NARSAD
The Brain and Behavior Research Fund

2010 NARSAD Independent Investigators

Paul P. Allen, Ph.D., Institute of Psychiatry/King's College London, United Kingdom, aims to establish biomarkers that predict the likelihood of adolescents developing psychosis after exhibiting the "At Risk Mental State" or ARMS. It is currently impossible to reliably predict which individuals with ARMS will develop psychosis, and the ability to do so would greatly advance clinical treatment. Dr. Allen will be evaluating elevated dopamine activity in the striatum of the brain and severe prefrontal cortex (PFC) dysfunction. This expands upon his earlier work.

Catalina Betancur, M.D., Ph.D., INSERM Universite Paris VI, France, plans to define new genetic variations associated with autism spectrum disorder, which has a complex inherited genetic component. Subjects for this genetic analysis will be recruited from the Paris Autism Research International Study (PARIS) and the Autism Genome Project databases. Data from this study should shed light on the complex genetic origins of this disease, and provide a basis for additional research and perhaps novel therapies for autism.

Geraldo F. Busatto, M.D., Ph.D., University of Sao Paulo, Brazil, seeks to prevent the misdiagnosis of adult onset Attention Deficit Hyperactivity Disorder (ADHD) as bipolar disorder by using improved MRI analysis and other novel diagnostic methods. Dr. Busatto will use high-dimensional pattern classification analysis of MRI scans to detect subtle differences in the brains of individual patients with ADHD and bipolar disorder. Misdiagnosis typically leads to the worsening of patients' symptoms.

Kenneth D. Carr, Ph.D., New York University, seeks to gain better understanding of the brain circuitry involved in the addictive process and its associative disorders. He will study the activity of a particular type of neurotransmitter receptor, which is stimulated by the dopamine pathway, in neurons of the nucleus accumbens in food-restricted versus non-food-restricted rats.

Hannie C. Comijs, Ph.D., Vrije University Medical Center, Amsterdam, seeks to gain further insight into the increased vulnerability of older adults to biological risk factors that can worsen depression and associated neurodegenerative disorders. Data from this study, the Netherlands Study of Depression in Older persons (NESDO), will be combined with data from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing epidemiological study of depression in 18 – 60-year-olds. Combined, this will represent the largest database yet available for the study of depression.

Gail L. Daumit, M.D., M.H.S., Johns Hopkins University, has designed a pilot study on effective weight-loss interventions via cell phone contact for people with serious mental illness. Intervention protocols include: automated reminders for meetings, healthy eating tips and prompts to self-monitor exercise and healthy eating. Heart disease contributes significantly to

early mortality in people with serious mental illness, and being overweight and obese are significant risk factors for developing heart disease.

Lynette C. Daws, Ph.D., University of Texas Health Science Center at San Antonio, seeks to gain further insight into the biological mechanisms underlying the tendency of young children, repeatedly exposed to high levels of stress, to develop mental illness later in life. This depends in part on which genetic variant of the serotonin receptor gene (5-HTT) one carries. Dr. Daws will test another highly efficient serotonin receptor for susceptibility to developing mental illness by blocking the highly efficient receptor with the stress hormone corticosterone in mice.

Faith B. Dickerson, Ph.D., M.P.H., Sheppard Pratt Health System/University of Maryland, will test the capability of biomarkers to more accurately diagnose and treat depression associated with acute bipolar disorder. Biomarkers have proven to be invaluable in the diagnosis and treatment of several major illnesses. This study is the most comprehensive to date to assess biomarkers specifically associated with bipolar disorder.

Amelia J. Eisch, Ph.D., University of Texas Southwestern Medical Center at Dallas, will investigate the neurobiological basis of resilience following exposure to extreme stress in individuals who are more susceptible to developing major depressive disorder and PTSD, and more resilient individuals. Dr. Eisch will use social avoidance as an indicator, in a mouse model of post-traumatic stress disorder.

