs. acetate obtained as a byproduct of alcohol metabolism in healthy controls.

**Yingjie Zhu, Ph.D.**, Stanford University, observes that circuitry of the paraventricular nucleus of thalamus (PVT) plays a role in mediating opioid withdrawal, and that this provides an opportunity to examine the contribution of drug withdrawal to drug-seeking behavior. Dr. Zhu will use DREADD technology (involving targeting artificial receptors with designer drugs) to try to selectively erase drug memory while leaving other memories intact. This will be done by silencing PVT output pathways in a mouse model of addiction/withdrawal during retrieval of a drug memory and examining its impact on the other memory.

## ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

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**Matthew Lovett-Barron, Ph.D.**, Stanford University, will study how neurons deep within the brain control alertness and attention. He will identify these neural circuits using zebrafish as a model and then apply that knowledge to understand how alertness is regulated in mammals. The results may reveal new targets for the treatment of disorders like ADHD.

**Pamela K. Douglas-Gutman, Ph.D.**, University of California, Los Angeles, will analyze a large data set including structural MRI (sMRI), functional MRI (fMRI), diffusion tensor imaging (DTI), and behavioral metrics from people with attention deficit-hyperactivity disorder (ADHD) at two time points: prior to initiation of stimulant treatment at the initial time of diagnosis, and after a 3-month course of medication. She will quantify linkages between neuroimaging information and clinical behavioral characteristics of ADHD, and determine if white matter microstructure changes can predict a beneficial response to stimulant treatment of ADHD.

**Yuwen Hung, Ph.D.**, Massachusetts Institute of Technology, aims to improve understanding of emotion regulation in adults suffering from attention-deficit/hyperactivity disorder (ADHD). Dr. Hung hopes to identify neural biomarkers in ADHD adults during cognitive reappraisal of negative emotions, a task in which individuals actively alter the perception and interpretation of an occurring negative emotional event.

**Jessica A. Church-Lang, Ph.D.**, University of Texas, Austin, will conduct a pilot study on attention deficit-hyperactivity disorder (ADHD) in which her team will collect a week of real-life measures of sleep and activity information from parent-child pairs. They will also collect resting functional connectivity MRI data from both family members to study changes in brain networks important for task control. Data will be collected from 60 child-parent pairs: 30 pairs in which the child has ADHD, and 30 in which the child is typically developing. Analyses will correlate child and parent sleep and brain data, and test for differences between children with and without ADHD, as well as between the parent groups.

**Kristina A. Neely, Ph.D.**, Pennsylvania State University, seeks to understand why a majority of children who are diagnosed with ADHD also suffer from deficits in motor skills. These skills often improve with stimulant medication. Dr. Neely will examine brain activity during a hand-grip task, both on and off stimulant medication, in young adults with ADHD and healthy controls to assess how stimulants affect the motor system of young adults with ADHD.

## ANXIETY

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**Thackery Ian Brown, Ph.D.**, Stanford University, will examine the impact of stress on the ability to plan for the future. Using functional magnetic resonance imaging to measure brain activity during a virtual spatial navigation task, Dr. Brown hopes to identify the neural mechanisms that enable thoughts about the future. The theory behind the research is that stress disrupts those mechanisms to limit future-oriented thought, leading to more habitual, and less efficient, behavior. This study aims to illuminate how pronounced stress, common in anxiety disorders, can impair memory and goal-directed actions.

**Bridget Laura Callaghan, Ph.D.**, Columbia University, hopes to define how childhood adversity affects memory development and may lead to chronic anxiety. Her team will examine whether memory formation in the hippocampus region differs among youths who have experienced hardship, such as international adoptees; whether those differences alter the storage of long-term memories; and whether these memory impairments predict anxiety. By exposing the neurodevelopmental pathways that lead to anxiety, Dr. Callaghan hopes to identify new targets for treating and preventing anxiety disorders among youth.

## AUTISM SPECTRUM DISORDER

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**Anahita Amiri, Ph.D.**, Yale University, will explore genetic activity that alters brain activity in autism spectrum disorders (ASD). Using advanced stem cell technology and next generation gene sequencing, Dr. Amiri's team plans to test lab-grown models of brain tissue to study DNA sequences that enhance the transcription of developmental genes linked to ASD. They believe that advanced understanding of these "enhancer" sequences will elucidate the pathology of ASD and point toward new targeted treatments for these conditions.

**Laura Christiana Andreae, Ph.D.**, King's College London, UK, aims to lay the foundation for drug treatments to address core symptoms of autism spectrum disorders (ASD). Looking at both human and rodent cellular models of ASD, Dr. Andreae will focus on two genes that direct communication within the brain and have been strongly implicated in ASD. Her study will test the effects of deleting these genes—which may in turn disrupt the brain's balance of excitatory and inhibitory connections—on cortical neurons, particularly their plasticity.

**Abhishek Banerjee, Ph.D.**, University Hospital Zurich, Switzerland, will study neuronal activity in the dentate gyrus of the hippocampus, the brain's memory center, in relation to a developmental disorder called Rett syndrome. Using an animal model of the X chromosome-linked disorder, which can cause severe cognitive impairment, Dr. Banerjee hopes to demonstrate that learning alters activity in the dentate gyrus, where new neurons form and create a cellular basis for memories. He will manipulate interneurons in the dentate gyrus to disrupt the balance of excitatory and inhibitory activity and measure any resulting disruptions to memory formation.

**Helen S. Bateup, Ph.D.**, University of California, Berkeley, will examine the role of neurons that release dopamine, and their critical role in behavioral flexibility, motor control, and social cognition, in leading to autism spectrum disorders (ASD). Dr. Bateup's team will use a genetic mouse model of ASD to test how mutations to the risk gene *Tsc1* affect the physiology and activity of dopamine neurons. They will also study how changes in neuronal activity alter behavior in ways relevant to ASD.

**Maria Chahrour, Ph.D.**, University of Texas-Southwestern Medical Center at Dallas, seeks to identify the normal function of a gene linked to autism spectrum disorders (ASD) and mutations of that gene that can lead to neurodevelopmental illness. Dr. Chahrour will create a mouse model lacking the gene *UBE3B*, connected to ASD and intellectual disability, to see how the gene's absence affects neuronal development and function. Her team further hopes to identify the proteins regulated by *UBE3B*, to identify a pathway of genetic mutations that lead to ASD and may hold the key to new treatments.

**Harrison Wren Gabel, Ph.D.**, Washington University, seeks to explore how autism and related neurodevelopmental disorders can result from disruption of a process called DNA methylation, which regulates the expression, or activity, of genes. Using cultured cells and mice, Dr. Gabel will study how a unique form of this process called non-CpG DNA methylation, which occurs in neurons, regulates normal gene expression and how disruptions can arise from mutations of a gene called *DNMT3*. In doing so, Dr. Gabel aims to shed light on the molecular causes of intellectual disability and autism in individuals carrying these mutations, laying the groundwork for new therapeutic strategies.

**Rocco George Gogliotti, Ph.D.**, Vanderbilt University, will examine autopsy samples from patients diagnosed with Rett syndrome with the goal of better understanding the molecular pathways involved in causing the disorder. He will focus on mGlu5, a protein preclinical data suggests could be a therapeutic target, and test whether molecules that alter its activity mitigate symptoms of Rett syndrome. Dr. Gogliotti will also perform RNA sequencing on the autopsy samples to compare the molecular pathways in patients who do and do not have a Rett syndrome-linked mutation called MECP2.

**Elizabeth Heron, Ph.D.**, Trinity College Dublin, Ireland, hopes to shed light on the problem of “missing heritability” in autism by studying the effects of epigenetic changes, which alter the expression of genes. Epigenetic changes can cause genes to function differently depending on their parent of origin, potentially explaining how some parents who are unaffected by autism can pass the disorder on to their children.

**Bruce E. Herring, Ph.D.**, University of Southern California, aims to enhance knowledge of how abnormalities in the transmission of the neurotransmitter glutamate may contribute to autism. Working with transgenic mice, he will focus on Trio, a gene crucial in the transmission of glutamate between neurons and that has been linked to autism. Dr. Herring hopes to provide a framework for understanding the role of Trio in the transmission of glutamate and to explore the potential effects of targeting Trio with drugs.

**Zhitao Hu, Ph.D.**, University of Queensland, Australia, will use the model organism *C.elegans* to investigate the role of the LIN-2 gene and the protein CASK in autism. Mutations of CASK, which is evolutionarily conserved in humans, have been linked to autism. Dr. Hu aims to shed light on how LIN-2/CASK regulates the excitation of neurons, as autism has been linked to imbalances of neuronal excitation and inhibition.

**Michele Nerissa Insanally, Ph.D.**, New York University, hopes to shed light on dysfunctional brain circuitry thought to contribute to autism. Using rats, she will record the activity of neurons to investigate the complex computations that occur in the auditory and prefrontal cortex during the performance of tasks. Dr. Insanally aims to define the processes by which groups of neurons in the auditory cortex interact with neurons in the prefrontal cortex to enable behavioral flexibility.

**Matthew Daniel Lerner, Ph.D.**, Stony Brook University School of Medicine, hopes to contribute to an integrative understanding of the role of social cognition in autism. He will use electroencephalography (EEG) to examine relations between social cognitive processes and their corresponding neural mechanisms in children with and without autism. Additionally, he will use a standardized, validated computer-based social-cognitive assessment tool (SELweb) to administer social cognitive assessment tasks and measure a variety of emotional and social responses.

**Harold Duncan MacGillavry, Ph.D.**, Utrecht University, Netherlands, will explore fundamental mechanisms that control neural communication in the brain. Neurons use chemical messengers to send signals across the brain, and disruption of this communication underlies neurodevelopmental disorders such as autism. Dr. MacGillavry will focus on the regulation of a protein known as mGluR and how altered control may contribute to neurodevelopmental disorders.

**Jessica Mariani, Ph.D.**, Yale University, will explore how changes in the 3D organization of DNA can alter gene expression and neurodevelopment, leading to autism spectrum disorders. Dr. Mariani will construct a 3D map of DNA interactions in ASD patients and their unaffected fathers using so called brain organoids. These findings will reveal how changes in DNA organization can orchestrate the disruption of molecular pathways implicated in neuropsychiatric disorders, and may provide new targets for therapeutic strategies.

**Ligia Assumpcao Papale, Ph.D.**, University of Wisconsin-Madison, will investigate how epigenetic mechanisms contribute to developmental disorders. In particular, Dr. Papale will focus on gender-specific susceptibilities as well as the contribution of oxytocin in prenatal stress-induced autistic-like behaviors. These findings could identify stress-related molecular targets in the brain that are influenced by environmentally sensitive epigenetic mechanisms and are involved in developmental brain disorders.

**Zhengan Qi, Ph.D.**, Massachusetts Institute of Technology, will explore the neurobiology underlying the substantial language deficits in many children with autism spectrum disorder. Decades of behavioral research have found that statistical learning is essential for typical language development, but this type of learning is impaired in ASD patients. Using a powerful combination of behavioral and neuroimaging methods, Dr. Qi will investigate how language impairment in ASD is grounded in defects in statistical learning.

**Maximiliano Rapanelli, Ph.D.**, Yale University, is interested in the role of the basal ganglia in autism spectrum disorder (ASD), using a new rodent model in which two specific types of interneuron in the striatum (the large input nucleus of the basal ganglia) are depleted. While originally applied to the study of Tourette syndrome, here it will be used to study profound deficits in social preference observed in these animals, similar to what has been described in genetic mouse models of ASD. To Dr. Rapanelli, this suggests that this striatal manipulation recapitulates core feature of ASD, not just tics. His team will manipulate affected striatal circuitry using a novel combinatorial chemogenetic approach that permits tight control of neuronal activity during specific time windows to test causal relationships within brain circuitry.

**Dorothy Schafer, Ph.D.**, University of Massachusetts Medical School, recently made the surprising discovery that microglia, brain immune cells, sculpt the developing brain by ‘eating’ or engulfing a subset of excitatory synapses. It is unknown whether microglia regulate the development of inhibitory neurons or their synapses, or how microglia respond to changes in the balance of excitatory/inhibitory signals in the nervous system. Her team will use a mouse model to genetically eliminate microglia or manipulate microglia-specific gene expression and determine how inhibitory neurons and synapses are disrupted, and assess how microglial gene expression and cellular responses change in mouse models of ASDs in which levels of inhibition are disrupted.

**Lukas Ian Schmitt, Ph.D.**, New York University, studies sensory abnormalities in the context of neurodevelopmental disorders like autism (ASD). Little is known about the neurobiology of sensory gating, and even less is known about its failure in disease. In this study, he will investigate how selective gating of information occurs in the thalamus, a structure which acts as a gateway through which most sensory input reaches higher order processing centers in the brain. The study focuses on the role of the thalamic reticular nucleus (TRN), the ‘guardian’ of the thalamic gateway. He will record neurons relaying auditory information through the thalamus in mice and assess the effect of suppressing the TRN on sensory representations of incoming sound stimuli, then study changes in sensory processing in a disease-relevant mouse model of TRN dysfunction.

