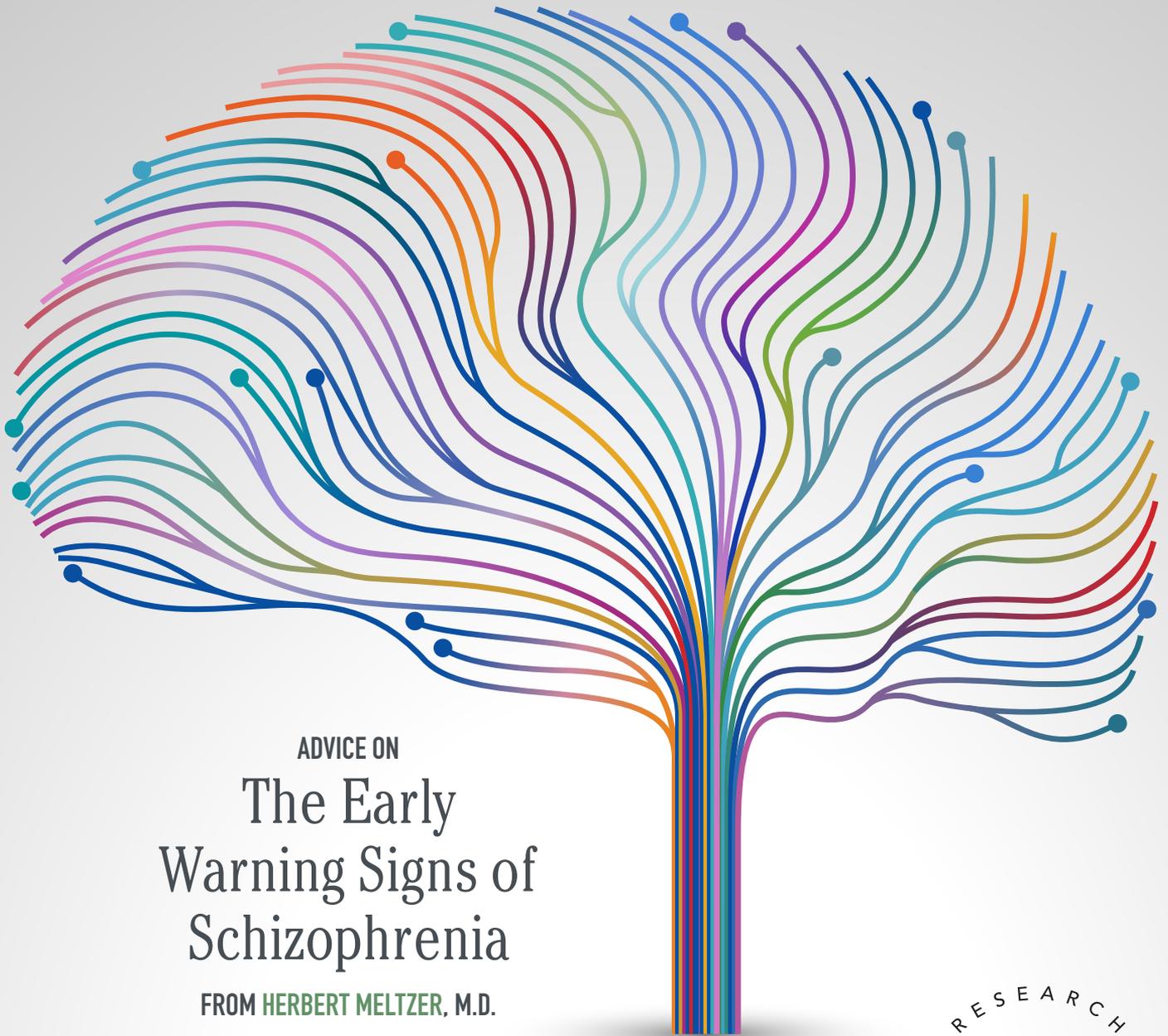


Brain & Behavior

MAGAZINE

Formerly "The Quarterly"

MARCH 2017



ADVICE ON
The Early
Warning Signs of
Schizophrenia

FROM HERBERT MELTZER, M.D.

FROM FOUNDATION YOUNG INVESTIGATOR TO
SCIENCE SUPERSTARS—NIMH DIRECTOR, JOSHUA
GORDON, M.D., PH.D. & KAY TYE, PH.D.

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Brain & Behavior Research Foundation

As the Brain & Behavior Research Foundation embarks on its 30 year anniversary, we begin the celebration by announcing the change of the name of the *NARSAD Research Quarterly* magazine to *The Brain & Behavior Magazine*.

When this publication was first circulated in 1989, its aim was to provide the most up to date information on cutting-edge neuroscientific research on mental illness. Now, more than 28 years later, we still hope we fulfill this goal, in addition to offering information that can be of practical use to families coping with the diagnosis of a behavioral disorder or mental illness in a loved one, and providing stories of inspiration about the people and families living with mental illness.

We'd also like to let you know that thanks to your support in 2016 the Foundation funded more than \$19 million in grants divided between our 15 Distinguished Investigator Grantees, approximately 80 Independent Investigator Grantees, and approximately 400 Young Investigator Grantees. As you know, our grants enable these outstanding scientists to pursue new, pioneering ideas to answer important questions or help identify new potentially game-changing targets for treatment in brain and behavior research.

For our Young Investigator Grantees especially, the awards function as seed funding for new directions in scientific research which would otherwise be impossible.

First awarded in 1987, the NARSAD Young Investigator Grant enables young scientists with innovative ideas to enter the neuropsychiatric field, garner pilot data, and often, go on to receive further funding based on their "proof of concept" for their work. Government funding for research has declined especially for young scientists, and we are at great risk of losing an entire generation of scientists.

Many scientists who have received Young Investigator Grants have moved on with distinguished and productive careers. One of the most notable is the new Director of the National Institute of Mental Health, Dr. Joshua Gordon, who received two Young Investigator Awards (2003 and 2001) and became a member of our Scientific Council in 2012. In this issue Dr. Gordon discuss the importance of those awards on his career (page 10).

We also highlight the work of another Young Investigator, Dr. Kay M. Tye, and the important new science she is researching on behavior (page 14). Dr. Tye began her research career under another former Young Investigator, Dr. Karl Deisseroth (2005), who are both conducting innovative research and are members of our Scientific Council.

Funding Young Investigator research provides support for the kind of out-of-the-box research that will offer our best hope for advancements.

We strive to make even greater scientific progress in 2017. I ask you to help us to sustain the remarkable accomplishments of scientists such as these. It is only through support for research that we can alleviate the pain and suffering of mental illness, and find the advances and breakthroughs that will result in better treatments and hope for cures.

Sincerely,

A handwritten signature in black ink that reads "Jeff Borenstein".

Jeffrey Borenstein
President & CEO

The 2016 Pardes Humanitarian Prize

On October 28, 2016 the Brain & Behavior Research Foundation hosted its 29th annual International Awards Dinner, honoring the year's Outstanding Achievement Prizewinners (featured in the Symposium story on page 6), as well as the recipients of the Pardes Humanitarian Prize in Mental Health, at the Pierre Hotel in New York City.

This year's Pardes Prize recipients were Vikram Patel, Ph.D., F.Med.Sci., for his transformative work in advancing mental health care in resource-poor countries and Charles F. Reynolds, III, M.D., for his pioneering work in geriatric psychiatry and the prevention and treatment of late-life depression. An Honorary Tribute was given to the late Senator Edward M. Kennedy for his powerful and unwavering commitment to advocating on behalf of people with mental illness.

The Pardes Humanitarian Prize in Mental Health is awarded annually to recognize individuals whose contributions have made a profound and lasting impact in advancing the understanding of mental health and improving the lives of people suffering from mental illness. It focuses public attention on the burden mental illness places on individuals and society, and the urgent need to expand mental health services globally. Established in 2014, The Pardes Humanitarian Prize in Mental Health is named in honor of noted psychiatrist Herbert Pardes, M.D., who leads the Foundation's Scientific Council.

Recognized by *Time* magazine in 2015 as one of the '100 Most Influential People in the World', Dr. Patel addresses the stunning void of mental health care in developing countries and the grave shortage of psychologists and psychiatrists. He has been a vocal advocate for the development of mental health services in these countries and promotes practical solutions to improving mental health care by teaching ordinary people to deliver front-line mental health care to address the unmet need for care for people with mental illnesses. His

2003 manual, "Where There Is No Psychiatrist," has been translated into a dozen languages and used by community healthcare workers worldwide.

Dr. Patel is the co-founder of Sangath, a Non-Governmental Organization (NGO) in Goa, India, which won the 2008 MacArthur Foundation's International Prize for Creative and Effective Institutions. Sangath is a pioneer in training lay people to deliver healthcare treatments and interventions to their communities.

Dr. Reynolds and his colleagues have made groundbreaking contributions to the prevention and treatment of depression in older adults. Depression has been identified by the World Health Organization as a leading cause of disability worldwide and a major contributor to the global burden of disease across the life cycle.

Dr. Reynolds helped to define a new global health priority as depression prevention in older adults, now recognized as a feasible public health goal. He and his colleagues have also demonstrated that depression treatment reduces both suicidal risk and cancer-related mortality risk in elderly medical patients, and his work has informed long-term treatment strategies to prevent recurrence and to delay dementia in depression with mild cognitive impairment.

Dr. Reynolds leads an NIMH study with the Goa Medical College/India and with Sangath to develop and test a scalable model of depression prevention. Building upon the contribution of Pardes Prize co-recipient Dr. Vikram Patel, this work uses lay health counselors for early intervention in mildly symptomatic older adults, thereby optimizing scarce mental health resources to prevent depression onset. The NIMH-sponsored center in late life mood disorders, which Dr. Reynolds directs at the University of Pittsburgh School of Medicine, has mentored 25 research-career development (NIH K) awardees since 1995.



