2015
Young Investigator Grant Program

ANNOUNCEMENT OF YOUNG INVESTIGATOR GRANTEES

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

ABOUT THE YOUNG INVESTIGATOR GRANT PROGRAM

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

The Foundation's NARSAD 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

- Every Young Investigator gets support and guidance from a scientific mentor designated by the Scientific Council

- 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 3,888 YI Grants

- More Than $230 Million Funded

- Resulting In More Than $2.3 Billion In Subsequent Research Funding

The Foundation is pleased to announce $13 million in 191 new two-year grant awards to support the work of promising young scientists with innovative ideas in mental health research. The grants for 2015 address outstanding research questions across diagnostic categories, from schizophrenia and depression to anxiety, PTSD, autism spectrum disorder, and ADHD, among others. About 60 percent of the projects funded are basic research, the wellspring of innovation in brain research as in all sciences.

Covering a broad spectrum of mental illnesses, these NARSAD Young Investigator Grants function as catalysts to get new ideas off the ground that may not otherwise be supported. We are very grateful to all of our donors for making these important awards possible.

On the following pages you will find our 2015 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 one-third of the 2015 grants fund projects that specifically aim to develop next-generation therapies.

- About 10 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: Canada, Holland, Italy, Australia, Germany, Israel, Ireland, Spain, the UK, Argentina, Austria, Finland, Japan, South Korea and Switzerland.

IN 2015

- 712 Applications

- 191 Grants Awarded

- $13 Million Funded

Honoring Herbert Y. Meltzer, M.D.
for 28 Years of Service
as the Chairman of the
Young Investigator
Grant Selection Committee
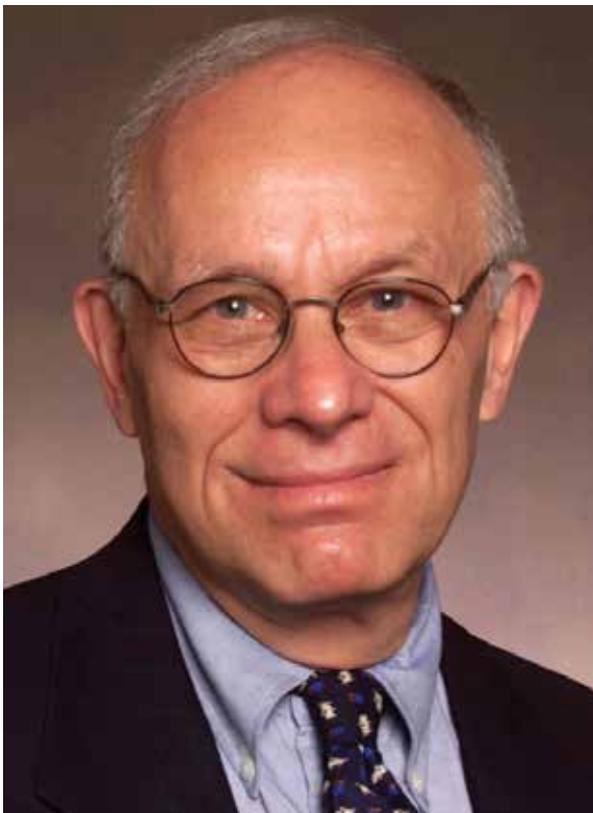
Herbert Y. Meltzer, M.D.

*Professor of Psychiatry and Behavioral Sciences
and of Physiology
Northwestern University, Feinberg School of Medicine*

Founding Member of the Scientific Council
Chair, Young Investigator Grant Selection Committee
Foundation Scientific Council

Dr. Meltzer has reviewed 14,784 grant applications since 1987

NARSAD Grants: Distinguished Investigator 1988, 1994, 2000 and 2007
Prizes: 1992 Lieber Prize for Outstanding Achievement in Schizophrenia Research

> *"In addition to a significant base of grants for basic brain research to understand what happens in the brain to cause mental illness, we also see an uptick in the number of grants focused on the development of next generation treatments and therapies. There is also an increasing trend in the number of investigators utilizing cutting-edge technologies to better study the brain."*

DR. MELTZER

Dr. Meltzer is an active clinician who directs a multifaceted research program in schizophrenia and bipolar disorder which is devoted to developing more effective treatments. He is one of a few clinical researchers also heavily engaged in basic research. He is particularly renowned for having been the principal investigator of the seminal trials that led to the approval of clozapine for treatment-resistant schizophrenia (1988) and patients who are at high risk for suicide (2003). He also is credited with articulating the theory that atypical antipsychotics such as clozapine owe much of their advantage over typical drugs to the balance between serotonin and dopamine receptor blockade (1989).

Dr. Meltzer's research interests span clinical, basic, and translational topics. The focus of his clinical research is the development of novel treatments for schizophrenia, particularly treatment resistant schizophrenia, optimizing the efficacy and minimizing the side effects of approved antipsychotic drugs, developing treatments to overcome the cognitive deficit of schizophrenia and understanding the cognitive effects of psychotropic drugs, and pharmacogenomic research to identify risk genes for psychotic disorders and genetic biomarkers to guide choice of treatments for psychosis. His basic research emphasizes clarifying the mechanism of action of antipsychotic drugs, animal models of cognitive impairment in schizophrenia, and illuminating the roles of glutamate, GABA, dopamine, serotonin, and acetylcholine in psychosis and cognition models. Dr. Meltzer's clinical work is directed towards the evaluation and treatment of patients with psychotic spectrum disorders, which includes schizophrenia and bipolar disorder.

Prior to joining Northwestern, Dr. Meltzer taught at Vanderbilt University, where he also directed the psychosis program. Beyond his various leadership positions at each stop in his career, Dr. Meltzer has served as president of the American College of Neuropsychopharmacology (ACNP) and the Collegium International Neuro-psychopharmacologicum (CINP). He has also been an editorial board member at numerous scientific journals.

> *"We all want to join in thanking Herb Meltzer for an outstanding job as head of our review committee for Young Investigators. Countless hours of hard work are necessary to read the thousands of applications and develop consensus and agreement from various reviewers on the grant awardees. This is and has been an enormously challenging task. Herb has always done this with knowledge, diplomacy and focus on how to do the best for our researchers. The Brain & Behavior Research Foundation is enormously appreciative of all his fine efforts."*

HERBERT PARDES, M.D.
President of the Scientific Council

BASIC RESEARCH

ADDICTION / SUBSTANCE ABUSE

Amit Agarwal, Ph.D., at Johns Hopkins University seeks to explore the effects of THC, the main active ingredient of marijuana, on the long-term cognitive development of adolescents. Dr. Agarwal will investigate THC's effects on astrocytes, a neural cell type. Using transgenic mice bred without signaling molecules called IP3 receptors, which allow astrocytes to regulate activity throughout the brain, Dr. Agarwal aims to show that THC dysregulates astrocyte activity, leaving adolescents vulnerable to long-term cognitive impairments.

Stephan Lammel, Ph.D., of the University of California, Berkeley will work to identify specific connections in the brain that can be altered by drug use. Drugs of abuse elicit long-lasting changes in the brain's reward system that is thought to contribute to the development of addiction. By identifying specific drug-induced changes within the brain's reward circuits, Dr. Lammel hopes to enable the development of new interventions to reduce drug use and relapse. BR ADD

Jocelyn Margaret Richard, Ph.D., of Johns Hopkins University, hopes to reveal mechanisms that drive relapse in addiction. Relapse is especially likely during times of stress. Dr. Richard and colleagues will investigate the brain region of the ventral pallidum as a potential center for interaction between environmental triggers and stress that contributes to relapse. Neurons in the ventral pallidum are excited by environmental cues that promise reward. Looking at individuals struggling with addiction, the team expects to show

that these neurons renew their previously strong response to alcohol when people are under stress; that these neurons' activity predicts alcohol-seeking; and that targeting inputs to the ventral palladium may reverse this activity. These results may hold a key to improved treatments.

Benjamin Thomas Saunders, Ph.D., of Johns Hopkins University will identify how different brain circuits contribute to reward-related behavior, which is distorted in conditions ranging from addiction and overeating to depression. Neurons orchestrate the reward system by releasing the neurotransmitter dopamine and so motivating behavior. In previous research, Dr. Saunders and colleagues found that different groups of dopamine neurons are responsible for distinct facets of reward, such as attraction to cues in the environment or positive reinforcement. To understand these facets, this project will use imaging techniques to monitor dopamine neurons during drug seeking and relapse, and will also manipulate some of those neurons to see how reward behavior is affected.

Lucas Sjulson, M.D., Ph.D., of New York University, will study brain activity in an animal model of cocaine addiction. In the cocaine conditioned place preference model (CPP), an animal exploring a multi-chamber space spends more time in the chamber where it previously received cocaine. CPP has been used extensively to demonstrate the rewarding properties of cocaine and to assess the potential therapeutic effects of different therapies. Yet the neural mechanisms underlying CPP are not clearly understood. This project will test the hypothesis that CPP involves the strengthening of particular connections between the hippocampus and the nucleus accumbens.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

Lisa Anne Briand, Ph.D., at Temple University will investigate the role of GRIP, a protein important in glutamate signaling, in the development of ADHD. Preliminary evidence suggests that disrupting GRIP function within the prefrontal cortex leads to impaired learning in mice. To further GRIP research, Briand will knock out GRIP in mice and will use a more comprehensive behavioral paradigm that assesses measures of cognitive flexibility such as strategy shifting and reversal learning. Dr. Briand seeks to determine how disruption of glutamate signaling in the prefrontal cortex, through deletion of GRIP, alters cognitive function and synaptic plasticity.

Joseph Stephen Ralker, Ph.D., of Florida International University, aims to improve our understanding of ADHD by assessing a system for distinguishing between, and differently treating, separate symptoms of the condition. ADHD involves different symptoms linked to neurocognitive deficits, including failures of working memory and inhibition of impulsive behavior. Dr. Ralker and colleagues plan to replicate previous findings that children with ADHD are more or less impaired across different symptoms. They will then, for the first time, evaluate whether those subgroups help predict the effects of methylphenidate, commonly known as Ritalin and prescribed to treat ADHD.

Shona Lee Ray-Griffith, M.D., of the University of Arkansas for Medical Sciences, will expand on research suggesting that children exposed in utero to acetaminophen (e.g., Tylenol) may be more at risk for developing ADHD. The risk is more pronounced for the children of women with psychiatric disorders, who typically use more nonprescription medications in pregnancy. Dr. Ray-Griffith's team will test whether greater exposure to acetaminophen in the womb corresponds with higher rates of psychiatric illness among mothers, greater exposure to medications as a whole, and ultimately higher rates of attention disorders. New findings could serve to refine treatment guidelines for pregnant women with neuropsychiatric illnesses.

Karen E. Seymour, Ph.D., of the Johns Hopkins University School of Medicine, will study disruptions in the regulation of emotions among children with ADHD. This research aims to identify the clinical features and brain regions involved in low frustration tolerance. Dr. Seymour's team will compare children with ADHD to children without the condition, testing their ability to tolerate frustration and their corresponding symptoms, such as difficulty focusing or anxiety and depression. Then they will use neuroimaging to probe the underlying brain circuits. They will also extend their study to children with ADHD and other psychiatric disorders.

Robert Whelan, Ph.D., University College Dublin, Ireland, studies impulsivity, a key feature of attention deficit hyperactivity disorder (ADHD). It can be measured using tests of "response inhibition," requiring a person to try and stop an already-started response. Individuals with ADHD tend to perform worse on such tests than controls. Dr. Whelan will recruit patients from an existing study of ADHD and anxiety. Using EEG he will evaluate the effects of emotion on response inhibition. By examining the timing of the resulting brain activity when participants either succeed or fail in inhibiting their responses, he hopes to gain insight into underlying neurocognitive processes.

ANXIETY

Jiook Cha Ph.D., at Columbia University will carry out a neuroimaging study in children with clinical anxiety. The long-term goal is to develop a neurobehavioral biomarker of anxiety. Dr. Cha will evaluate fear generalization, or the propensity to react with fear to stimuli bearing perceptual similarities to a conditioned stimulus, in anxious children. Dr. Cha will investigate the relationship between this disrupted functional mechanism and anxiety symptom severity in children using fMRI and physiological responses within a fear generalization task.

Jacek Debiec, M.D., Ph.D., at the University of Michigan will investigate mechanisms underlying maladaptive anxiety observed in children with anxiety disorders. Emotional trauma is one of the best known environmental risk factors for anxiety disorders. Dr. Debiec will use one of the most commonly used experimental models of emotional trauma, fear conditioning, with rodents to study the mechanisms of fear learning in infancy. He aims to contribute to the development of early preventive and therapeutic interventions that will diminish the impact of maladaptive anxiety in childhood.

Edward Korzus, Ph.D., of the Neuropsychiatric Institute & Hospital at the University of California, Los Angeles will investigate neurons in the brain's prefrontal cortex that may help prevent an animal from developing fear of harmless stimuli. He will develop new methods of studying the activity and roles of specific populations of prefrontal cortex cells during discriminative fear learning, working toward understanding the mechanisms that control the fear memory accuracy.

Sabine Krabbe, Ph.D., of the Friedrich Miescher Institute, Switzerland, will study the impact of local interneurons on sensory processing and the acquisition of fear. About 20 percent of the neurons in the brain are interneurons, which tightly control the signaling of other cells. Dr. Krabbe will investigate the actions of one class of interneurons in the brain's basal lateral amygdala, those that express vasoactive intestinal peptide, on other interneurons in fear learning circuits.