**Oleksandr (Alex) Shcheglovitov, Ph.D.**, University of Utah, will test the theory that loss of SHANK3 in human neurons results in the loss of specific neuronal inputs on these neurons when grafted into the prefrontal cortex of the mouse brain. He will test this hypothesis by transplanting SHANK3-deficient iPSC-derived human neurons into mouse brains and determining whether these cells receive abnormal neuronal inputs from other neurons in different brain regions. This proof-of-principle study will provide a platform for studying how mutations in synaptic proteins affect the connectivity of human neurons in the brain and advance our understanding of the molecular, cellular, and circuitry deficits associated with ASDs.

**Stephen Edward Paucha Smith, Ph.D.**, Seattle Children’s Research Institute, employs quantitative multiplex immunoprecipitation (QMI) to measure the physical interactions among a network of synaptic proteins whose genes have been linked with autism. These proteins form tiny molecular machines that control communication between neurons. In this research Dr. Smith will use two independent mouse models (the Shank3 and VPA models), in which a specific sub-network of interactions centered on Homer1 is strongly upregulated. Data suggest that Homer1 may be an important network hub that is dysregulated in multiple genetic version of ASD. The team will examine the behavior of this sub-network in the Shank3 knockout mice and their wild-type littermates.

**Hume Akahori Stroud, Ph.D.**, Harvard Medical School, hopes to identify the genetic mechanisms behind Rett Syndrome, an X chromosome-linked autism spectrum disorder that can cause serious cognitive impairments, usually in girls. Rett Syndrome stems from mutations in the protein MeCP2, levels of which typically increase throughout development and is part of chromatin, the structure that bundles DNA. Dr. Stroud will use a combination of biochemistry, genetics, and genomics tests to study how MeCP2 functions in normal cells. He hopes that understanding the protein’s normal functions will help clarify how disruptions of MeCP2 lead to Rett Syndrome.

**Yesser Hadj Belgacem Tellier, Ph.D.**, University of California, Davis, will investigate how the Sonic hedgehog (Shh) signaling pathway, known for its role in the early development of the central nervous system, may be involved in autism. In an interdisciplinary effort, Dr. Tellier seeks a better understanding of how the Shh pathway influences later development, maturation, and physiology of the brain.

## BIPOLAR DISORDER

**Alessandro Colasanti, M.D., Ph.D.**, King's College London, UK, is pursuing evidence that brain cells, in bipolar disorder, appear to be inefficient in energy production. Indeed, patients may experience either increased or reduced levels of energy. The result of an inefficient 'oxygen metabolism' traceable to cellular energy factories called mitochondria, could be damaging the brain cells and lead to disease progression and cognitive decline, he theorizes. He will study people with and without bipolar disorder with MRI, to measure oxygen consumption, while experimentally "stretching" the energy production of mitochondria. This is a pilot study aimed at testing the ability of this procedure to demonstrate a reduced 'oxygen metabolic reserve' in people with bipolar disorder.

**Jasmin Lalonde, Ph.D.**, Massachusetts General Hospital and Harvard University, will investigate the activity, molecular basis, and function of structures known as store-operated calcium entry (SOCE) in patients with bipolar disorder. She aims to determine whether these structures are compromised during neuron development. Working in patient-derived inducible pluripotent stem cells (iPSCs), Dr. Lalonde will use calcium imaging to compare the activity of SOCE in a representative set of patient and healthy controls.

**Rupali Srivastava, Ph.D.**, Johns Hopkins University, wants to understand how defects related to calcium signaling in the brain could contribute to pathology in bipolar disorder (BP). Genome-wide association studies have shown possible contributions of ion channel genes such as voltage-gated calcium channels (VGCC). Dr. Srivastava will study the functioning of these channels in a clinically stratified subset of BP patients. The hypothesis is that weaker calcium dynamics through the VGCC activation results in compromised activity of calcium-stimulated potassium channels (Kca), such as the big conductance potassium (BK) channel. Normal functioning of BK channels is essential for proper neuronal excitability and firing capabilities. This in turn, is crucial for normal brain functioning.

**Laura Stertz, Ph.D.**, University of Texas Health Science Center, Houston, will use human induced pluripotent stem cell (hiPSC) technology to study the interaction between astrocytes and neuronal cells in the context of bipolar disorder (BD). The team's hypothesis is that astrocytes from BD patients have a pathological phenotype, leading to impairment of neurogenesis and toxicity in healthy neuronal cells. To test this hypothesis, they will develop hiPSC-derived cortical neuronal cells and astrocytes, from both BD patients and healthy controls. They will evaluate the effect of BD-derived astrocytes on neurogenesis and neuron survival and characterize the role of BD-derived astrocyte-neuron interaction in regulation of gene expression and signaling pathways.

## DEPRESSION

**Aaron Samuel Andalman, Ph.D.**, Stanford University, will explore the neural bases of responses to "inescapable stress," hoping to shed light on hopelessness as a key symptom of major depressive disorder. In rodent models of depression, a passive response to persistent stress reflects an animal's degree of hopelessness. Dr. Andalman will extend these findings to larval zebrafish, a model organism in which scientists can measure the activity of every individual neuron. For this study, he will shock the zebrafish and then use light field microscopy to measure the short- and long-term effects on their brain activity to create a neural model of the inescapable stress response. Dr. Andalman hopes the results will identify underlying neural mechanisms that can be targeted to treat major depression.

**Ipek Yalcin Christmann, Ph.D., Pharm.D.**, Centre National de la Recherche Scientifique (CNRS), University Pierre & Marie Curie, France, seeks to reach a cell-type specific genetic and epigenetic level of understanding of molecular alterations in brain neural networks in depression. The focus will be on the anterior cingulate cortex (ACC), in which have been observed functional and morphological alterations in depressive states. The team will use mouse models of depression to determine and compare the genetic and epigenetic alterations occurring in distinct neuronal populations of the ACC. They will also assess molecular traits of ACC neurons projecting to the basolateral nucleus of amygdala (BLA). This could generate a molecular blueprint of stress- and pain-induced depression, and to determine how the ACC and its connectome are remodeled with different etiologies of depression.

**Nils Christian Gassen, Ph.D.**, Max-Planck Institute for Psychiatry, Germany, will build from work showing that markers of autophagy in blood cells of depressed patients correlate with treatment success. Autophagy is a process through which cells dispose of waste. He will explore how a stress protein called FKBP51 affects the initiation of autophagy, and, in turn, alters communication between neurons in a manner that may give rise to depression. He will also study how a newly identified compound mediates this pathway to produce antidepressant-like effects in mice.

**Albert Giralt, Ph.D.**, French Institute of Health and Medical Research (INSERM), France, aims to gain a better understanding of which types of brain cells operate in different stages of the chronic stress periods which may lead to major depression. Using mice that have been genetically modified to display depressive-like behaviors, he will detect and characterize highly specific populations of neurons and will explore the role of Pyk2, an enzyme that is enriched in brain regions involved with major depression, in giving rise to such behaviors.

**Elizabeth A. Heller, Ph.D.**, University of Pennsylvania, will explore a potential link between epigenetic changes, which modify the expression of genes, and depression. She will examine the role of Cdk5, a gene shown to underlie stress responsiveness in various brain regions in rodent models of depression. Dr. Heller will study how changes in Cdk5 expression affect social-defeat stress behavior in mice, a well-established behavioral model that mimics that chronic nature of depression.

**Georgia Eve Hodes, Ph.D.**, Icahn School of Medicine at Mount Sinai, will explore the role of the peripheral immune system, which controls immune responses everywhere outside of the brain, in depression. Recognizing that most pre-clinical research has focused almost exclusively on male lab animals, despite the fact that depression is more common among females, she will investigate how dysregulation of the peripheral immune system may contribute to sex-linked differences in depression-like behaviors in mice.

**Carrie Holmberg, M.D., Ph.D.**, Stanford University, will probe circuitry in the brain involved in recalling autobiographical memories and making subjective judgments, seeking to better understand how dysfunction within this circuitry can contribute to depression. Using rodent models, she will examine the evolution of dysfunction in the default mode network, as chronic stress gives rise to depression-like behaviors. Dr. Holmberg will use cutting-edge optogenetic-based tools to precisely control and measure activity in defined groups of neurons while the animals are engaged in a behavioral memory task.

**Mary Claire Kimmel, M.D.**, University of North Carolina at Chapel Hill, will study the impact of variation in the maternal gut microbiota, bacteria and other organisms that populate the intestinal tract, on postpartum depression. She will use a metagenomic approach, which makes it possible to sequence the genomes of all of the microorganisms within a sample, to analyze the microbial composition of maternal gut microbiota over the course of pregnancy. Dr. Kimmel will also investigate how maternal gut microbiota composition may affect the performance of mothers and infants in established social and physical stress tests.

**Jie Liu, Ph.D.**, Columbia University, will explore the non-genetic route through which depression is transmitted multi-generationally. The research is based on an ongoing longitudinal study of families at low- and high-risk for depression. Over its 30-year course, the research has expanded from proband groups (Generation 1, G1), to their biological children (Generation 2, G2), and to grandchildren (Generation 3, G3). Each of the 6 data waves contains a comprehensive battery of family history and behavioral development, with DNA and MRI data collected at wave 5 and 6. This study investigates the heritability of neuroimaging-based phenotypes associated

with familial risk for depression across generations, using SOLAR-ECLIPSE software, a newly developed genetic imaging tool, to quantify the heritability of brain morphology and white matter anomalies.

**Jenna Ann McHenry, Ph.D.**, University of North Carolina, Chapel Hill, plans to study how sex hormones influence the neural circuitry underlying depression and other affective disorders. Women are more than twice as likely as men to experience depression, especially during hormonal flux, but it is not clear how hormones influence the neural circuits that mediate motivation. Dr. McHenry will monitor and manipulate the activity of neurons in the brain that respond to hormones, providing invaluable insights into how both sex and stress impact neural circuits and the risk for affective disorders.

**Caroline Menard, Ph.D.**, Icahn School of Medicine at Mount Sinai, will investigate how changes in the blood-brain barrier contribute to depression. Dr. Menard has found that loss of a key component of the barrier, known as claudin-5, can induce depressive-like symptoms in mice. She plans to extend these findings by looking further into the molecular mechanisms regulating claudin-5 expression in mice and exploring how chronic stress affects the permeability of the blood brain barrier.

**Janitza Liz Montalvo-Ortiz, Ph.D.**, Yale University, will explore why sexual abuse during childhood is a major risk factor for the development of depression later in life. Dr. Montalvo-Ortiz will focus on how abuse alters chemical tags, known as methylation marks, across the genome in women. Changes in these marks influence gene expression, providing a possible mechanism by which childhood sexual abuse confers risk for depression in women.

**David Elliot Moorman, Ph.D.**, University of Massachusetts Medical School, will characterize how neurons in the hypothalamus, a brain region that controls fundamental behaviors such as sleep and waking as well as motivation, are disrupted in chronic stress models of depression. Dr. Moorman will identify how signaling by specific classes of neurons is disrupted in rat models of depression and tease apart the roles of these neurons in reward- and stress-related behaviors.

**Alexander R. Nectow, Ph.D.**, Princeton University, will investigate the role of a brain area called the dorsal raphe nucleus (DRN), in both depression and feeding-related behaviors. The dorsal raphe is a remarkably complex structure, comprised of numerous cell types, and Dr. Nectow plans to functionally dissect the role of the DRN's component cell types in the healthy and depressed states. His goal is to elucidate the neural circuit mechanism underlying depression, which may ultimately aid in the development of novel therapies.

**Yuliya Nikolova, Ph.D.**, Centre for Addiction and Mental Health, University of Toronto, Canada, aims to shed new light on pathways underlying depression and possibly open novel avenues for intervention. In the past, researchers have explored molecular changes within neuron classes as well as the broad functional changes in the brain associated with depression. Dr. Nikolova seeks to provide a novel and comprehensive evaluation of previously unexplored links between these changes in behaviorally relevant properties of the brain and region-specific cellular function.

**Jocelien Danielle Attalie Olivier, Ph.D.**, University of Groningen, Netherlands, aims to tease apart the effects of depression and antidepressant use during pregnancy on offspring. Using an advanced rat model for depression, Dr. Olivier will identify changes in social behavior and microbiome in offspring due to depression during pregnancy, antidepressant treatment, or the combination.

**Bin Pan, M.D., Ph.D.**, Medical College of Wisconsin, aims to understand the neural link between chronic pain and depression. Dr. Pan will explore the molecular basis of changes in specific regions of the brain, including the medial prefrontal cortex and the endocannabinoid system, that will provide insights into how chronic pain can lead to depression. The project hopes to lay the groundwork for developing new therapies for depression and other disorders triggered by chronic pain.

**Shenfeng Qiu, M.D., Ph.D.**, University of Arizona, seeks to understand how neural circuit connectivity within the prefrontal cortex may be relevant to depression and if future therapeutic strategies may be devised precisely to target these important circuits. Combining state-of-the-art functional and anatomical techniques in animal models, the project aims to generate a breakthrough understanding of the role of specific limbic circuits in depression.