Chang-Gyu Hahn, M.D., Ph.D., University of Pennsylvania School of Medicine, seeks to determine the molecular and biochemical basis for the hypofunctioning of the N-methyl-D-aspartic acid (NMDA) receptor in the prefrontal cortex of the brain, which is well documented in schizophrenic individuals. Dr. Hahn will identify which proteins in the NMDA receptor complex are linked to the hypofunctioning of the NMDA in patients with schizophrenia by analyzing post-mortem tissue samples. Data from these studies will suggest possible targets for novel therapeutics.

Beng-Choon Ho, M.D., University of Iowa, seeks to first establish biomarkers associated with the development of schizophrenia in young, asymptomatic relatives of schizophrenic individuals using the latest highly sophisticated microarray and bioinformatic approaches. In the second phase of the study, state-of-the-art brain imaging studies will examine brain anatomic structures and neuronal activity profiles and correlate them with the biomarker data from the first phase. The ultimate goal of this project is to improve the ability of clinicians to identify young people who are at the highest risk of developing schizophrenia, thus mitigating or even preventing the onset of schizophrenia in those individuals.

Eun-Kee (EK) Jeong, Ph.D., University of Utah, aims to optimize an MRI-based technique to better understand metabolic energy levels in the brains of patients with major depressive disorder (MDD). Current brain MRI techniques are not used with patients with MDD due to the long duration of 1.5 to 2 hours, but Dr. Jeong and colleagues hope to decrease duration time to half an hour. This will enable them to measure the activity of creatine kinase (CK), an enzyme critical to maintaining metabolic energy levels. Ultimately they seek to establish brain CK activity as a robust biomarker of MDD.

Marc J. Kaufman, Ph.D., McLean Hospital/Harvard University, has designed a pilot study adapting a special imaging technique associated with MRI to better measure and analyze glycine levels in the brains of patients with schizophrenia. The ability to absorb and metabolize glycine varies from patient to patient and alters the effectiveness of antipsychotic medications in the treatment of schizophrenia. Dr. Kaufman and colleagues seek to optimize glycine augmentation therapy with these new results, thus improving the efficacy of antipsychotic medications.

Lawrence S. Kegeles, M.D., Ph.D., Columbia University, will examine the underlying neurobiology of the response of healthy 'control' patients to ketamine, an anesthetic sometimes used as a recreational drug. Ketamine is known to induce schizophrenia-like symptoms. These experiments will provide further insight into the neurophysiology of NMDA receptor-related dysfunction in schizophrenia. This study may also highlight mechanisms by which ketamine can have positive therapeutic effects in obsessive-compulsive disorder and major depression.

Danny Koren, Ph.D., University of Haifa, Israel, has designed a large, community-based epidemiological study to correlate diagnoses of schizophrenia in Israeli citizens ages 25 and under with their previous records from the school counseling system (SCS). It is predicted that the SCS samples will be a reliable predictor of the tendency to develop schizophrenia. If this is borne out, the SCS can be enhanced to collect genetic and environmental data on students referred to them, which would make the SCS a very valuable resource for more detailed analysis of genetic and environmental contributions to the development of schizophrenia.

David E. Krantz, M.D., Ph.D., University of California, Los Angeles, will use knowledge of the basic biology of neurotransmitter release at neuronal synapses in fruit flies, or Drosophila, to identify potential novel drugs to treat various psychiatric disorders. Dr. Krantz will screen up to 20,000 compounds over two years in Drosophila larvae, observing physical or molecular changes that point to potential treatments.

Tatiana G. Kutateladze, Ph.D., University of Colorado Denver, will study the cAMP response element-binding (CREB) binding protein and the role its deficiency plays in alcohol and drug addiction, depression and the Rubenstein-Taybi Syndrome, which leads to severe mental retardation. Dr. Kutateladze will complete a very comprehensive biochemical and molecular characterization of CREB, which is essential for learning, long-term and emotional memory, and neuronal plasticity (the ability of neurons to change or make new connections with other neurons). The insights gained from this work will provide a critical basis for the development of pharmacological interventions that can ameliorate CREB-based diseases.

