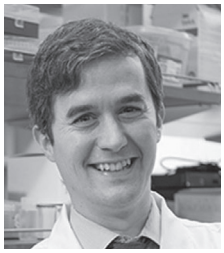
TOP 10 ADVANCEMENTS & BREAKTHROUGHS by Foundation Grantees in 2016

Listed in Order of Occurrence

1

BASIC RESEARCH: DEPRESSION, SCHIZOPHRENIA

New Experiments Reveal Brain Circuitry Behind Inability to Experience Pleasure



Anhedonia, or the inability to feel pleasure or enjoyment, is a key symptom in several mental illnesses including major depression and schizophrenia. This sense of pleasure is generated partly by the brain's neural pathways involved in seeking and experiencing reward. The new research tells us much more. Using optogenetics to control the activity of dopamine neurons in a part of the brain called the medial prefrontal cortex, the team* was able to produce symptoms of anhedonia in rodents. Brain imaging helped reveal that this cortical reward circuitry can in turn suppress activity in other parts of the brain, such as the striatum, that are involved in reward-seeking behavior.

JOURNAL: *Science* January 1, 2016

CONOR LISTON, M.D., PH.D.
Weill Cornell Medical College

2016 Freedman Prizewinner Honorable Mention
2013 NARSAD Young Investigator

KARL DEISSEROTH, M.D., PH.D.
Stanford University School of Medicine

Scientific Council Member
2005 NARSAD Young Investigator Grant

*Team included: 2012 Young Investigator Amit Etkin, M.D., Ph.D.; 2003 Young Investigator Brian Knutson, Ph.D.; and 2012 Young Investigator Melissa R. Warden, Ph.D.

2

BASIC RESEARCH: SCHIZOPHRENIA

A Milestone in the Search for Schizophrenia's Causes

Research by a large international team that included Drs. Sullivan and O'Donovan, who are leaders of the Psychiatric Genomics Consortium, points to one of the likely causes of schizophrenia in some people: overactive pruning of synapses - connections between nerve cells - in the brain's prefrontal cortex during the early years of life. The team focused on variation in genes giving rise to a vital group of proteins called the major histocompatibility complex (MHC). MHC proteins are part of the mechanism used by the immune system to fight off foreign invaders. The team found that variations in the expression of genes known as complement component 4 (C4) genes specifically impacted neuronal synapses, dendrites, axons, and cell bodies. In mice, C4 mediated synapse elimination during postnatal development. Excessive C4 activity may help explain the reduced numbers of synapses in the brains of individuals with schizophrenia.

JOURNAL: *Nature* January 27, 2016

PATRICK F. SULLIVAN, M.D., FRANZCP
University of North Carolina at Chapel Hill

2014 Lieber Prizewinner
2010 NARSAD Distinguished Investigator Grant

MICHAEL O'DONOVAN, M.D., PH.D.
Cardiff University

2012 Lieber Prizewinner

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NEW TECHNOLOGY: AUTISM, SCHIZOPHRENIA, INTELLECTUAL DISABILITY

Genetic Anomalies Frequently Associated with Neurodevelopmental Disorders Can Now Be Efficiently Recreated in the Lab

A new method for recreating large-scale genetic anomalies known as copy number variations (CNVs) will make it easier for scientists to study the effects of those mutations, many of which have been linked to autism and other neurodevelopmental disorders. Drs. Gusella, Talkowski and colleagues have already used the approach, called SCORE, to create human cells that carry too many or two few copies of chromosomal regions known as 15q13.3 and 16p11.2 – CNVs associated with disorders such as autism, schizophrenia, and intellectual disability. The achievement paves the way for studying exactly what goes wrong in cells that carry such defects, and could help researchers find ways to correct those problems. SCORE is an important application of CRISPR, a research tool that is changing the way scientists "edit" genomes in the lab.