Ekaterina Likhtik, Ph.D., of Columbia University will investigate the neural circuitry that evaluates and responds to safety and threats, focusing on communication between the brain's prefrontal cortex and the amygdala, an important structure for processing threats. In experiments with mice, she will investigate whether boosting communication between the prefrontal cortex and the amygdala before fear learning or during recall of fear memories can improve animals' ability to discriminate between threatening and non-threatening stimuli. By better understanding these neural circuits, Dr. Likhtik hopes to identify new strategies for treating anxiety disorders.

Dean Mobbs, Ph.D., of Columbia University, will study how the brain responds to, learns to avoid, and gauges threat, with implication for anxiety disorders. Employing behavioral and imaging techniques Dr. Mobbs and colleagues will track the activity of emotional circuits involved in threat response and attempt to identify crucial points in brain circuits that can translate a normal threat response into symptoms of anxiety. The developed model will then be tested on anxiety patients to verify this study's efficacy in helping to characterize anxiety disorder, which manifests with a diverse range of symptoms.

Ilya E. Monosov, Ph.D., of Washington University, will investigate circuits in the brain underlying perceptions of uncertainty, which are implicated in a wide range of clinical disorders of mood and motivation. Dr. Monosov previously studied a brain region that processes and transits information about outcome uncertainty while contributing to anxiety and depression. This study will test whether signals communicating uncertainty affect emotion and behavior through connections between the anterior brain and medial forebrain. Results may reveal neural mechanisms underlying excessively negative expectations of the future, resulting from uncertainty. This has implications for disorders like anxiety and depression that involve pessimism.

AUTISM SPECTRUM DISORDER

Brendon M. Nacewicz, M.D., Ph.D., of the University of Wisconsin-Madison, will characterize neurotransmitter release in the amygdala, a brain region associated with emotional response to social interactions and implicated in psychiatric disorders that include autism and anxiety. Using a novel functional imaging technique, Dr. Nacewicz and colleagues will track these neurochemical responses to stress in relation to heart rate and pupil dilation. Their goal is to use amygdala activation to identify possible targets in the brain signaling high stress for pharmacological treatment.

Kimberly Lynn Hills Carpenter, Ph.D., at Duke University Medical Center will investigate the relationship between anxiety and a phenomenon called sensory over-responsivity (SOR). SOR is characterized by heightened and unusual reactivity to sensory stimuli, such as touch and sound. Carpenter hypothesizes that SOR reflects dysregulation in the brain systems linking sensory processing to threat appraisal and that this dysregulation is moderated by a diminished ability to (1) reduce one's response to repeated or irrelevant sensory stimuli and (2) shift attention away from sensory stimuli. Dr. Carpenter will explore this hypothesis by assessing preschool aged children with and without ASD using parental report, child observation, and EEG measures.

Daniel H Ebert, M.D., Ph.D., at Johns Hopkins University School of Medicine will investigate a genetic mutation that causes Rett syndrome, a disorder with features of autism. Major gaps in knowledge remain in understanding how this mutation regulates gene expression in the brain and how dysfunction of this gene leads to neuropsychiatric disorders. Dr. Ebert will explore a hypothesized interaction between this gene and a molecular system in the brain called the NCoR co-repressor complex. He hopes findings from this study will advance understanding of molecular mechanisms that contribute to the development of a range of neuropsychiatric disorders including autism.

Min Fu, Ph.D., at Duke University will investigate core symptoms of autism spectrum disorder: social interaction and social communication deficits. Studies have shown that the prefrontal cortex (PFC) plays a crucial role in social cognition. How PFC neurons mediate social recognition and regulate social behaviors remains largely unknown, however. Dr. Fu will record large populations of PFC neurons using a brain imaging system that allows mice to move freely (required for social interaction behaviors). Results may provide novel insights into neural substrates underlying social recognition, and how this process might be abnormally altered in mouse models of autism.

Theofanis Karayannis, Ph.D., of New York University will explore the role of the CASPR4 gene, which is often present in abnormal amounts in people with autism. He will study mice lacking one copy of the gene, as well as mice that lack CASPR4 only in specific cell types in the brain, to determine how these abnormalities affect brain activity and behavior.

Miranda M. Lim, M.D., Ph.D., of Portland VA Medical Center and Oregon Health and Science University will use prairie voles to investigate how sleep disturbances impact brain development and social functioning, to determine whether impaired sleep contributes to the brain pathology of autism spectrum disorder. Prairie voles are highly social and form lifelong pair bonds. Dr. Lim will study whether disrupting the sleep of prairie vole pups during a sensitive developmental period influences their social behavior as juveniles or pups, and evaluate the animals' brains for markers associated with autism.

Olga Penagarikano, Ph.D., of the University of the Basque Country, Spain, will study dysfunction in the release of the neurotransmitter oxytocin, which is associated with social deficits in autism and other psychiatric disorders. This project will expand on past findings revealing the social effects of oxytocin to probe how oxytocin interacts with two other neurotransmitters extensively linked to social behavior: dopamine and serotonin. Looking at brain activity in mice, the team will also examine how oxytocin and its interactions with the dopamine and serotonin systems are affected by environmental factors. They hope to help identify candidates for therapeutic intervention early in human development that may improve social deficits.

Susan B. Perlman, Ph.D., of the University of Pittsburgh, will explore the neural correlates of social reciprocity, the capacity for back-and-forth social interaction that is often impaired in autism spectrum disorders. This study will measure the correlation between brain activity in two people interacting with each other. Using the imaging technique of near-infrared spectroscopy, the team will examine activity in the medial prefrontal cortex and temporo-parietal junction—brain regions associated with social reciprocity—while children with autism interact with a parent or experimenter. The amount of speech will also be analyzed as a measure of social interaction. Dr. Perlman hopes this study will introduce new measures of interaction that can be used to test the efficacy of autism treatments, and will also point toward brain-based ASD treatments.

Tyler K. Perrachione, Ph.D., of Boston University, plans to investigate the brain bases of phonological working memory deficits in children with autism spectrum disorder. Phonological working memory refers to the skills that allow for the short-term maintenance of speech sounds in the brain. Deficits in this kind of working memory can severely impair vocabulary growth and speech perception. To investigate the physical roots of these deficits, Dr. Perrachione and colleagues will track brain activity in children with autism while they complete tasks used in the clinical diagnosis of communication impairments.

Caroline Elizabeth Robertston, Ph.D., of the Massachusetts Institute of Technology, will investigate the atypical visual perception that helps define autism. Individuals with autism report exceptionally quick, accurate perception of small details in their environments—which can also cause difficulties in filtering out redundant and conflicting visual information. Dr. Robertson's team will combine imaging and behavioral measures to expand on previous findings of a specific visual deficit in autism: a weakened ability to inhibit conflicting information perceived across both eyes. The team will test whether this deficit is linked to levels of the neurotransmitter GABA.

Stephan J. Sanders, BMBS, Ph.D., of the University of California, San Francisco, hopes to detect subtle changes in the location and size of cells during brain development to track the effects of genes that contribute to autism spectrum disorder. Genes associated with autism are present throughout the brain, shape all stages of brain development, and perform a wide range of biological functions. Dr. Sanders' team will test new methods for assessing cells affected by autism-related genes and changes to those cells throughout development. They will then use this method to study how cell location and size change in response to mutations in autism-linked genes. The team hopes to enrich our understanding of autism's causes.

Nasim Vasli, Ph.D., Centre for Addiction and Mental Health, University of Toronto, Canada, will assess 100 Iranian patients with autism spectrum disorder (ASD) and their parents, all from related-by-blood (consanguineous) marriages, in order to probe genetic causes of their disorder and to detect new autosomal recessive (AR) genes via whole-genome sequencing. In autosomal recessive diseases, two copies of an abnormal gene must be present for a disease or trait to develop. The team will attempt to further validate any AR genes in a cohort of 200 other ASD cases and their parents, to assess which of the genes are most frequently disrupted.

BIPOLAR DISORDER

Ezra Wegbreit, Ph.D., Brown University, notes that fMRI imaging studies have shown that adults with bipolar disorder (BD) have altered neural activity and connectivity compared to healthy controls in a prefrontal cortex-amygdala-striatal circuit during facial emotion perception, which is a crucial social skill. Young people with BD also show consistent neural alterations in this circuit. Dr. Wegbreit will directly compared brain behavioral alterations in BD-youths to those in BD-adults. The goal is to advance models of the developmental trajectory of BD, potentially leading to improved assessment, diagnosis, and treatment of youths and adults.

DEPRESSION

Agustin Anastasia, Ph.D., at Weill Cornell Medical College will investigate the underlying brain circuitry contributing to mood disorders observed in patients with Parkinson's Disease (PD). A certain polymorphism, or gene variation called Val66Met is thought to be associated with a higher risk of various mood disorders, such as depression and anxiety. Dr. Anastasia will examine the effects of this alteration within the brains of transgenic mice bred with this polymorphism. He hopes to show that this polymorphism leaves a person with PD more susceptible to psychiatric symptoms such as depression or anxiety.

David Bulkin, Ph.D., at Cornell University will investigate the neural underpinnings of depression with the latest optical technology to manipulate neurons. Pairing experimental molecules called calcium indicators with a lens implanted deep into the brain, Dr. Bulkin can measure the activity of neurons optically with a miniature microscope. He will focus on a brain region implicated in depression called the lateral habenula. The experiments aim to provide new insight into depression physiology.

Ramesh Chandra, Ph.D., at the University of Maryland will investigate energy homeostasis and its role in the development of depression. Previous studies demonstrate that stress, which can lead to depression, alters energy metabolism in certain brain areas. Dr. Chandra will study energy metabolism in a mouse model of depression called the chronic social defeat stress model, in which mice are either susceptible to stress and display depression-like behaviors or are resilient to stress and display no depression-like behaviors. Based on this work Dr. Chandra seeks to better understand how mitochondrial functioning is differentially altered between the two mouse models.

Revathy U. Chottekalapanda, Ph.D., at the Rockefeller University will investigate the cellular and molecular mechanisms that contribute to depression and to responsiveness to pharmacological treatments for depression. Cellular responses to antidepressants are complex and involve many distinct cell types in multiple brain regions. Cytokines are one such cell type, whose role in influencing the response to antidepressants is unknown. The research aims to better understand cytokine functioning in response to chronic antidepressant treatment, to look for cytokines that interact with known biomarkers of depression, and to validate the role of cytokines in depressive-like behavior and antidepressant responses.

Esther M. Berrocoso, Ph.D., at the University of Cadiz, Spain, will study neural mechanisms behind the relationship between chronic pain and the development of mental disorders. She will investigate a pathway between brain regions called the locus coeruleus (LC) and the anterior cingulate cortex (ACC), which is thought to be responsible for modulating chronic pain. Using a rat model of neuropathic pain, a type of chronic pain, Dr. Berrocoso aims to show that pain-induced depression can cause the functional reorganization of neuronal networks. The project also will attempt to determine whether the sensory component of pain is functionally disconnected from its psychological components.

George Dragoi, M.D., Ph.D., at Yale University's School of Medicine will investigate brain circuitry underlying a cognitive process altered in patients with depression – one by which we generate internal representations. The hippocampus is the primary brain structure involved in this process, and Dr. Dragoi has recently discovered that preconfigured hippocampal network activity called 'preplay' indicates that internal representations are integrated within a network of pre-existing knowledge. Using rats, he will investigate how these patterns are shaped by positive and negative early-life experiences and how they are affected by the experimental antidepressant, ketamine.

Fernando S. Goes, M.D, at Johns Hopkins University will use genomic sequencing to identify novel rare genetic variants that lead to depression. There have been comparatively few studies of rare genetic variation in MDD. In this study, Dr. Goes will perform genome sequencing in 40 individuals selected from 10 families with early onset, recurrent MDD. The study could identify important targets for future drug development and may stimulate larger-scale efforts aimed at identifying rare variation associated with major depression.

Olivia Engmann, Ph.D., at Mount Sinai's Icahn School of Medicine will investigate the effects of caffeine on the circadian system called CLOCK that regulates sleep. Because sleep disturbances are often observed in those with depression, the CLOCK system is also thought to play in role in modulating depression. Dr. Engmann

seeks to establish significant interactions between the caffeine-CLOCK pathway using genetic sequencing and other molecular techniques to identify new candidate molecules to target in future treatments.

Liisa Hantsoo, Ph.D., of the University of Pennsylvania will investigate how hormonal changes associated with the menstrual cycle can affect stress and reactivity to arousing stimuli in women with premenstrual dysphoric disorder. She will also investigate how treatment with selective serotonin reuptake inhibitors (SSRIs) mitigates these effects.

Poornima A. Kumar, Ph.D., of McLean Hospital and Harvard University will investigate how major depression affects the brain's ability to learn about rewards and punishments. Reduced reward learning and increased punishment learning may contribute to many of the symptoms of depression, including depressed mood, inability to feel pleasure, inability to make decisions, and excessive guilt. Dr. Kumar will investigate the neurological basis for these learning deficits with molecular and functional imaging of two brain regions involved in reinforcement learning, the basal ganglia and the lateral habenula, in individuals with and without major depression.

Tara Anne LeGates, Ph.D., of the University of Maryland School of Medicine will investigate how stress alters brain circuitry and increases the risk of depression. Dr. LeGates hypothesizes that stress weakens connections in the brain's reward circuitry and that restoring these connections is a critical for effective antidepressant therapy. She will examine how connections between two regions of the brain, the hippocampus and the nucleus accumbens, change in response to chronic stress and whether antidepressant medications strengthen those connections.

Kathryn M. Lenz, Ph.D., of Ohio State University will explore the relationship between stress in early life, brain development, and the immune system. Early life stress can trigger robust activation of mast cells—immune cells that synthesize a variety of compounds that contribute to brain development and play a role in mood disorders, including serotonin, histamine, and inflammatory cytokines. Dr. Lenz will investigate whether mast cells mediate the impact of early-life stressors on later-life vulnerability to mood disorders by regulating the permeability of the blood brain barrier and thereby altering brain development.