Dr. Herbert Pardes

Dr. Jeffrey Borenstein, Dr. Vikram Patel, Dr. Herbert Pardes, Dr. Charles Reynolds and Patrick Kennedy—Pardes Humanitarian Prize and Honorary Prizewinners

Drs. Eric and Denise Kandel

Lieber & Maltz Prizewinners—Dr. William Horan, Dr. Amanda McCleery, Dr. Michael Green and Dr. Stephen Marder of UCLA

in Mental Health

Dr. Vikram Patel said, "I am honored and humbled to receive the Pardes Humanitarian Prize. Mental illness is a global issue affecting millions, the majority of whom live in the developing world and who have limited access to appropriate mental health care and often live terrible lives on the margins of their communities. I accept this Prize on behalf of them and pledge to redouble my efforts to address the burden of mental health problems globally, and especially amongst those who are socially disadvantaged or living in low resource settings."

Dr. Charles F. Reynolds, III, said, "It is a privilege and an honor to be a recipient of the Pardes Humanitarian Prize. In our youth-focused culture, the elderly and their struggles with mental illness are often overlooked and neglected. Late-life depression is a global health priority that has immense impact on older individuals and their families. It is my sincere hope that as a society we can work to restore the joy of living to older adults affected by mental illness."

Dr. Pardes commented, "Dr. Patel and Dr. Reynolds exemplify what it means to be a humanitarian. Dr. Patel's mission is to bring desperately needed psychiatric care to people living in countries where access to these services is limited or non-existent. Dr. Reynolds is a pioneer in geriatric psychiatry whose mission is to help the elderly lead full and productive lives in their later years. We honor them both for their outstanding commitment to alleviating the pain and suffering of mental illness."

Each year the esteemed International Selection Committee also chooses an Honorary Pardes Humanitarian Prize recipient. This person is a public figure whose chosen field of work is outside the mental health arena but whose extraordinary contribution has been transformative and of great magnitude to those living with mental illness and their families.

Senator Edward M. Kennedy was recognized posthumously with a Pardes Humanitarian Prize honorary tribute. His unflagging dedication to mental health embodies the essence of the Prize. His tireless efforts to affect lasting change through critical government legislation have had a profound and enduring impact on advancing the understanding of and advocacy for mental health. The honor was accepted by former Congressman Patrick J. Kennedy on behalf of his distinguished father. Patrick Kennedy continues to carry the Kennedy family torch for the mentally ill with passion, vision and unbridled energy.

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Highlights from the International Mental Health Research Symposium

On October 28, 2016, The Brain & Behavior Research Foundation held its' 28th International Mental Health Research Symposium, with presentations by top researchers in the field of mental illness. The symposium at the Kaufmann Music Center in New York City was moderated by Dr. Robert Hirschfeld and featured research talks by nine of the foundation's 2016 outstanding achievement prizewinners, along with two promising young investigator grantees.



Symposium Moderator,
Dr. Robert Hirschfeld

Symposium Commentator,
Dr. Alan Schatzberg

Keynote Speaker,
Robert Boorstin

2016 LIEBER PRIZE FOR OUTSTANDING ACHIEVEMENT IN SCHIZOPHRENIA RESEARCH

Michael F. Green, Ph.D.

Professor

*Semel Institute for Neuroscience and Human Behavior
at UCLA*

Director

*VA Research Enhancement Award Program (REAP) on
Enhancing Community Integration for Homeless Veterans*

Director

*Treatment Unit, VA VISN 22 Mental Illness
Research, Education, and Clinical Center (MIRECC)*

Dr. Green discussed what he called one of the largest mysteries about schizophrenia: why daily functioning is so difficult. The impaired domains that influence daily functioning in schizophrenia include cognition, social cognition and motivation. Problems in social cognition (i.e., identifying emotions in faces and voices, inferring other people's thoughts and feelings) are common in schizophrenia, even at the beginning of the illness.

Recent developments in social neuroscience give us insights into the systems that comprise the human social brain and help people to navigate their social worlds, Green said. His lab has focused on understanding several of these social processing systems in schizophrenia using non-invasive approaches, such as functional magnetic resonance imaging (fMRI) and electrophysiology (EEG). By building a social neuroscience roadmap with these data, it is possible to divide social processing systems into those that are intact versus those impaired in schizophrenia. Such a roadmap also has implications for new ways to treat schizophrenia. This information about brainbased social processing systems in the disorder provides ways to thoughtfully develop pharmacological and training interventions for these processing deficits.

"We have a large, productive and cohesive research team thanks in large part to the fact that most members of our team received NARSAD grants at critical junctures in their careers," Green said at the symposium. "In many respects, my receipt of the Lieber Award reflects collaborations with colleagues who initially established and then maintained their careers based on the vision and generosity of the Liebers."

Stephen R. Marder, M.D.

Daniel X. Freedman Professor of Psychiatry Vice Chair for Education in Psychiatry, and Director, Section on Psychosis

*Semel Institute for Neuroscience and Human Behavior
at UCLA*

Director

*VA Desert Pacific Mental Illness Research, Education,
and Clinical Center*

2011 Distinguished Investigator

Dr. Marder, also a 2016 Lieber Prizewinner, led the NIMH-MATRICES (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative with Dr. Green, to address key issues in the development of medications for improving cognition in schizophrenia. In his symposium presentation, Dr. Marder provided an overview of recent progress in discovering treatment approaches that may improve patients' functioning and quality of life.

He and his colleagues have focused on characterizing the impairments in schizophrenia that are most closely related to functioning, improving our understanding as to how these impairments are related to brain circuits, and encouraging the development of pharmacological and nonpharmacological interventions that address these problems.

Dr. Marder presented findings from his study of a psychosocial training intervention developed by Dr. Green and Dr. William P. Horan, Ph.D., that focuses on social cognition. The researchers found that doing this along with medication works to learn empathy skills.

2016 MALTZ PRIZE FOR INNOVATIVE & PROMISING SCHIZOPHRENIA RESEARCH

William P. Horan, Ph.D.

Research Psychologist

*Department of Psychiatry and Biobehavioral Sciences
University of California, Los Angeles*

Clinical Research Psychologist

Veterans Administration Greater Los Angeles

Faculty

*VA VISN 22 Mental Illness Research, Education,
and Clinical Center (MIRECC)*

2008, 2004 Young Investigator

Amanda McCleery, Ph.D.

Assistant Research Psychologist

*Semel Institute for Neurosci-
ence and Human Behavior
at UCLA*

*VA Greater Los Angeles Health-
care System VISN 22 MIRECC*

2015 Young Investigator



Drs. McCleery and Horan

Drs. Horan and McCleery discussed their work in better understanding the impairment of social cognition in schizophrenia and applying this knowledge to new interventions that target social cognition as a means to improving how patients with schizophrenia function in communities. Dr. McCleery reviewed recent developments in the effort to develop non-invasive methods for assessing neuroplasticity—the ability of the brain to reorganize itself based on experiences—in humans. More research on neuroplasticity may be helpful for understanding both the causes and treatment of cognitive impairment in schizophrenia. In his talk, Dr. Horan discussed a new group-based intervention to improve social cognition in schizophrenia, which addresses factors such as the ability to recognize social cues in faces and in non-verbal gestures, empathy, and the ability to understand social situations from the perspective of others.

2016 COLVIN PRIZE FOR OUTSTANDING ACHIEVEMENT IN MOOD DISORDERS RESEARCH

Francis J. McMahon, M.D.

Senior Investigator and Chief

Human Genetics Branch

National Institute of Mental Health
Intramural Research Program

2006, 1998 Independent Investigator

1994 Young Investigator

Thomas G. Schulze, M.D.

Professor and Director

Institute of Psychiatric Phenomics and Genomics (IPPG)
Medical Center of the University of Munich

Adjunct Faculty

Department of Psychiatry and Behavioral Sciences
Johns Hopkins University

Associated Investigator

Human Genetics Branch

National Institute of Mental Health Intramural Program

2007, 2002 Young Investigator

Pamela Sklar, M.D., Ph.D.

Founding Chief

Division of Psychiatric Genomics

Vice-Chair

Department of Genetics and Genomics Sciences

Professor

Departments of Psychiatry, Neuroscience,
and Genetics and Genomic Sciences
Icahn School of Medicine Mount Sinai

Scientific Council Member

2006 Independent Investigator

1998, 1995 Young Investigator

Drs. McMahon, Schulze and Sklar are all pioneers in the field of psychiatric genetics, which has made substantial contributions to our understanding of schizophrenia and bipolar disorder over the past two decades. At the symposium, Dr. Schulze discussed his work on large-scale collaborative efforts and major developments in molecular biological technologies, in particular genome-wide association studies (GWAS) that have helped identify well over one hundred vulnerability genes for schizophrenia. By studying common genetic markers, Dr. McMahon and his colleagues have found that many different genes are associated with bipolar disorder as well. They have also discovered that some of the same genetic markers associated with bipolar disorder influence risk for depression and other mental illnesses. In Dr. Sklar's research, she and her colleagues have shown that a very large number of schizophrenia genetic risk regions are also responsible for genetic risk of bipolar disorder, a discovery that is leading to a re-evaluation of the classification of the major psychiatric disorders.



Dr. Pamela Sklar

2016 RUANE PRIZE FOR OUTSTANDING ACHIEVEMENT IN CHILD & ADOLESCENT PSYCHIATRIC RESEARCH

John L.R. Rubenstein, M.D., Ph.D.