Francis S. Lee, M.D., Ph.D., Weill Cornell Medical College, endeavors to gain more understanding of the role of genetic variants to provide a basis for improved diagnosis and treatment of post traumatic stress disorder (PTSD). He will study the role of genetic variants of the brain derived neurotrophic factor (BDNF) gene in mediating response to classic treatments for PTSD. BDNF is thought to play a major role in the response of PTSD victims to anti-depressants, the most common treatment for PTSD. Currently, as many as 40 percent of PTSD patients do not respond to treatments with anti-depressants.

Sarah F. Leibowitz, Ph.D., Rockefeller University, will study the effect of prenatal exposure to low or moderate doses of nicotine in rats, with a hypothesis that it is related to compulsive behavior in adolescents. Dr. Leibowitz will study cellular and molecular events that occur in the hypothalamus and limbic region that by extrapolation should shed some light on these events in humans born to mothers who smoke while pregnant.

Yijun Liu, Ph.D., University of Florida, will use fMRI-based analytical techniques to map signaling between the three brain structures repeatedly implicated in depression. Signaling between the amygdala, orbital frontal cortex and anterior cingulate cortex will be mapped in healthy patients not being treated with medications, but recently diagnosed with major depressive disorder. Dr. Liu will gain insight into the causal (inhibitory and/or stimulatory) relationships between the three brain structures in emotion processing and at rest, and will provide additional insight into how the brain processes emotions and how these processes are altered in depression.

Xin-Yun Lu, M.D., Ph.D., University of Texas Health Science Center at San Antonio, seeks to further understand the observed clinical correlation between obesity and the incidence of depression and anxiety. Dr. Lu will study the role of reduced levels of adiponectin – a small protein fragment that regulates metabolism – in depression and anxiety.

James H. MacCabe, M.B.B.S., Ph.D., Institute of Psychiatry/King's College London, United Kingdom, will take advantage of well-documented and maintained psychiatric records in Israel to determine whether there is a statistically significant correlation between intelligence, creativity and incidence of bipolar disorder. Dr. MacCabe recently completed a study of 900,000 Swedish students, age 16, and found that those who performed best on exams had a four-fold risk of developing bipolar disorder in adulthood. Other similar studies have shown similar results.

Dara S. Manoach, Ph.D., Harvard Medical School, will build upon her earlier studies revealing that memory processing associated with schizophrenia is impaired due to faulty memory processing over time and during sleep. Dr. Manoach now seeks to distinguish between deficits in memory consolidation that occur in the waking state and during sleep in patients with schizophrenia.

Olivier J. Manzoni, Ph.D., INSERM Universite Paris VI, France, aims to gain further insight into the brain/neuronal mechanisms underlying the development of Fragile X Syndrome, which is associated with a range of mental, physical, psychological and emotional disorders. He will test the hypothesis that neuronal function is altered in the nucleus accumbens in Fragile X Syndrome and that resulting defects may be corrected by administering drugs.

Andrew M. McIntosh, M.D., University of Edinburgh, United Kingdom, seeks to identify genes that influence a quantitative decrease in white matter integrity in people with bipolar disorder and their relatives, even those not exhibiting any bipolar symptoms. Previous brain imaging studies on these groups have revealed a decrease in white matter and this study will correlate those finding with genomic data.

Robert K. McNamara, Ph.D., University of Cincinnati, will examine the biosynthesis of docosahexaenoic acid (DHA), an omega-3 fatty acid that is a major component of neuron and red blood cell (RBC) membranes, in patients with bipolar disorder-1 (BD-1). Previous studies showed that the cell membranes of neurons and RBCs of those with this disorder, which often manifests in childhood, are deficient in DHA. Comparisons are expected to show a correlation between the severity of the disease and levels of DHA. Data from this study will provide a basis on which to conduct further genetic and molecular studies to analyze heritability of BD-1.