Byungkook Lim, Ph.D., of the University of California, San Diego will investigate the neural circuits that mediate depression-like behaviors in mice following exposure to stress. Dr. Lim will examine the anatomy and function of circuits in the ventral pallidum, a major component of the brain's reward circuitry, and evaluate how these circuits are affected by the stress of repeated social defeat. This type of stress causes behavioral changes in rodents that resemble symptoms of major depressive disorder, including impaired social interaction, lack of motivation, helplessness, and

inability to feel pleasure. Understanding how stress changes the brain's neural circuits to produce these behavioral effects could help researchers develop better treatments and diagnostic tools for major depression.

Brittany Leigh Mason, Ph.D., of the University of Texas Southwestern Medical Center at Dallas, will compare how the presence of gut bacteria affects anxiety and depression. Many individuals with mood disorders show gastrointestinal and appetite disturbances. This study will examine the relationship between gut bacteria and mood across people showing only anxiety symptoms, only depression symptoms, and symptoms of both conditions. Blood samples will be collected to test for immune factors, which are regulated by bacteria. Initial results suggest that people with depression and anxiety symptoms show a unique pattern of gut bacteria.

Bradley Ress Miller, M.D., Ph.D., of Columbia University, will use an imaging study to test the role of serotonin in emotional behavior, with implications for anxiety and depression. Serotonin levels have long been theorized to contribute to major depression, which often occurs with symptoms of anxiety. Imaging the brains of mice, this project will use imaging to track the activity of neurons that produce serotonin during emotional behavior. The team will also selectively limit the activity of these neurons. Dr. Miller expects to show that serotonin neurons are necessary for healthy emotional behavior and that stress triggers depression and anxiety by changing these neurons' activity

Veronica Musante, Ph.D., of Yale University, will expand findings on dopamine transmission in brain in mechanisms implicated in major depressive disorder. Dopamine plays a major role in reward, motor and pleasure signaling and is emanates from the striatum. Dr. Musante and colleagues will study mice to investigate a particular version of a gene that affects dopamine pathways in the striatum. They hope their project will reveal the specific role of this gene, in particular its regulators and interactions, in driving major depressive disorder.

Sarah Ordaz, Ph.D., Stanford University, will assess how levels of a mother's warmth to her child may reduce depressive episodes among adolescent girls. Dr. Ordaz's team will interview girls ages 13 to 16 for their depressive symptoms and experiences of warmth from their mothers, supplementing this information with interviews of the mothers. Over a five-month period, they will continue to track depressive symptoms while also conducting imaging scans of the teenagers' brains. These methods will allow the team to gauge how maternal warmth can mitigate depression, and whether these effects stems from activity in brain regions involved in executive control, rumination and processing the relevance of stimuli. Understanding the biological mechanisms of maternal warmth as treatment may identify biomarkers for measuring this treatment's effects and also support its overall efficacy.

Jodi Lynn Pawluski, Ph.D., of the University of Rennes, will expand on recent work suggesting that the use of SSRI antidepressants during pregnancy may negatively affect children in utero. Pregnant rats will be treated with the commonly prescribed SSRI fluoxetine (Prozac) and their offspring tested for any resulting impact on their behavior and brain activity. Some rats will be subjected to stress, to help identify the impact on offspring of a stressful environment in mothers who take fluoxetine. The researchers expect to characterize any long-term effects of SSRI exposure in utero.

Marta Pecina, M.D., Ph.D., of the University of Michigan, will investigate the neural bases of the placebo effects in depression. Many studies have found that people's symptoms of depression can improve after they use the equivalent of sugar pills. Understanding the causes of these improvements will shed light on brain chemistry that can give rise to depression symptoms, with potential impact for treatment. In this study, Dr. Pecina and colleagues will test their hypothesis that the release of opioids—chemicals with anesthetic effects—drive the placebo effect by acting on emotion centers in the brain, such as anterior cingulate cortex.

Joaquin Piriz, Ph.D., of the National Scientific and Technical Research Council (CONICET), Argentina, will test approaches to altering activity in the brain's so-called "disappointment center," with promise for treating major depressive disorder. Depression has been tied to the brain's lateral habenula (LHb), linked with disappointment because it helps assign negative value to stimuli and actions and shows increased activity when an outcome is worse than expected. LHb hyperactivity may lead to strong pessimism in depression. Dr. Piriz's team hopes to unpack LHb activity by studying its unusual function, releasing opposite kinds of neurotransmitter—one that promotes communication and another that limits it. Understanding these communication points will help in targeting LHb for novel depression treatments.

Peter Rudebeck, Ph.D., of the Icahn School of Medicine at Mount Sinai, will explore a new method for treating anhedonia, the inability to experience pleasure that is common in depression. Dr. Rudebeck and colleagues will investigate the unique brain characteristics that may give rise to anhedonia in individuals whose depression has not responded to standard treatments. They will examine the connections between part of the anterior cingulate cortex, a brain region associated with anhedonia, and two other brain regions that connect to anterior cingulate cortex. Understanding how these regions communicate to shape the experience of positive emotion may shed light on how anhedonia is reduced by deep brain stimulation.

Jonathan B. Savitz, Ph.D., of the Laureate Institute for Brain Research, will investigate whether the flu vaccine is less effective among young people with major depressive disorder. The flu vaccine is known to be less protective among the elderly, especially those experiencing psychological distress, and in some studies has also been shown less effective in stressed college students. Dr. Savitz and colleagues believe that an immune system strained by depression has trouble producing antibodies against the flu. Their team will compare stress levels, antibodies produced in response to the flu vaccine and behavioral symptoms between 40 women with depression and 40 women without the disorder. Only women will be studied because they respond more to the flu vaccine than do men. The results will help determine whether younger people with depression should forego the vaccine.

Neil Schwartz, Ph.D., of the University of California, San Francisco, will investigate brain mechanisms that control responses to negative stimuli in the environment and how they are disrupted in depression. These mechanisms are largely directed in the nucleus accumbens, a brain region that helps translate motivation into action. Dr. Schwartz and colleagues will plant electrodes in the nucleus accumbens of rats to measure the region's activity during a task with negative feedback. They will then see how activity changes as the rats learn to avoid the negative feedback. Dr. Schwartz hopes this work will lead to more targeted depression treatments.

Desiree Rosa Maria Seib, Ph.D., of the University of British Columbia, Canada, will examine how new neurons formed in the brain contribute to the ability to work for future rewards, an ability hindered by depression. To study this, the team will halt the formation of new neurons in rats. The rats will then be tested during a task in which they can either get a smaller reward immediately or a larger reward after a short delay. Preliminary results suggest that rats lacking new neurons are more likely to settle for smaller rewards. Dr. Seib's team will also test how the rats lacking new neurons cope with negative feedback and whether the addition of neurons directly contributes to motivation to work.

Marisa S.P. Toups, M.D., University of Texas Southwestern Medical Center at Dallas, seeks to untangle the relationship between stress, inflammation, tryptophan metabolism, and depression. Tryptophan metabolism is regulated by inflammatory molecules called cytokines as well as by cortisol. Dr. Toups will conduct a computerized stressor task in adults with depression. Her team will measure tryptophan, its metabolites, and other factors, before and after the stressor. They hypothesize that subjects who do not complete the stressful tasks will show greater overall activation of tryptophan metabolism than subjects who tolerate the stress. They also predict that those intolerant of the stressor will show greater increase in inflammatory cytokines and increase of downstream tryptophan metabolites thought to contribute to depression through neurotoxicity. If true, tailored therapy for a subset of depressed patients may be achieved by developing methods to alter tryptophan metabolism.

MULTIPLE DISORDERS

Todd Hancock Ahern, Ph.D., at Quinnipiac University will investigate gene-environment interactions that could result in marked differences in social behaviors. He hypothesizes that early environmental factors, such as differences in family structure, can influence the genes responsible for shaping adult social behaviors. Using prairie voles, a well-established animal model for studying sociability, Dr. Ahern aims to demonstrate how early environmental conditions affect the genes that encode oxytocin and vasopressin receptors, two molecules involved in chemical signaling systems that regulate sociality.

Samuel Alan Barnes, Ph.D., at University of California, San Diego will investigate the mechanisms underlying reward processing, which is often dysfunctional in patients with psychiatric disorders. Dr. Barnes will use optogenetics to manipulate the neuronal activity of rats while they perform a task that evaluates their reward processing skills. Dr. Barnes will manipulate activity in certain brain regions, such as the nucleus accumbens and the amygdala, which are thought to be involved in reward processing.

Anna Verena Beyeler Ph.D., at Massachusetts Institute of Technology will investigate the neural circuits responsible for encoding emotion. When predicting a certain outcome, different parts of the brain are activated depending on what kind of outcome is anticipated. For example, Dr. Beyeler has found that amygdala neurons connected to the nucleus accumbens are selectively excited during cues predicting positive outcomes whereas neurons connecting to the central part of the amygdala are excited by cues during negative outcomes. She seeks to further characterize the circuitry within the amygdala as well as study the emotional circuitry of the hippocampus.

Gwendolyn Gabrielle Calhoon, Ph.D., at Massachusetts Institute of Technology will investigate brain circuitry responsible for the ability to associate environmental cues with their outcomes and to then assign emotional value to those cues. A region of the brain called the basolateral amygdala complex (BLA) contains two separate populations of neurons responsible for encoding positive and negative values to environmental outcomes. Using optogenetics as well as electrophysiological and anatomical brain slice techniques, Dr. Calhoon seeks to explore these neuronal populations to determine how they interact with one another and neurons elsewhere to which they are connected.

Daniel Cavanaugh, Ph.D., at the University of Pennsylvania will study the circadian system and its relation to psychiatric disorders. Previous research has suggested that circadian disruption can have severe consequences, and Dr. Cavanaugh hypothesizes that this may occur in part through aberrant control of stress responses. To better understand the connection between circadian disruption, stress responses, and psychiatric disorders, Dr. Cavanaugh will determine the genes, molecules, and neuronal circuits that couple the circadian clock to behavioral outputs such as sleep and wakefulness in fruit fly models.

Catherine Christian, Ph.D., at the University of Illinois will investigate molecules that may have similar effect to benzodiazepines but are naturally occurring in the brain. Peptides called diazepam binding inhibitors (DBI) have been shown to work like benzodiazepines in some parts of the brain but not in others. Dr. Christian will use mice lacking DBI to infer the role of DBI in modulating the hippocampus, a brain structure that plays a key role in learning and cognition and that is affected in many psychiatric disorders.

Joanna Molly Dragich, Ph.D., at Columbia University will investigate how biological pathways govern the formation of white matter axonal tracts. The goal is to deepen understanding of how genes can impact cognitive function. Dr. Dragich will study genetic mutations with a gene called WDFY3 that have appeared in patients with schizophrenia and in one patient with ASD. Studying mice carrying these mutations, she hopes to elucidate the mutations' impact on brain signaling, specifically in white matter.

Monica Dus, Ph.D., at the University of Michigan will investigate how abnormal behaviors may contribute to the establishment of chronic disease. She aims to describe the molecular and neural steps involved in transforming initial abnormal behavior into a chronic maladaptive condition by studying rats' overconsumption of palatable food in the absence of hunger. The results of these experiments may reveal fundamental properties of how abnormal behavioral patterns can affect the activity of neuronal circuits and the regulated behaviors they control.

Christina Marie Gremel, Ph.D., at the University of California in San Diego will investigate the neural mechanisms behind commonly observed difficulties with decision making in people with psychiatric disorders. Patients often have difficulties making judgments about their actions and the associated consequences. Dr. Gremel aims to study the role of neurons in a brain region called the orbital frontal cortex (OFC) in goal-directed behavior in mice. Using a behavioral task that can differentiate between mice acting in a habitual or goal-directed manner, she will explore the hypothesis that increased activity in OFC neurons is necessary for goal-directed actions and that certain molecular systems can inhibit this activity.

Michael M. Halassa, M.D., Ph.D., of New York University wants to find targeted ways to treat sleep problems in people with neurodevelopmental disorders. Inadequate sleep is detrimental to mental functioning; but medications that artificially put the brain to sleep cannot enhance mental function when sleep problems are caused by brain circuit abnormalities, as they are in schizophrenia, autism, and ADHD. To better understand and treat such disorders, Dr. Halassa will investigate brain circuits that control the flow of sensory input during both sleep and waking attention.

Gretchen L. Hermes, M.D., Ph.D., of Yale University will explore the relationship between mitochondrial dysregulation and abnormal glutamate and glutamine signaling in the brain. Transmission and cycling of the neurotransmitters GABA and glutamate, processes that are implicated in a wide variety of neuropsychiatric illness, are major consumers of energy in the brain. Mitochondria support neuronal activity as suppliers of cellular energy. Dr. Hermes will use a mouse model in which mitochondrial responses to energy demands are impaired to test the hypothesis that mitochondrial dysregulation is an important cause of glutamate/glutamine signaling abnormalities in psychiatric disease.

Kathryn Leigh Humphreys, Ph.D., of Tulane University will investigate potential mechanisms through which stress in early life increases the risk of mental and physical health problems. There is evidence that high stress levels can accelerate the shortening of the protective caps at the ends of chromosomes called telomeres, a process associated with aging. Dr. Humphreys will examine the associations between early life stress and telomere length in children, and correlate these to both irritability—a common characteristic of several psychiatric disorders—and physical health.