Nina Ireland Distinguished Professor in Child Psychiatry

University of California at San Francisco

Scientific Council Member

1997 Distinguished Investigator

1992, 1990 Young Investigator

Dr. Rubenstein spoke about his 30 years of research towards explaining fundamental genetic mechanisms that control multiple steps in the development of brain structures (specifically the cortex and basal ganglia) that are at the core of human cognition and emotion. His laboratory's research has led to many discoveries, including an understanding the function of genes that increase autism spectrum disorder risk; deciphering the components of the gene-transcribing circuitry which will facilitate understanding of gene network defects in neuropsychiatric disorders; seeking and describing the mechanisms that underlie subtypes of neuropsychiatric disorders; and devising stem cell approaches for understanding and treating these disorders.

2016 GOLDMAN—RAKIC PRIZE FOR OUTSTANDING ACHIEVEMENT IN COGNITIVE NEUROSCIENCE

Earl K. Miller, Ph.D.

Picower Professor of Neuroscience

Massachusetts Institute of Technology

Dr. Miller discussed how he and his colleagues use experimental and theoretical approaches to study the neural basis of high-level cognitive functions. His focus is on the frontal lobe, the region of the brain most studied in humans and linked to neuropsychiatric disorders. His laboratory has provided insights into how categories, concepts and rules are learned, how attention is focused, and how the brain coordinates thought and action. Innovative techniques developed in Dr. Miller's lab help to study the activity of many neurons in multiple brain areas simultaneously, which has provided insight into how different brain structures interact and collaborate. This work has established a foundation upon which to construct more detailed accounts of how cognitive control is implemented in the brain, and its dysfunction in diseases such as autism spectrum disorder, schizophrenia and attention deficit disorder.

The Prizewinners are selected by special committees of the Foundation's Scientific Council, a volunteer group of 173 preeminent mental health professionals in brain and behavior research. The day's presenters also included keynote speaker Robert O. Boorstin, Senior Vice President of Albright Stonebridge Group, who spoke about his per-

2016 YOUNG INVESTIGATOR PRESENTATIONS

Tracy Butler, M.D.

Research Assistant Professor of Neurology and Psychiatry

New York University

Medical Director

NYU Center for Brain Health

2015 Young Investigator

Timothy Mariano, M.D., Ph.D., MSc.

Instructor

Harvard Medical School

Associate Psychiatrist

Brigham and Women's Hospital

2015 Young Investigator

Dr. Butler discussed her research on military personnel diagnosed with post-traumatic stress disorder (PTSD) and depression, and the evidence for whether some of these patients with a history of traumatic brain injury may actually be suffering from chronic traumatic encephalopathy or CTE. Results from this project could have significant implications for the diagnosis, treatment and understanding of both PTSD and brain injury. Dr. Mariano presented his research on a noninvasive form of brain stimulation, called transcranial direct current stimulation (tDCS), and its use in treating the anxiety and depression that may result from chronic low back pain. If successful, his study would be a first demonstration of tDCS's ability to alleviate the depressive symptoms of chronic pain.



Drs. Tracy Butler and Timothy Mariano, 2015 Young Investigator Grantees

sonal and political reflections on mental health after his diagnosis with manic depression in 1987.

Later that evening, the nine Outstanding Achievement Prizewinners were honored at the Foundation's International Award Dinner at the Pierre Hotel in New York City.

Photo Credit: Chad David Kraus and Charles Manley



Two Early NARSAD Grants Helped Launch the Career of the Nation's New NIMH Director

JOSHUA GORDON, M.D., Ph.D.

*Director, National Institute of Mental Health
Scientific Council*

2003 & 2001 Young Investigator

BY PETER TARR, Ph.D.

Joshua Gordon, M.D., Ph.D., remembers being deeply impressed during college with a mentor who was devoted not just to research—about genes whose activation sends cells on a path toward cancer—but also to using knowledge about these “oncogenes” to help doctors all over the world assess their patients’ tumors, enabling better treatment decisions.

“That marriage between learning something basic about how biology works and intimately linking it with issues of direct relevance to patient care” not only impressed Gordon, but became a model for his future work in neuroscience.

In July 2016, the Director of the National Institutes of Health, Dr. Francis Collins, announced that Dr. Gordon, most recently of Columbia University, would become the next Director of the National Institute of Mental Health (NIMH), filling a vacancy left by the departure of Dr. Thomas Insel, who led the Institute for the past 13 years.

Dr. Gordon, who received career-shaping NARSAD Young Investigator Grants in 2001 and 2003, was described by Dr. Collins as “a visionary psychiatrist and neuroscientist with deep experience in mental health research and practice.” He is the fifth individual with important connections to the Foundation to lead our nation’s agency devoted to advancing research and treatment of mental illness—the largest such institution in the world.

Past leaders of the NIMH include Herbert Pardes, M.D., Founder and President of the Brain & Behavior Research Foundation’s Scientific Council, and Foundation Scientific Council Members Frederick Goodwin, M.D., Stephen Hyman, M.D., and Lewis Judd, M.D.

We spoke with Dr. Gordon about his goals for the NIMH and about his own research on brain circuitry whose promise helped catapult him into a position of international prominence in neuroscience. One of Dr. Gordon’s foremost priorities at the NIMH echoes the lesson of his college mentor. “I have an interest in trying to move from techniques that enable us to learn about the brain—by studying how its neural circuits work—toward ways of using this new knowledge to develop new treatments.” His own lab’s recent research demonstrates how the two paths—basic and applied research—can support and amplify one another. (See side bar, next page)

In both mental health and mental illness, the importance of neural circuits—whose trillions of connections give rise to consciousness, enable perception, and make possible all of our

responses to the world around us—is self-evident. But how

to make sense of these myriad linkages over which messages between hundreds of millions of neurons pass every second and how to mobilize this knowledge in developing next-generation treatments—these are among the great questions of modern science.

Dr. Gordon’s devotion to the brain and to a career in neuroscience began with neural circuits. In 1990, he was attending a conference in Washington, D.C. and heard a lecture about micro-stimulation. “The investigators used small electric currents to change the activity patterns in a monkey’s brain. As the patterns changed, so did the monkey’s behavior. That was astonishing to me. It was a fascinating, if rudimentary, example of the relationship between patterns of brain activity and patterns of behavior,” Dr. Gordon remembers.

Immediately upon returning to San Francisco, where he was then in the early part of his medical school training at U.C. San Francisco, Gordon told those in charge that he was switching his focus from molecular biology to neuroscience.

When he applied for his first NARSAD Young Investigator Grant in 2000, Dr. Gordon was in the fourth and final year of his medical residency and performing research in the laboratory of René Hen, Ph.D., at Columbia University (a 2009 and 2003 Distinguished Investigator, a 1998 Independent Investigator, and a member of the Scientific Council). Gordon’s project involved recording patterns of brain activity during behavior, which called for equipment the Hen lab did not have.

Nobel prizewinner Dr. Eric Kandel (also of the Scientific Council) graciously offered Gordon access to equipment in his own lab, but Gordon’s research time was limited. “I applied for a ‘NARSAD,’ and when I received that first grant I went out and bought myself a rig. It was the fact that I could go to NARSAD and get this early support that enabled me to launch my career,” Dr. Gordon says.

His second NARSAD Young Investigator Grant was awarded in 2003, when Gordon was a research fellow at Columbia, “and it completely enabled me to jump start things when I joined the faculty in 2004.” At Columbia, as elsewhere in the U.S., a new assistant professor is obliged to secure research funding, usually from the government, to sustain a laboratory over a period of years. “Without that second Young Investigator Grant I honestly wouldn’t have had nearly enough time on the equipment I needed to produce the data that enabled me to get that essential government award and make the



Joshua Gordon, M.D., Ph.D.

transition to research independence. Dr. Gordon was, in other words, the perfect example of the sort of researcher the Young Investigator Grants seek to identify and help: one who is unlikely to gain independence until s/he can generate experimental results of sufficient promise to draw a much larger and sustaining government grant.

Partly because of the way grants are reviewed at the government level—the need for positive early results before multi-year support is extended—one appreciates the importance of the Foundation and other philanthropies that support promising but as yet unproven young people beginning a career of research, whether in neuroscience or clinical psychiatry.

“Just looking at my case it’s pretty clear there are gaps, where government funding isn’t there,” Dr. Gordon says. “And while it’s reasonable to ask how we might fill those gaps from a government perspective, the fact that a philanthropic organization like the BBRF can jump in, in a much more flexible way, is incredibly crucial to the research enterprise.”

CONTINUING THE CONVERSATION WITH DR. GORDON

IN SCHIZOPHRENIA, THE PROSPECT OF RESTORING NEURAL SYNCHRONY TO ADDRESS COGNITIVE DEFICITS

Long before the advent of modern neuroscience, those who have cared for and spent time with people living with schizophrenia have described the disorder in terms of a “disconnection.” Patients who experience the hallucinations and delusions that characterize psychosis, for example, may seem to be “disconnected” from the reality that others around them are experiencing.

The research of Dr. Joshua Gordon and his colleagues has provided scientific support for the notion of schizophrenia as a kind of “disconnection syndrome,” although in a way that is not at all obvious, and in fact doesn’t refer to dramatic, manifested symptoms like a person hearing voices. Rather, Dr. Gordon’s work has shed new light on the so-called cognitive symptoms of schizophrenia: debilitating yet less visible deficits in memory, attention and learning. These are aspects of the illness that tend to, more often than other symptoms, prevent people from integrating successfully in society. That’s because they directly affect their capacity to think clearly, communicate, and work.

