2021 Leading Research Achievements

by BBRF Grantees, Prizewinners & Scientific Council Members

Presented in order of publication.

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

Diagnostic Tools/Early Intervention: ADHD

Low Maternal Vitamin D in Early Pregnancy Is Linked With ADHD Risk in the Child

Andre Sourander, M.D., Ph.D.

University of Turku, Finland

2008 BBRF Independent Investigator

Journal of the American Academy of Child & Adolescent Psychiatry,
January 1, 2021

Researchers discovered that a low level of maternal vitamin D during the early part of pregnancy raises the odds that a child born of that pregnancy will develop clinically diagnosed ADHD by adolescence. The team studied 1,067 mother-child pairs in which the child was diagnosed with ADHD within 12 years of birth, and an equal number of mother-child pairs, matched demographically, in which the child was not diagnosed with ADHD. Maternal vitamin D levels were based on blood samples taken in the first or early second trimester of pregnancy. Vitamin D receptors, expressed in the brain, help regulate calcium signaling between brain cells; the nutrient also impacts factors which help neurons mature and grow. It is theorized that vitamin D depletion can lead to alterations in dopamine signaling, possibly giving rise to "hyperlocomotion" and increased activity.

The research team included: **David Gyllenberg M.D., Ph.D.**, 2015 BBRF Young Investigator; **Alan S. Brown, M.D., MPH**, 2019 BBRF Lieber Prize, 2015 BBRF Distinguished Investigator, 2004 and 2000 BBRF Independent Investigator, 1996 and 1993 BBRF Young Investigator.

New Technologies: Eating Disorders

New Technology Enables Manipulation of Neurons in Peripheral Organs & Reveals Mechanism of Appetite Suppression

Sung Il Park, Ph.D.

Texas A&M University

2018 BBRF Young Investigator

Nature Communications,
January 8, 2021

Dr. Park and his team invented a new technology called optoelectronics that enabled them to activate and deactivate neurons in peripheral organs via tiny wireless devices; testing it, they discovered an unexpected mechanism for suppressing appetite. In contrast to optogenetic technology, which can manipulate neuronal activity within the brain only, optoelectronic devices are powered by extremely small light-emitting diodes with soft, highly flexible tethers that can be implanted successfully in peripheral organs. The focus of the team's test of the technology were endings of the vagus nerve within the stomach, known to be important in the regulation of appetite. By activating specific vagus nerve endings in a specific area of the stomach in mice, appetite was suppressed—to the point of almost complete suppression when the stimulation was increased in intensity. This could have future implications in the treatment of eating disorders as well as obesity.

Next-Generation Therapies: PTSD

Repeated Ketamine Infusions Over 2 Weeks Significantly Reduced Chronic PTSD Symptoms

Adriana Feder, M.D.

Ichan School of Medicine at Mount Sinai

2015 BBRF Independent Investigator, 2002 BBRF Young Investigator

American Journal of Psychiatry, February 1, 2021

A small clinical trial showed that repeated infusions of the drug ketamine over a 2-week period can significantly reduce PTSD symptom severity, while also helping to reduce depression symptoms that often accompany PTSD. The first randomized study to test the efficacy of a course of repeated infusions in individuals with PTSD, the study recruited 30 chronic PTSD patients with moderate to severe symptoms, half of whom received 6 infusions of ketamine over 2 weeks while half received placebo infusions. Those responding to ketamine (reduction in symptoms of 30% of more) were followed until their symptoms returned. The positive results suggest the team can now test whether FDA-approved esketamine has similar benefits in chronic PTSD; and whether psychotherapy, added to a course of ketamine or esketamine, might reduce the likelihood of relapse once the infusions end.

The research team included: **Dennis S. Charney, M.D.**, BBRF Scientific Council, Emeritus, 2019 BBRF Colvin Prize; **James W. Murrough, M.D.**, 2009 BBRF Young Investigator; **Laura Bevilacqua, M.D.**, 2017 BBRF Young Investigator.

Diagnostic Tools/Early Intervention; Basic Research: Schizophrenia, Psychosis

Study Links Schizophrenia Medicines' Anticholinergic Impact to Risk of Cognitive Impairment

Yash B. Joshi, M.D., Ph.D.

University of California, San Diego

2018 BBRF Young Investigator

Gregory A. Light, Ph.D.