**Matthew James Robson, Ph.D.**, Florida Atlantic University, studies serotonin neurotransmission in the context of major depression. Signals carried by this neurotransmitter are under tight regulation by antidepressant-sensitive, high-affinity, serotonin transporters (SERT). Recent studies have found that aberrant immune system function is also associated with several neuropsychiatric disorders, including MDD. Dr. Robson aims to determine if cytokine signaling in concert with IL-1R1 activation within serotonergic neurons is required for immune system-induced alterations in SERT activation and consequent anxiety-like behaviors. To pursue these questions, they have generated mice suitable for the conditional elimination of IL-1R1.

**Julia Sacher, M.D., Ph.D.**, Max-Planck Institute for Brain Research, Germany, notes that the perimenopausal transition is a time of increased vulnerability for women. Yet it is not known how stress-related changes in the body and the brain during perimenopause relate to females' heightened risk for mood disorders. This project will test the idea that since estrogen can protect from harmful metabolic and inflammatory effects of stress, the relationship between visceral abdominal fat compared to subcutaneous abdominal fat increases during the perimenopause versus age-matched premenopausal women, and that perimenopausal women with increased visceral abdominal fat will also have lower hippocampal volume, which will predispose to higher levels of depressive symptoms. These theories will be tested in a sample of age-matched premenopausal and perimenopausal women (n=160).

**Jaclyn Marie Schwarz, Ph.D.**, University of Delaware, who studies postpartum depression, seeks to determine how microglia, the immune cells of the brain, change throughout pregnancy and the postpartum period; and examine whether changes in microglia function impact postpartum behaviors (mood, anxiety and maternal care or motivation). The specific hypothesis she and colleagues will test is that pregnancy induces a dramatic change in the function of microglia that continues immediately postpartum, and that the change in microglia function increases the risk of disordered mood and anxiety, precipitated by events that activate the immune system.

**Maggie M. Sweitzer, Ph.D.**, Duke University Medical Center, notes that cigarette smoking and depression are highly comorbid. Smokers with a history of depression are at greater risk of relapse even in the absence of current depressive symptoms, suggesting a shared underlying neurobiological vulnerability. Dr. Sweitzer seeks to learn more about social reward processing, which may contribute to comorbidity. She will examine group differences in reward-related activation and connectivity in response to an fMRI social 'likeability' task among smokers and non-smokers with and without a history of depression; and explore associations between brain activation and self-reported measures of social anhedonia and smoking history. Participants will be young adults, aged 18–25.

**Eric Steven Wohleb, Ph.D.**, Yale University School of Medicine, observes that stress-induced depressive symptoms are linked to pyramidal neuron atrophy and synaptic deficits in the medial prefrontal cortex (PFC). While this likely contributes to depressive-like behavior, it is unclear how these deficits develop in stress-induced models of MDD. His project will focus on microglia, immune cells in the brain, directed by neuron-derived signals which have a functional role in modulating synaptic plasticity. In animal models, his team will study molecular and cellular mechanisms that mediate microglia function during stress conditions with the hope of uncovering novel pathways by which microglia can contribute to stress-induced synaptic deficits and behavioral consequences.

**Bun Yamagata, M.D., Ph.D.**, Keio University, Japan, will investigate female-specific intergenerational transmission effects on functional and anatomical brain connectivity and structure within corticolimbic circuitry in depression. Specifically, Dr. Yamagata will use neuroimaging techniques to evaluate whether depressed-mother/high-risk daughter pairs have significantly greater associations in the corticolimbic regions of the brain, compared to depressed-mother/high-risk son and depressed-father/high-risk offspring pairings. Prior research in the series has spurred this research; they indicated that mother and daughter's corticolimbic morphology was more similar than other parent-offspring pairs. This approach may help to answer critical questions regarding maternal effects on brain development and female susceptibility to developing depression.

## EATING DISORDERS

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**Haijiang Cai, Ph.D.**, University of Arizona, will study a set of neurons that may play a key role in connecting emotion processing to eating disorders. Studying mice with virus-labeling and microendoscopic techniques, Dr. Cai will test whether different neurons in the brain's central amygdala, important for emotion, activate feeding behavior as compared to anxiety. The study will look further at whether these neurons form different connections to signal feeding versus anxiety. Dr. Cai hopes to identify specific brain circuits underlying emotion that help to control appetite, which may be targeted to treat eating disorders.

**Frank Julius Meye, Ph.D.**, Rudolf Magnus Institute of Neuroscience, Utrecht University, Netherlands, aims to provide a fundamental understanding of the brain circuit changes that drive binge eating. Using mice as a model, Dr. Meye, will explore how connections between different regions of the brain respond to anxiety and potent food cues. The work will provide insights that may help refine treatment strategies for binge eating-related disorders,

which are among the most prevalent and pernicious psychiatric conditions today.

**Jessica Werthmann, Ph.D.**, King's College London, UK, will conduct a randomized clinical trial using attention bias modification aimed at reducing food avoidance in people with anorexia nervosa, a severe mental disorder characterized by fear of food and avoidance of eating. Participants will be randomized, one set receiving food cues (active condition) the other a control condition without disorder-relevant cues. Behavioral outcome measures include attention bias for food, food anxiety and food intake pre- and post-training. To investigate neural underpinnings of change associated with brain changes in bias modification training, and in food avoidance, the team will select 32 participants for fMRI scanning.

## MENTAL ILLNESS

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### GENERAL

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**Jason Aoto, Ph.D.**, University of Colorado-Denver, will study a poorly understood brain region that regulates levels of the pleasure-related chemical dopamine, crucial in many illnesses including schizophrenia, depression and drug addiction. Looking at the brain's ventral subiculum, the researchers will investigate two types of interneurons that facilitate communication throughout the brain: parvalbumin (PV) and cholecystokinin (CCK) interneurons. Dr. Aoto will first probe the normal function of PV and CCK interneurons, and then measure how their activity is affected by disruptions to a gene that has been linked to schizophrenia and drug addiction. His team hopes to identify new pharmaceutical targets for treating both conditions.

**Raymundo Baez-Mendoza, Ph.D.**, Massachusetts General Hospital-Harvard University, hopes to identify the neuronal activity that drives social interaction. Dr. Baez-Mendoza's team will train rhesus macaques to play an adapted version of the Prisoner's Dilemma game, in which partners make decisions that either benefit or hurt each other. They will measure how the behavior of individual neurons changes during the game, particularly in the dorsal anterior cingulate cortex and basolateral amygdala, brain regions whose impact on social behavior is not well understood. Aiming to develop a basic understanding of social interaction at the neuronal level, Dr. Baez-Mendoza also hopes to build a framework for testing common behavioral interventions like medication and deep brain stimulation.

**Tahsin Stefan Barakat, M.D., Ph.D.**, University of Edinburgh, UK, will probe the origins of neurodevelopmental disorders, including intellectual disability. Dr. Barakat predicts that many neurodevelopmental disorders without a clear cause stem from mutations to “enhancers,” or genetic elements that control DNA transcription during early embryonic development. His team will use a novel sequencing technique to identify active enhancers in brain development, test them for mutations among patients with neurodevelopmental disorders, and then study lab-created tissue to determine how enhancer mutations affect neurons.

**Tracy Bedrosian, Ph.D.**, Salk Institute for Biological Studies, will seek the genetic origins of individual differences in personality and emotional reactivity that predict susceptibility to mental illness, including depression, anxiety, and addiction. Dr. Bedrosian expects to find that variations in early life experiences cause certain genetic elements to act on different parts of neurons, setting the stage for further disparities in interactions with the environment that lead to personality differences. Dr. Bedrosian hopes to elucidate the role of these flexible DNA elements in increasing susceptibility to disorders and apply this knowledge to help prevent and treat mental illness.

**Silvia Bernardi, M.D.**, Columbia University, will investigate how the brain represents contextual information to regulate emotion, a process that is disrupted in many psychiatric disorders. Using multichannel electrophysiology in monkeys, Dr. Bernardi will record single neuron activity from three brain regions—the amygdala, hippocampus, and anterior cingulate cortex (ACC)—associated with memory and emotion regulation, during a task that requires an understanding of context. Dr. Bernardi expects to identify different roles in context processing for each brain region, including a leadership role for the ACC, elucidating fundamental mechanisms behind emotional health that can be targeted to treat symptoms of mental illness.

**Erin S. Calipari, Ph.D.**, Icahn School of Medicine at Mount Sinai, will compare the effects of different receptors in the brain for the pleasure-associated neurochemical dopamine, linked to psychiatric disorders including addiction, depression, schizophrenia, post-traumatic stress disorder, eating disorders, and ADHD. Dr. Calipari plans to use imaging techniques in mice to measure the effects of two dopamine receptors, D1 and D2, in response to pleasurable and painful stimuli, determining which receptor drives people to seek experience and which receptor drives people to avoid it. She will also study how these behaviors change with cocaine use, potentially highlighting avenues for treating addiction.

**Jerry Lu Chen, Ph.D.**, Boston University, is interested in neural oscillations in the brain, which have long been associated with cognition. Abnormalities in such activity patterns have been identified in a wide-range of neurological disorders and thus can serve as a useful non-invasive biomarker for patient diagnosis. This research aims to directly assess the role of neural oscillations in information selection and routing in the cortex by establishing an integrated methodological approach combining optical and electrophysiological recording techniques across multiple scales in the awake behaving animal.

**Evan Feinberg, Ph.D.**, University of California, San Francisco, notes that behaving adaptively requires us to associate environmental stimuli with consequences such as reward and punishment. Several lines of evidence suggest that dopamine (DA) neurons drive this process, and aberrant DA activity is associated with a host of disorders from schizophrenia to addiction. He will develop an experimental paradigm to decipher the sensory signals encoded by dopamine neurons. He will combine an optical preparation he previously developed and the full arsenal of mouse genetics to identify the circuits that relay sensory signals to DA neurons. His premise is that a better understanding of sensory responses of DA neurons will facilitate efforts to understand what DA signals encode, and how altered signaling can cause neuropsychiatric disease.

**Il Hwan Kim, Ph.D.**, Duke University Medical Center, will explore the Arp2/3 complex, a downstream signaling target of many neuropsychiatric candidate genes. When Arp2/3 is knocked out in mice, their social behavior becomes impaired. Dr. Kim will use a novel circuit-selective gene manipulation method that he developed to study the networks within the frontal cortex, amygdala, and perirhinal cortex regions of the brains of such mice. Through this work, he hopes to uncover the neural network mechanism responsible for these social symptoms.

**Daniel Allen Lee, Ph.D.**, California Institute of Technology, studies sleep misregulation, a factor in a wide range of psychiatric disorders including schizophrenia, anxiety disorders and mood disorders. He seeks to understand the molecular and genetic basis of sleep regulation, using zebrafish as a model system. His focus is neuropeptide VF precursor (NPVF), which preliminary studies have shown to decrease locomotor activity and increase sleep in zebrafish and worms. Pharmacological inhibition of receptors for NPVF promotes arousal and inhibits sleep. This study seeks to learn how NPVF peptides and their receptors regulate sleep and will test the hypothesis that NPVF-expressing neurons are necessary and sufficient to promote sleep.

**Pieter Naude, Ph.D.**, University of Cape Town, South Africa, seeks to understand how maternal stress during pregnancy can be transmitted to an infant, conferring an increased risk of neurodevelopmental disorders. Part of the larger Drakenstien Child Health Study, this work will evaluate how the immune system and gut bacteria vary in pregnant women and their children in response to stress. The work could ultimately lead to the identification of new strategies to prevent the detrimental effects of stress in pregnant women on their offspring.

**Ashley Elizabeth Nordsletten, Ph.D.**, Karolinska Institute, Sweden, will investigate how children are affected by having two parents diagnosed with major psychiatric disorders. Such unions are common among psychiatric populations, with people occasionally finding partners who share the same disorder but more commonly choosing a mate with a different diagnosis. Dr. Nordsletten aims to understand what role these types of nonrandom matings play in the risk of major psychiatric diagnoses for children.

**Angela Macia Ortega, Ph.D.**, University of California, San Diego, will investigate how repeated sequences in the human genome contribute to neural function. One repeated DNA sequence, known as LINE-1, can copy and insert itself anywhere in the genome, constituting 17% of the human genome on average. Dr. Ortega will analyze the impact of LINE-1 element on brain development, and how its activity changes between normal and healthy individuals, providing insight into how LINE-1 may drive differences in cognitive behavior.

**Hyun-Jae Pi, Ph.D.**, Cold Spring Harbor Laboratory, will investigate neuronal mechanisms underlying impulsivity. Severe impulsivity can lead to poor decisions, even in the face of negative consequences, and is implicated in diverse psychiatric conditions including addiction, aggression, bipolar disorder, attention deficit-hyperactivity disorder, and borderline personality disorder. Using state-of-the-art tools in animal models, Dr. Pi aims to quantify impulsive behaviors and identify the neural circuits that drive impulsivity.