Dr. Gordon’s research has centered on the concept of neural synchrony. “Synchrony,” he explains, “literally means things that are happening together in time.” In the brain, synchrony can be measured in two basic ways. “At the local level — say, in a single area of the brain like the hippocampus or the cortex, synchrony can mean that neurons within that area tend to fire together, and become silent together.” In the language of neuroscience, neurons within brain regions can exhibit synchrony in activation and inhibition.

The other fundamental kind of synchrony in the brain is coordination across different brain regions. “This makes intuitive sense,” Dr. Gordon suggests. “Imagine, for instance, that the hippocampus needs to work together with the prefrontal cortex on a particular task. To accomplish this work, you would imagine that things work better when the two regions are working in synchrony.”

While a logical idea, in science, this is really nothing more than a hypothesis. It needs to be proven in order for us to learn anything useful from it. This is exactly what some of Dr. Gordon’s research has accomplished. It turns out that different kinds of synchrony have been observed in the brain using different technologies. Watching parts of the brain function in an MRI scanner while a person performs a task has, for instance, revealed certain patterns of activity within and between brain regions. Those patterns play out on a time scale of seconds.

The kind of patterns Dr. Gordon scrutinizes occurs over much more compressed time intervals, on the order of hundredths of a second. His focus is on patterns that arise from electrical activity in the brain—activity that helps move messages from neuron to neuron in the almost incomprehensibly dense thicket of cells and the “wires” that are packed into our most complex organ. Electrical patterns—popularly referred to as brain waves—have long been measurable with a technology called EEG—electroencephalography.

With EEG, characteristic patterns of fluctuation in electrical activity within and across brain regions have been delineated. Within a structure like the hippocampus, for example, one fluctuation in electrical signals, called a theta wave, warbles

eight times per second in what Dr. Gordon describes as a kind of “up—and—down, up—and—down” pattern. At the same time, other types of waves “ride” on top of that signal. Gamma waves in the hippocampus fluctuate 40 times per second. When the hippocampus is in synch, the relation of the slower wave to the faster is such that together they appear almost to regulate one another—the frequency of each keying off of and thus appearing to keep that of the other “in synch.”

These patterns are more than mere scientific curiosities. In 2010, Dr. Gordon, working with his frequent collaborator Dr. Joseph A. Gogos of Columbia University, an authority on the genetics of schizophrenia who has developed and studied several important mouse models of the illness, studied brain waves in mice as they tried to navigate through a maze. Their experiments showed that there is synchrony not only locally, within two key brain regions—the hippocampus and the medial prefrontal cortex—but between them as well.

“Not only can we measure that there is synchrony, but we can measure how strong it is,” Dr. Gordon explains. “It depends on what the animal is doing, behaviorally.” In making its way through a maze, a rodent has to process information about where it is—spatial information—and it must remember where it has just been—tapping short-term memory—if it is to reach the piece of cheese at the end of the maze. In a healthy mouse, “when the animal is doing a working memory task [like remembering where it has just been], you see an enhancement in synchrony between the hippocampus and the prefrontal cortex,” says Dr. Gordon. But here’s the key point: things were different in the mice that Dr. Gogos had developed to mimic some of the key symptoms of schizophrenia.

These mice were bred with a genetic defect called 22q11 deletion syndrome—a mutation on chromosome 22 that is seen in a subset of people with schizophrenia and is thought to be powerful enough to cause the illness. When these mice navigated a maze, synchrony between the hippocampus and prefrontal cortex was weaker than in healthy mice. “This suggested to us that perhaps working memory is impaired in schizophrenia because those two brain regions are not working together properly,” Dr. Gordon says.

In the “schizophrenia” mice, the two regions were not dis-connected so much as dys-connected; they did not seem to be working in optimal synchrony. Interestingly, these experiments revealed that there was no problem with synchrony among neurons within each of the two regions, only between them. This led to more experiments, culminating in a 2015 paper in which Dr. Gordon and colleagues intentionally dis-

rupted long-range connections between the two regions in healthy mice, and observed impairments in the animals’ working memory capacity. Disrupting specific kinds of brain waves led to another interesting observation: what is specifically lost in the observed dys-synchrony between the prefrontal cortex and hippocampus was the mouse’s ability to encode new information and thus keep in mind the spatial location of its goal as it navigated a maze.

In 2016, another exciting step forward in the research: in mice with 22q11 deletion syndrome, modeling human schizophrenia, Dr. Gordon and colleagues confirmed that working memory deficits precisely affected the animals’ ability to mentally represent the location of their goal, due to a lack of synchrony between the hippocampus and prefrontal cortex. What remains to be shown, Dr. Gordon says, is whether the problem identified in the 22q11 mice crops up in mice with

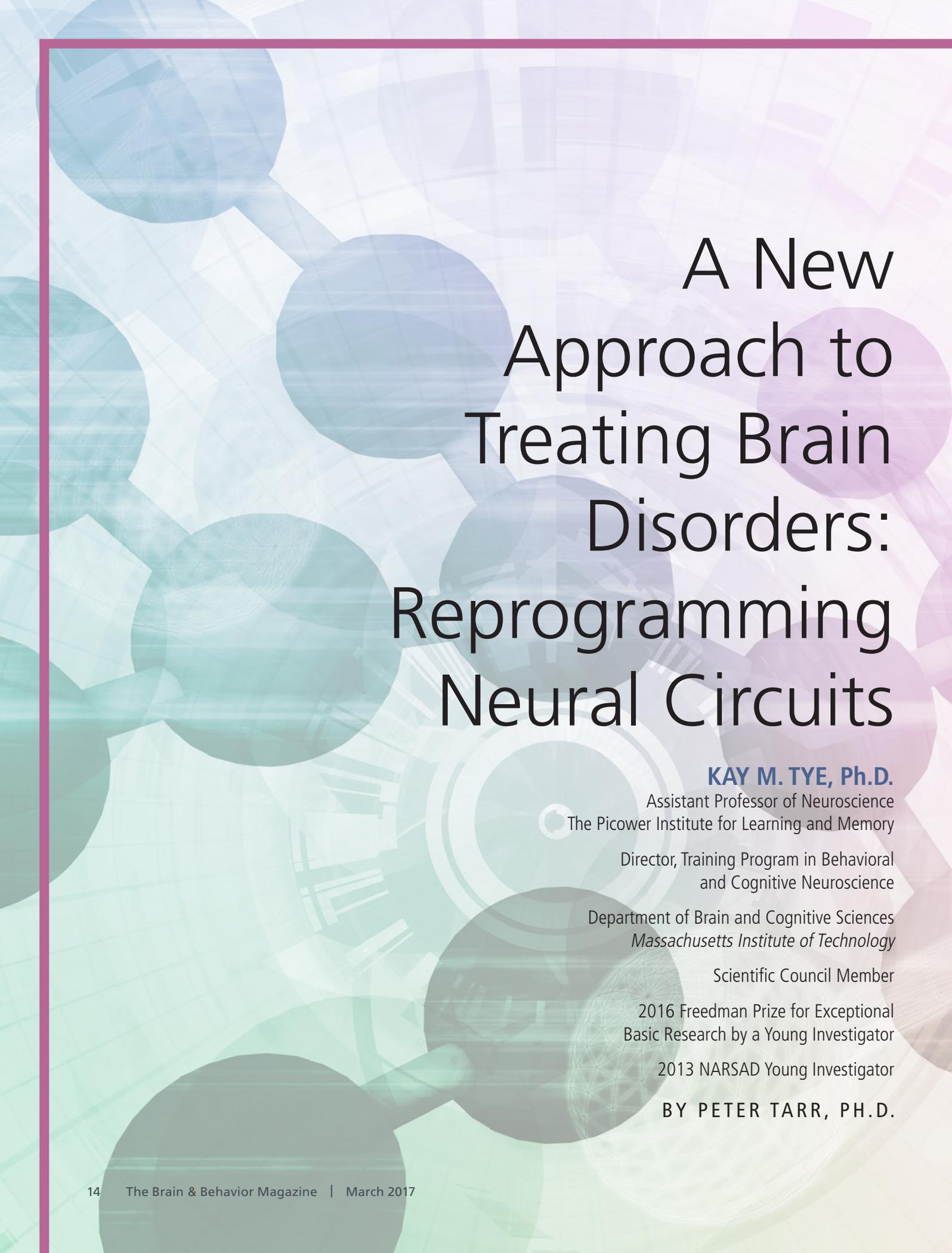
other genetic defects that give rise to schizophrenia-like symptoms. Another question, more difficult to answer, is whether people with 22q11 deletion syndrome have the synchrony problem that mice do.

The most exciting question, if the synchrony problem is confirmed in people, is whether it can be reversed. Dr. Gordon thinks there are several ways to attempt this, and with Dr. Gogos and colleagues has already tested one in mice, with results he calls “flabbergasting.” In mice with

22q11 deletion syndrome, the scientists gave a drug during the fetal development period. The drug inhibits GSK3, one of many proteins disrupted because of the 22q11 mutation. Administering this drug appeared to restore the integrity of long-range connections from the prefrontal cortex to the hippocampus and boosted working memory in the mice, after birth. “Whether this will be applicable in people I don’t know,” Dr. Gordon says, “but it is an astounding and wonderfully promising result.”

In a recent article in the journal *Science* reviewing advances made by another neuroscience team studying the brain, Dr. Gordon likened a brain affected by a serious neurodevelopmental disorder to “a tangled mess of threads.” The point of the metaphor, he noted in our conversation, is not to stress the tangle, but rather the absolute necessity of “following the threads all the way through,” wherever they lead. “That’s how we learn something about these devastating illnesses. We have to have the patience to learn how to untangle what is tangled—something I vividly remember my mother helping me to do when I was very young.”