University of California, San Diego

2009 BBRF Independent Investigator, 2001 BBRF Young Investigator

American Journal of Psychiatry, May 14, 2021

A study of antipsychotic and other medications commonly prescribed to people with chronic schizophrenia has concluded that medicines with anticholinergic effects can "substantially" contribute to the risk of long-term cognitive impairment. The study assessed the total burden of anticholinergic medications (blocking action of the neurotransmitter acetylcholine) taken by 1,120 chronic schizophrenia outpatients, many of whom take medicines for comorbid health conditions that also have anticholinergic effects. Overall, 63% of participants had a significant burden, which the team associated with generalized impairments in cognitive functioning. Results, if validated, could help guide prescribing physicians make medication decisions that reduce patients' cognitive impairment risk.

The research team included: **Ming T. Tsuang, M.D., Ph.D.**, BBRF Scientific Council, 2010 BBRF Lieber Prize, 1998 BBRF Distinguished Investigator; **Raquel E. Gur, M.D., Ph.D.**, BBRF Scientific Council, 2009 BBRF Lieber Prize, 1999 BBRF Distinguished Investigator; **Neal R. Swerdlow, M.D., Ph.D.**, 2016 BBRF Distinguished Investigator, 1995 BBRF Independent Investigator, 1990 BBRF Young Investigator; **Bruce I. Turetsky, M.D.**, 2001 BBRF Independent Investigator; **Debby W. Tsuang, M.D., Ph.D.**, 2009 BBRF Independent Investigator, 2001 BBRF Young Investigator; **Tiffany A. Greenwood, Ph.D.**, 2008 BBRF Young Investigator; **William S. Stone, Ph.D.**, 2000 and 1997 BBRF Young Investigator; **Ruben C. Gur, Ph.D.**, 2007 BBRF Distinguished Investigator; **David L. Braff, M.D.,** 2014 BBRF Lieber Prize, 2007 BBRF Distinguished Investigator; **Juan Molina, M.D.**, 2020 BBRF Yong Investigator.

Basic Research; Next-Generation Therapies: Depression

Brain Lesions and Treatment Targets in Depression Are Found to Affect the Same Circuitry, Suggesting New Treatment Possibilities

Shan H. Siddiqi, M.D.

Harvard Medical School, Brigham & Women's Hospital

2019 BBRF Young Investigator

Nature Human Behaviour, July 8, 2021

Researchers discovered that the brain circuitry underlying depression is the same or similar in a wide variety of patients and circumstances. Specifically, their work revealed that physical brain damage, or "lesions," that result in depression affect the same or similar brain circuitry as the circuitry targeted by both invasive and non-invasive brain stimulation therapies that alleviate depression symptoms. These and other results of the study could lead to identification of new treatment targets in depression and possibly other neuropsychiatric disorders.

The research team included: **Helen S. Mayberg, M.D.**,BBRF Scientific Council, 2007 BBRF Falcone Prize, 2002 BBRF Distinguished Investigator, 1995 BBRF Independent Investigator, 1992 BBRF Young Investigator; **Mark S. George, M.D.,** BBRF Scientific Council, 2008 BBRF Falcone Prize, 1998 BBRF Independent Investigator, 1996 BBRF Young Investigator; **Robin Cash, Ph.D.**, 2020 BBRF Young Investigator; **Ki Sueng Choi, Ph.D.**, 2016 BBRF Young Investigator; **Darin Dougherty, M.D.**, 2003 BBRF Young Investigator; **Paul Fitzgerald, Ph.D.**, 2005 BBRF Young Investigator; **Alvaro Pascual-Leone, M.D., Ph.D.**, 1998 BBRF Independent Investigator.

Basic Research; Diagnostic Tools/Early Intervention: Anxiety

Excessive Sensory Response at Birth May Signal Risk for Later Anxiety, Research Suggests

Chad M. Sylvester, M.D., Ph.D.

Washington University, St. Louis

2017 BBRF Young Investigator

American Journal of Psychiatry, August 1, 2021

The response of various brain systems to unexpected stimuli provides insights into processes in the brain that enable individuals to respond to salient information and to suppress responses to stimuli that are not relevant or helpful in a given context. New evidence in infants connects sensory overresponse to unexpected auditory stimuli and risk of anxiety disorder. Brain network activity levels in the newborns were shown to be correlated with their mothers' scores on a standard measure of anxiety, suggesting their potential utility as biomarkers. In older children and adults with anxiety disorder, researchers have noted weakened inhibitory responses. Results of this study suggest neural stimulus-response properties near birth signal risk for processes in the brain that generate later-life anxiety and elevated risk in adulthood of depression, substance-use disorders, eating disorders, and bipolar disorder.

The research team included three BBRF Scientific Council members: **Joan Luby, M.D.**, BBRF 2020 Ruane Prize, 2004 BBRF Klerman Prize, 2008 and 2004 BBRF Independent Investigator, 1999 BBRF Young Investigator; **Daniel Pine, M.D.**, 2011 BBRF Ruane Prize, 2000 BBRF Independent Investigator; **Deanna Barch, Ph.D.**, 2013 BBRF Distinguished Investigator, 2006 BBRF Independent Investigator, 2000 and 1995 BBRF Young Investigator.