**Caitlin Kantrowitz Rollins, M.D.**, Children's Hospital, Boston, will test the theory that in utero neuroprotective therapies may prevent or reduce neurodevelopmental sequelae for patients with certain forms of congenital heart disease. This study will use fetal MRI to investigate brain abnormalities in utero. Dr. Rollins and team will describe whether congenital heart disease affects specific brain regions more than others and determine the timing of onset during pregnancy. They will also examine whether fetal brain findings in this population relate to toddler cognitive and psychological functioning. The study will employ innovative structural MRI techniques, using cutting edge post-processing tools to correct for fetal motion. Pregnant women will undergo fetal MRI twice during pregnancy, and after birth, children will undergo neurodevelopmental testing at age 2.

**Ludovic Tricoire, Ph.D.**, Centre National de la Recherche Scientifique (CNRS), University Pierre & Marie Curie, France, seeks to understand mechanisms involved in the dynamic regulation of dopaminergic (DA) neurotransmission depending on brain states and contextual information. Dysfunction of glutamatergic and dopaminergic functions is thought to be linked to psychiatric disorders such as schizophrenia. Dr. Tricoire hopes to forge a new link between DA and glutamatergic neurotransmission through the crosstalk between mGlu5 and the GluD1 receptor present on DA neurons, knowledge that could help us understand the pathophysiology of psychiatric disorders.

**Cheng Wang, M.D., Ph.D.**, University of California, San Francisco, aims to understand the transmission of emotion-regulating behavior and its origins in neural networks, distinguishing genetic and environmental contributions. Using resting-state functional MRI imaging, his team will focus on corticolimbic circuitry associated with a variety of conditions that show intergenerational effects such as depression and, anxiety. The study group will comprise 48 families with children born through IVF, now aged 8-11. Comparing parent-offspring covariation of corticolimbic circuitry in three IVF groups will allow us to disentangle genetic, prenatal and postnatal effects. They expect to find parent-sibling correlation in the corticolimbic system, especially in mother-daughter dyads; they also anticipate both genetic and environmental influence on the corticolimbic system but with matrilineal and patrilineal-specific patrilineal-specific patterns.

**Kai Xia, Ph.D.**, University of North Carolina, Chapel Hill, seeks to develop novel machine-learning procedures using data from two well-characterized population cohorts studied from birth through 2 years of age. Machine-learning variable selection will be used to build a predictive model for cognitive development which incorporates genome-wide genetic information and developmental trajectories of cortical thickness (CT) and surface area (SA). Dr. Xia hypothesizes that genes involved in dendritic development and synaptogenesis will be primary contributors to individual differences in CT and SA development in infancy and that genetic influences will show circuit-specific associations with working memory, gross motor development, visual reception, fine motor development, expressive language, and receptive language skills. The results could be generally applied to our understanding of infants with psychiatric disorders and cognitive delays.

**Mingshan Xue, Ph.D.**, Baylor College of Medicine, will combine novel molecular genetic manipulations with cutting-edge electrophysiology, imaging and optogenetic techniques to understand the molecular mechanisms underlying the proper relationship between excitation and inhibition, often referred to as the E/I ratio. It is now unclear how abnormal E/I ratios affect cortical computations, thereby contributing to the behavioral deficits

in mental illnesses. Failure to establish or maintain a proper E/I ratio will lead to cortical circuit dysfunction. The research seeks to understand how genetic mutations involved in autism and schizophrenia affect cortical E/I ratios and sensory processing.

**Gwyneth Zai, M.D., Ph.D.**, University of Toronto, Canada, is interested in shared genetic liabilities that have been seen in obsessive-compulsive disorder (OCD), schizophrenia, and attention-deficit hyperactivity disorder (ADHD). Dr. Zai's team will recruit 200 people with a psychiatric disorder and DNA already collected from previous research studies, as well as 100 healthy siblings and 100 healthy controls. They seek to identify DNA variations that contribute to the risk of developing cognitive deficits in patients with psychiatric disorders. Identification of genetic factors that contribute to cognitive dysfunction will support the goal of identifying those who may benefit from cognitive behavioral therapy and/or cognitive rehabilitation.

## MENTAL ILLNESS

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### MULTIPLE

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**Bénédicte Amilhon, Ph.D.**, Douglas Mental Health University Institute, McGill University, Canada, will investigate mechanisms in the brain's memory center, the hippocampus, that affect memory formation during intensely emotional experiences—with implications for post-traumatic stress disorder (PTSD) and anxiety disorders. Dr. Amilhon's work will focus on a lower section of the hippocampus, called the ventral third, or vHP, which receives many signals from neurons releasing the mood-regulating chemical serotonin. Using optogenetics and behavioral studies in mice, Dr. Amilhon will test the unique properties of serotonin neurons communicating with vHP, the effect of that communication on vHP cells, and any associated behavioral changes.

**Rita Baldi, Ph.D.**, Vanderbilt University, will investigate brain circuits that may promote resilience to stress and so explain strong differences among people in their stress vulnerability. Cannabis products have been shown to reduce stress by acting on particular connections in the amygdala, an emotion center in the brain, by increasing levels of a chemical called 2-AG. This study aims to identify the specific circuits that affect stress susceptibility and the sensitivity of these circuits to 2-AG levels. Dr. Baldi's team hopes that uncovering these molecular mechanisms behind stress responses could help treat and prevent conditions like post-traumatic stress disorder and major depression.

**Erin Nicole Bobeck, Ph.D.**, Icahn School of Medicine at Mount Sinai, will investigate a novel target for treating stress- and fear-related behaviors that contribute to conditions like anxiety, post-traumatic stress disorder, and depression. Dr. Bobeck will focus on BigLen-GPR171, a system of receptors commonly found in brain regions such as the amygdala, hippocampus, and prefrontal cortex that play a role in pathological fears. Her research will use viral techniques to stimulate or block the receptor system in mice and then measure behavioral effects on stress and fear, as well as any impact of these emotions on cellular expression in the receptors themselves. She hopes to reveal BigLen-GPR171's potential as a new therapeutic target.

**Donna J. Calu, Ph.D.**, University of Maryland School of Medicine, will test whether a particular pathway in the brain leads to post-traumatic stress disorder and drug addiction in vulnerable individuals. Dr. Calu expects to show that connections between the central nucleus of the amygdala, an emotion center in the brain, and a region known as the bed nucleus of the stria terminalis, heighten fear responses, as well as stress-related drug use. Her team will measure whether such effects are stronger among people who are predisposed to react more strongly to trauma and drug use. They hope the research will illuminate mechanisms that drive post-traumatic stress disorder when it develops alongside addiction.

**Bo Cao, Ph.D.**, University of Texas Health Science Center at Houston, hopes to determine whether a unique brain characteristic linked to schizophrenia results from the natural progression of psychiatric illness, rather than medication taken to treat the disorder. Using brain imaging, Dr. Cao's team will study whether abnormally high connections between the prefrontal and cingulate cortex are found in schizophrenia compared to bipolar disorder, among patients not taking medication. They will also measure how connectivity affects schizophrenia symptoms, such as working memory as well as verbal and visual learning. The team hopes to lay the foundation for tools to predict, and so better treat, related psychiatric disorders.

**Alexandre Charlet, Ph.D.**, Centre National de la Recherche Scientifique (CNRS), University Pierre & Marie Curie, France, seeks to understand how oxytocin is able to modulate such a broad spectrum of behaviors and emotions. Oxytocin, a neuropeptide released by the hypothalamus, impacts a wide range of complex behaviors such as fear, pain, social interaction and sexual behavior. Dr. Charlet will address whether there are several different subpopulations of oxytocinergic neurons, some recruited during negative emotion (e. g. anxiety, pain) via nor-adrenalin projections, and others recruited during positive emotion (e. g. social interaction, sexual arousal) via dopaminergic projections.

**Paula Louise Croxson, Ph.D.**, Icahn School of Medicine, Mount Sinai, wants to learn more about the relation of adolescent cannabis use and risk for neuropsychiatric disorders, including schizophrenia and psychosis. Her team will use adolescent cannabis exposure in non-human primates to model changes to higher-order cognitive functions, particularly working memory, and the brain structures involved. They will also investigate the mechanistic changes underlying these alterations by characterizing epigenetic changes that occur during development. The aim is to secure unique insights into mechanisms underlying development of psychosis and schizophrenia in adolescence, as well the effects of cannabis on the developing adolescent brain, in a model that is very close to the human.

**Alexis Edwards, Ph.D.**, Virginia Commonwealth University, will study co-occurrence and the relation between depression and alcohol misuse in order to improve outcomes. Dr. Edwards will merge individual-level phenotypic and genetic data for two large and longitudinally assessed samples, with experimentally confirmed tissue-specific functional genomic information. One sample (N~15,000) has been followed since birth into current young adulthood. The second sample (N~6000) has been followed from late adolescence into young adulthood. Analysis will support evaluation of the extent to which, for example, genetic variants with regulatory roles in brain tissue account for depression/alcohol misuse comorbidity during adolescence vs. young adulthood, or how variation in transcripts expressed in liver vs. specific brain regions impacts comorbidity across development.

**Ozgun Gokce, Ph.D.**, Ludwig-Maximilians University, Germany, aims to shed light on the neural underpinnings of behavior disorders such as depression and addiction within a brain region called the striatum, known to contribute to many cognitive processes and disorders. Dr. Gokce will build upon previous results that uncovered a new subtype of medium spiny neuron (MSN), the primary type of neuron found in the striatum. Using single neuron transcriptome analysis, imaging, and functionality testing on mice, he will investigate the role of this newly discovered MSN subtype in these behavior disorders.

**Sarah A. O. Gray, Ph.D.**, Tulane University, hopes to contribute to the improvement of mental health outcomes for people exposed to trauma early in life by exploring the connection between emotion dysregulation and psychopathology. She will investigate a potential physiological marker of emotion regulation known as Respiratory Sinus Arrhythmia in patients who were exposed to potentially traumatic events in childhood. Dr. Gray will also explore the effects of synchronous parenting behavior on emotion regulation.

**Brad Alan Grueter, Ph.D.**, Vanderbilt University Medical Center, aims to elucidate how interactions between the nervous and immune systems can contribute to autism and schizophrenia in cases of developmental abnormalities and chronic exposure to phencyclidine (PCP). He will explore the behavioral and neural consequences of altering microglia, a type of brain cell involved in immune defense of the central nervous system, in mice.

**Weizhe Hong, Ph.D.**, University of California, Los Angeles, seeks to explore the medial amygdala (MeApd), a brain region that previous work in lab animals has shown can control distinct social behaviors and anxiety. Using techniques including optogenetics to manipulate MeApd circuits in animal models, Dr. Hong will study how distinct populations of MeApd neurons activate during social behaviors and regulate anxiety.

**Mihaela D. Iordanova, Ph.D.**, Concordia University, seeks to gain insight into the basic neurobiological mechanisms of extinction based interventions, such as abstinence for addiction and exposure therapy for anxiety, which are characterized by high rates of relapse to problem behaviors. Using lab animals whose neurons have been genetically modified to be activated by particular drugs or colors of laser light, Dr. Iordanova will study how extinction manifests at the level of circuits within the brain. Dr. Iordanova will use an established set of behavioral tasks to model extinction therapy.

**Roselinde Henderson Kaiser, Ph.D.**, Harvard Medical School, strives to improve understanding of the cognitive effects of mood disorders and provide a framework of mood pathology that complements traditional diagnoses. She will image the brains of patients diagnosed with a mood disorder as well as healthy controls while they perform a battery of well-validated cognitive tasks designed to capture executive functioning and reinforcement learning. Dr. Kaiser will investigate how large-scale brain networks that are putatively involved in cognitive control work together in the brains of healthy people as well as those with mood disorders.

**Seung Suk Kang, Ph.D.**, University of Minnesota, will investigate the role of a brain region known as the claustrum in “positive” symptoms schizophrenia, which include hallucinations and delusions. The claustrum is thought to be a center of consciousness in the brain. Dr. Kang will use functional magnetic resonance imaging (fMRI) and electroencephalographic (EEG) recordings to study whether the functional connectivity within the claustrum is linked to the severity of positive symptoms in schizophrenia patients.

**Marian Lee Logrip, Ph.D.**, Indiana University, aims to identify and explore neural circuits underlying depression and anxiety. Specifically, Dr. Logrip is looking to explain why these mental illnesses are more common in women than men. Her studies will employ cutting edge techniques to interrogate how specific regions of the rat brain differ between males and females in the hopes of identifying improved therapies for both women and men.

**Nikolaos Mellios, M.D., Ph.D.**, University of New Mexico, is working to understand the complex mechanisms that underlie neuropsychiatric disorders, including schizophrenia and bipolar disorder. His work is focused on the role of an emerging class of noncoding RNAs known as circular RNAs (cricRNAs). Dr. Mellios aims to elucidate the function of schizophrenia- and bipolar disorder-associated circRNAs in manipulating gene expression and neuronal development to shed light on the unexplored role of these messages in brain function.

**Ian Mendez, Ph.D.**, University of California, Los Angeles, will study the relationship between neural circuits that govern 'wanting' and 'liking.' Dr. Mendez will investigate how two chemical messengers, called dopamine and enkephalin, interact, offering valuable insight into how motivation and related behaviors are regulated. The work will provide a basis for the development of treatment strategies aimed at regulating altered motivational states in disorders such as depression, schizophrenia, and addiction.