Katherine M. Nautiyal, Ph.D., of Columbia University, hopes to delineate the roots of impulsive aggression, a key feature of psychiatric disorders such as schizophrenia, bipolar disorder, post-traumatic stress disorder, attention deficit hyperactivity disorder, and conduct disorder. A better understanding of the development of aggressive behaviour and the underlying neural circuits will promote interventions and targeted treatments for excessive aggression found in psychiatric disorders. Dr. Nautiyal proposes to study the effects of receptors for serotonin, implicated in many mood disorders. Looking at a novel model of serotonin signaling in mice, her team will map circuits involved in aggressive behaviour and contributing to a critical period in the lifespan when aggression is likely to develop.

Ramin Pashale, Ph.D., of University of Wisconsin-Milwaukee, will examine how the activity of brain cells relates to blood flow in the brain. Blood flow within the brain is disrupted in illnesses such as stroke, hypertension and Alzheimer's disease. Using the latest technology in optical brain imaging, electrophysiology, and molecular genetics, this project will focus on a possible mediator between blood flow and neuronal activity: astrocytes, the most abundant non-neuronal brain cells. The team will investigate astrocyte activity in relation to the brain's blood flow and related changes in neuronal activity.

Robert Mark Richardson, M.D., Ph.D., of the University of Pittsburgh, will study how connections in the brain allow expectations of reward or punishment to influence planned movements in ways that affect motivation. Motivation is significantly reduced in Parkinson's, a disorder that affects motion, as well as in apathy, one of Parkinson's most common symptoms. Researchers have had success treating motor symptoms in Parkinson's with deep brain stimulation (DBS). In this study, individuals with Parkinson's will be tested to see whether DBS can alter the brain activity associated with both motivated and unmotivated movements. The team also will test individuals with late-life depression that resists treatment.

Nicolas W. Simon, Ph.D., of the University of Pittsburgh, will examine the brain circuits underlying motivation in behavior, both the seeking of reward and the avoidance of predicted negative outcomes. Disruptions to motivation are found in a range of psychiatric disorders. Dr. Simon's team will investigate whether motivation is shaped by neurons that produce dopamine in the brain's ventral tegmental area (VTA), implicated in depression, schizophrenia and substance abuse. They predict that connections between the VTA and nucleus accumbens, which helps translate motivation into action, control the processing of rewarding stimuli. The processing of negative stimuli is expected to result from VTA projections to prefrontal cortex, which regulates our emotions and impulses.

Nien-Pei Tsai, Ph.D., University of Illinois at Urbana-Champaign, studies hyperexcitable brain circuit, a neurological abnormality observed in patients with various psychiatric and neurodevelopmental disorders. It is linked with clinical symptoms such as hypersensitivity to sensory stimuli, anxiety and seizures. Dr. Tsai seeks to better understand the mechanisms by which neurons fine-tune their excitability in order to develop new routes to control hyperexcitability in serious psychiatric disorders. The focus will be on an enzyme called Mdm2 and its substrate, the tumor suppressor p53, which are involved in a mechanism through which neurons reduce their excitability when they are chronically challenged by higher activities. This work has the potential to impact pharmaceutical development.

Taehong Yang, Ph.D., University of California, San Francisco, wants to know what is responsible for the striking sex differences in incidence, prevalence and outcome of many mental illnesses, including autism spectrum disorder, attention deficit hyperactivity disorder, anxiety, major depression, and PTSD. Dr. Yang looks to sex hormones such as estrogen and testosterone that differ between the sexes, which are critical for development and activation of

neural circuits underlying social interactions. This study will dissect the molecular and neural circuit control of female social interactions by estrogen. Using genetic techniques, the team will study relevant gene activity with the hope of obtaining molecular insights into how estrogen exerts control over distinct social behaviors.

Erika Yeh, Ph.D., University of California, San Francisco, will study how mutation of a protein called BRAF affects the maturation of neurons and the development of synapses, in three neuronal types linked with brain disorders. Mutations in BRAF cause cardio-facio-cutaneous (CFC) syndrome, symptoms of which include increased risk for behavioral disorders. BRAF is involved in cognitive systems, social processes, and arousal regulatory systems, which are all part of the symptomology of the five major psychiatric disorders: ASD, ADHD, bipolar disorder, major depression, and schizophrenia. Results could be useful in screening for these disorders, and in establishing underlying biological linkages between these disorders.

OBSESSIVE-COMPULSIVE DISORDER

Patricia A. Gruner, Ph.D., at Yale University will investigate problems with causal reasoning frequently observed in those with obsessive compulsive disorder (OCD). Previous research has shown that during tasks in which an individual is asked to learn causal associations, those with OCD learn them less well than their control counterparts. Gruner will use an fMRI-compatible version of these behavioral tasks to examine causal learning at the behavioral and neural level in individuals with OCD. This project aims to advance understanding of the pathophysiology of OCD and the neural bases of belief formation.

Joshua L. Plotkin, Ph.D., of the State University of New York at Stony Brook, plans to identify links between brain regions that may explain the overlap between obsessive compulsive disorder (OCD) and anxiety. One brain region associated with OCD is the dorsal striatum, crucial for action selection and habit formation, two behaviors that go awry in OCD. The amygdala also plays a major role in mediating anxiety. A direct link between these regions would suggest the possibility that anxiety influences a part of the brain deciding which behaviors to allow and which to suppress. The project will assess how the amygdala functionally connects to the dorsal striatum, and how this connection is altered in a mouse model of OCD.

POST-TRAUMATIC STRESS DISORDER

Mark Paul Brandon, Ph.D., at McGill University/Douglas Mental Health University Institute, Canada, will use optogenetics and a behavioral task with mice to determine the role of the nucleus reunions (NR) in spatial map retrieval. Previous behavioral evidence has shown that patients with PTSD have difficulty discriminating between safe and dangerous contexts. The nucleus reunions (NR), a region of the thalamus involved in a neuronal circuit connecting the prefrontal cortex and the hippocampus, is thought to contribute to the ability to discriminate between different contexts. Understanding this circuitry better would provide an important biological explanation for a patient's inability to discriminate between safe and dangerous contexts.

Nikolaos P. Daskalakis, M.D., Ph.D., at Mount Sinai's Icahn School of Medicine will investigate novel biomarkers for identifying brain changes brought about by PTSD. The hypothalamic-pituitary-adrenal axis (HPA axis) is the central coordinator of the neuroendocrine stress response and appears to be dysregulated in PTSD. Dr. Daskalakis aims to identify critical gene networks underlying HPA-axis involvement in PTSD pathophysiology. Using genetic techniques and animal modeling, he hopes to uncover a biomarker for the glucocorticoid stress hormone, which might lead to novel therapeutic targets for treating PTSD.

Diasynou Fioravante, Ph.D., at the University of California's Davis Medical Center will study the cerebellum and its role in fear processing. Fear-related disorders such as PTSD are not yet well understood. Using mouse models and optogenetic techniques, Dr. Fioravante will explore the anatomical and functional relationships between the cerebellum and amygdala-based fear networks to analyze the role of the cerebellum in learned and innate fear.

Talya Greene, Ph.D., at the University of Haifa, Israel, will explore how symptoms that emerge during trauma exposure predict symptoms that persist or emerge after the exposure. Dr. Greene's hypothesis is that ongoing trauma symptoms will predict longer term symptoms in those with and without serious mental illness. Those with serious mental illness may have a different pattern of symptoms. To explore this hypothesis, Dr. Greene will utilize traditional questionnaires as well as data gathered from electronic questionnaires sent twice daily to her subjects—people who were exposed to rocket fire between July 8 and August 26, 2014 in fighting between Israel and Hamas.

Dmitri Young, Ph.D., University of California, San Francisco, will extend an ongoing study that investigates the impact of mutations in a gene called FKBP5 and trauma on PTSD symptoms and abnormalities in the stress system response. In all, 504 adult participants who are acutely traumatized victims of interpersonal violence (e.g. sexual assault, gunshot wounds, stabbings, etc.) and are receiving mental healthcare will be studied. The aim is to further personalize mental healthcare by identifying and using biomarkers in conjunction with standard clinical data to determine treatment approaches.

Moriel Zelikowsky, Ph.D., California Institute of Technology, will use a novel mouse model of PTSD to investigate the neural circuits underlying trauma as well as trauma-induced enhancements in fear learning, elevated aggression, disrupted sexual behavior and resistance to fear extinction. The aim is to elucidate the neural circuitry that controls the fear-sensitized brain. With an estimated 18.1% of Americans afflicted with some form of anxiety disorder, understanding the sensitized brain and the specific neural circuits that control trauma-related behaviors is vital.

SCHIZOPHRENIA

Renata Batista-Brito, Ph.D., at Yale University will explore the role of regulatory brain cells known as interneurons in the development of schizophrenia. She will use mice that lack a gene that has been linked to schizophrenia, ErbB4. To assess the effects of this absent gene, Dr. Batista-Brito will use a visual task both model mice and humans with schizophrenia respond to similarly. The aim is to determine how changes in the activity of interneurons contribute to schizophrenia.

Estefania Pilar Bello, Ph.D., at Columbia University will investigate brain circuitry alterations thought to contribute to the development of schizophrenia. Previous research has shown that an excess of dopamine in a part of the brain called the striatum is linked to development of the illness. However, studies have also found a reduction of dopamine in a part of the brain called the prefrontal cortex (PFC). Using novel mouse models that have these alterations, Dr. Bello seeks to better understand if and how these opposing changes interact, if one causes the other, and what symptoms each change is responsible for.

Francois Bourque, M.D., at McGill University/Douglas Mental Health University Institute, Canada, will investigate environmental factors thought to contribute to the onset of schizophrenia. Previous research with European migrant populations has demonstrated that migrant and ethnic minority groups are at higher risk for psychotic disorders than native populations in their host country. Dr. Bourque

aims to investigate this finding by studying immigrants in a North American context. This research hopes to identify potentially preventable social and environmental exposures contributing to the development of schizophrenia.

Michael Edward Cahill, Ph.D., at Mount Sinai's Icahn School of Medicine will investigate a brain signaling pathway whose dysfunction is thought to contribute to the development of schizophrenia. Structures called dendritic spines are important for communication of brain signals between neurons; a signaling pathway known as the Rap1-Akt-mTOR pathway may be important for their proper development. Dr. Cahill will study the pathway's influence on dendritic spine development in mice and then examine how this pathway might be altered by the environment in which the mice are raised.

Alana May Campbell, Ph.D.,, University of North Carolina at Chapel Hill, is studying interactions between two kinds of symptoms in schizophrenia: problems in interpreting emotional content (affect) and deficits in cognition. Using EEG, her team will characterize neural electrophysiological measures of executive-affective interactions across multiple domains of executive functioning and across both positive and negative emotional responses. The team will relate these to clinical symptoms and their severity in patients, and will analyze the brain circuits underlying these phenomena. The ultimate aim is to devise new and more effective treatment strategies.

Francesco Errico, Ph.D., at Ceinge Biotecnologie Avanzate, Italy, will investigate a novel biomarker of antipsychotic drug activity. Previous research has shown that reduction of D-asparate is linked to impaired brain activity in those with schizophrenia. Dr. Errico has found that an enzyme which breaks down D-asparate, called DDO, is modulated by second-generation antipsychotic medication. Dr. Errico aims to demonstrate antipsychotic-dependent changes in D-aspartate levels in mice that overexpress DDO in order to provide evidence for a novel biomarker of antipsychotic activity.

Ragy R. Girgis, M.D at Columbia University will assess the timing of brain changes that occur during a period before the onset of schizophrenia known as clinical high risk (CHR). A large body of evidence suggests that increased dopamine transmission in the associative striatum (AST) is a key pathophysiological phenomenon in schizophrenia. What is unknown is whether dopamine abnormalities outside the striatum co-occur, precede, or follow dopamine dysregulation in the striatum, especially during the CHR. Using PET imaging techniques, Girgis' research will provide insight into this question.

Jill R. Glausier, Ph.D., at the University of Pittsburgh will investigate underlying mechanisms of working memory in order to identify novel therapeutic targets for patients with schizophrenia. Working memory is a core cognitive function impaired in schizophrenia that depends upon activation of prefrontal cortex (PFC) circuitry. People with schizophrenia show reduced PFC activation while performing working memory tasks. The underlying cellular and circuitry alterations must be determined in order to identify therapeutic targets. This research focuses on determining whether reduced excitation in a key neural microcircuit for cognitive processes such as working memory contributes to lower PFC activation in schizophrenia.

Jacob Gratten, Ph.D., at the University of Queensland, Australia, will investigate the hypothesis that sex differences in gene expression underlie sex differences in major mental disorders. Based on observations that there are more cases of schizophrenia in men and more cases of depression in women, Dr. Gratten proposes that there may exist male-specific and female-specific genetic risk factors for each disorder. To explore this he will perform statistical analysis on several genomic databases. Elucidating the mechanisms responsible for sex differences in schizophrenia and major depression will improve understanding of disease etiology for these disorders, and may point to general mechanisms that apply to other mental disorders.

John A. Gray, M.D., Ph.D., at the Davis Medical Center of the University of California will investigate the role of two molecules, glycine and D-serine, in glutamate neurotransmission during development in young mice. Abnormalities in glutamate neurotransmission have been implicated in the pathophysiology of schizophrenia, particularly deficiencies in NMDA-type glutamate receptors. Unique to NMDA receptors is the fact that they require glycine or D-serine to activate. By replacing normal NMDA receptors with mutant ones, Dr. Gray seeks insight into the normal function of glycine and D-serine toward the end of developing new therapeutic drugs that target this binding site.