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Synchrony literally means things that are happening together in time.
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A New Approach to Treating Brain Disorders: Reprogramming Neural Circuits

KAY M. TYE, Ph.D.

Assistant Professor of Neuroscience
The Picower Institute for Learning and Memory

Director, Training Program in Behavioral
and Cognitive Neuroscience

Department of Brain and Cognitive Sciences
Massachusetts Institute of Technology

Scientific Council Member

2016 Freedman Prize for Exceptional
Basic Research by a Young Investigator

2013 NARSAD Young Investigator

BY PETER TARR, Ph.D.

If you want a glimpse into the future, to know where brain research is taking us, just ask Dr. Kay M. Tye. A NARSAD Young Investigator grantee in 2013, Dr. Tye in the eight years since earning her Ph.D. in neuroscience at the Massachusetts Institute of Technology has won a bevy of top fellowships including the Society for Neuroscience Young Investigator Award as well as the NIH Director's New Innovator Award. She has been named one of the world's "35 Top Innovators Under 35" by *Technology Review*. And she has secured an assistant professorship in the Department of Brain and Cognitive Sciences at MIT's Picower Institute for Learning and Memory. This past year Dr. Tye was the recipient of the Foundation's prestigious Freedman Award, and, separately, was named a member of the Foundation's Scientific Council.

Dr. Tye speaks with infectious enthusiasm about the subject at the focus of her research: the neural circuits of emotions. Although hard to describe in rigorous scientific terms, emotions come in essentially two flavors, she says: pleasure and pain. So much of behavior has at its root the pursuit of one and the avoidance of the other. And yet, "even during the years I was in graduate school and just getting into neuroscience, most people weren't very confident that 'emotion' was something that you could come up with a mechanistic explanation for."

She was eager to take on the challenge. "What I'm most passionate about is the experience of emotion. When you think about mental illness, it comes down to the way people subjectively experience the world around them, things that are happening to them. People have long tried to describe these experiences, but what motivates me is figuring out the mechanisms that underlie the things that we think and feel."

In 2014, a head-turning viewpoint article written by Dr. Tye appeared in the prestigious journal *Neuron*. It began with this provocative sentence: "If I were to describe a future therapy for chronic, relapsing neuropsychiatric diseases, where patients with anxiety, depression, or addiction could receive a painless treatment over a few days and emerge permanently cured without any undesirable side-effects, you might think this was science fiction. "Yet this is where Dr. Tye believes brain research is heading. And we may not be as far from this vision as one might imagine, she says, although for the moment, all of Dr. Tye's research is conducted in animals, typically rodents, whose brains are remarkably similar to the human brain. Her basis for such optimism is the fact that scientists have invented technologies that enable meaningful explorations of the brain's neural circuitry—the incredi-

bly complex sets of connections within and between brain regions that carry the information underlying all of our mental processes, emotions included.

One transformative technology enabling Dr. Tye's work is optogenetics, which enables scientists to manipulate individual neurons and groups of neurons, consequently altering the operation of entire neural circuits, in some cases causing an animal's behavior to change as a result. Optogenetics performs this magic with focused beams of colored laser light that are carried into the brain via thread-thin optical fibers. It was developed by a 2005 recipient of a Young Investigator Grant, Karl Deisseroth, M.D., Ph.D. of Stanford University and colleagues, in whose lab Dr. Tye performed her postdoctoral research (winning Stanford's Post-Doctoral Award in 2010).

Dr. Tye is among the pioneers in "neural circuit reprogramming," an activity made possible in part by Dr. Deisseroth's breakthrough. Her aim is to advance therapies for psychiatric disorders beyond the current paradigm, which stresses using pharmaceuticals to tweak brain chemistry, mainly neurotransmitters, the brain's chemical messengers. Our current drugs are certainly needed now Dr. Tye fully acknowledges. But she, Dr. Deisseroth and others hope that by gaining a highly sophisticated knowledge of how particular brain circuits inform specific behaviors, a much more individualized form of treatment involving targeting specific circuits—and even specific synapses (connections between neurons) within specific circuits—will make possible the kind of therapy Dr. Tye wrote about in 2014.

"The ultimate goal," she says, "is not to have a drug treatment for depression or anxiety—a band-aid that you put on every day, often with side effects. The idea is to mobilize the brain's own resources to heal itself in some way." She means healing that lasts long-term, using methods of manipulating cells and synapses to induce plasticity—changing the strength of connections among specific neurons.

HOW IS SUCH A THING POSSIBLE?

Dr. Tye puts it this way: "The way I think about brain disease is, circuits are working, but something is a little off. Maybe there's too much transmission here, and that gives rise to anxiety; or too little transmission there, and that generates depression. We aren't quite sure what the brain's stable baseline of transmission activity is, whether locally or across regions. But whatever the baseline happens to be, it might be possible to nudge the brain to a new stable baseline, where those symptoms are not longer experienced."

In thinking, for example, about where anxiety comes from—what in our circuits actually goes wrong—Dr. Tye reminds us that everyone experiences anxiety, and that there’s a powerful reason for it. Simply stated, anxiety is “adaptive”—it helps us survive, up to a point, of course. “You’re supposed to be worrying about things, supposed to avoid essential threats. You want to be able to escape from predators—and there are many circuits in the brain that support this. In the same way, some of the behaviors associated with depression help us survive: resources are scarce, competition is intense, and there are many threats. In some situations, it makes sense to withdraw; to conserve energy, to stop seeking rewards—until the situation changes and you are no longer directly threatened.”

The key in both examples, Dr. Tye stresses, is that “when the situation changes,” a healthy brain “will go into a new state,” in which anxiety is no longer felt, or reward-seeking resumes. “Our brains can shift into one state and then into another state. It’s all about understanding what the trigger points are for a change in brain state.”

Where do researchers look for the kind of knowledge that would inform what to do when the brain gets “stuck” in anxiety or depression? Dr. Tye’s first decade of research provides a good example. A number of her projects have involved a careful review of information revealed by brain imaging studies. Functional MRI imaging of people and animals both at rest and performing mental tasks generates signals that indicate regions in which neurons are activated. Such imaging has limited resolution, but “gives us an estimation of where certain things are happening, which gives a clue about where to start looking” using extremely high-resolution techniques like projection-specific manipulations in optogenetics.

Pinpointing problems in individual neural circuits is something like finding a few needles in a gigantic haystack, and so, Dr. Tye says, “it’s really useful if one can divide that haystack into 100 small piles.” Using high resolution methods to comb those small piles then becomes what she calls a “community effort.”

“No scientist is an island,” Dr. Tye says. “Nobody can do this themselves. That’s the beautiful thing about the scientific community—you can build on the work someone else has already done, often in a different field. To me, this is what is exciting about the BBRF. It brings different parts of the neuroscience community together, people who have the same goals but use different approaches, and may be sharing their results at different scientific meetings. The thing about the Foundation that really impresses me is that its influence goes way beyond the NARSAD Grants, as important as they are.

Karl [Deisseroth] and I were supported by the Foundation, and now four members of my lab at MIT themselves are Young Investigator grantees. This gives you a sense of the community that the Foundation builds, uniting people to work together for the greater good. I’m really grateful for that.”

In 2014, Dr. Tye was part of an effort that included Dr. Deisseroth and Robert C. Malenka, M.D., Ph.D., also a member of the Scientific Council. They introduced a new method called fiber photometry which enabled them “to optically record natural neural activity” in particular portions of brain circuits. This

made it possible for the first time to observe in real-time how specific neuronal projections within a circuit operated as an animal engaged in social interactions. Using optogenetics to manipulate portions of this circuit, which stretched between two important brain regions—the ventral tegmental area (VTA) and the nucleus accumbens (NAC)—the team learned that they could change the way animals interacted socially, but could not change the way the animals interacted with inanimate objects.

A needle in the brain’s colossal haystack of mechanisms? Perhaps, but one that suggests one place to experiment with circuit manipulations if one is interested in changing particular social behaviors. Another “needle”: in a 2013 paper appearing in *Nature*, first author Tye and many colleagues including Dr. Deisseroth used optogenetics to demonstrate that bi-directional control of dopamine neurons in the midbrain had the effect of “immediate modulation of multiple depression symptoms caused by chronic stress.” Translation: by inhibiting or exciting

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It’s all about
understanding what
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Kay M. Tye, Ph.D.

specific neurons that are activated by the neurotransmitter dopamine, the team could at will induce depression symptoms in mice and relieve these symptoms. In January 2015, Dr. Tye led a team reporting in *Cell* that they had succeeded in identifying “a neural circuit that selectively controls compulsive sugar consumption, providing a target for potential interventions.” This circuit runs from lateral hypothalamus (LH) into the VTA, and was previously understood to be involved in “reward processing,” e.g., the quest for sweets. Yet the new research pinpointed that of the two types of connections sent between the two regions, it was specifically the ones that activate inhibitory GABA neurons (and not excitatory dopamine neurons) that “drives feeding behavior.”

These are all major discoveries. Dr. Tye is working right now on a variety of projects with equally astonishing potential. To cite just one: a recurring focus of her lab has been the very complicated mechanism underlying anxiety disorders. In other words, anxiety that is chronic and debilitating to an individual; anxiety that is maladaptive, that prevents the individual from functioning successfully in life. This condition affects an estimated 18 percent of adults, and is experienced at some point over a lifetime by 28 percent of adults—tens of millions of people in the U.S. alone.