**Anna Victoria Rotberg Molofsky, M.D., Ph.D.**, University of California, San Francisco, plans to investigate how interactions between the immune system and nerve cells in the brain contribute to schizophrenia. Specifically, Dr. Molofsky will explore how unique populations of immune cells in the brain eat away at the connections between neurons in a process known as pruning, providing insight and potential new drug therapies for psychiatric diseases including schizophrenia and autism.

**Sara Morrison, Ph.D.**, University of Pittsburgh, will investigate how the brain performs cost-benefit analyses in order to make decisions. Using rats as a model system, Dr. Morrison will focus on two specific areas of the prefrontal cortex to determine how neural circuits can represent and interpret cost and integrate it with the possibility of reward. The results are likely to set the stage for understanding, and potentially mitigating, decision-making that has gone awry in psychiatric disorders such as depression and schizophrenia.

**Anirvan Nandy, Ph.D.**, Salk Institute for Biological Studies, aims to understand neural mechanisms underlying attention in order to develop treatments for disorders in which attention fails, such as schizophrenia and ADHD. By focusing on specific areas of the macaque brain, Dr. Nandy hopes to provide the framework for a circuit-level model of attention and pave the way for better understanding disorders in which attention fails.

**William Paul Nobis, M.D., Ph.D.**, Northwestern University, will explore how stress affects neural circuits and alters subsequent behavior. Stress has been found to alter neural anatomy in specific regions of the brain, and Dr. Nobis will dissect the molecular pathways that are responsible for these changes. His work will focus on the role of a protein known as beta-arrestin in an extended area of the amygdala, in the hopes of providing new insights and potential target for treatment of stress and anxiety disorders.

**Elizabeth A. Olson, Ph.D.**, McLean Hospital-Harvard University, will explore neural circuits that link PTSD with other mental disorders including alcohol/ substance abuse, and suicidal behavior. Dr. Olson will focus the study on two regions of the brain, the nucleus accumbens and anterior insula that are involved in decision-making. This work has the potential to help identify people with PTSD that are at particularly high risk for impulsive behaviors, and ultimately may lead to the development of new targets for novel treatments.

**Ina P. Pavlova, Ph.D.**, Research Foundation for Mental Hygiene, Inc./NYSPI at Columbia University, seeks to elucidate the mechanisms underlying stress resilience and guide the development of effective prophylactic treatments. Stress exposure is a major risk factor for mood disorders, but some people are resilient and able to adapt. This resilience is thought to require neurogenesis, or the birth of new neurons in adulthood, but ketamine injections can similarly induce resilience in mouse models, independent of neurogenesis. Dr. Pavlova aims to identify the neural pathways underlying both neurogenesis-dependent and -independent stress resilience.

**Nadine Provencal, Ph.D.**, Max-Planck Institute for Psychiatry, Germany, aims to understand how maternal stress during pregnancy increases the risk of mental health problems for children later in life. Dr. Provencal will focus on the role of glucocorticoid hormones, the main regulators of our response to stress, and how these hormones influence gene expression through chemical tags, called epigenetic modifications, across the genome. The study combines both cell culture models and neuroimaging in newborns to identify new targets that may prevent the development of disease.

**Steve Ramirez, Ph.D.**, Harvard University, seeks a mechanistic account of how chronically activated circuits supporting positive memories may reprogram neural activity and behaviors. His team will test whether or not chronic reactivation of positive memories prior to prolonged stress is sufficient to induce stress resilience. They hypothesize that chronically stimulating positive memory-bearing hippocampus cells prior to stress can prevent anxiety and depression-like states from precipitating at the cellular level, including preventing neuronal atrophy, as well as the behavioral level, including preventing social impairments, aberrant risk-assessment phenotypes, and anhedonia. They will later perform brain-wide analyses to identify key cellular loci mediating memory's potential prophylactic capacity.

**Danielle Roubinov, Ph.D.**, University of California, San Francisco, will use two unique datasets of community samples of children to test novel hypotheses of the bidirectional, longitudinal relations between physiological activity and internalizing disorders. Data were collected from 180 children during infancy and toddlerhood (6, 18, 36, and 48 months of age) and 324 children across the kindergarten year (fall and spring). Each study collected repeated measurements of adversity, physiological reactivity across multiple stress responses systems (autonomic nervous system and the hypothalamic-pituitary-adrenal axis), and internalizing symptoms in early childhood. The research will test an integrated, multisystem developmental cascades model. The ultimate aim is implementation of novel, tailored clinical interventions to reduce disorder and promote resilience among children exposed to adversity.

**Esther Serrano Saiz, Ph.D.**, Columbia University, notes that dopamine neurons are important for the control of motivated behavior and are involved in the pathophysiology of several major neuropsychiatric disorders, including schizophrenia and drug abuse. Recent studies have shown that some ventral midbrain dopamine (DA) neurons are capable of glutamate (Glu) cotransmission. She will perform experiments to reveal fundamental regulatory mechanisms for the proper function of the Glu-DA neurons. This might facilitate future experiments in which she would genetically manipulate specifically the Glu-DA neurons of the VTA to see if this affects DA transmission.

**Dongju Seo, Ph.D.**, Yale University School of Medicine, wants to know more about factors linking major depression (MDD) and alcohol abuse, which, when comorbid, result in poor treatment outcomes, frequent relapse, and greater likelihood of suicidal attempts than in people with MDD alone. Dr. Seo hypothesizes that compromised function and connectivity in the VmPFC-left DLPFC circuit may contribute to mood and HPA axis dysregulation and comorbid alcohol abuse, and predict prospective depression and mood-related alcohol drinking in individuals with MDD. To test this he will lead a 2-year study composed of three groups including MDD, MDD

comorbid with alcohol abuse, and healthy controls (20 subjects each, demographically-matched). The study will utilize the simultaneous fMRI and HPA axis monitoring technique combined with prospective clinical design to identify neurobiological markers for depression and comorbid alcohol abuse.

**Stephen Vincent Shepherd, Ph.D.**, The Rockefeller University, is interested in altered emotional signaling, which may play a causal role in dysfunction and treatment of human social pathology in both autism and schizophrenia. Investigation of the neural mechanism for emotional signaling will be greatly facilitated, Dr. Shepherd proposes, through the use of cutting-edge electrode microarrays, which permit better localization of brain activity under more naturalistic circumstances compared with traditional, acute microelectrode recordings. By using electrode microarrays to record neural activity along the pathway converting perceived to produced emotional expressions, he will investigate how our brains coordinate our emotional states with those of our social partners.

**Gek Ming Sia, Ph.D.**, University of Texas Health Science Center at San Antonio, has been studying sushi repeat protein X-linked 2 (SRPX2), a synaptogenic protein which increases the density of excitatory synapses in cortical neurons. This project seeks to characterize the molecular, cellular and behavioral phenotypes associated with SRPX2 deletion in mice. SRPX2 deletion in mice results in abnormal ultrasonic vocalization in infant pups, and also impairs their performance a social approach task, both of which relate to symptoms in autism spectrum disorder (ASD) as well as negative symptoms of schizophrenia. Dr. Sia hypothesizes that SRPX2 deletion leads to abnormal circuitry formation in the brain which affects the development of both language and social behaviors.

**Aline Silva de Miranda, Ph.D.**, Federal University of Minas Gerais, Brazil, will study the incidence of psychiatric sequelae following traumatic brain injury (TBI) in a Brazilian population, following on evidence that neuroinflammatory processes are involved in such injuries, as well as depressive and anxiety symptoms. Dr. Miranda will evaluate the incidence of depressive and anxiety symptoms following a TBI event in young adults; and study a potential inflammatory biomarker of TBI-associated psychiatric sequelae. The study will have a prospective case-control design, with 100 cases and 100 controls.

**Philip Tovote, Ph.D.**, Friedrich Miescher Institute, Switzerland, notes that fear and anxiety trigger defensive responses, which in turn spur neuronal signals that are fed back to the central nervous system. This process, termed interoception, makes a major contribution to aversive emotions such as fear and anxiety. Dr. Tovote will use multiple methods to identify the neuronal circuit elements within a part of the brain called the midbrain periaqueductal grey (PAG) mediating autonomic responses to threat; characterize circuit mechanisms of integration of cardiac interoceptive information into PAG output pathways; and investigate how differential regulation of PAG circuits contributes to distinct types of fear and anxiety.

**Mirjam van Zuiden, Ph.D.**, University of Amsterdam, Netherlands, aims to identify causal factors in life history and genetic make-up associated with vulnerability for mental health problems after trauma. Dr. Zuiden will investigate whether prenatal adversity increases vulnerability for trauma-induced mental health problems. The team will also investigate whether this developmental programming effect is influenced by common variants in genes regulating the glucocorticoid system. The team will use the Dutch Famine Birth Cohort study, which has followed adults born in Amsterdam around the time of the Dutch Famine at the end of WWII. About half of the cohort was exposed to malnutrition in the womb, while the other half was not.

**Neide Vieira, Ph.D.**, University of Minho, Portugal, seeks to learn more about the role of a brain-enriched protein called SNX27 in the nervous system, specifically, how its expression and function changes during aging and in the presence of environmental stressors. It is one of the “sorting neurexins” (SNXs), whose expression levels are altered in the brain in aging, in a way that correlates strongly with cognitive performance in rodents. By exposing rodents to chronic mild stress, a model of depression, the team found SNX27 expression significantly decreased in the pre-frontal cortex (PFC), and its levels to correlate strongly with corticosterone levels. They now will perform a molecular and multidimensional behavioral analysis of the SNX27 mouse model, during aging and under exposure to stress (CMS) to learn more.

**Minghui Wang, Ph.D.**, Cold Spring Harbor Laboratory, is interested in understanding why some individuals are susceptible to stress while others are resilient, a question that bears on several brain disorders including depression and anxiety disorders. Dr. Wang and colleagues have observed in mice that inactivation of a gene called *Ophn1* in parvalbumin (PV) inhibitory neurons, in the brain’s medial prefrontal cortex (mPFC), is sufficient to induce a depression. Inactivation of the gene has also been shown to cause a form of X-linked intellectual disability. They seek now to unravel the underlying mechanisms, at a cellular and molecular level, and among other things identify genes regulated by *Ophn1* in mPFC PV interneurons in stress responses.

**Romy Wichmann, Ph.D.**, Massachusetts Institute of Technology, notes that impaired social interest and social withdrawal are classic features in many psychiatric disorders, including depression, posttraumatic stress, and anxiety disorders. Dr. Wichmann seeks to explain how mesolimbic dopamine (DA) signaling—linked to social behaviors—differs between males and females. The focus will be on how non-social stressors impact female mice, using cutting-edge tools to identify the downstream target(s) mediating DA- and stress-induced effects on social behavior; and identifying different VTA DA subpopulations as well as different target areas of the VTA. Overall, this research will provide details about the fundamental neurobiological principles mediating social interaction.

**Guang Yang, Ph.D.**, The Hospital for Sick Children, University of Toronto, Canada, will test the hypothesis that gestational diabetes interacts with genetically-defined perturbations in the enzyme glyoxalase 1 (Glo1) to cause short-term alterations in embryonic neural precursors, neurogenesis and neural development and, ultimately, to cause altered adult forebrain structures and cognitive behaviors relevant to ASD and schizophrenia. Hyperglycemia in diabetes induces an overproduction of the toxic metabolite methylglyoxal, levels of which are normally held in check by Glo1. To test the hypothesis, Dr. Yang will use a genetic mouse model of gestational diabetes and a conditional Glo1 mutant mouse.

**Tim Ziermans, Ph.D.**, Leiden University, Netherlands, will assess social attention in adolescents with ASD and psychotic symptoms as well as a healthy comparison group. His aim is to establish the extent to which compromised “social brain” functions may predispose those with ASD to psychosis. They are at elevated risk for developing psychosis later in life. Dr. Ziermans will use eye-tracking technology to assess whether known shared vulnerability markers as manifest in eye movements and pupil dilation are already present before the onset of psychosis.

## OBSESSIVE-COMPULSIVE DISORDER

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**Daigo Homma, Ph.D.**, Massachusetts Institute of Technology, strives to identify new therapeutic targets for obsessive-compulsive disorder (OCD) by investigating pathways within the ventral striatum, a brain area known to be involved in the disorder’s pathogenesis. Dr. Homma will test the hypothesis that cholinergic interneurons control repetitive behavioral acts by regulating brain activity known as beta oscillations in response to the release of the neurotransmitter dopamine in the ventral striatum. To do this, Dr. Homma will administer behavioral tasks to transgenic rats and monitor the correlation of beta oscillation and dopamine release.

**Minseok Song, Ph.D.**, Weill Cornell Medical College, will follow up on research showing that deletion of four genes in mice, *Hoxb8*, *Sapap3*, *Cx3cr1*, and *Slitrk5*, leads to pathological behaviors including adult-onset excessive grooming with mild-to-severe hair loss and self-injury – symptoms that model human obsessive-compulsive disorder (OCD). The proposed studies are intended to directly address the molecular role of BDNF/TrkB on the pathogenesis of OCD-like phenotypes, especially in the context of OCD-related neuronal circuitry. These studies are relevant to understanding the pathogenesis of OCD and to the development of novel target-based therapies to treat these debilitating conditions.