Stephanie Mary Groman, Ph.D., at Yale University's School of Medicine will investigate the neural mechanisms underlying decision-making impairments in schizophrenia. Two types of learning systems, the model-free and model-based systems, are thought to allow for regular decision-making abilities. Dopamine alterations in schizophrenia may disrupt the model-based system, but this hypothesis is difficult to test. To work around limitations, Dr. Groman will use a whole-brain neuroimaging system in a neurodevelopmental animal model of schizophrenia while assessing the animal's model-free and model-based learning abilities.

Marc Aaron Heiser, M.D., Ph.D., of the University of California, Los Angeles will examine a brain network called the mirror neuron system in people who are at increased risk for developing schizophrenia. The mirror neuron system is believed to be important for facilitating social behavior and social emotions such as empathy. Dr. Heiser hypothesizes that diminished mirror neuron activity contributes to social problems that affect people in this high-risk group, as well as people who have been diagnosed with schizophrenia.

Jonathan D. Hommel, Ph.D., of the University of Texas Medical Branch at Galveston will investigate a potential cause of cognitive deficits in schizophrenia. He believes that overactive serotonin receptors in the brain's memory center, the hippocampus, contribute significantly to these symptoms. He will use animal models to determine whether reducing signaling from the 5-HT7 serotonin receptor restores normal levels of neurotransmitters in the hippocampus and improves memory.

Shantanu P. Jadhav, Ph.D., of Brandeis University will investigate the physiological interactions between the brain's hippocampal and prefrontal cortex regions that support learning and memory-guided behavior. The two structures are important for different aspects of memory formation, storage, and retrieval, and impaired hippocampal-prefrontal interactions have been implicated in neurological disorders related to cognition, including memory disorders and schizophrenia.

Abigail Susan Kalmbach, Ph.D., of Columbia University will investigate how changing the firing patterns of dopamine-producing neurons affects how cells release and respond to the neurotransmitter. She will also explore in mice whether dopamine signaling deficits can be reversed in adulthood. Defects in dopamine signaling are a potential cause of cognitive symptoms in patients with schizophrenia, and better understanding those defects could help researchers identify potential avenues for treatment.

Said Kourrich, Ph.D., of the University of Texas Southwestern Medical Center at Dallas will look for cellular and molecular alterations that contribute to psychosis in people with schizophrenia. Some studies have suggested that hyperactivity of cells in the hippocampus, a brain region critically involved in learning and memory, may play a key role in the development of psychosis. Dr. Kourrich will use a mouse model to investigate the physiological consequences of molecular alterations in the hippocampus that are associated with psychosis.

Viviane Labrie, Ph.D., of the Centre for Addiction and Mental Health, University of Toronto, Canada, will investigate whether sequence changes and epigenetic disturbances that affect genetic enhancers alter brain function to cause schizophrenia. Enhancers are regulatory segments of DNA that influence when and where genes are turned on. Dr. Labrie will examine enhancer regions where sequence changes have been associated with schizophrenia, surveying differences in the chemical marks that influence gene activity. By determining what genes are affected by abnormally regulated enhancers in schizophrenia, she will shed light on biological pathways that may be disrupted in people with the disorder.

Hanmi Lee, Ph.D., of Stanford University will explore the link between immune molecules and neurological dysfunction in schizophrenia. Genetic studies have found that abnormalities within genes for immune molecules called human leukocyte antigens (HLAs), which play central roles in tissue rejection responses as well as during infection, are common among people with schizophrenia. Dr. Lee will investigate the role these immune molecules may play in remodeling connections between neurons during a critical period of brain development.

Makino, Ph.D., of the University of California San Diego, is studying how we form perceptions of the environment, with implications for hallucinations experienced in schizophrenia. Perception results from both "bottom-up" processes that involve processing external information, and "top-down" processes projecting our expectations onto the world. Some researchers believe that learning is what shifts bottom-up processing to top-down. Using advanced imaging techniques and optogenetics to alter and measure activity in mouse brains, Dr. Makino and colleagues will test this claim by looking at the response of visual neurons to both processing types. They will then extend their investigations to hallucinations, by examining whether sensory expectations alone can create false visual perceptions in the mice, even in the absence of external stimuli.

Amanda McCleery, Ph.D., of the University of California Los Angeles, will probe brain mechanisms that may give rise to cognitive symptoms in schizophrenia. Cognitive impairments include deficits in basic thought processes, such as being able to remember new information temporarily. Researchers have proposed that these impairments result from abnormalities in cortical plasticity. Using a new method for testing electrical activity in the brain, Dr. McCleery and colleagues will test whether cortical plasticity truly is disrupted in schizophrenia and whether phenomena associated with plasticity, like learning and memory, are also affected.

Alex S. Nord, Ph.D., of the University of California, Davis, aims to improve diagnosis and treatment of schizophrenia by studying epigenetic factors contributing to the condition. Schizophrenia is believed to result from the interaction of environmental and genetic factors. Dr. Nord and colleagues will look at the activity of genes in fetal mice and also profile the activity of their frontal cortex after they are exposed to maternal immune system activity in utero, a response to stress. Their hope is to determine how that immune activity drives genetic changes in ways that contribute to schizophrenia, to identify possible biomarkers for diagnosing the illness and potential drug targets for treatment.

Gaurav H. Patel, M.D., Ph.D., of New York State Psychiatric Institute/Columbia University, plans to uncover how activity across different communication networks in the brain contribute to the social deficits experienced in schizophrenia. To improve our understanding of the underlying brain activity, Dr. Patel and colleagues will study the activity in areas that direct attention and face processing—both important for social interaction—among schizophrenia patients watching film clips of social encounters. Dissecting brain function during social behaviors will help characterize deficits in social interaction skills across different psychiatric conditions, paving the way for more targeted treatments.

Albert R. Powers, M.D., Ph.D., of Yale University, hopes to connect the neural activity underlying hallucinations experienced in schizophrenia to the actual experience of hallucinations. In previous research, his team found that people with schizophrenia may be particular vulnerable to conditioned hallucinations, or the experience of phantom stimuli in response to associated real stimuli. To understand this aspect of schizophrenia, this project will identify behavior linked to hallucinatory experiences and connect that behavior to brain and clinical measures of hallucination severity. This work may form the basis for tests to identify and help treat different types of hallucination, perhaps manipulating forms of stimulation, inhibition and feedback to relevant brain circuits.

Matthew David Puhl, Ph.D., of McClean Hospital/Harvard University, will investigate elevated levels of certain chemicals in the brain associated with schizophrenia. Previous research has found high levels of the neurotransmitters glutamate, which promotes communication in the brain, and GABA, which inhibits communication. Dr. Puhl's team seeks to distinguish whether these elevated levels are the result of more being produced or unique patterns relating to their degradation after being released in the brain. These studies will lead to a better understanding of changes in brain chemistry during schizophrenia, potentially identifying novel targets for treatment and biomarkers that may help diagnose the disease.

Stephen Ripke, M.D., Ph.D., of Charite—University Medicine Berlin, Freie Universitat Berlin, Germany, will use genome-wide association study to help identify the origins of schizophrenia. Collecting data from large samples—2,500 individuals with schizophrenia and 2,500 without—Dr. Ripke will look for gene variants that appear to correlate with schizophrenia, lending insight into the genetic basis for the illness. He will further evaluate the influence of especially unusual gene sets that show an association with schizophrenia, to understand how these pronounced cases of genetic variety contribute to the illness' development.

Antonio Sanz-Clemente, Ph.D., of Northwestern University, will investigate changes in the molecules at communication points between neurons that contribute to cognitive symptoms in schizophrenia. To study this, Dr. Sanz-Clemente's team will use drugs to induce cognitive impairments among rats. They will then examine the rat brains for any effects of cognitive symptoms on proteins at communication points between neurons, any redistribution of these points, and changes to the chemical structures driving communication. The team will further analyze the effects of haloperidol and lurasidone, two drugs used to treat schizophrenia. They hope that their findings relating to molecular changes in the brain will help identify new drug targets for treating cognitive deficits.

Jeffrey N. Savas, Ph.D., of Northwestern University, will examine molecular at synapses between neurons that are associated with schizophrenia, as well as how these are affected by the antipsychotic medications often used to treat the illness. Using advanced technology to examine proteins at synapses, the team will study the effects of phencyclidine (PCP). It is used to model cognitive deficits associated with schizophrenia because it reduces activity at NMDA receptors in the brain, crucial for learning and memory. Using PCP to simulate schizophrenia, Dr. Savas' team will study protein activity, any changes to that activity caused by the antipsychotic medication lurasidone, and any related behavioral effects. This work may shed light on the physiological causes of schizophrenia.

Shushruth Shushruth, M.B.B.S., Ph.D., of Columbia University, will investigate deficits in cognitive performance associated with schizophrenia and other disorders. Dr. Shushruth and colleagues propose that a cause of such deficits is the failure of calculations made in association cortex, brain regions that shape our associations between sensory experiences. The team will test the cognitive effects of controlling activity in different regions of association cortex in primates. They hope this approach will not only allow more detailed study of the causes of cognitive impairments, but will also lay the foundation for treating impairments.

Katharine Natasha Thakkar, Ph.D., of University Medical Center Utrecht, Holland, seeks to understand at the biological level a feature of schizophrenia and psychosis long observed in the clinic, involving disturbances to the patient's sense of self. She theorizes that a match between anticipated and actual sensory events following an action engenders a sense of agency—and that a mismatch causes the subjective experience that sensations are caused by an external agent (a frequent claim in hallucination and delusion). fMRI imaging will be used to determine regions that are differentially involved in generation or transmission of corollary discharge signals in schizophrenia patients, focusing on the mediodorsal thalamus. Diffusion tensor imaging and magnetization transfer imaging will be used to investigate microstructural abnormalities in thalamo-cortical pathways.

Marie-Eve Tremblay, Ph.D., Laval University, Quebec, Canada, will investigate the implication of basic neuroimmunological mechanisms in the development of neurodevelopmental disorders. State-of-the-art imaging of microglia and synapses will be performed across development, adolescence and adulthood in mouse models of prenatal infection, a major environmental risk factor for neurodevelopmental disorders. Changes in microglial functions and their consequences on the maturation of neuronal circuits will be correlated with the developmental trajectory of behaviors relevant to either autism spectrum disorders or schizophrenia. This work will provide fundamental insights into the roles of microglia-synapse interactions, and new evidence regarding their vulnerability to environmental risk factors.

Christiaan H. Vinkers, M.D., Ph.D., University Medical Center Utrecht, Holland, has developed a new method to measure glutamate levels across the brain in unprecedented detail. To shed light on the longstanding theory that glutamate dysfunction plays a causal role in at least some fraction of schizophrenia, Dr. Vinkers will look for distinct and local changes in glutamate throughout the brain in schizophrenia patients. The project will compare high-resolution data about glutamate levels in patients and healthy controls. In patients, glutamate levels also will be related to severity of psychotic and cognitive symptoms as well as brain connectivity.

Gemma Margaret Williams, MBBCh, Cardiff University, UK, notes that high-frequency oscillatory activity in the brain is required for cognitive processing and is impaired in patients with schizophrenia performing cognitive tasks. She will use an electrical recording method called magnetoencephalography (MEG) to see if abnormal oscillatory activity in the brain can provide a link between impaired sensory processing and cognitive function in schizophrenia and neurochemical hypotheses of how the illness is caused. Specifically, she will test the theory that patients with rare genetic changes affecting pathways for neurotransmitters GABA and glutamate will display altered neural synchronization, as measured by MEG, as compared to those with rare genetic changes that don't hit these pathways as well as controls without any rare genetic changes.

Ki-Jun Yoon, Ph.D., Johns Hopkins University, has developed mouse models that enable the study of a type of genetic mutation seen in autism and schizophrenia. The mutation involves extra copies or missing copies of DNA in a region of chromosome 15 called 15q11.2. One gene within this region is called CYFIP1. The model mice show the effects of gaining or losing copies of this gene. The project aims to demonstrate the impact on neuronal development, neural systems and behavior. This could provide molecular insights into the functional roles of CYFIP1 as a factor in neuropsychiatric disorders.

OTHER DISORDERS

ANOREXIA NERVOSA

Summer Fontaine Acevedo, Ph.D., at the Southwestern Medical Center of the University of Texas in Dallas hopes to show that a certain protein in the brain that is important for social functioning, the oxytocin receptor, could serve as a useful biomarker for those suffering from Anorexia Nervosa (AN). Dr. Acevedo will study the gene that encodes for the oxytocin receptor by comparing the gene's level of expression, or activity, with the gene's level of methylation, chemical "tags" that suppress activity. Dr. Acevedo hopes to show that these expression and methylation levels correspond to the severity of AN symptoms, specifically, limited social functioning abilities.

EATING DISORDERS

Elisa S. Na, Ph.D., of the University of Michigan, aims to improve treatment of childhood obesity by investigating the neurobiological mechanisms that drive the condition. In particular, her team will examine the developmental trajectory of early onset obesity as a consequence of alterations to maternal diet, looking at changes to dietary patterns among children as a result of exposure to high fat and high calorie food while they are still in the womb. This study will identify interactions between genetic predisposition to obesity and in utero environment to broaden our understanding of childhood obesity, paving the way for appropriate pharmaceutical treatments.

"The Foundation believes that scientific breakthroughs come from encouraging people to think outside the box. By having the best scientists in the field select the most promising research projects to fund, the Foundation has consistently sponsored research that has led to important advances to improve the lives of those with mental illness."

ERIC KANDEL, M.D.
Nobel Prizewinner and Scientific Council Member

NEW TECHNOLOGIES

AUTISM SPECTRUM DISORDER (ASD)

Kwanghun Chung, Ph.D., at Massachusetts Institute of Technology will utilize a new genetic manipulation technique called CRISPR to better understand how the brain's architecture, neuronal connectivity, molecular machinery, and genomic network bring about mental function. Chung aims to overcome certain limitations of CRISPR technology and will use it on mouse brains to ask how genes associated with autism spectrum disorder cause functional, structural, and molecular abnormalities in a cell-type and brain region-specific manner.