Anxiety has been likened by Dr. Tye to “too much of a normal thing,” referring to the concept that it is perfectly normal to feel anxious, but not to feel anxious continuously, without rational cause. In an October 2015 review paper in *Nature Neuroscience*, Dr. Tye and a colleague (Dr. Gwendolyn Cal-

hoon, Ph.D., a recent NARSAD Young Investigator grantee in the Tye Lab) discuss such concepts as “interpreting threats on the level of microcircuits”—specific ensembles of connections within larger circuits; discovering “nodes” of connection among these microcircuits and how they act together; how such neural wiring enables us to evaluate threats, and how the interpretation of those threats is regulated in the brain. As in so many instances, much of what specific brain areas “process” ends up being sent to the cerebral cortex—the highest processing center—for integration and evaluation, as a prelude to an individual taking action based on a perceived threat.

Here is what Dr. Tye’s paper concludes, based on what is known so far: “Because disruption to any one part of a highly interconnected system results in changes to the whole, effective solutions require interventions that consider the dynamics of the entire system. Hence, future therapies for anxiety disorders must take a circuit-level approach. Targeted plasticity, perhaps via transcranial magnetic stimulation (TMS) or focal ultrasound [both non-invasive and painless] directed at certain nodes in the reciprocal loops described in this review, could elicit positive downstream changes, ameliorating undesirable anxiety.”

It is safe to assume we will be hearing much more in the years just ahead as a broad circuit-level approach to brain dysfunction leads science toward entirely new ways of treating the disorders that affect the human brain.

2016 Distinguished Investigator Grants

The NARSAD Distinguished Investigator Grants provide support for experienced investigators (full professor or equivalent) conducting neurobiological and behavioral research. One-year grants of \$100,000 each are provided for established scientists pursuing particularly innovative ideas.

Grantees are selected by members of the Foundation's Scientific Council, a prestigious



Jack D. Barchas, M.D.

Chair, Distinguished Investigator,
Selection Committee
Scientific Council Member

Chair, Department of Psychiatry,
NewYork-Presbyterian Hospital /
Weill Cornell Medical Center

group of 173 leaders in brain and behavior research. This year's 15 Distinguished Investigators were selected from 152 applicants. Their projects demonstrate the variety of ways in which our knowledge about mental illness and brain and behavior disorders is advancing. Some of these studies represent multidisciplinary collaborations, while others take a deep look using a single discipline. "We received a

large number of outstanding proposals. Many of the applications involved knowledge that could inform several illnesses, such as schizophrenia and depression, the overlaps between disorders, or, the multiple forms of what is considered a single illness. Several applications also dealt with basic science that reveals new neurobiological or behavioral targets for understanding of illness and potential treatment. Some were based on exciting new basic science, others on translational scholarship, and still others deal with early treatment trials which center on a new approach or new ways to combine forms of treatment."

152 APPLICATIONS
15 GRANTS AWARDED
\$1.5 MILLION TOTAL
FUNDING

Funds from these NARSAD Grants can be considered as seed capital which permits important steps. The results will be important whether positive or negative—if positive, they may represent a direction that will need to be replicated and extended; if negative, they provide an important answer about a step which may not now require follow up or which may need further work in the future when there is still more related knowledge.

BIPOLAR DISORDER



Roel A. Ophoff, Ph.D., of the *University of California, Los Angeles*, will explore how disruptions in circadian rhythms—our internal 24-hour clock—influence bipolar disorder. Dr. Ophoff has collected tissue samples from 100 patients with severe bipolar disorder as well as 100 samples from healthy individuals, and has generated cell cultures from these samples. Dr. Ophoff will use the cultures to examine

the molecular regulatory mechanisms underlying the circadian clock. The goal is to use data-driven statistical tools to objectively identify genes and gene clusters that show clock-like patterns of expression. Dr. Ophoff hopes that this work will lay the foundation for systematic investigation of the involvement of the circadian clock in bipolar disorder.



Uwe Rudolph, M.D., of *McLean Hospital/Harvard Medical School*, will investigate the pathways that are disrupted in depression. Specifically, he will focus on the interplay between two neural signaling pathways: the GABAergic and glutamatergic systems, which, respectively, are inhibitory and excitatory. Using highly specific chemogenetic tools (genetically engineered proteins that interact with small molecules),

he will explore how increasing the activity of GABA receptors affects biochemical signaling in the medial prefrontal cortex, a brain area required for decision-making and memory. Dr. Rudolph will also assess how modulation of GABA receptor function affects behavior in animal models of depression. This work will provide insight into a novel, potentially pharmacological pathway underlying depression.

DEPRESSION



Jay M. Baraban, M.D., Ph.D., of the *Johns Hopkins University School of Medicine*, will explore the role of unconventional molecular pathways in depression. Much of our current knowledge and treatments for depression are focused on a few narrow pathways. Unfortunately, many patients do not respond to current therapies, suggesting that additional pathways may contribute to depression.

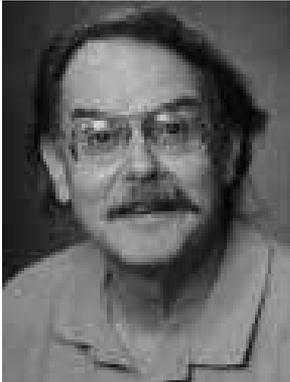
Dr. Baraban will focus on a group of cellular signaling molecules known as microRNAs. In previous studies, reduced levels of microRNAs have been associated with depression-like behavior in mouse models of the illness. Dr. Baraban is working to understand how the machinery that is responsible for microRNAs degradation affects behavior. His goal is to find inhibitors for this pathway that may serve as novel alternative treatments for depression.



Etienne L. Sibille, Ph.D., of the *Centre for Addiction and Mental Health*, Canada, is working to identify new molecular targets for drug development for depression. The majority of current drugs target a single molecular pathway, that of the neurotransmitter serotonin; little is known about other pathways that may contribute to the disease. Dr. Sibille will focus on defining the role of other sig-

nals in depression, such as somatostatin (SST)-positive GABA neurons. He has found that reduced SST expression and function is associated with depression in both humans and animal models of the illness. He will explore how deficiencies in SST-positive neurons contribute to depression and assess whether modulation of these neurons is a potential avenue for antidepressant development.

MENTAL ILLNESS—MULTIPLE



Richard Scott Jope, Ph.D., of the *University of Miami*, hopes to develop a potentially revolutionary new method to alter protein levels in the hippocampus, the center of learning and memory in the brain. Dr. Jope is using a potent class of signaling molecules known as siRNAs to control gene expression. He has found that, when administered

through the nose, siRNAs accumulate in the hippocampus of mice. Dr. Jope plans to use this method to modulate the levels of genes that play an important role in a range of mental illnesses. His preliminary studies will focus on genes, such as GSK3 and histone deacetylases, that have been challenging to target with traditional methods. Dr. Jope hopes that his new method will produce highly targeted treatments with limited side effects for patients suffering from a wide variety of mental illnesses.



Andres V. Maricq, M.D., Ph.D., of the *University of Utah*, will study how an auxiliary protein influences the function of a key neuronal receptor, called the NMDA receptor that is critical for learning and memory. This receptor has been implicated in numerous mental illnesses, including autism spectrum disorders, depression, Alzheimer's disease and schizo-

phrenia, which make it an attractive target for new therapies. Dr. Maricq is working to understand how the receptor is regulated in an effort to identify additional avenues for drug development. Dr. Maricq has identified a protein known as NRAP-1 that is required for NMDA activity. He has proposed to define how NRAP-1 biochemically interacts with the NMDA receptor to control its activity. Dr. Maricq is hopeful that this work will lead to novel pharmacological therapies for diseases like depression and schizophrenia.



Kwang-Soo Kim, Ph.D., of *McLean Hospital/Harvard Medical School*, will work to identify the biological mechanisms that determine how a person reacts to trauma. For example, children who are exposed to abuse are much more likely to suffer from depression and addiction as adults. Still, a small percentage of these children remain resil-

ient despite their traumatic experiences. Using rodent models, researchers have gained insight into the hormone and chemical signaling that influence these behaviors. Dr. Kim now proposes to extend these findings to humans. Dr. Kim will generate stem cells from two groups of adult patients who were abused as children. One group will have a diagnosis of depression, while the other group will not exhibit any symptoms of mental illness. The stem cells from people in each group can be coaxed to form any adult neural cell type, thus enabling Dr. Kim to attempt to define the molecular, cellular, and physiological properties that underlie biological resilience.



Marina R. Picciotto, Ph.D., of *Yale University*, will examine the role of an unstudied group of neurons in anxiety and depression. The so-called ChAT-positive neurons are a rare group of inhibitory cells in the hippocampus, the center of learning and memory in the brain. Dr. Picciotto hypothesizes that these neurons form an important network that

is critical for oscillations in the hippocampus that lead to an increase in anxiety- and depression-like behaviors in rodents. Using a combination of molecular genetic, pharmacological, electrophysiological, and behavioral strategies, Dr. Picciotto will determine the effect of ChAT-positive neurons on neural signaling and behavior. The results will be the first functional and behavioral evaluation of this population in the hippocampus, and will provide a novel role for these neurons in behaviors related to anxiety and depression.



Gustavo X. Turecki, M.D., Ph.D., of McGill University, Canada, will study molecular changes in the brain that occur after severe child abuse. Children who have experienced these traumatic events are more likely to suffer from mental illnesses, including severe depression and addiction. Dr. Turecki will gather rare postmortem human brain sam-

ples to robustly and specifically characterize changes in the expression of genes and in chemical changes to DNA called methylation that are specifically associated with early-life adversity. He will focus on excitatory pyramidal neurons that are largely responsible for cognition. His goal is to improve our understanding of the molecular mechanisms underlying the impact of child abuse, and ultimately propose novel avenues for intervention.