## PSYCHOSIS

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**Daniel Scott, Ph.D.**, University of Texas Southwestern Medical Center at Dallas, seeks to identify the neural correlates of psychosis, which he conceptualizes as a memory disorder, induced by hippocampal hyperactivity as indicated by human imaging and postmortem tissue studies. He hypothesizes that hyperactivation of the CA3 directly mediates specific behaviors associated with psychosis. To induce a hyperactive state in CA3, he infuses a virus containing a Designer Receptor Exclusively Activated by Designer Drugs (DREADD), under the control of a pyramidal cell-specific promoter directly into the dorsal or ventral CA3 of wild-type mice. This approach allows the team to induce firing of the infected neurons in a cell-type, spatial, and temporally specific manner, and assess the resulting behavior. They will carry this work forward, to determine the range of symptoms induced by hippocampal hyperactivity, as well as the role activity within the other hippocampal subfields and associated cortical regions.

**Stefania Tognin, Ph.D.**, Institute of Psychiatry, King's College London, UK, seeks to understand how the experience of stress is related to the onset of psychosis. To clarify which environmental factors influence coping strategies in the early stages of psychosis, Dr. Tognin will use a smartphone app to collect real-time information about the appraisal of physical and interpersonal environment, the appraisal of self, and ways of coping, in people at clinical high risk of psychosis, who have experienced a first episode of psychosis vs. a group of healthy controls. This is designed to reveal which coping strategies are adopted by individuals in the early stages of psychosis and how these strategies are affected by the environment's appraisal.

## POST-TRAUMATIC STRESS DISORDER

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**Rosalina Fonseca, M.D., Ph.D.**, Gulbenkian Institute of Science, Portugal, will address the dynamics of memory, combining cellular physiology with behavioral approaches in the context of PTSD. She proposes that traumatic events alter synaptic plasticity in amygdala synapses. Her team has found that synapses receiving inputs from thalamic and cortical projections, circuitry known to be key in fear responses, can re-enforce each other. The temporal window in which thalamic and cortical synapses cooperate is determined by endocannabinoid signaling. Using a model of PTSD they will test whether the development of PTSD leads to a change in thalamic and cortical synaptic cooperation. They will also test whether modulation of endocannabinoid signaling can bring about reversal of PTSD-induced synaptic modifications.

**Justin Michael Moscarello, Ph.D.**, New York University, is working to identify neural circuits responsible for resilience, or the ability to 'bounce back' following trauma. This proactive behavior helps people cope with stress, lessening the impact of trauma. Using rats as a model, Dr. Moscarello will explore how specific neural circuits in the brain resolve the conflicting behaviors that are derived from innate fear response and resilience.

**Christine A. Rabinak, Ph.D.**, Wayne State University, studies brain response to trauma, and is interested in fatty acid amide hydrolase (FAAH), an enzyme that regulates the body's natural endocannabinoid system. She will use imaging genetics coupled with a standard Pavlovian fear conditioning paradigm to investigate the contribution of FAAH genetic variation to inter-individual variability in extinction-related brain function. Individual variability in FAAH-mediated endocannabinoid function may offer a neurobiological explanation for why some people are more prone to develop PTSD following trauma exposure and provides a functional target for development of novel pharmacotherapies for PTSD.

**Stephanie Trouche, Ph.D.**, University of Oxford, UK, notes that fear memories, once extinguished, sometime return spontaneously. She will combine multichannel neuronal recordings, optogenetic tools and cellular imaging in mice to directly test whether spontaneous recovery of fear memories is mediated by the reactivation of fear neurons in the basal amygdala (BA), possibly through a reduction of inhibitory activity from parvalbumin-expressing (PV+) interneurons in the BA. The project may enable identification of potential novel treatments for PTSD that selectively and permanently inactivate a pool of neurons (fear neurons) whose activation causes fear disorders such as PTSD.

## SCHIZOPHRENIA

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**Atheir Ibrahim Abbas, M.D., Ph.D.**, New York State Psychiatric Institute of Columbia University, will investigate brain circuits that drive cognitive impairments in schizophrenia, an aspect of the illness that does not improve sufficiently under existing treatments. The research will focus on two types of cells that inhibit brain activity: parvalbumin and somatostatin neurons. Working with mice, Dr. Abbas will test how deactivation of these two neuron types affects connectivity in the brain, and, in turn, disrupts working memory function. The results will shed light on the potential for targeting these neurons to treat cognitive dysfunction in schizophrenia.

**Marta Busnelli, Ph.D.**, Institute of Neuroscience of the National Research Council, will explore the molecular mechanisms through which the neurochemical oxytocin relieves symptoms of schizophrenia. Dr. Busnelli's team will examine whether oxytocin addresses schizophrenia by interacting with the release of dopamine, a key neurochemical for the brain's reward system and motor control. Studying mouse models of schizophrenia, they plan to pinpoint chemicals that treat the disorder by altering both oxytocin and dopamine release.

**Kayla A. Chase, Ph.D.**, University of California, San Diego, will test the theory that environmental insults exert their biological effects through changes to chromatin, the bundles of DNA and protein that package our genetic material. She is specifically interested in dopaminergic signaling, which is strongly implicated in the etiology of schizophrenia. Dopamine acts on GABAergic medium spiny neurons (MSNs), which constitute the two major output pathways of the striatum. She has developed a novel genetic technique that will allow direct examination of the effect of prenatal environmental insults on chromatin structure in dopamine type 1 and 2 receptors on MSNs.

**Youngsun Theresa Cho, M.D., Ph.D.**, Yale University, will use translational neuroimaging and other methods to test if cognitive performance changes in response to rewards, and if the magnitude of cognitive deficits predicts the lack of desire to engage in pleasurable activities often seen in schizophrenia, and how the brain may carry out these processes in patients with schizophrenia. Dr. Cho and colleagues have designed a state-of-the-art neuroimaging task that explicitly manipulates short-term versus long-term task-performance incentives. The aim is to examine if severity of motivational deficits in schizophrenia is relatively constant irrespective of task condition (i.e. despite cognitive demands) or if it presents as more severe when maintenance of reward is needed over time (i.e. with cognitive demands).

**Timothy Hanks, Ph.D.**, University of California, Davis, hopes to develop new treatments for the cognitive symptoms of schizophrenia by gaining a better understanding of circuits in the brain that are involved. Focusing on the flexibility of decision making that is profoundly impaired in schizophrenia, he will use tools including optogenetics and computational analysis to study such neural circuits in mice. In doing so, Dr. Hanks strives to bridge the gap between interventions that act at the molecular level and clinical symptoms that are manifested by neural circuits.

**Laurence Tudor Hunt, Ph.D.**, University of London, UK, aims to improve understanding and treatment of schizophrenia and psychosis by studying the role of the neurotransmitter glutamate. He will use a drug called ketamine, which acts upon glutamate receptors, to model the experience of psychosis in healthy human volunteers and in non-human primates. Dr. Hunt will record neural activity from the brains of both the ketamine and placebo groups while the subjects perform a simple decision-making task, as the delusions of schizophrenia patients affect decision-making.

**Jee-Yeon Hwang, Ph.D.**, Albert Einstein College of Medicine, seeks to explore N-methyl-D-aspartate receptors (NMDARs), structures found on neurons that are critical to the formation of neural circuitry and to higher cognitive functions. A hallmark feature of NMDARs is a developmental switch in structure, and Dr. Hwang aims to identify mechanisms underlying this switch, particularly in a brain region called the hippocampus. Dr. Hwang will test the hypothesis that this developmental switch is regulated epigenetically, meaning through changes in gene expression, and that the dysregulation of this process may contribute to schizophrenia.

**Jason Karl Johannesen, Ph.D.**, Yale University, will use the McGurk effect, a well-studied illusion that arises when the timing of auditory and visual components of speech are offset, to study schizophrenia in adolescents. Dr. Johannesen contends that the McGurk effect can be used to assess the integration of information gained through multiple senses in schizophrenia. Building upon previous work in adults suggesting that people with schizophrenia are less sensitive to this effect, he will administer an electroencephalographic (EEG) version of the McGurk task to adolescents with schizophrenia and healthy adolescents.

**Esther Soon Kim, Ph.D.**, Columbia University, hopes to elucidate molecular mechanisms through which environmental factors influence the development of schizophrenia. She will test the hypothesis that neurons differentiated from induced pluripotent stem cells (iPSCs) sampled from childhood-onset schizophrenia patients are more susceptible to negative environmental factors such as hypoxia, or oxygen deprivation. Dr. Kim will also investigate whether dysfunctions in subcellular components called mitochondria can impair the ability of neurons from schizophrenia patients to mitigate hypoxia.

**Vishnu P. Murty, Ph.D.**, University of Pittsburgh, seeks to provide a mechanistic understanding of how deficits in a specific inhibitory neurotransmitter, known as GABA, can contribute to schizophrenia. Focusing on a region of the brain called the hippocampus, Dr. Murty will investigate how loss of GABA can lead to the aberrant engagement of the dopaminergic system in schizophrenia.

**Dhakshin Ramanathan, M.D., Ph.D.**, University of California, San Francisco, notes that deficits in both micro-circuits (gamma oscillations) and macro-circuits (coherence in lower oscillations) have been observed in association with cognitive deficits occurring in schizophrenia. This project will investigate the specific neural circuits that underlie cognitive deficits in a rodent-model of schizophrenia, using a new approach for simultaneous recordings across cortical, sub-cortical and cerebellar brain regions. Dr. Ramanathan will directly apply electrical stimulation to specific brain regions, at specific frequencies tailored to the neural deficits, seeking to learn the degree to which these interventions can normalize neural circuits and remediate cognitive deficits in a rodent model of schizophrenia.

**Tade Souaiaia, Ph.D.**, University of Southern California, wants to elucidate the genetic etiology of schizophrenia, in view of large-scale patient data analysis suggesting that over 20,000 casual variants with very minor effects may be involved in etiology. The team will develop a multi-dimensional model which incorporates RNA-seq data from a set of neural precursor cell lines [Cultured Neuronal cells derived from Olfactory Neuroepithelium (CNON)] developed from people with and without schizophrenia. They propose development of a multi-dimensional learning model to integrate CNON expression data with complimentary genomic and transcriptomic data to better understand the mechanisms that distinguish the schizophrenia phenotype from genotype.

**Toral S. Surti, M.D., Ph.D.**, Yale University, notes that cognitive remediation, i.e., exercises that target under-functioning neural activity, has been shown to help people with schizophrenia improve their cognition and their independence to a limited extent. One reason, says Dr. Surti, for the limited effects may be problems with sleep and sleep-dependent learning in schizophrenia. Since sleep plays a central role in some forms of normal learning, and sleep-dependent learning may be disrupted in schizophrenia, Dr. Surti will study sleep spindles, which are short bursts of neural oscillations measured by EEG that occur during sleep and are associated with cognitive ability. These can be increased or decreased by different psychiatric medications. This study will test whether the reduction of sleep spindles in schizophrenia predicts deficient sleep-dependent learning on two tasks.

**Ai-Hui Tang, Ph.D.**, University of Maryland School of Medicine, will perform research on deficits of the glutamate system at both synapse and circuit levels in the context of schizophrenia. Dr. Tang's super-resolution microscopy studies have demonstrated presynaptic glutamate release is organized to occur at sites directly opposing postsynaptic receptor nanoclusters by an aligned distribution of key synaptic proteins. This provides an unexpected new mechanism to control synapse strength, disruption of which can dramatically weaken synaptic function and may play a role in causing schizophrenia. The new project will test whether a disruption of this aligned architecture in animal models contributes to the glutamate hypofunction thought to occur in schizophrenia.

## OTHER DISORDERS

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### PARKINSON'S DISEASE

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**Maria Soledad Esposito, Ph.D.**, Friedrich Miescher Institute, Switzerland, will study a part of the brainstem that shows extensive neurodegeneration in postmortem studies of Parkinson's disease patients—the Mesencephalic Locomotor Region (MLR), a key structure involved in modulation and execution of locomotor functions. Dr. Esposito seeks to elucidate at the circuit level how MLR dysregulation leads to the generation of abnormal motor outputs. The team will use mouse genetics, viral tools, optogenetics and single-unit recordings in freely moving animals to dissect neuronal circuitry of identified neuronal populations according to cell identity and/or projection target during natural behavior and to compare how ablation of different key circuit elements may alter the function of specific pathways resulting in disturbed motor performance.