JOURNAL: *Nature Neuroscience* February 1, 2016

JAMES F. GUSELLA, PH.D.
Harvard University/Massachusetts General Hospital

2007 NARSAD Distinguished Investigator Grant

MICHAEL E. TALKOWSKI, PH.D.
Harvard University/Massachusetts General Hospital

2012 NARSAD Young Investigator Grant

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NEXT-GENERATION TREATMENTS: DEPRESSION

Opioid Medication Combo Helps Patients Who Don't Respond to Antidepressants

Reviving an old treatment for mood problems, researchers find that adding certain opioid medications to depression treatment can help patients who don't respond well to conventional antidepressants. When Dr. Fava's team gave a combination of opioid medication and antidepressants as an adjunct therapy to patients who had not responded to antidepressants alone, these patients saw greater improvements than their peers who received only antidepressants. The drug combination consisted of buprenorphine, an opioid medication, and samidorphan, an opioid antagonist included to block those effects of buprenorphine that are associated with its addictive potential. All patients continued on their current antidepressant therapy and on the same dosage throughout the course of the study.

JOURNAL: *American Journal of Psychiatry* February 12, 2016

MAURIZIO FAVA, M.D.
Harvard University/ Massachusetts General Hospital

1994 NARSAD Young Investigator Grant

*Team included: 2002 Independent Investigator and 1992 Young Investigator Madhukar H. Trivedi M.D.

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NEXT-GENERATION TREATMENTS: SUICIDE, DEPRESSION

Important Discovery by Foundation-Supported Researchers Explains How Ketamine Exerts its Rapid Antidepressant Effects

Ketamine, a drug approved long ago as an anesthetic but used recently on an experimental basis to treat resistant major depression, exerts rapid antidepressant effects in many patients, including those contemplating suicide. The new research suggests it may be possible to separate ketamine's benefits from its serious unwanted side effects. Inside the body, ketamine is broken down and forms several new compounds, called metabolites. The team discovered that one of these metabolites—a molecule called hydroxynorketamine (HNK)—can by itself generate the antidepressant effects seen in keatamine. Efforts are under way to develop and test an HNK-like drug in animals and then people.

JOURNAL: *Nature,* May 4, 2016

TODD DENTON GOULD, M.D.
National Institute of Mental Health (NIMH/NIH)

2013 NARSAD Independent Investigator Grant
2010 & 2004 NARSAD Young Investigator Grant

CARLOS A. ZARATE, M.D.
National Institute of Mental Health (NIMH/NIH)

2011 Foundation Bipolar & Mood Disorder Research Prizewinner
2005 NARSAD Independent Investigator Grant
1996 NARSAD Young Investigator Grant

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NEXT-GENERATION TREATMENTS: MULTIPLE ILLNESSES

Treatment with Immune-Regulating Gut Bacteria May Boost Immune System Against Stress

Risk for psychiatric disorders ranging from depression to PTSD to schizophrenia is thought by some scientists to be linked to elevated levels of inflammation. By exposing mice to bacteria that help regulate the immune system, a team* led by Dr. Lowry was able to prevent stress from causing harmful inflammation, and in some cases, symptoms of illness. The researchers injected mice with a bacterium *called M. vaccae, w*hich is abundant in soil and has immune system-regulating effects. This prevented mice from getting colitis when put in highly stressful situations. In stressed mice, the treatment had anti-anxiety and fear-reducing effects. The findings can help researchers develop microbiome- and immunoregulation-based strategies to prevent disorders related to stress**.**

JOURNAL: *Proceedings of the National Academy of Sciences,* May 31, 2016

CHRISTOPHER A. LOWRY, PH.D.
University of Colorado, Boulder

2010 & 2007 NARSAD Young Investigator Grant

*Team included: 2005 Independent Investigator Monika Fleshner, Ph.D. and 2013 NARSAD Independent Investigator Charles L. Raison, M.D

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NEXT-GENERATION TREATMENTS: DEPRESSION

Brief Course of Psychotherapy Benefits Moms with Major Depression and Their Children

Children whose mothers have depression are more likely than others to develop childhood psychiatric illnesses. Dr. Swartz and colleagues now show that these children do better when their mothers are treated for depression and their symptoms improve. Previously, such studies had involved women whose depression was treated with medication, not psychotherapy. 168 mothers participated in nine 45-minute psychotherapy sessions over three months. For one group, the therapy was specifically focused on the mother's relationship with her child. Treatments helped all mothers, but those children whose mothers were in the latter group had fewer mental health visits and were prescribed fewer antidepressant medications during the study than children whose mothers underwent the general therapy.