Simon Keith Warfield, Ph.D., of Children's Hospital, Boston, will use innovative new technology to build structural maps of the connections between neurons in the developing fetal brain during pregnancy. Dr. Warfield has developed new technology that allows researchers to image the brain even while the fetus is moving. This motion-robust MRI

and other imaging enables quantitative analysis of neural connections in the early brain. Using this technology, Dr. Warfield will analyze both healthy and at-risk fetal MRI cases. The at-risk population will include fetuses with identified maternal risk factors for developing mental health disorders, including those who have experienced stressful events during pregnancy or obstetric hypoxic complications. Dr. Warfield hopes motion-robust imaging will differentiate between abnormal and normal brain development, which will facilitate the identification of fetuses that are at risk for developing mental health disorders.

WHAT THEY SAID

Jay M. Baraban, M.D., Ph.D.

"I am deeply honored by being selected for this Award. It will allow us to move ahead on research aimed at developing a novel class of anti-depressants."

Beng-Choon Ho, M.D.

"It is a great honor to receive the 2016 Distinguished Investigator Award. I am very grateful of the Foundation's support over the years. NARSAD Grants have been key to the growth of my research program enabling it to extend into new and novel directions."

Elliot Hong, M.D.

"Putting a new and complex brain imaging idea into actual experiment is always challenging. Receiving this generous NARSAD Grant to support its initial development gives us great encouragement!"

Richard S. Jope, Ph.D.

"Many new drugs never reach clinical use because of difficulties entering the brain or side effects caused by actions outside of the brain. This Distinguished Investigator Grant will be put toward the hurdles that this study aims to overcome to allow the clinical use of drugs that previously did not adequately enter the brain."

Kwang-Soo Kim, Ph.D.

"I am so excited about this great news because it will allow me and my colleagues to explore the underlying biological basis of neuropsychiatric resilience versus susceptibility."

Andres Villu Maricq, M.D., Ph.D.

"I am grateful and honored to receive a NARSAD Distinguished Investigator Award. We recently discovered a novel auxiliary protein that is required for NMDAR—mediated signaling, and we now plan mechanistic studies of this protein. We are hopeful that the identification and characterization of this novel protein will contribute to the development of new pharmacological strategies for the treatment of brain disorders."

Marina R. Picciotto, Ph.D.

"This NARSAD Award will allow us to explore a completely new idea on how signaling in the hippocampus can contribute to depression. New ideas are inherently risky, so this funding will invest in providing support for this novel hypothesis so that we can work toward getting broader investment in this area."

POST-TRAUMATIC STRESS DISORDER



Rachel Yehuda, Ph.D., of the *Icahn School of Medicine at Mount Sinai*, seeks to understand the neurobiological mechanisms involved in resilience to trauma and to define markers that will allow researchers to predict how a person will respond to trauma. Dr. Yehuda has identified neuroendocrine (hormonal) and molecular predictors of

resilience and markers of recovery from PTSD. Now, she will examine these predictors in combination with markers of brain structure and function. Dr. Yehuda will scan 15 trauma-exposed individuals with PTSD and 15 trauma-exposed individuals without PTSD. Her goal is to identify neural circuits associated with resilience to trauma as well as neuroimaging biomarkers of treatment response to cognitive therapy in PTSD. More broadly, Dr. Yehuda hopes that improved biomarkers for a patient’s response to trauma or the treatment of trauma will advance our understanding of the molecular mechanisms that underlie behavior.

SCHIZOPHRENIA



Beng-Choon Ho, M.D., of the *University of Iowa*, will work to develop a method to measure neuroinflammation in neuropsychiatric disorders. Dr. Ho will test a diagnostic known as advanced diffusion magnetic resonance imaging (dMRI) to determine if it can serve as a marker of brain immune activation triggered by obstetric complications. The

work will take advantage of a unique and highly informative Dutch birth cohort which has been evaluated from prenatal life until mid-adolescence and is still ongoing. The project holds the promise to advance our knowledge of the mechanisms that govern neuroinflammation and provide insight into how maternal infections increase schizophrenia susceptibility, which may allow for earlier intervention and the development of improved therapeutics.

SCHIZOPHRENIA



Elliot Hong, M.D., of the *Maryland Psychiatric Research Center*, hopes to build a comprehensive map of the brain based on both biochemical interactions and electrical signals. Our current understanding of the brain is largely derived from discrete maps that are based on unrelated structural, functional, chemical or electrical information.

Yet complex diseases, like schizophrenia, are likely caused by defects in multiple pathways at once. Using a combination of technical and conceptual advances, Dr. Hong proposes to create the first large-scale map of the brain’s synchronized electro-chemical dynamics. His hope is that this integrated image of the brain will provide insight not only into how chemical signals regulate neural activity, but will also identify abnormalities and network-dysfunctions that are commonly observed in patients with schizophrenia.



Neal R. Swerdlow, M.D., Ph.D., of the *University of California, San Diego*, will work to test an alternative approach to treating schizophrenia. For more than 50 years, antipsychotic drugs have been the main therapy for patients with schizophrenia, but these treatments often fall short in treating various cognitive aspects of the illness. Recent

research suggests that patients may benefit from so-called pharmacologically augmented cognitive therapies (PACTs), which pair targeted drugs with cognitive therapies. The dual treatment may have synergistic effects. Dr. Swerdlow will treat schizophrenia patients with range of doses of the pro-attention psychostimulant, d-amphetamine, in addition to conventional antipsychotics. The drug treatment will be paired with cognitive therapy that is specifically targeted to develop attention skills. Dr. Swerdlow hopes that this investigation will provide compelling data that expands the use of PACTs to treat schizophrenia.



Dawn I. Velligan, Ph.D.,

of the *University of Texas Health Science Center at San Antonio*, will look for new biomarkers that are associated with particularly severe cases of schizophrenia. These markers will be used to assess a new treatment, known as the MOtiVation and Engagement (MOVE) Program. The method builds on existing therapies

with comprehensive, home-based, multi-modal approaches, and results have been promising so far. Dr. Velligan will focus

on inflammatory markers as potential biomarkers. She will examine the relationship between the amount of inflammatory markers circulating in the blood of patients and the severity of their negative symptoms. Dr. Velligan will also assess the impact of MOVE on levels of these molecules. This work has the potential to uncover novel biomarkers associated with the negative symptoms of schizophrenia, which may offer a path to more targeted, improved treatments.

WHAT THEY SAID

Etienne Sibille, Ph.D.

"Receiving a NARSAD Distinguished Investigator Grant is a beautiful recognition and feedback from the field of neuropsychiatry for our efforts to unravel the molecular mechanisms of depression and other brain disorders!"

Neal R. Swerdlow, M.D., Ph.D.

"As clinicians and scientists, we are mindful of both the terrible suffering imparted by brain disorders, and the tremendous potential in the nervous system for plasticity and healing. Support from NARSAD makes it possible to test novel learning-based paradigms for engaging natural restorative mechanisms in the brain, and to harness them within empowering treatments for our patients struggling with serious mental illness."

Gustavo Turecki, M.D. Ph.D.

"It is a great privilege to receive the NARSAD Distinguished Investigator Grant. This grant will provide me with a unique opportunity to apply innovative approaches to investigate how traumatic experience modifies brain function at the molecular level in individual cells. This knowledge will set the stage for more refined approaches to understanding psychopathology and suicide risk."

Dawn I. Velligan, Ph.D.

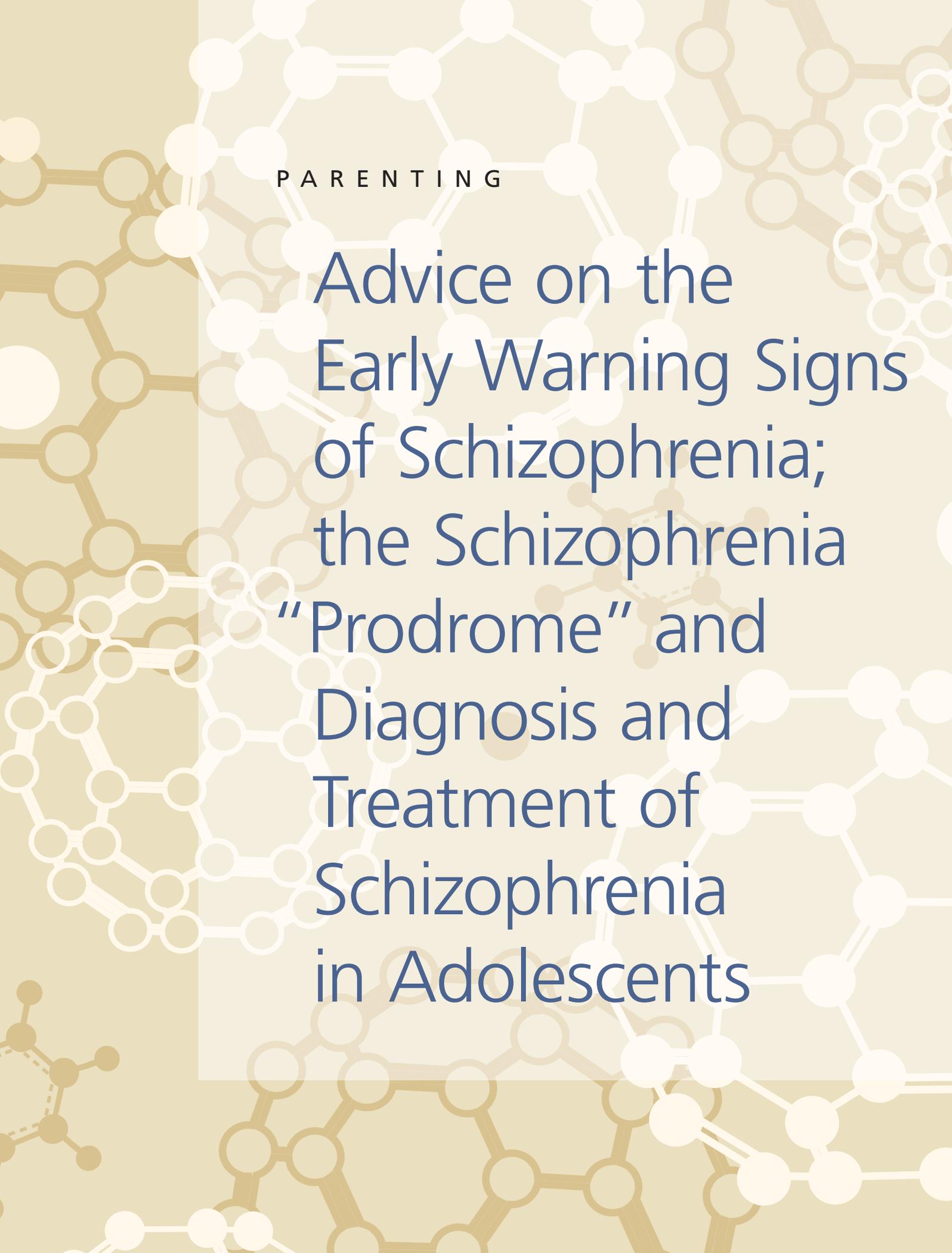
"Getting this NARSAD grant will allow our research group known for developing evidence-based psychosocial treatments for individuals with schizophrenia to begin to assess their impact on immune system activity. Motivation and Engagement Training (MOVE) is a novel psychosocial treatment found to improve persistent negative symptoms. By using MOVE as a probe for changes in inflammatory markers with treatment we will be able to understand more about the underlying pathophysiological processes involved in negative symptoms. This is likely to spur the development of personalized medicine to treat negative symptoms."