# NEW TECHNOLOGIES

## ADDICTION

**Silvia De Santis, Ph.D.**, Cardiff University, UK, will develop new technology needed to better understand the brain. His project ADDICT seeks to produce innovative imaging technology to characterize the changes produced by long-term alcohol drinking and abstinence. He proposes a novel strategy to take non-invasive MRI-like 'pictures' with a range of different focuses and measure biomarkers such as axonal density and diameter, heterogeneity index and tract-specific myelination. He seeks to fully characterize the link between advanced diffusion MRI metrics and brain microstructure, and to apply the new framework to a rat model of alcohol use disorders

## AUTISM SPECTRUM DISORDER

**Christos G. Gkogkas, Ph.D.**, University of Edinburgh, UK, seeks to explore a protein synthesis pathway known as mTOR that is commonly dysregulated in autism. He will use the genome editing tool CRISPR/Cas9 to mutate genes that control the activity of a protein called 4E-BP2, which plays a role in the mTOR pathway and may regulate the production of other proteins that are crucial to normal brain development. Dr. Gkogkas hopes that this work will highlight new biomarkers and potential drug targets.

**Krishanu Saha, Ph.D.**, University of Wisconsin-Madison, has developed several human stem cell models of Rett Syndrome, an autism spectrum disorder (ASD). In this research Dr. Saha and colleagues will test a new platform to array microscale islands of astrocyte-neuron co-cultures, gene-edit them in high-throughput, and analyze them in situ with high content analysis without dissociating the cultures. This novel system effectively separates neurons from dense cultures into isolated 'islands' that can be easily analyzed for complexity. The hypothesis is that automated analysis of spatially isolated astrocyte-neuron co-cultures derived from Rett patients will dramatically increase our ability to understand neuronal biology and advance drug discovery/toxicology.

**Ying Yang, Ph.D.**, Stanford University, will combine novel optical and chemical techniques with molecular engineering to study the dynamics of newly produced proteins in living neurons. Fragile X syndrome (FXS) is the best-understood cause of autism as well as mental retardation. It is caused by loss of expression of the Fragile X mental retardation protein (FMRP). In the brain, FMRP regulates the production of proteins that locate near synapses. Dr. Yang will identify signaling pathways required for the preferential localization of PSD95, a synaptic structural protein that is crucial for learning and regulated by FMRP. Dr. Yang will observe how various FMRP mutants (including mutations identified in patients) affect the process. These experiments may reveal potential drug targets.

## DEPRESSION

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**Hee-Dae Kim, Ph.D.**, University of Arizona, hopes to determine whether modulation of a protein called SIRT1 constitutes a potential therapeutic approach for depression. A recent study in humans revealed SIRT1 as the first robust reproducible marker linked to depression. Using mice, Dr. Kim will use the CRISPR/Cas9 genome editing system and optogenetics to study the pathways in the brain through which SIRT1 signaling regulates depression-like behaviors.

## MENTAL ILLNESS

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### MULTIPLE

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**Casey Harrison Halpern, M.D.**, Stanford University, strives to improve a responsive neurostimulation treatment, in which a device is implanted in the nucleus accumbens of the brain, for disabling compulsive behaviors such as gambling and binge eating. By studying both mouse models of binge eating behavior and human patients diagnosed with obsessive compulsive disorder, Dr. Halpern will examine and characterize candidate electrographic biomarkers for optimizing this treatment.

**Jakob Hartmann, Ph.D.**, Harvard University-McLean Hospital, will investigate how stress-related psychiatric disorders such as major depression and post-traumatic stress disorder may be linked to epigenetic modifications, which are thought to alter the way genes are expressed in response to life events. The gene FKBP51 has been linked to stress-related psychiatric disorders in numerous ways. Using mice, Dr. Hartmann will use the genome-editing tool CRISPR/Cas9 to explore the role of FKBP51 in causing stress-related psychiatric disorders and open new avenues for discovery by creating better models for these disorders.

## PSYCHOSIS

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**David Reid Roalf, Ph.D.**, University of Pennsylvania, notes that malfunctioning neurotransmitter systems, such as glutamate, are implicated in disease progression of psychosis, but the role of glutamate, particularly early in the course of psychosis and those at risk, remains unclear. Changes in brain glutamate in psychosis likely have several sources, including changes in oxidative stress. Dr. Roalf's work focuses on glutathione, an antioxidant that works to eliminate environmental toxins that damage neurons. This project studies glutamate and glutathione using a novel 7 Tesla MRI glutamate imaging technique in young patients with psychosis and those at high clinical risk.

### SCHIZOPHRENIA

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**Eric Hau-Yun Chang, Ph.D.**, Feinstein Institute for Medical Research, seeks to better understand the effects of antipsychotic drugs on the brain. Past research has linked these drugs with decreases in white matter integrity and volume, but may be limited in their applicability due to irregularities among tested patients in illness severity, concomitant substance abuse, and drug-induced changes in metabolic status. Dr. Chang's project will be the first to use the new technology called CLARITY, in which brain matter is rendered transparent, to study the effects of antipsychotics on white matter by assessing myelin- and axon-associated proteins in normal mice that have been treated with aripiprazole and risperidone.

**Tonya Marie Gilbert, Ph.D.**, Massachusetts General Hospital-Harvard University, hopes to illuminate the role of epigenetic pathways, which alter the expression of genes, in the development of schizophrenia. Dr. Gilbert will explore how dysregulation of a family of enzymes called histone deacetylases (HDAC) may contribute to schizophrenia using a non-invasive imaging tool developed in her lab called [11C]Martinostat, which quantifies HDAC expression across the living human brain. Through a combination of imaging, cognitive tests, and experiments on induced pluripotent stem cell-derived neurons, she hopes to uncover a new method for early schizophrenia diagnosis via aberrant HDAC expression levels as well as new therapeutic targets.

**Ethan Lippmann, Ph.D.**, Vanderbilt University, aims to develop personalized models of human brain tissue that can be used to identify new avenues for treating schizophrenia. He seeks to improve the drug screening process by creating a three-dimensional tissue model of the vascularized human brain using induced pluripotent stem cells (iPSCs). Dr. Lippmann hopes to help inform clinical trials and treatment strategies by constructing and testing this tissue model with iPSCs derived from different patient populations, to establish correlations between drug efficacy and patient genetics.

**Emma Sprooten, Ph.D.**, Icahn School of Medicine at Mount Sinai, will conduct the first study of non-invasive imaging of intracortical myelination in schizophrenia that harnesses the power of high-field imaging at 7 Tesla (7T) coupled with a novel computational algorithm. The aim is to study brain morphology, white matter and resting state functional connectivity in schizophrenia patients (n=20) and demographically matched controls (n=20), and to examine case-control differences in myelination that will inform about the degree and regional distribution of myelin abnormalities. This project will demonstrate the capability of the new method to quantify myelin abnormalities in schizophrenia and the potential to identify causal mechanisms underlying dysconnectivity between brain areas that will enhance our understanding of symptoms.

**John-Paul J. Yu, M.D., Ph.D.**, University of Wisconsin, has generated a CRISPR/Cas9-based Disc1 rat model of schizophrenia that provides an exciting opportunity to explore the impact of a well-known de novo genetic variant of large effect in the causation of schizophrenia. This will be accomplished through the examination of gene-specific changes in global neural structure and organization as observed using diffusion tensor imaging (DTI) technology. The impetus for the research is evidence of disruptions in neural connectivity and structure in patients with chronic schizophrenia. These findings, while encouraging, have been inconsistent across multiple studies.

# NEXT GENERATION THERAPIES

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## ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

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**Gustavo Adolfo Angarita, M.D.**, Yale University, will examine the potential of Vitamin D to treat ADHD when given with commonly used stimulant medications. Stimulants can treat ADHD symptoms by boosting the brain's dopamine system, but they may have negative side effects and do not work for all patients. Dr. Angarita's team will coordinate a pilot study in six patients to test whether an active form of Vitamin D, called calcitriol, increases dopamine in the brain when given with stimulants compared to placebo pills. They expect to demonstrate calcitriol's benefits over placebo, paving the way for larger trials to investigate this treatment option.

## AUTISM SPECTRUM DISORDER

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**Meagan Ruth Talbott, Ph.D.**, University of California Davis Medical Center, notes that social-communication impairments experienced by young children with Autism Spectrum Disorder (ASD) from very early in life have cascading effects on development across all areas. Increasing social attention and social learning is the target of most early behavioral treatments, yet there are only three known studies that have reported on brain-based changes in response to behavioral treatment for ASD. Dr. Talbott will investigate relations between behavioral change observed

in the context of high quality, empirically validated behavioral treatment for toddlers with ASD, and brain-based measures of the mechanisms hypothesized to underlie this change. The goal is to identify mechanisms through which successful behavioral treatments for ASD work to improve social communicative symptoms of ASD.

## ANXIETY

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**Yoon-Hee Cha, M.D.**, Laureate Institute for Brain Research, will investigate the potential for transcranial magnetic stimulation (TMS), a noninvasive technique, to treat chronic fear by altering brain activity. Studying people with a phobia of public speaking, Dr. Cha will map connections between the ventromedial prefrontal cortex, a brain region that underperforms at reducing fear in people with anxiety, and higher-up parts of the brain. Dr. Cha will also test whether applying TMS to these connections changes their activity and, in turn, normalizes fear responses, whether by stimulating or inhibiting the connections. The research aims to identify a therapeutic pathway to difficult-to-reach brain networks that can be targeted to treat anxiety.

## DEPRESSION

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**Clémentine Bosch-Bouju, Ph.D.**, Université Bordeaux II, France, seeks to identify the mechanisms through which omega-3 fatty acids can prevent depression, providing an alternative to current pharmaceutical treatments. Dr. Bosch-Bouju's team will use pharmacological and electrophysiological tests in male and female mice to measure how omega-3 levels affect the plasticity of points of connection, or synapses, in the brain. They will also investigate how the most common omega-3 in the brain (docosahexaenoic fatty acid) protects synaptic plasticity in two mice models of depression, comparing effects by gender. The study aims to improve understanding of omega-3's effects on the brain to expand treatment options for depression and other mental disorders.

**Sjoerd Jehannes Finnema, Ph.D.**, Pharm.D., Yale University, aims to determine whether the rapid acting antidepressant ketamine normalizes synaptic density at the time of its greatest antidepressant effect in people with major depression (MDD). Ten people with MDD will participate in two 11C-UCB-J PET scans to determine SV2A binding before and 24 hours after ketamine administration. Mood assessment and cognitive measures will be administered before and after ketamine administration. Relationships between PET outcome parameters and mood and cognitive assessment measures will be evaluated. SV2A-PET may prove a promising in vivo imaging biomarker for rapid antidepressant response and facilitate novel antidepressant drug discovery by providing a surrogate endpoint in individuals with MDD.

**Ye Han, Ph.D.**, Northwestern University, will investigate a new drug candidate for treating major depressive disorder. Dr. Han will expand upon previous work suggesting that a lack of structures called hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, or the TRIP8b molecules that regulate their activity, produces antidepressant-like behavior in lab animals. Using mice, Dr. Han will evaluate the ability of a therapeutic candidate called SNL-CP to promote antidepressant-like behavior by disrupting the interaction between HCN and TRIP8b.

**Brent Michael Kious, M.D., Ph.D.**, University of Utah, will explore a novel strategy for the treatment of depression in women based on growing evidence for a link to reduced oxygen levels, known as hypoxia. Dr. Kious will investigate whether administering molecules known as creatine and 5HTP can help to mitigate hypoxia-related depressive symptoms. He will conduct a placebo-controlled clinical trial to determine whether creatine and 5HTP can effectively augment treatment with existing drugs called selective serotonin reuptake inhibitors (SSRIs).

**Sho Moriguchi, M.D.**, University of Toronto, Canada, will investigate a possible cause of treatment resistance in depression. Dr. Moriguchi hypothesizes that commonly used current treatments do not target elevated levels of monoamine oxidase B (MAO-B), a protein that helps remove chemicals from the brain that normally improve mood. Dr. Moriguchi will measure MAO-B levels in patients with depression and determine if levels correlate with the severity of depressive symptoms, in the hopes of identifying MAO-B inhibitors as a potential treatment for clinical depression.

**Desmond Jay Oathes, Ph.D.**, University of Pennsylvania, aims to advance a novel noninvasive treatment for depression. Previous research has shown that an area deep in the brain called the subgenual anterior cingulate cortex (sgACC) is overactive in patients with depression. Currently, surgery is the only option to modulate the activity of this brain region, but Dr. Oathes is working to develop an alternative, noninvasive therapy based on repetitive transcranial magnetic stimulation, to reduce activity in the sgACC.

**Karina Quevedo, Ph.D.**, University of Minnesota, will develop a novel treatment for severely depressed adolescents using real-time neurofeedback functional magnetic resonance imaging (fMRI-NF). Participants will try to change their brain activity (depicted as a bar graph next to a picture of their own smiling face) by thinking of happy memories while receiving neurofeedback from the anterior cingulate cortex, a brain region associated with self processing. Dr. Quevedo hopes that the results will generate a new mode of treatment for adolescents.

**Marcia J. Ramaker, Ph.D.**, University of California, San Diego, is studying rapid-acting antidepressants. She will examine the necessity of induction of the neural growth factor BDNF in the medial prefrontal cortex (mPFC) or hippocampus for the behavioral antidepressant effects of scopolamine and ketamine as compared to the SSRI antidepressant fluoxetine. She will also use Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) and a two-virus approach to determine whether activity of ventral tegmental area (VTA)-to-mPFC projections is necessary for fast-onset antidepressant effects in these three antidepressant agents.