Andrea Mechelli, Ph.D., Institute of Psychiatry/King's College London, United Kingdom, has designed a clinical trial that will identify those most likely to develop schizophrenia within a population of individuals that exhibit a pre-schizophrenic condition known as the "At Risk Mental State" (ARMS). This state is often identified in teenagers who exhibit isolated psychotic symptoms. Only a third of these individuals ever develop schizophrenia. In the interest of providing early intervention and treatment of schizophrenia in this group, Dr. Mechelli and colleagues will assess multiple factors, including genetic vulnerability, environmental stressors and cognitive performance.

Jouko A. Miettunen, Ph.D., University of Oulu, Finland, and his colleagues are creating an internet database to organize an enormous amount of disparate data from multiple epidemiological studies of schizophrenia. This database will be made available to the public, making it extremely useful to clinicians and researchers. It will foster new collaborations, and aid in the development of consensus on a wide range of scientific and medical issues related to schizophrenia, including risk factors and outcomes of treatment.

Gregory E. Miller, Ph.D., University of British Columbia, Canada, will study underlying molecular mechanisms of caregivers for seriously ill relatives. These caregivers are under considerable chronic stress and often experience serious mental and physical health problems, particularly depression and heart disease, as a result. Dr. Miller and colleagues will examine whether stress-related genetic modifications are responsible for observed changes in gene expression in monocytes, blood cells that release pro-inflammatory cytokines, from caregivers.

Guo-li Ming, M.D., Ph.D., Johns Hopkins University, will use stem cells to study the expression of genes being affected in schizophrenia. Dr. Ming and his colleagues will create "induced pluripotent stem cells" (iPSCs) from skin cells of patients identified as having either multiple copies or deletions of the CYFIP1 gene, which is associated with schizophrenia. These iPSCs will be reprogrammed to simulate neurogenesis, and the developmental process will be monitored to see how these genetic abnormalities may affect neuronal development.

Lisa M. Monteggia, Ph.D., University of Texas Southwestern Medical Center at Dallas, will investigate the molecular and biochemical mechanisms by which ketamine exerts its fast-acting antidepressant effects. Ketamine – an anesthetic sometimes used as a recreational drug – temporarily inhibits N-methyl-D-aspartic acid (NMDA) receptor signaling and increases bone derived neurotrophic factor (BDNF) in hippocampal neurons in mice. The goal of this project is to determine the time-dependent effect of elevated BDNF levels on NMDA receptor signaling, in order to further clarify the molecular events that mediate ketamine's fast-acting antidepressant

effects. This may, in turn, provide a basis for developing anti-depressants that act much faster than the currently available SSRIs.

Ziad Nahas, M.D., Medical University of South Carolina, has obtained preliminary data showing that bilateral epidural prefrontal cortical stimulation (EpCS) is highly effective in relieving severe treatment-resistant depression (TRD) in five patients with TRD. An estimated 3.2 million Americans suffer from TRD, but very few have received effective treatment. The goal of the proposed project is to conduct a full-fledged randomized, double-blind controlled clinical trial of EpCS in patients with TRD.

Julie V. Patterson, Ph.D., University of California, Irvine, seeks to define a biological characteristic, in particular, an electrophysiological marker of bipolar disorder. Dr. Patterson will compare the electrophysiological responses to controlled, timed, simple sounds in healthy individuals and individuals with bipolar disorder in an attempt to identify the electrophysiological marker.

Isabel Perez-Otano, Ph.D., University of Navarra, Pamplona, Spain, seeks to further understand the role of synaptic pathways in schizophrenia. Dr. Perez-Otano will examine in humans, on a cellular and molecular basis, the role of the immature N-methyl-D-aspartic acid (NMDA) receptor in normal brain development and in schizophrenia. A mature and properly functioning NMDA receptor is critical for synaptic plasticity, or the strengthening or weakening of neuronal transmission through a synapse, but in the brains of adult schizophrenic patients, the immature form of the NMDA receptor still exists. Dr. Perez-Otano's work may suggest therapeutic targets for the treatment of schizophrenia.