JOURNAL: *Journal of the American Academy of Child & Adolescent Psychiatry,* June 2016

HOLLY A. SWARTZ, M.D.
University of Pittsburgh

2006 NARSAD Young Investigator Grant

*****Team included: 2006 Ruane Prizewinner and 2001 Distinguished Investigator David A. Brent, M.D.; 1998 Distinguished Investigator Ellen Frank, Ph.D.; and 2002 Independent Investigator John C. Markowitz, M.D., Pharm.D

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EARLY INTERVENTION/DIAGNOSTIC TOOLS: PSYCHOSIS

New Tool Calculates Patients' Personal Psychosis Risk

Most people who develop schizophrenia and other disorders involving psychosis (including some cases of bipolar disorder and depression) experience subtle changes in belief, thought, and perception that precede the onset of full psychosis. But fewer than 35 percent of people with these subtle changes actually develop full psychosis within three years of being identified as high-risk. Those who do become ill fare best when treated early. A team* led by Dr. Cannon developed a new risk calculator to identify them, using data from 596 high-risk individuals. Dr. Carrión led another team* that validated the risk calculator in a separate group of 210 high-risk individuals. The most important warning signs were: higher levels of unusual thought content and suspiciousness, as compared with others; lower verbal learning and memory capacity, slower cognitive processing, and greater decline in social functioning.

JOURNAL: *American Journal of Psychiatry,* July 1, 2016 [both papers]

TYRONE D. CANNON, PH.D.
Yale University

2006 NARSAD Distinguished Investigator Grant
1997 NARSAD Independent Investigator Grant

RICARDO E. CARRIÓN, PH.D.
Zucker Hillside Hospital Campus of the Feinstein Institute for Medical Research

2012 NARSAD Young Investigator Grant

*More than a dozen NARSAD grantees helped develop and validate the risk calculator. Dr. Cannon's team included: 2005 & 2003 Young Investigator Carrie E. Bearden, Ph.D.; 1999 & 1992 Young Investigator Kristin Cadenhead, M.D.; 1990 Young Investigator Robert Heinssen, Ph.D.; Scientific Council Member, 2007 Independent Investigator & 2001 Young Investigator Daniel H. Mathalon, M.D., Ph.D.; 1997 Distinguished Investigator Thomas H. McGlashan, M.D.; 2004 & 1998 Independent Investigator Larry J. Seidman, Ph.D.; Scientific Council Member, 2010 Lieber Prizewinner and 1998 Distinguished Investigator Ming T. Tsuang,M.D., Ph.D., D.Sc.; 1989 Distinguished Investigator Elaine F. Walker, Ph.D.; and 2005 Distinguished Investigator and 1998 Independent Investigator Scott W. Woods, M.D.

Dr. Carrión's team included 2004 Young Investigator Andrea Auther, Ph.D.; Scientific Council Member, 2001 Klerman Prizewinner, 2007 Distinguished Investigator, 1997 & 1994 Young Investigator, Cameron S. Carter, M.D.; 2012 Young Investigator Tara A. Niendam, Ph.D.; and 1996 Young Investigator Stephan F. Taylor, M.D.