**Adam Philip Stern, M.D.**, Harvard Medical School, wants to better understand why Transcranial Magnetic Stimulation (TMS), a non-invasive treatment approach to medication-refractory depression, doesn't work for some patients. He will explore whether non-responders in standard high frequency TMS protocols may be consistently converted to experience responses using a distinct stimulation approach known as intermittent theta burst stimulation (iTBS). First, the team will demonstrate that TMS-induced modulation of corticospinal excitability at a frequency used in clinical treatment protocols will predict clinical response over a full course of treatment. Then they will investigate intermittent theta burst stimulation to determine if greater degrees of response can be achieved in depressed patients.

**Samuel Wilkinson, M.D.**, Yale University School of Medicine, will lead a randomized, controlled trial of patients with treatment-resistant depression to investigate the potential of cognitive behavioral therapy (CBT) to sustain ketamine's antidepressant effects. Ketamine can rapidly relieve treatment-resistant depression, though its effects are short-lived after a single dose and there are concerns about long-term administration. To take advantage of the purported window of opportunity that begins about 24 hours following ketamine administration, CBT or the control will be administered 24–48-hr following each treatment in ketamine-responding patients, who will be randomized to receive CBT or intensive medication management plus psychoeducation (control). The team will measure group difference in relapse rates 4 and 8 weeks following the final ketamine treatment.

**Nolan Ryan Williams, M.D.**, Stanford University, is interested in the opioid properties of ketamine. He seeks to determine if ketamine's rapid antidepressant effects are mediated through the opioid system by exploring the potential for naltrexone (which reverses the effect of opioids) to block opioid receptors and therefore the antidepressant response in known ketamine responders. Another objective is to determine if the dissociative effects of ketamine are mediated through the opioid system, given that these effects are correlated with response in depression. He will conduct a clinical trial in which ketamine responders will be randomly assigned to two groups, one receiving ketamine plus naltrexone, the other ketamine plus placebo.

## POST-TRAUMATIC STRESS DISORDER

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**Chuan Huang, Ph.D.**, Stony Brook University School of Medicine, aims to determine a pretreatment marker of the effectiveness of nasal continuous positive airway pressure (CPAP) treatment during sleep in post-traumatic stress disorder (PTSD) patients. Nasal CPAP can alleviate sleep disordered breathing (SDB), which has been shown to contribute to PTSD. Dr. Huang will test the hypothesis that nasal CPAP treatment decreases the secretion of molecules that cause inflammation, reducing brain inflammation and resulting in improved PTSD symptoms.

**Benjamin Kelmendi, M.D.**, Yale University, hopes to learn more about the pathophysiology and treatment models for post-traumatic stress disorder (PTSD) by investigating a drug known as MDMA as a potential treatment. He will conduct a randomized, double-blind, placebo-controlled study of the effects of MDMA on PTSD patients. To measure some of the acute effects of MDMA, Dr. Kelmendi will use functional magnetic resonance imaging (fMRI) to measure blood oxygen level (BOLD) response.

## SCHIZOPHRENIA

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**Andrew Wayne Bismark, Ph.D.**, VA San Diego Healthcare System at the University of California, San Diego, hopes to identify factors that predict the effectiveness of a computer-based treatment for schizophrenia called targeted cognitive training (TCT). Dr. Bismark will measure behavioral indicators of attentional control, reward-based learning, and effortful motivation, which are disrupted in schizophrenia. He predicts that higher baseline scores in these behaviors will lead to greater cognitive improvements after 10 weeks of TCT, which relies on patients' ability to respond to reward feedback so that they improve their information processing and, in turn, their quality of life.

**Wing Chung Chang, FHKCPsych**, Chinese University of Hong Kong, notes that motivational impairment is one of the key symptoms in schizophrenia and strongly predicts functional disability. Despite its clinical significance, motivational impairment doesn't respond very much to medication and psychosocial interventions. Dr. Chang will conduct a prospective 1-year follow-up study on a representative cohort of first-episode schizophrenia patients (n=45), to examine their effort-based decision making ability using a well-validated computerized task. Results will shed light on the longitudinal course of effort-allocation deficits in the initial year of treatment, and relationships of these deficits with various variables, particularly motivational impairment and functional outcome. Clemens

**Christian Bauer Hoss, M.D., Ph.D.**, Massachusetts Institute of Technology, hopes to demonstrate that mindfulness therapy can reduce activity of the brain's default mode network that has been linked to schizophrenia. The default mode network is a set of connections in the brain that activate when someone is not engaged in a distinct task, and it shows abnormally high connectivity and stimulation in schizophrenia. Dr. Hoss expects to show that schizophrenia patients can use mindfulness therapy, coupled with feedback on their brain activity, to quiet the default mode network and so improve their clinical and cognitive symptoms of schizophrenia. His team will also test the safety of this intervention to set the stage for more robust clinical trials.

**Britta Galling, M.D.**, Feinstein Institute for Medical Research, hopes to improve clinical procedures for preventing onset of schizophrenia by comparing the effects of two psychotropic drugs, fluoxetine and aripiprazole, on patients with symptoms known to precede psychosis. Dr. Galling will examine their effects on a variety of factors related to schizophrenia onset, including social functioning, alterations to medication regimens, and levels of brain derived neurotrophic factor (BDNF), a chemical which supports processes in the brain that appear to be disturbed during schizophrenia onset. To do this, Dr. Galling will expand a pilot study on patients at risk of schizophrenia.

**Laura Magdalen Tully, Ph.D.**, University of California Davis Medical Center, will use non-invasive brain stimulation technology called transcranial direct current stimulation (tDCS) to target brain mechanisms underlying impaired cognitive control of emotion in schizophrenia. While tDCS is known to improve cognitive control of emotion in healthy individuals, the brain mechanisms of tDCS-induced improvements are not yet understood. Dr. Tully seeks to identify tDCS-induced behavioral changes in cognitive control of emotion during negative social evaluation, and will use fMRI to identify tDCS-induced changes in the frontal-limbic network supporting cognitive control of emotion during negative social evaluation. This could reveal underlying brain systems that contribute to social difficulties in schizophrenia.

**Remko van Lutterveld, Ph.D.**, University of Massachusetts Medical School, will conduct the first study to assess the association between a neurofeedback signal and meditation quality in people with schizophrenia. The aim is to help determine the feasibility of using mindfulness training as an alternative to antipsychotic therapy in schizophrenia. The team will use neurofeedback from the posterior cingulate cortex (PCC) in 25 patients to provide real-time feedback on the quality of mindfulness meditation practice based on brain activity. In this way, individuals have an unbiased 'mental mirror' which directly informs them on their meditation quality in real time in an unbiased way. This study tests whether patients with schizophrenia can voluntarily modulate EEG neurofeedback, and if so, whether there is an impact on schizophrenia symptoms.

## OTHER DISORDERS

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### FRAGILE X SYNDROME

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**Manavi Chatterjee, Ph.D.**, Yale University, is studying Fragile X syndrome (FXS), which is usually caused by a switched-off Fmr1 gene that encodes Fragile X mental retardation protein (FMRP). FMRP normally functions to suppress protein synthesis of select messenger RNAs. Loss of FMRP leads to increased translation of some of these mRNAs. One of the mRNAs regulated by FMRP encodes an enzyme in the central nervous system called STEP, levels of which are elevated when FMRP is lost. In this project, Dr. Chatterjee will test whether a compound called TC-2153, which inhibits STEP, is of therapeutic value in mouse models of FXS. L

# DIAGNOSTIC TOOLS & EARLY INTERVENTION

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## AUTISM SPECTRUM DISORDER

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**Robert Wayne Emerson, Ph.D.**, University of North Carolina, Chapel Hill, will use neuroimaging to longitudinally study the brain and behavior of infants at high familial risk for developing autism. Specifically, he aims to (1) verify a new early detection method that he has recently developed, (2) explore the possibility of using neuroimaging to predict an individual's future behavioral profiles, and (3) study how early behaviors affect longitudinal changes in the brain's functional organization. If successful, these studies will make the first important steps toward developing an early detection method in 6-month-old infants and identifying an infant's specific behavioral risks.

**April Robyn Levin, M.D.**, Children's Hospital in Boston, aims to develop an early predictive biomarker of autism and biologically related disorders by examining neural network "noise" in infants. Dr. Levin will analyze encephalographic (EEG) recordings collected from infants with an older sibling with autism, whose risk of developing autism is approximately 20%, and infants with a typically developing older sibling, whose risk of developing autism is approximately 1%. She aims to determine whether children who develop autism will show increased neural network noise on EEG, which is present even before behavioral manifestations of autism become recognizable.

**Tiziano Prampero, Ph.D.**, University of California, San Diego, seeks to discover predictors of early treatment response for children with autism spectrum disorder (ASD). Using different statistical and bioinformatic approaches on a large, existing dataset, Dr. Prampero will mine quantitative measures of individual biological variability collected pre-treatment to identify biological predictors of evidence-based behavioral treatment. The goal is to improve the development of predictors for a better-targeted and more effective response to early behavioral treatment in ASD intervention programs.

## BIPOLAR DISORDER

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**Sergi Papiol, Ph.D.**, Ludwig-Maximilians University-Munich, Germany, aims to develop diagnostics that will improve the treatment and prognosis of patients living with bipolar disorder. Dr. Papiol plans to identify biological markers in peripheral blood that make it possible to predict, for example, if a patient who suffers from bipolar disorder will respond to pharmacological treatment, will develop a more severe form of the disease, or will suffer a less pronounced cognitive decline. The research may enable doctors to personalize treatment priorities according to their predicted outcome over time.

## DEPRESSION

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**Ki Sueng Choi, Ph.D.**, Emory University, aims to develop a means to subtype patients with major depressive disorder (MDD) that will serve to guide clinical management of individual patients. To complement biomarkers now being tested which predict remission or nonresponse to SSRI medication and cognitive behavioral therapy, Dr. Choi wants to characterize the impact of chronicity, severity, and recurrence and will develop multivariate tools to examine the impact of grey and white matter lesions on both structural and functional connectivity and overall network integrity at distinct clinical stages. The study is a step in the development of precision medicine algorithms for the treatment of MDD at all stages of illness.

**Xuejun Hao, Ph.D.**, Columbia University, aims to facilitate prevention and early intervention for major depressive disorder (MDD) by discovering potential biomarkers indicative of risk. Dr. Hao will study individuals at high familial risk for MDD. Using advanced imaging technology called 1H Magnetic Resonance Spectroscopy (MRS), Dr. Hao will investigate whether levels of a brain metabolite called N-Acetylaspartate (NAA) are linked to changes in brain structure and function in individuals at high-risk for MDD, comparing with low-risk individuals.

## MENTAL ILLNESS

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### GENERAL

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**Stacy Tzoumakis, Ph.D.**, University of New South Wales, Australia, seeks to determine the prevalence of psychopathology in middle childhood, which will help to determine potential unmet mental health service needs in the population. Dr. Tzoumakis will characterize how symptoms of psychopathology group together, determining the population prevalence of co-occurrences of psychopathology. The study will identify risk factors and use these to predict the development of mental health disorder in early adolescence and assist in the development of well-targeted intervention and prevention programs. The basis for the project is population data from the New South Wales Child Development Study, which includes 22,000 children.

## MENTAL ILLNESS

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### MULTIPLE

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**Lisanne Michelle Jenkins, Ph.D.**, University of Illinois at Chicago, aims to identify biomarkers that predict recurrence of major depressive disorder and bipolar disorder. She will use magnetic resonance imaging (MRI) to study the brain activity of patients with either major depressive disorder or bipolar disorder as they perform a task that assesses their inhibitory control. In particular, Dr. Jenkins will test the hypothesis that inhibitory control networks in the brain will be more impaired in patients who experience disease recurrence than those who do not.

**Alyson Kay Zalta, Ph.D.**, Rush University Medical College, will conduct a pilot study to explore the relationships between parent traumatic stress, offspring psychopathology, offspring biological aging, and psychological and biological risk factors that have been implicated in the intergenerational transmission of trauma, including parenting style, attachment, fear conditioning, and stress system neuroendocrine dysregulation. Dr. Zalta will recruit 40 military families with a biological child age 7-12, in which the father was deployed in the service of the US military and experienced a military-related traumatic event.

## SUICIDE RESEARCH / PREVENTION

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**Jeremy Gordon Stewart, Ph.D.**, McLean Hospital, Harvard University, seeks to identify novel markers that predict suicide attempts in a high-risk population of adolescents. He will use electroencephalography to measure individual differences in adolescents' sensitivity to rejection. The research will probe feedback-related negativity (FRN), an event-related potential that signals negative or worse-than-expected outcomes (e.g., the receipt of rejection). Developing objective, task-based markers of suicide risk is crucial because some patients conceal or minimize suicidal thoughts and thus, basing clinical decisions solely on patient report is often unreliable. The proposed study will recruit 40 depressed adolescent suicide attempters and 40 non-attempters within 48 hours of admission to an acute, residential hospital program.



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