William T. Regenold, M.D., University of Maryland School of Medicine, has designed a preliminary study to test the efficacy of nonconvulsive electrotherapy (NET) in patients with major medication-resistant depression. Traditionally, electro-convulsive therapy (ECT), which induces seizures, has proven effective in relieving medication-resistant depression. However, the side effects associated with the seizures, including confusion and memory problems, are a drawback. NET, which specifically stimulates the brain's frontal lobes and does not induce seizures, may provide relief from medication-resistant depression without the side effects associated with ECT.

Jonathan L. Sebat, Ph.D., University of California, San Diego, proposes to conduct a genomic analysis of a large cohort of schizophrenia patients and healthy matched controls in order to confirm the results of a previous study in which two gene copy number variations (CNVs) associated with schizophrenia were identified. These two CNVs had not been identified previously in any known study as being associated with schizophrenia. If the correlation of these CNVs with schizophrenia is proven, analysis of the function of these two novel genes will provide new insights into the etiology of schizophrenia, which could potentially lead to the development of new therapies.

Simone G. Shamay-Tsoory, Ph.D., University of Haifa, Israel, has designed a study to determine whether oxytocin, which possesses both hormonal and neuromodulatory properties, will improve measures of empathy and affect anatomical changes in the amydgala in

schizophrenic individuals. The proposed study is based on previous studies from Dr. Shamay-Tsoory's lab and others showing that oxytocin levels are directly related to empathic response and improved perception of social cues, which is lacking in those with schizophrenia. It is expected that oxytocin will improve empathy and social cognition in schizophrenic subjects.

Vandana Shashi, M.D., M.B.B.S., Duke University, works with children with chromosome 22q11.2 deletion syndrome (22q11.2DS), which is associated with a high risk of developing schizophrenia. Dr. Shashi will recruit 30 subjects with 22q11.2DS, ages 10 – 17 years, from an ongoing study and test whether a computerized cognitive remediation program will improve cognitive development.

Paul D. Shepard, Ph.D., University of Maryland, seeks to understand the neurobiology underlying new findings showing that deep brain stimulation (DBS) of the habenula region of the brain dramatically mitigates symptoms of treatment-resistant, severe major depressive disorder. Previous studies have shown increased metabolic activity in the habenula in depressed patients relative to that in healthy control subjects.

Helen Blair Simpson, M.D., Ph.D., NYSPI/Columbia University, will employ some of the most advanced MRI-associated techniques to better understand what happens in the brains of patients with obsessive compulsive disorder (OCD). Dr. Blair Simpson will collect data on total tissue glutamate, a neurotransmitter, in the caudate nucleus region of the brain in subjects with OCD and in healthy control subjects without OCD. The imaging technique used in this study, unlike those employed previously, can distinguish between glutamate activity and the activity of other glutamate-related neurotransmitters, believed to be important in OCD.

Shanthini Sockanathan, Ph.D., Johns Hopkins University School of Medicine, seeks to gain further insight on the genesis of several mental illnesses, including schizophrenia, autism and epilepsy. Dr. Sockanathan will use advanced molecular techniques in a mouse model created in her lab to understand the role of retinoic acid (RA), a vitamin A derivative, in the development of newborn cortical neurons. RA is known to play a critical role in the proper development of cortical neurons, and accumulating evidence suggests that abnormal development of cortical neurons is central to the genesis of these mental illnesses.

Albert Hung Choy Wong, M.D., Ph.D., FRCPC, University of Toronto, is interested in determining whether environmental factors can exert influence on genetic variants of the disrupted-in-schizophrenia (DISC1) gene. Carriers of mutated variants of this gene most often develop schizophrenia, but can also develop major depressive disorder, cognitive impairment or other mental illnesses. Data from this study will provide a basis on which to more accurately understand the molecular etiology of DISC1-associated mental illnesses, and should ultimately lead to improved treatments for these conditions.