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NEXT-GENERATION TREATMENTS: DEPRESSION

Treating Metabolic Problems Improves Symptoms of Some Patients with Refractory Depression

Dr. Pan and colleagues* have discovered that some people who suffer from major depression may benefit from the diagnosis and treatment of metabolic deficiencies. These are abnormal levels of the byproducts of basic bodily and cellular functions -- in this case as detected in the blood, plasma, urine, and cerebrospinal fluid (which circulates in the spinal cord and brain). In a study of patients with treatment-resistant depression, about two-thirds had metabolic deficiencies that affect the brain's ability to produce neurotransmitters. Patients' depression symptoms declined significantly when these metabolic problems were treated. Some reached remission. The most common of the deficiencies observed in participants was in levels of cerebral folate, which is treatable with folinic acid.

JOURNAL: *American Journal of Psychiatry* August 13, 2016

LISA A. PAN, M.D.
University of Pittsburgh School of Medicine

2012 NARSAD Young Investigator Grant

*Team included: 2006 Ruane Prizewinner and 2001 Distinguished Investigator David A. Brent, M.D.

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BASIC RESEARCH: SCHIZOPHRENIA

Researchers Catalog Subtle but Widespread Schizophrenia-Associated Differences in Gene Activity

Dr. Sklar led a large team* that identified nearly 700 genes whose activity levels differ in the brains of people with schizophrenia compared to those without it. Most of the differences were subtle, consistent with the idea that variations in many genes contribute to the risk of schizophrenia, each alone having a small effect. The team compared the activity of genes within the brain whose sequences had previously been shown to vary in small but significant numbers of patients. They manipulated the activity of five of the schizophrenia-linked genes in zebrafish (a "model organism" often used for genetics experiments), and found three genes whose alteration disrupted brain development. Other researchers can now extend the team's findings by further exploring genes on the list to begin teasing out the molecular basis of schizophrenia.

JOURNAL: *Nature Neuroscience* September 26, 2016

PAMELA B. SKLAR, M.D., PH.D.
Icahn School of Medicine at Mount Sinai

Scientific Council Member
2016 Colvin Prizewinner
2006 NARSAD Independent Investigator Grant
1998 & 1995 NARSAD Young Investigator Grant

*Team included: 2016 Independent Investigator and 2012 Young Investigator and Kristen Jennifer Brennand, Ph.D.; Scientific Council Member Joseph D. Buxbaum, Ph.D.; Scientific Council Member, 2009 Lieber Prizewinner and 1999 Distinguished Investigator, Raquel E. Gur, M.D., Ph.D.; 2010 Independent Investigator, 2002 and 2000 Young Investigator and Chang-Gyu Hahn, M.D., Ph.D.; 1996 Distinguished Investigator Vahram Haroutunian, Ph.D.; 1997 Young Investigator Scott E. Hemby, Ph.D.; Scientific Council Member, 2005 Lieber Prizewinner and 2008 Distinguished Investigator David A. Lewis, M.D.; 1994 Young Investigator Barbara K. Lipska, Ph.D.; 2013 Young Investigator Edwin C. Oh, Ph.D.; 2006 Young Investigator Shaun Matthew Purcell, Ph.D.; 2013 Young Investigator Panagiotis Roussos, M.D., Ph.D.; 2015 Young Investigator Douglas Ruderfer, Ph.D.; 2013 Young Investigator Eli Ayumi Stahl, Ph.D.; and 2014 Lieber Prizewinner and 2010 Distinguished Investigator Patrick F. Sullivan, M.D., FRANZCP

The Brain & Behavior Research Foundation is committed to alleviating the suffering of mental illness by awarding grants that will lead to advances and breakthroughs in scientific research. The Foundation funds the most innovative ideas in neuroscience and psychiatry to better understand the causes and develop new ways to treat brain and behavior disorders.

Since 1987, the Foundation has awarded more then $360 million to fund more than 4,000 leading scientists around the world. This has led to over $3.5 billion in additional funding for these scientists.

100% of donor contributions for research are invested in our grants leading to advances and breakthroughs in brain and behavior research. This is made possible by the generous support of two family foundations which cover all of the Foundation's operating expenses.

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