DEPRESSION

Priti Balchandani, Ph.D., at Mount Sinai's Icahn School of Medicine aims to overcome current limitations on 7T (Tesla) MRI imaging. MRI machines operating with the power of 7T are able to image finer and more subtle abnormalities in brain regions known to be affected by psychiatric disease. But these machines still have physical and technical limitations. In this study, Dr. Balchandani hopes to construct an MRI procedure that overcomes these limitations while capturing key differences in the brains of those suffering from major depressive disorder (MDD).

George M. Slavich, Ph.D., of the University of California, Los Angeles, will study how neuronal activity and the immune system may be associated with depression risk and stress response in adolescent girls. Dr. Slavich's team will use cellular reprogramming to generate functional neurons using blood samples from girls aged 12 to 15. Half of these girls will have a biological mother with depression but no history of psychiatric illness themselves, and the other half will have no personal or maternal history of mental illness. Thus the team will be able test how the neurons they create respond to immune system chemicals in girls at higher risk for depression, compared to girls at lower risk. The girls' moods will also be measured, in order to assess how any depressive symptoms they experience relate to neuronal activity.

Mariano Soiza-Reilly, Ph.D., of INSERM, France, will study the development and maturation of neural pathways connecting the medial prefrontal cortex (mPFC) and the dorsal raphe nucleus, which are involved in stress and emotional responses and are impaired in mood disorders. Does dysregulation of this process contribute to vulnerability to stress and mood disorders? The team will use a new technique called array tomography along with in utero electroporation to selectively visualize and manipulate the activity of neural circuits. This may provide new insights into the possible role of mPFC neurons in the developmental origins of stress-related and mood disorders and will provide a plausible neural substrate for developing preventive tools and therapeutics.

Amber Leaver, Ph.D., of the University of California, Los Angeles will develop strategies for improving the effectiveness of neurostimulation therapies for brain disorders by tailoring the placement of electrodes to individuals' unique brain anatomy. Her studies will determine how variations in electrode placement affect therapy-stimulated brain activity during transcranial direct-current stimulation of the dorsolateral prefrontal cortex, which is used for the treatment of major depressive disorder.

MULTIPLE DISORDERS

Renato Pollmanti, Ph.D., of Yale University, will apply an innovative technique to understand genetic predisposition to psychiatric disorders. Analysis known as genome-wide association studies (GWAS) have helped researchers identify which gene variants may give rise to different psychiatric disorders. This proposal will expand on these studies by introducing evolutionary analysis to the GWAS approach, examining how evolution across the human genome may contribute to attention deficit hyperactivity disorder, bipolar disorder, major depressive disorder and schizophrenia, or multiple disorders. After identifying genes associated with psychiatric illness, the team will investigate pathways related to any significant interactions between these genes.

Daniel Schmidt, Ph.D., of the University of Minnesota, hopes to develop new ways of exploring the molecular and cellular mechanisms that underlie brain cell activity. Researchers transfer certain genes into brain tissue to alter and measure the activity of different types of neurons. Dr. Schmidt's team plans to expand on techniques for doing this by introducing a method that targets neurons based on their receptors and the channels that regulate their electrical activity. This new method would allow for more specific genetic manipulation of neuron types, expanding researchers' tools for understanding how neurons communicate. In turn, a better understanding of neuron activity will help in identifying how that activity gets disrupted in a range of psychiatric disorders.

POST-TRAUMATIC STRESS DISORDER (PTSD)

Tracy A. Butler, M.D., at New York University School of Medicine will use a new type of PET scanning that identifies deposition of the protein tau in neurofibrillary tangles in the brain. The second most common disease due to tau accumulation is called chronic traumatic encephalopathy (CTE). A recent finding suggests that many CTE cases in young patients is misdiagnosed as PTSD. Dr. Butler aims to use tau PET scans to identify individuals misdiagnosed with PTSD who are actually suffering from CTE.

SUICIDE PREVENTION

Megan Lee Fitzgerald, Ph.D., at Columbia University will utilize stem cell technology to study postmortem brain tissue of those whose depression ultimately led to suicide. Human induced pluripotent stem cells (hiPSCs) can be generated from postmortem tissues, and neurons developed from these hiPSCs would allow direct examination of the equivalent of mature cells from people who died by suicide. Brain tissue will be taken from nine matched pairs of suicides and controls. Dr. Fitzgerald hopes these studies might contribute to a more complete portrait of the biological correlates of depression and suicide.

SCHIZOPHRENIA

Jose Alejandro Cortes-Briones, Ph.D., at Yale University will evaluate a method for estimating relapse risk for patients with schizophrenia. 80-90% of patients have one or more relapses within five years of their first schizophrenic episode; therefore, searching for a reliable biomarker capable of detecting changes in brain activity indicative of an increase in relapse risk would be invaluable. Dr. Cortes-Brione seeks to demonstrate that an electroencephalography (EEG) measure called the Lempel-Ziv complexity, which measures the amount of neural noise occurring in the brain, might serve as a useful estimate of relapse risk. He will study 30 patients with schizophrenia aged 18-45 years who will be assessed four times over a two year period.

Erik Michael DeBoer, Ph.D., at the University of Pennsylvania will utilize innovations in stem cell technology to explore brain connectivity deficiencies observed in those with schizophrenia. Newly developed technology allows stem cells to be generated from the skin of patients of neuropsychiatric ailments and then rapidly converted into cortical neurons. Dr. DeBoer will take advantage of this technique to study stem cell-derived neurons from patients with the most common genetic cause of schizophrenia, called 22q11.2 deletion syndrome.

Edmund Lalor, Ph.D., of Trinity College Dublin, Ireland, will investigate two new electroencephalogram (EEG) methods that he has developed to monitor the activity of visual processing systems in the brain that may be dysfunctional in people with schizophrenia. The new EEG methods offer greater precision and control than traditional approaches, and Dr. Lalor hopes to use them to uncover the neural mechanisms that underlie specific visual processing deficits often experienced by people with schizophrenia. That, in turn, could help identify new targets for drug development.

Aviv Abraham Mezer, Ph.D., of Hebrew University, Israel, will investigate the role of white matter abnormalities in people with schizophrenia. White matter in the brain encompasses connections that transmit signals, and researchers have long proposed that schizophrenia is caused by disrupted connectivity. Dr. Mezer's project will use a new imaging technique to collect new insights on white matter pathways, how they change in relation to each other, and whether all these features correspond with certain genetic variations. He hopes this project will lead to improved techniques for analyzing white matter, with possible implications for a range of psychiatric conditions.

OTHER DISORDERS

FRAGILE X

Manish Saggar, Ph.D., of Stanford University, will use a new approach in understanding the brain activity underlying fragile X syndrome, an inherited vulnerability of the X chromosome that typically leaves children mentally disabled. Working with data from individuals with and without fragile X syndrome, his team will attempt to improve current imaging technologies used to study resting state activity in the brain. Identifying patterns of resting state activity linked to fragile X syndrome may point toward biomarkers. Further, the team will study transitions between processes in the brain during resting states to see if these transitions also mark conditions-- for example, if "rapid" transitions reflect attention-based disorders, while unsuccessful transitions may characterize depression.

"Research generates more questions than answers, as it should, and it has become my defining characteristic. That statement is no less true today than it was when I began as a medical student at Yale."

HERBERT MELTZER, M.D.
Foundation Scientific Council Member
Chair, Young Investigator Grant Selection Committee

NEXT GENERATION THERAPIES

ADDICITON/SUBSTANCE ABSUSE

David Louis Pennington, Ph.D., of the Northern California Institute for Research and Education, University of California, San Francisco, aims to improve the treatment of veterans who consume alcohol at hazardous levels. His team will examine the efficacy of Alcohol Approach Bias Modification (AABM), a training technique aimed at reducing people's motivation to acquire and drink alcohol. AABM will be tested for effectiveness in reducing alcohol approach and use, and in reducing or reversing neurocognitive deficits associated with alcoholism. Positive results will support adding AABM to more widespread treatments for individuals with alcohol addiction and the cognitive, emotional and behavioral impairments with which they struggle.

James J. Prisciandaro, Ph.D., of the Medical University of South Carolina, will conduct research aimed at simultaneously treating substance abuse and bipolar disorder, conditions that often co-occur and together produce worse outcomes than either disorder alone. Both have been linked to dysfunction of the prefrontal cortex (PFC), which directs cognitive control and planning of behavior. These findings have led to the model Dr. Prisciandaro plans to test—that abstinence from alcohol and/or drugs can restore the PFC in ways that also treat bipolar disorder. Imaging will be used to test for this PFC improvement, reflected by activity of the neurotransmitter glutamate.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

Merideth Alice Addicott, Ph.D., at Duke University aims to improve treatment for those with ADHD by improving doctors' ability to identify a specific subtype of the disorder caused by problems with the dopamine system. She seeks to evaluate the diagnostic ability of a behavioral test called the 6-armed bandit task (6ABT). Dr. Addicott will test subjects with and without ADHD using 6ABT and will then test these subjects again when they are taking either a placebo or methylphenidate, the most commonly prescribed ADHD medication. Addicott hopes to use these results to relate the behaviors observed in the test to ADHD symptomatology, dopamine function, and medication efficacy.

Hadi Hosseini, Ph.D., of Stanford University will test a treatment designed to improve executive function such as working memory and mental flexibility, in individuals with ADHD. Dr. Hosseini will evaluate effects of the intervention, which integrates neurofeedback with cognitive rehabilitation, on neural networks associated with executive function as well as on children's behavior. Validation of the technique could provide a foundation for improving executive function in a variety of disorders, including major depressive disorder and autism spectrum disorders.

ANXIETY

Dylan Grace Gee, Ph.D., at Weill Cornell Medical College will investigate a core feature of anxiety disorder observed in children and evaluate a novel therapeutic approach to ameliorating it. Children with anxiety disorders have been observed to have difficulty identifying when situations that have been experienced as threatening in the past are no longer dangerous. This research will test the efficacy of a kind of learning called safety signal learning as a novel method of fear reduction. Dr. Gee will adapt a paradigm used in animal studies to test the efficacy of safety signals across development in healthy children and adolescents, and in those with anxiety disorders.

Catherine Alexandra Hartley, Ph.D., of Weill Cornell Medical College will study whether active coping can alter fear-related brain networks and help adolescents regulate fear. The primary behavioral treatments for anxiety disorders are exposure therapies, which desensitize fear associations through repeated passive exposure to a fear-eliciting stimulus, but these therapies may be less effective during adolescence. Learning to exert control over a feared stimulus may be an alternative strategy for mitigating subsequent fear.

Emily Sue Kappenman, Ph.D., of the University of California, Davis Medical Center will investigate an emerging brain stimulation technology known as transcranial direct current stimulation (tDCS) as a potential treatment for anxiety. Her laboratory has shown that tDCS can modulate neural signatures of error monitoring, a brain process that is significantly elevated in anxious individuals. She now plans to characterize the mechanisms of tDCS-induced modulations in error-related brain activity and examine the role of tDCS in modulating that activity in a model of anxiety.

Stephen Eric Nybo, Ph.D., of Ferris State University, will pilot a new method for engineering E. coli bacteria to aid in the production of a new medication to treat anxiety and stress. Valerenic acid has shown promise as an anti-anxiety and sedative compound that affects the transmission of GABA, the chief neurotransmitter that inhibits communication in the brain. But this acid cannot be efficiently produced by current synthetic methods. Dr. Nybo's team hopes to use genetic and engineering techniques to produce compounds with chemical profiles similar to valerenic acid, paving the way for new drugs to treat stress and anxiety by targeting GABA activity.

Lauren M. Osborne, M.D., of Johns Hopkins University, will investigate the relationship between the immune system and anxiety levels among pregnant women. Looking at women with and without anxiety disorder, Dr. Osborne and colleagues seek to determine if symptoms of obsessional anxiety in pregnancy correspond with changes in immune system function. They will also test whether those changes correspond with levels of the important hormone progesterone and its metabolites. Cognitive behavioral therapy will be tested as a possible treatment for anxiety during pregnancy that, accordingly, resolves abnormal immune response.

Laura Sagliano, Ph.D., of Second University of Naples, Italy, will evaluate the effectiveness of an innovative treatment for anxiety and obsessive compulsive disorders (OCD) called transcranial direct current stimulation (tDCS). Dr. Sagliano's team will use tDCS to modulate activity in prefrontal cortex, which is believed to have reduced activity in anxiety and OCD and so decrease an avoidance of threatening stimuli. They will test the ability of tDCS to lower the amount of attention paid to threat, compared to the therapeutic effects of general cognitive training and attention-focused training. This project, they hope, will help establish procedures for detecting early symptoms in, treating and preventing anxiety and OCD.

Simona Scaini, Ph.D., of San Raffaele Vita-Salute University, Italy, will develop non-invasive tools to recognize emotional reactivity among children with anxiety symptoms compared to children without anxiety. Children with and without anxiety, as well as the children of adults with anxiety disorders, will view emotional expressions while having their own facial expressions and physiological responses recorded. Dr. Scaini's team will analyze this data and compare it to questionnaires and clinical examinations of the children's emotions, to see where bodily reactions and reported emotions match up with the observations or self-reports. Their goal is to translate these match-ups into a reliable clinical tool for assessing patients' description of their emotional states against their body language, adding another layer of information to inform treatment.