Next-Generation Therapies: Depression

Positive Preliminary Results in Highly Personalized Deep-Brain Stimulation Therapy for Treatment-Resistant Depression

Katherine W. Scangos, M.D., Ph.D.

University of California, San Francisco

2018 BBRF Young Investigator

Andrew D. Krystal, M.D.

University of California, San Francisco

1997, 1993 BBRF Young Investigator

Nature Medicine, October 4, 2021

Researchers reported initial success in using a novel, highly personalized, and technologically advanced deep-brain stimulation (DBS) approach to rapidly relieve symptoms, eliminate suicidal thoughts, and by 4 months, achieve remission in a patient with lifelong and severe treatment-resistant depression. The team used a form of brain stimulation called closed-loop neuromodulation, in which prior extensive mapping of the patient's neural circuitry preceded the implantation, via surgery, of a battery-powered deep-brain stimulation (DBS) device. The device was "tuned" to activate briefly (in 6-second bursts) throughout each day in response to signals within the brain sensed by the device and which had been linked with the onset of the patient's depressed moods.

Next-Generation Therapies: Depression

Non-Invasive Brain-Stimulation Protocol for Treatment-Resistant Depression Enabled 79% to Experience Remission Following 5-Day Treatment Course

Nolan R. Williams, M.D.

Stanford University

2019 BBRF Klerman Prize; 2018, 2016 BBRF Young Investigator

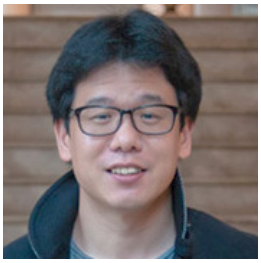
American Journal of Psychiatry, October 29, 2021

In its first randomized, placebo-controlled test, an enhanced form of non-invasive brain stimulation called SNT (Stanford Neuromodulation Therapy, formerly called SAINT) generated "a large antidepressant effect" that enabled 79% of treatment-resistant patients to experience remissions within 4 weeks of the conclusion of the 5-day course of treatment. Over a 4-week period following the treatment course, over 85% of participants who received SNT responded (symptom reduction of 50% or greater). In addition to other possible applications, the brevity of the SNT treatment course compared with standard rTMS therapy and its high rate of effectiveness suggests its potential utility in treating patients in emergency or inpatient settings.

The research team included **Alan Schatzberg, M.D.**, BBRF Scientific Council member.

Basic Research, Next-Generation Therapies: Depression

Two Signaling Pathways Involved in Regulating Synaptic Plasticity Suggest Novel Targets for Rapid-Acting Antidepressants



Kanzo Suzuki, Ph.D.

Vanderbilt University

2018 BBRF Young Investigator

Lisa Monteggia, Ph.D.

Vanderbilt University

BBRF Scientific Council, 2014 BBRF Distinguished Investigator, 2010 BBRF Independent Investigator, 2005 BBRF Freedman Prize, 2003, 2001 BBRF Young Investigator

Ege Kavalali, Ph.D.

Vanderbilt University

2012 BBRF Distinguished Investigator

Cell Reports,
November 2, 2021

Researchers reported the involvement of two chemical signaling pathways in generating homeostatic plasticity, which they suggest plays a key role in rapid antidepressant action such as that seen following the administration of the drug ketamine. The research could advance the search for novel drugs that will have ketamine's rapid action, but fewer side effects. It suggests how changes in pathways "downstream" of the NMDA receptor—thought to be the target of ketamine and precipitated by ketamine's blockade of the receptor—may produce homeostatic plasticity, which appears to modulate circuit function globally in the brain, and does not directly affect synaptic plasticity mechanisms that process and store information. Drugs targeting homeostatic mechanisms thus might preserve memory and cognitive function.

Basic Research: Addiction

Researchers Propose a New Understanding of Dopamine's Role in Learning and Memory

Erin S. Calipari, Ph.D.

Vanderbilt University

2016 BBRF Young Investigator

Munir Gunes Kutlu, Ph.D.