Shari A. Steinman, Ph.D., of New York State Psychiatric Institute, Columbia University, will test a new way of reducing return of fear following cognitive behavioral therapy (CBT). This will be the first test of a novelty-facilitated extinction paradigm vs. a standard extinction paradigm. 80 patients with pathological anxiety will take part, half receiving standard therapy and half the new therapy. If novelty-facilitated extinction similarly affects those with pathological anxiety as it does healthy people, this study will be the foundation for research evaluating effects of adding novelty to exposure therapy (e.g., pairing a tarantula with a surprising, novel stimulus during exposure treatment for spider phobia, as opposed to pairing a tarantula with the absence of a negative outcome).

Richard Michiel van Rijn, Ph.D., Purdue University, seeks to determine the exact manner by which a signaling protein called β-arrestin assists in the modulation of anxiety and depression, knowledge that may help in developing novel therapeutics for those disorders. The project will investigate how β-arrestin-induced signaling

can reduce anxious behavior in mice. To isolate the functional relevance of the β-arrestin signaling pathway in living animals, the team will use so called designer receptors that can only exclusively be activated by designer drugs (DREADDs).

AUTISM SPECTRUM DISORDER (ASD)

Marta Biagioli, Ph.D., at the University of Trento, Italy, will investigate a novel gene therapy for autism spectrum disorder (ASD). A genetic mutation causing a reduction of a protein called CHD8 has been shown in several studies to be linked to ASD. Dr. Biagioli aims to develop innovative RNA tools to increase CHD8 expression and reverse alterations observed in both cellular and animal models of ASD.

Julien Christian Roger Dubois, Ph.D., at California Institute of Technology will seek out neural markers for ASD, specifically markers for the altered social functioning. Using extensive fMRI analysis, Dr. Dubois will image subjects with and without ASD before and after they undergo a 14–16 week-long social skills training program. Dr. Dubois hopes measurements from this study can be used to better diagnose and predict treatment outcomes in ASD.

BIPOLAR DISORDER

Alexis Estelle Whitton, Ph.D., Maclean Hospital/ Harvard University, studies bipolar disorder. Her current research seeks to get at one of the reasons for the documented delay between symptom onset and diagnosis, which is over 10 years, on average. It concerns recognizing hypomanic behavior—less than fully manic, but marked by talkativeness, great energy and expressions of great confidence. Such episodes sometimes predict full blown mania and onset of BDP. Dr. Whitton has used scalp-recorded EEG to differentiate people with BD from those with unipolar major depression. This project uses fMRI and MRS (magnetic resonance spectroscopy) imaging to elucidate the underlying molecular and neural mechanisms contributing to these scalp-recorded differences—to improve diagnosis of both depression and BPD

DEPRESSION

Melynda Diane Casement, Ph.D., at the University of Pittsburgh will study the relationship between chronic inflammation and depression in young women with moderate to severe depressive symptoms. Research suggests that inflammation might contribute to depression by damaging brain regions that allow us to feel pleasure or accomplishment. Dr. Casement will explore this by experimenting with the women's sleep conditions. She hopes to show that sleep extension might serve as a low-risk intervention that could reduce inflammation, improve pleasure-related brain function, and decrease symptom severity in young women with moderate to severe depressive symptoms.

Evangelia G. Chrysikou, Ph.D., at the University of Kansas aims to better understand transcranial direct current stimulation (tDCS) as a noninvasive and painless neuromodulation method for treating depression. Using proton magnetic resonance spectroscopy, a technique that measures metabolic function in the brain, and functional magnetic resonance imaging, a technique measuring brain activity, Chrysikou seeks to identify the changes in brain chemistry and neural activity induced by tDCS.

Laura K. Fonken, Ph.D., at the University of Colorado will investigate late-life depression. Little is known about how late-life depression develops. Based on previous research, Dr. Fonken hypothesizes that immune system hyperactivity due to the effects of aging contributes to the development of late-life depression. A molecule called HMBG1 is known to stimulate immune cells, so to further understand the role of HMBG1, Dr. Fonken will test an HMBG1 inhibitor as a potential therapy.

Brian M. Iacoviello, Ph.D., of the Icahn School of Medicine at Mount Sinai has developed a cognitive training program to enhance the control of emotional information processing. Preliminary studies have found that the training program, called the Emotional Faces Memory Task, can reduce the symptoms of major depression. Dr. Iacoviello will now investigate the effects of the training on brain circuits that process emotional information.

Dawn F. Ionescu, M.D., of Massachusetts General Hospital and Harvard University will investigate the mechanism by which the drug ketamine decreases depression in anxious depression patients. She will measure how ketamine affects activity of the insula, an area of the brain that has been found to be dysfunctional in patients with anxious depression. The drug's effects will be compared between patients with anxious depression, patients with non-anxious depression, and healthy controls.

Clare Kelly, Ph.D., of Trinity College Dublin, Ireland, will assess active coping strategies in adolescent girls with and without depressive symptoms. Active coping strategies, which influence individuals' resilience to stress, involve brain circuits involved in emotion and reward processing that have been implicated in depression. Dr. Kelly's study will evaluate how age and depressive symptoms affect girls' performance of an active coping task, as well as the underlying circuitry, which could help researchers identify individuals most at risk for major depression.

Donel M. Martin, Ph.D., of the University of New South Wales, Australia, will test the efficacy of non-invasive brain stimulation in treating depression, particularly in people who have not responded to more common depression treatments. His team will use transcranial direct current stimulation (tDCS), stimulation of the scalp, which has previously been shown to reduce symptoms moderately. Participants will undergo tDCS in combination with emotional brain training, which has promoted antidepressant effects in other studies. Participants will also report on their symptoms as long as three months after getting the treatment, to gauge how long any effects of tDCS last, and have their brain activity measured to help determine exactly how tDCS might help overcome treatment-resistant depression.

Mark J. Niciu, M.D., Ph.D., of the National Institute of Mental Health, will study the efficacy of the medication ketamine in specifically treating depression among individuals with a family history of alcohol abuse. Ketamine is thought to have antidepressant effects by acting on NMDA receptors. Predicting that low-dose ketamine enhances the brain's ability to adjust its connections in response to learning, known as neural plasticity, Dr. Niciu's team will examine how ketamine changes plasticity in relation to a family history of alcoholism. Their findings may help treat depression, especially among individuals predisposed to alcohol addiction.

Darren Michael Opland, Ph.D., of Yale University, will develop a novel treatment for a specific aspect of major depressive disorder: anhedonia, the inability to feel pleasure. Previous research suggests that anhedonia stems from dopamine signaling in the ventral striatum of the brain, involved in our reward system. This project will try reactivating ventral striatal neurons in mice using optogenetic techniques, which genetically sensitize brain cells to pulses of light. The activity of these neurons will be measured before and after depression symptoms are induced. These findings may broaden our understanding of the way striatal neurons track reward and so help identify new possible targets for treating depression-related anhedonia.

Leah H. Somerville, Ph.D., of Harvard University, will test whether measures of brain network integrity (measured with resting state fMRI) can be used to prospectively identify individuals at risk for an uptick in depression and anxiety symptoms during adolescence. She will use a unique dataset which characterizes brain networks and symptoms of depression and anxiety in 125 youth aged 9–15. The study seeks to distinguish between two groups based on the network integrity of two brain networks: the frontoparietal control network and the salience network, which play a critical role in the generation of emotion and regulatory processes. These analyses aim to identify what particular features of these brain networks 'carry information' about risk for mood dysregulation through adolescence, and by extension, throughout the lifespan.

Marie Spies, M.D., of the University of Vienna, Austria, will investigate if the rapid-acting experimental antidepressant ketamine binds to the serotonin transporter (SERT) in humans, and will relate its binding pattern to antidepressant response. Since ketamine has acute and short-term anti-depressant effects and treatment must be followed by long-term antidepressant treatment, the team aims to investigate if the response to ketamine can be used to predict response to subsequent SSRI treatment. This double-blind control study involving 20 patients with severe unipolar depression and 20 age and sex matched healthy controls will help explore how ketamine can be incorporated into long-term antidepressant treatment strategies.

Oren Tene, M.D., of Tel Aviv University, Israel, will conduct a prospective double blind cross-over study to learn the effect of deep transcranial magnetic stimulation (dTMS) on women with premenstrual dysphoric disorder (PMDD), a hormone-dependent mental condition that causes significant distress in 5% of women of reproductive age. An estimated 15% of symptomatic women attempt suicide; 70% of all who are symptomatic suffer from major depression. dTMS is a technique of electrically induced neurostimulation and neuromodulation. It has been used experimentally with some success in treating refractory depression.

Erin Christine Tully, Ph.D., Georgia State University, studies negatively-biased processing of emotional faces and excessive empathy and shame responses to others' emotions, particularly parents' sadness and anger, theorizing they may be early-risk markers for depression. Dr. Tully will modify a well-validated emotional face processing task to incorporate elements used to elicit empathy and shame. Children will view parents' facial expressions in addition to strangers' faces. The project will follow up at age eight to nine years-old, a sample of 40 children (25 high-risk, 15 low-risk) who participated at ages five to six years-old, in a study of risks for internalizing problems. Using fMRI and other technologies, the study seeks to identify a pattern of neural activation consistent with poor modulation of emotion processing, excessive empathy, and shame. This would be a boon to early identification of depression risk.

Ryan Van Lieshout, M.D., Ph.D., McMaster University, Canada, seeks to determine the impact of cognitive behavioral therapy (CBT) group treatment for women with postpartum depression (PPD) upon their children—in their neurophysiological development and their ability to regulate their emotions. Both are important predictors of subsequent mental health. Dr. Van Lieshout will enroll 30 depressed and 30 non-depressed mothers within 3 months of delivery in a clinical trial. Depressed mothers will participate in a nine week group CBT treatment for PPD. Just before the CBT group, immediately after its completion, and three months after it has finished, emotion regulation and neurophysiological development will be assessed in infants. At six months a comparison will be made to age-matched infants born to non-depressed mothers.

Christian Anthony Webb, Ph.D., Maclean Hospital/ Harvard University, will test the theory that abnormalities in neural reward circuitry play a central role in adolescent depression. Depressed teens exhibit blunted neural response in the ventral and dorsal striatum, as well as hyper-activation in the medial prefrontal cortex (mPFC), to reward-related stimuli (e.g., monetary gains). Dr. Webb will examine the extent to which these neural abnormalities correspond with anhedonic and other depressive symptoms. The aim is to predict the onset of depressive symptoms in adolescents. Study participants will include 50 adolescents aged 12–14 who are at high-risk of developing major depres-sion on the basis of elevated anhedonia.

MULTIPLE DISORDERS

Satoru Ikezawa, M.D., Ph.D., of the National Center of Neurology & Psychiatry, Japan, plans to develop integrated cognitive training for children, with the goal of preventing or reducing the severity of mental illness and developmental disorders. He will evaluate the effectiveness of a neurocognitive training program that integrates computer-based training and physical exercise to strengthen executive function.

Nicole Rachel Kozloff, M.D., of St. Michael's Hospital and the University of Toronto, Canada, will evaluate the effects and economic impact of a program called Housing First on homeless youth with mental illness. Housing First gives homeless people with mental illness immediate access to housing of their choice and intensive mental health services without mandating sobriety or psychiatric treatment. In a research trial in Canada, Housing First reduced the use of emergency shelters, hospital emergency rooms, and other expensive services among homeless adults. The effects of the program have not yet been studied among young people.

Timothy Y. Mariano, M.D., Ph.D., M.Sc., of Brown University, will investigate whether a non-invasive form of brain stimulation can effectively treat lower back pain, which can contribute to anxiety and depression. Chronic pain is often treated in the short-term with medications, sometimes having serious side effects, and in the longer term with invasive surgery or electrode implantation. Transcranial direct current stimulation (tDCS) stimulates the scalp without requiring surgery and has not been shown to have severe side effects. Dr. Mariano and colleagues will test whether tDCS reduces the experience of lower back pain, while also screening for any related changes in brain activity. The success of tDCS would mean a portable, cheap and comparatively simple treatment for chronic pain.

Andrada Delia Neacsiu, Ph.D., of Duke University Medical Center, plans to build a new approach to treating mental disorders that involve mismanagement of negative emotions. This study will investigate the efficacy of repetitive transcranial magnetic stimulation (rTMS), a non-invasive procedure, in people using cognitive restructuring, an evidence-supported treatment for problems with emotional management. Dr. Neacsia and colleagues expect that rTMS will enhance the positive effects of cognitive restructuring. Such findings would point toward neuroscience-supported behavioral interventions for psychiatric deficits that contribute to a broad spectrum of mental illness.

Ueli Rutishauser, Ph.D., of Cedars-Sinai Medical Center at the University of California Los Angeles, will study rhythms of electrical activity in the brain that impact memory. Dr. Rutishauser will investigate the theta rhythm in the hippocampus, a brain region crucial for memory formation. His team will directly test how coordination of brain activity by the theta rhythm affects the strength of memory. If theta influences memory formation, electrical stimulation and medication that modify this rhythm may help in slowing, reversing or even preventing memory loss, a major symptom of neurological disorders such as epilepsy, Alzheimer's and post-traumatic stress disorder.

Antonios S. Zannas, M.D., Max-Planck Institute for Psychiatry, Germany, is studying epigenetic changes associated with accelerated aging to see if they contribute to the causation of neuropsychiatric disorders. Epigenetic changes involve changes in gene expression caused by factors that do not alter underlying DNA sequences. Lasting changes in one kind of epigenetic mechanism, DNA methylation, are known to be caused by psychological stressors. Dr. Zannas will correlate DNA methylation markers with measures of brain structure living subjects, as measured via MRI imaging, in the hope of identifying epigenetic biomarkers. Such markers might flag subjects at risk for accelerated aging-related changes in brain structure associated with various neuropsychiatric disorders.

OBSESSIVE-COMPULSIVE DISORDER (OCD)

George McConnell, Ph.D., of Duke University, plans to identify the precise processes by which deep brain stimulation (DBS) treats obsessive compulsive disorder (OCD). Though medication is often prescribed for OCD, up to half of patients do not respond, including those who are most seriously impaired. Working as a pacemaker for the brain, DBS is now being used as an alternative treatment. Yet its mechanisms of action are not known. Looking at mice, Dr. McConnell's work will examine how changes in brain circuit activity across the cortex, thalamus and basal ganglia relate to DBS efficacy in treating OCD, hoping to elucidate the mechanisms of this promising treatment.

POST-TRAUMATIC STRESS DISORDER (PTSD)

Lynnette Astrid Averill, Ph.D., at Yale University will evaluate the effects of ketamine on the cognitive functioning of patients with PTSD. Those with PTSD often suffer from cognitive impairments. Ketamine interacts with glutamate receptors, which are important for regular cognitive functioning. Using specialized MRI imaging techniques, Dr. Averill will explore the effects of ketamine on functional connectivity in PTSD patients with the hope of establishing ketamine's pro-cognitive effects.

Isaac Galatzer-Levy, Ph.D., at New York University's School of Medicine will evaluate the efficacy of a drug called dexamethasone in preventing the development of PTSD. The goal is to determine if a single dose of dexamethasone, a commonly utilized cortisol-suppressing steroid, when administered in the emergency room immediately following a traumatic event, will prevent the development of PTSD by altering expression of the gene FKBP5. Dexamethasone has been shown to both reduce cortisol and reduce FKBP5 expression in animal models, making it a plausible treatment for acute PTSD by altering the initial neurobiological response to trauma.

Jamie Lynn Peters, Ph.D., of the Medical University of South Carolina, plans to study a form of memory that may point the way to treating posttraumatic stress disorder (PTSD) and substance abuse. Although PTSD and substance abuse often co-occur, few treatments target both at once. Dr. Peters and colleagues will investigate the proposal that PTSD and substance abuse both arise from a failure in extinction memory, the formation of a new memory to replace an old one. This proposal will test the therapeutic potential of new designer drugs to activate a brain area associated with extinction therapy, the infralimbic region of prefrontal cortex. This research aims to develop a model of comorbid PTSD and cocaine addiction in particular while testing a drug to treat extinction memory failure as an underlying cause of both disorders.

Basant K. Pradhan, M.D., of Cooper University Hospital & Cooper Medical School of Rowan University, plans to replicate his prior pilot study supporting the use of ketamine with cognitive behavioral therapy to treat posttraumatic stress disorder (PTSD). Ketamine regulates levels of glutamate. Dr. Pradhan and colleagues have found that ketamine treats PTSD most effectively when combined with a form of therapy known as TIMBER—Trauma Interventions using Mindfulness Based Extinction and Reconsolidation of trauma memories. Extending their pilot findings would help support novel pharmacological treatments for PTSD.

SUICIDE PREVENTION

Emily B. Ansell, Ph.D., at Yale University will investigate neural system dysfunctions underlying suicidality and explore a possible drug intervention for high-risk individuals—in this case, people diagnosed with Borderline Personality Disorder (BPD). Suicidality is thought to be a result of dysregulation in a part of the brain called the prefrontal cortex (PFC). A compound called Guanfacine HCl has been shown to ameliorate PFC dysregulation. Thirty patients with BPD will undergo brain imaging before receiving either Guanfacine or placebo and eight weeks after treatment. Dr. Ansell hopes these results will identify Guanfacine as a pharmaceutical method of reducing suicidality as well as provide further evidence for the PFC's role in emotional and impulse regulation.

Haggai Sharon, M.D., of Tel Aviv University, Israel, will examine the use of oral ketamine to treat suicidal urges. Traditionally used as an anesthetic, ketamine can reduce depressive symptoms within hours. However, its usage is limited when it has to be taken intravenously. Dr. Sharon will examine the efficacy of a more convenient form of ketamine, by administering oral ketamine every day for three weeks to hospitalized and community patients immediately following a suicide attempt. The patients will be monitored on their immediate and ongoing clinical response and will also receive neuroimaging scans. If successful, this approach may introduce a new treatment approach in clinical psychiatry and improve outpatient treatment of suicidal patients.

SCHIZOPHRENIA

Anthony Olufemi Ahmed, Ph.D., at Weill Cornell Medical College will investigate a neurocognitive treatment called cognitive rehabilitation training (CRT), which has been shown to improve cognition and also decrease verbal and physical aggression in people with schizophrenia. Ahmed hopes to show that this training improves cognition and decreases aggression by improving emotional regulation and impulse control. He will compare subjects who undergo CRT with those who undergo CRT plus additional training that focuses on emotional regulation and impulse control. To measure emotional control and impulsivity, he will utilize a system called the International Affective Picture System, a task in which a series of pictures are presented to a subject while physiological responses are recorded.

Lisa Anne Buchy, Ph.D., at University of Calgary, Canada, will evaluate the efficacy of a neurocognitive intervention designed to improve prospective memory. Prospective memory is the ability to remember to perform tasks in the future. Those with schizophrenia have demonstrated impaired prospective memory skills. Dr. Buchy's study will evaluate the brain changes that occur in 40 people with schizophrenia following a five week prospective memory training program called ProMT.

Sasja Noriko Duijff, Ph.D., at the University Medical Center of Utrecht, Holland, will test a cognitive training program called cognitive remediation (CR) as a potential intervention for those at high risk for schizophrenia. CR is a strategy to improve neuropsychological deficits such as attention, verbal memory and executive function. Dr. Duijff will study 50 patients at high risk due to a genetic deletion they carry, in order to evaluate the efficacy of CR in preventing or delaying the onset of psychosis.

Anne-Kathrin J. Fett, Ph.D., at Vrije Universiteit, Holland, will evaluate a mobile application intervention to treat social functioning problems observed in schizophrenia. Dr. Fett says that traditional methods of improving social functioning often do not take place within the real-world environments patients live in; as a result, there is a high clinical demand for personalized interventions that adapt to the patient's specific needs and that offer structure and support within everyday life contexts. This study will assess the efficacy of a mobile intervention application that aims to improve patients' real-life social outcomes and wellbeing by incorporating interactive, tailored feedback and guidance.

Daniel John Foster, Ph.D., at Vanderbilt University Medical Center will investigate a kind of receptor in the brain known as the M4 muscarinic receptor, which may serve as a potential therapeutic target in schizophrenia. Current antipsychotic medications have significant side-effects that limit their long-term utility. Using an integrated approach of electrophysiological and behavioral studies along with novel pharmacological tools and genetically-modified mice, Dr. Foster aims to show that M4-PAM, a molecule designed to target the M4 muscarinic receptors, has promise as an antipsychotic target.

David Gyllenberg, M.D., Ph.D., at the University of Turku, Finland, aims to develop profiles of premorbid cognition in relation to psychotic disorders. Studies that examine cognitive functioning before the onset of disease offer a possibility for prediction and early intervention. Dr. Gyllenberg will utilize machine learning techniques to analyze a large database of people with psychotic disorders established through a collaboration between Columbia University and Turku Unviersity. Through this analysis, he aims to provide a better understanding of premorbid cognition.

Carol Jahshan, Ph.D., of the University of California, Los Angeles will explore whether transcranial direct current stimulation (tDCS), a brain stimulation therapy, can improve visual processing in patients with schizophrenia. Research in healthy subjects has demonstrated that when applied to the occipital cortex, tDCS can lead to perceptual changes. Dr. Jahshan's study will evaluate the technique's potential to treat perceptual deficits in schizophrenia, which can impact patients' cognitive skills and real-world functioning.

Heeyoung Lee, Ph.D., of the University of Pittsburgh will implement a pilot study evaluating the effectiveness of a home-based physical activity program in improving cognitive function in older adults with schizophrenia or schizoaffective disorder. His team will compare the effects of the physical activity program, in which participants will be instructed to engage in brisk walking for 30 to 45 minutes a day at least five days a week, to the effects of a health education program. Both neurocognitive function and levels of brain-derived neurotrophic factor, a neuron-supporting factor that can be measured in the blood, will be evaluated at the end of the 12-week exercise program and again 12 weeks later.

Shupeng Li, M.D., Ph.D., of the Centre for Addiction and Mental Health, University of Toronto, Canada, will test whether a potential new therapeutic, a peptide called TAT-D2, can reverse developmental problems in the brain and eliminate symptoms of schizophrenia. TAT-D2 disrupts the interaction between dopamine receptors and a protein called Disrupted-in-Schizophrenia-1 (DISC1), which is sometimes mutated in people with schizophrenia, bipolar disorder, or major depression. Abnormal DISC1 can cause prolonged activation of dopamine receptors, leading to schizophrenia-like behavior in mice.

Rachel L. C. Mitchell, Ph.D., of King's College London, UK, will examine how impaired social inferences might develop among individuals with schizophrenia, who may have trouble accurately judging other people's intentions. She and colleagues believe schizophrenia patients have distorted perceptions of time and causality, or the extent to which one event leads to another, due to abnormal communication in the brain. They will test this theory based on the ability of schizophrenic patients to judge causality between events based on their timing, as well as their psychological well-being and electrical activity in their brains during perception. Patients will also undergo non-invasive brain stimulation to see if this intervention regulates time perception, pointing toward a possible treatment for damaging social inferences in schizophrenia.

Nigel Craig Rogasch, Ph.D., of Monash University, Australia, will develop a new system for testing a system in the brain that can contribute to schizophrenia. The brain tissue of patients has shown irregularities in the system regulating GABA, the main inhibitory neurotransmitter. This project will investigate whether non-invasive electrical stimulation of the brain alters GABA levels. In turn, the team will also measure whether any changes in GABA levels brought on by brain stimulation affects the experience of cognitive symptoms, such as impaired memory and attention, and activity in prefrontal cortex, which oversees much of cognition. Cognitive symptoms are among the most common traits in schizophrenia, and the most clearly in need of improved treatment.

Jerri M. Rook, Ph.D., of Vanderbilt University Medical Center, notes that current drug treatments for schizophrenia help reduce hallucinations, paranoia and delusions but have little effect on cognitive impairments or symptoms reflecting a lack of normal sensations, such as pleasure. Altering levels of the neurotransmitter acetylcholine may help treat cognitive symptoms. Dr. Rook and colleagues have developed a compound that regulates activity at docking ports for acetylcholine in the brain, receptors that may be compromised in schizophrenia. They will test whether their compound improves cognitive function and social interaction in patients.

Douglas Ruderfer, Ph.D., of the Icahn School of Medicine at Mount Sinai, aims to apply findings on gene sets associated with schizophrenia to improving treatment of the disorder. Studying the effects of nearly 2,000 drugs, the team will evaluate how genes targeted by antipsychotics change their activity based on rare variations in their structures. They will also look at the activity of genes that otherwise interact with psychiatric drugs or are associated with schizophrenia risk. This study will provide an overview of how a wide range of genes influence the activity of different medications, which could potentially be better used to treat schizophrenia.

OTHER DISORDERS:

ANOREXIA

Sahib Khalsa, M.D., Ph.D. of the University of Tulsa will investigate a new approach to making eating less anxiety provoking for individuals with anorexia nervosa. He will assess the impact of infusions of isoproterenol on anticipatory meal anxiety and eating behavior in individuals with the disorder. The drug will be administered during meal anticipation to systematically link increased cardiorespiratory sensations to the experience of anxiety, a form of exposure therapy.

Pei-an (Betty) Shih, Ph.D., of the University of California, will study how biological traits that reflect vulnerability to anorexia nervosa affect the symptoms and clinical outcomes of the disorder. The team will study a marker of anorexia called sEH (soluble epoxide hydrolase), an enzyme that is more active in anorexia and produces inflammation in the body. They will test whether high sEH activity corresponds with anorexia symptoms such as anxiety and perfectionism and also examine the impact of genes that encode sEH. By identifying how sEH and the genes that code for it affect anorexia, this project aims to improve biological methods for predicting anorexia onset and monitoring illness progression as well as treatment response.

BORDERLINE PERSONALITY DISORDER

Vanessa Nieratschker, Ph.D., of the University of Tübingen, Germany, will study how genetic factors interact with the environment in a treatment for borderline personality disorder (BPD). Established treatments for BPD include dialectical behavioral therapy, which targets patients' environments. Dr. Nieratschker and colleagues plan to assess how this kind of therapy affects the expression of genes that have already been associated with BPD. This testing is needed to check the theory that therapy and other comparable treatments work by promoting methylation, the adding of methyl groups to DNA (an epigenetic process).

Investing in Breakthroughs
To Find a Cure

OUR MISSION:

The Brain & Behavior Research Foundation is committed to alleviating the suffering caused by mental illness by awarding grants that will lead to advances and breakthroughs in scientific research.

OUR VISION:

To bring the joy of living to those affected by mental illness—
those who are ill and their loved ones.

HOW WE DO IT:

100% of our donor contributions for research are invested in NARSAD Grants leading to innovative ideas in neuroscience and psychiatry to better understand what causes and how to effectively treat brain and behavior disorders. These disorders include depression, bipolar disorder, schizophrenia, autism, attention-deficit hyperactivity disorder, anxiety, borderline personality disorder, chemical dependency, obsessive-compulsive disorder and post-traumatic stress disorders.

OUR CREDENTIALS

For more than a quarter of a century, we have awarded more than $340 million to fund more than 5,000 grants to more than 4,000 scientists around the world.