Vanderbilt University

2019 BBRF Young Investigator

Current Biology,
November 8, 2021

Researchers proposed a markedly new way of understanding the role of dopamine in the brain. Ubiquitous throughout the brain and body, and serving a variety of functions, dopamine has long been regarded as key to the brain's reward system, and thus has often been thought of as playing a key role in the biology of addiction. Dysregulation of the dopamine system has also been hypothesized in depression, anxiety, and schizophrenia. For the last 20 years, dopamine has been thought to be central in a mechanism that enables individuals to adapt once expected rewards do not materialize. The new research suggests "reward-prediction error" is only part of what dopamine does. While rewards increase dopamine levels in the brain, so do stressful stimuli: dopamine helps encode information about all types of important and relevant events and drives adaptive behavior—regardless of whether it is positive or negative. The revised view has potentially broad implications for our understanding of behavioral control and a number of psychiatric disorders.

The research team also included **Cody A. Siciliano, Ph.D.**, 2017 BBRF Young Investigator

2021 Leading COVID-Related Discoveries

by BBRF Grantees, Prizewinners & Scientific Council Members

Presented in order of publication.

BRAIN & BEHAVIOR RESEARCH FOUNDATION
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People With Schizophrenia Have Increased Risk of Dying From COVID-19

Donald C. Goff, M.D.

NYU Langone Medical Center

2009, 2003 BBRF Independent Investigator

JAMA Psychiatry,
January 27, 2021

A study conducted in a major New York City hospital system found that people with schizophrenia have 2.7 times the overall risk of dying within 45 days if they are infected with the COVID-19 virus. Higher mortality was not seen in people with depression or anxiety who contracted the virus.

The research team included: **Mark Olfson, M.D., MPH**, 2005 BBRF Distinguished Investigator

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A Close Look at How COVID-19 Infection Can Damage the Brain

Maura Boldrini, M.D.

Columbia University

2014 BBRF Independent Investigator, 2006, 2003 BBRF Young Investigator

JAMA Psychiatry,
March 26, 2021

Neuropsychiatric symptoms in COVID-19 patients suggest independent brain damage attributable to viral infection, researchers said. Symptoms include cognitive and attention deficits ("brain fog"), anxiety, depression, psychosis, seizures, and suicidal behavior. Inflammation in the central nervous system is a likely contributor, they said. The researchers noted that COVID-19 proteins have been found in the lining of blood vessels in the brain. They suggested various means by which viral particles might leak through the blood-brain barrier, a membrane designed to protect the brain from viruses, toxins, and other harmful factors.

New Evidence Suggests COVID May Enter the Brain via Cellular 'Trojan Horses'

Lu Wang, Ph.D.

University of California, San Diego

2019 BBRF Young Investigator

Nature Medicine,
July 9, 2021

Researchers published new evidence suggesting how the COVID virus gains access to the brain. They found that cells called pericytes which surround the brain's blood vessels may act as "Trojan horses," providing a path for the virus to enter, replicate, and then infect surrounding brain cells and tissue. The team discovered that pericytes contain ACE2 receptors, a known passageway for COVID entry into cells elsewhere in the body. ACE2 receptors are found in abundance in the lungs, arteries, heart, kidney and intestines, but were not previously known to be produced in human pericytes.

Study Sheds Light on Prevalence of 'Long-COVID,' Including Cognitive and Psychiatric Symptoms

Paul J. Harrison, M.D. FRCPsych

Oxford University, UK

2004 BBRF Independent Investigator

PLOS Medicine, September 28, 2021

In a study involving over 273,000 patients, researchers provided a detailed picture of "long COVID"—how common its 9 core symptoms are and who is most likely to experience them. Most commonly reported was depression/anxiety, experienced by 22% within 6 months of diagnosis and 15% 3 to 6 months after diagnosis. Among other observations: long-COVID features were recorded in children and young adults, and also in more than half of non-hospitalized patients, confirming that they occur even in young people and those with relatively mild illness. This is significant in public health terms given that most people with COVID-19 are in the latter group, the researchers noted.

Negative Symptoms in Schizophrenia Worsened Under Pandemic Conditions

Gregory P. Strauss, Ph.D.

University of Georgia

2018 BBRF Young Investigator

European Archives of Psychiatry & Clinical Neuroscience, October 30, 2021

Researchers found that social distancing and isolation stemming from the pandemic caused a significant worsening of negative symptoms (flattened emotions, reduced motivation, difficulty speaking, a disinclination to socialize or seek pleasure) in schizophrenia patients, and to a lesser degree in those at clinically high risk of developing psychosis.

Research for Recovery

30+ years

For more than 30 years the Brain & Behavior Research Foundation has fostered new research pathways and transformative breakthroughs.

70k+ donors

Our 70,000 donors have joined together in the great challenge of modern medical science–overcoming mental illness.

$430M+ awarded

Since 1987 the Foundation has awarded more than $430 million to fund more than 6,200 grants.

5,100+ researchers

Grants have been given to more than 5,100 leading scientists around the world.