Simon K. Warfield, Ph.D.

"I am extremely honored and humbled to be one of the recipients of the 2016 NARSAD Distinguished Investigator Grant. This grant will play a crucial role in stimulating my work in imaging the disruption of neural circuitry that is the basis of mental health disorders, such as schizophrenia, at the earliest possible ages."

Rachel Yehuda, Ph.D.

"The NARSAD Grant will enable us to understand how brain function changes in combat veterans with PTSD who show marked improvement following psychotherapy. This is an exciting frontier because we are still in the early stages of discovery about how one can achieve resilience. My team and I are grateful and honored by this opportunity."



P A R E N T I N G

Advice on the
Early Warning Signs
of Schizophrenia;
the Schizophrenia
“Prodrome” and
Diagnosis and
Treatment of
Schizophrenia
in Adolescents

Herbert Y. Meltzer, M.D. is Professor of Psychiatry and Behavioral Sciences, Pharmacology and Physiology at Northwestern University Feinberg School of Medicine. Dr. Meltzer directs a multifaceted research program in schizophrenia and bipolar disorder which is devoted to developing more effective treatments. 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 second generation antipsychotics such as clozapine owe much of their advantage over first generation drugs to the balance between serotonin and dopamine receptor blockade (1989). He received Distinguished Investigator grants in 1988, 1994, 2000 and 2007, and is the 1992 Lieber Prizewinner for Outstanding Achievement in Schizophrenia Research.

WHAT ARE SOME OF THE EARLY SIGNS OF SCHIZOPHRENIA THAT PARENTS SHOULD BE ON THE LOOKOUT FOR?

A typical adolescent who later experiences a psychotic episode is one who may be doing very well in high school, having normal interests in activities, getting along well with others, but may show non-psychotic problems like being somewhat withdrawn, lacking motivation or have odd likes and dislikes, compared to other children in the family. Then, over a period of months to several years, the family notices that the child's school work begins to deteriorate, interest in sports, musical performance and other activities dissipates, and the child becomes much more isolated.

Next, the child might report—if they do report at all—short-lived psychotic experiences such as hearing voices for a few hours, delusional ideas of a paranoid nature, or bizarre thoughts and experiences. The important thing to note is that these experiences are transient at this point, and thus, it is easy to dismiss them. These are part of what we call the prodromal period—the early stage of psychosis in an adolescent who has a high risk of experiencing a prolonged psychotic episode at some later date.

It is important to note that these early symptoms do not always signal a full-blown psychotic episode. However, adults who pick up these early signs in the prodromal period can seek professional help for the child that can confirm whether some type of mental illness may be emerging or is already present. Professionals can look for some of the risk factors for impending psychosis: family history of serious mental illness, such as schizophrenia, bipolar disorder, ADHD; and substance abuse, especially marijuana, PCP, ketamine, cocaine, metham-

phetamine. Moderate to severe stress will enhance whatever genetic vulnerability may be present. Thus, limiting stress is a key step in delaying or forestalling a psychotic episode.

The onset of sleep disturbance—inability to fall asleep, stay asleep, early morning awakening—is additional evidence that a psychotic episode might be emerging.

BUT DISRUPTED SLEEP COULD BE A SIGN OF A NUMBER OF THINGS, INCLUDING NORMAL LEVELS OF ANXIETY, RIGHT?

Yes. There is no absolute predictor of psychosis. And keep in mind that transient psychotic experiences can occur without necessarily leading to full-blown schizophrenia or bipolar disorder. This is why it is important to seek the opinion of a skilled mental health professional who has lots of experience with adolescents and early psychosis.

I want to reemphasize substance abuse. Marijuana in particular is known to transition adolescents who are at higher risk for psychosis into the full-blown syndrome. Drugs like ketamine (sometimes called “Special K”), as well as PCP (angel dust or phencyclidine), cocaine and amphetamines have been demonstrated to bring about psychosis in high-risk individuals.

Sometimes patients with schizophrenia have been diagnosed with ADHD, and are treated with Ritalin or amphetamines. While these may help the ADHD, they can also bring out the paranoia and psychosis of schizophrenia and the schizophrenia prodrome.

WHAT IS IT ABOUT DRUG ABUSE THAT SEEMS TO PUSH FORWARD PSYCHOSIS?

PCP and ketamine are both antagonists for a receptor, or docking port, on neurons that are activated by the neurotransmitter glutamate. These receptors whose action is blocked by these drugs are called NMDA receptors. These receptors are present on inhibitory neurons in the brain which release the neurotransmitter GABA. Blocking the action of NMDA receptors can disturb the delicate balance in the healthy brain of excitatory and inhibitory neuronal activity. Virtually everyone who takes PCP will experience a dissociative state, a kind of “out-of-body” experience. So this is a new danger for parents to know about, since ketamine has come to be used more frequently in the last year or two in clinics all over the country, even without FDA approval, for depression.

**YOU’VE MADE REFERENCE TO YOUTHS “AT HIGH RISK.”
WHAT CRITERIA PUT SOMEONE AT HIGH RISK?**

One factor is having one or two parents, siblings, or grandparents with schizophrenia or bipolar disorder. A second factor is a cluster of prodromal symptoms, such as transient psychosis, decline in academic performance, and social withdrawal.

IT WOULD SEEM, THOUGH, THAT SOME OF THESE SYMPTOMS ARE NON-SPECIFIC-THEY MIGHT HAVE OTHER CAUSES. I DON’T MEAN PSYCHOTIC SYMPTOMS, BUT THE OTHERS. HOW CAN A PARENT KNOW WHEN THEY ARE INDEED POINTING TO SCHIZOPHRENIA?

It is admittedly difficult. The most careful attempt to identify and treat high-risk individuals was led by Dr. Patrick McGorry [2015 Lieber Prizewinner for Outstanding Achievement in Schizophrenia Research] in Melbourne, Australia. Even his team was only successful in predicting who goes on to develop a psychosis in one of four high-risk youths.

However, a third did make the transition into full blown psychosis or to bipolar disorder. We’re not very good at distinguishing between those two illnesses early on. Family history is not very reliable in that regard. If there is a sibling who has been diagnosed with schizophrenia, then having prodromal symptoms is more likely to resolve as schizophrenia than bipolar disorder. But if you have a bipolar mother and an offspring who is showing telltale prodromal symptoms, then that young person could still develop schizophrenia rather than bipolar disorder.

The genetic signatures of bipolar disorder and schizophrenia overlap a lot but newer methods of analysis are likely to improve our ability to predict which type of clinical course is more likely. We now know hundreds of risk genes for both disorders. For some individuals, the weight of the genetic evidence will strongly suggest one disorder rather than the other. The clinician should make certain that a family history is taken and that she or he knows whether first-degree relatives have had a positive history of a psychiatric disorder and if so, what their response to treatment and course of illness have been. The treatment information can be a valuable guide for the treatment of the other family members.

WHAT PREDICTS HOW SOMEONE WITH SCHIZOPHRENIA WILL FARE IN THE LONG-TERM?

Strong evidence shows that the cognitive impairment associated with schizophrenia is the most important predictor of functional outcome. It is highly valuable to seek a full cognitive battery, one which assesses verbal and spatial memory, working memory, semantic memory, speed of processing

information, attention and social cognition. This will yield a composite score and an IQ. A good clinician will use this information to assist in recommendations regarding many aspects of treatment and prognosis.

Cognitive function can and should be retested periodically to mark the progression of the illness. A steady decline in one or more domains is an ominous sign. There is evidence that typical antipsychotic drugs, such as haloperidol or fluphenazine, can cause worsening while atypical antipsychotic drugs, such as lurasidone, olanzapine, and risperidone, are likely to produce improvement in some areas.

IF THERE IS DECLINE, WHAT SHOULD A PARENT DO?

I would make sure that no first-generation (sometimes called “typical”) antipsychotic drug is being administered. I would check for signs of motor side effects from the antipsychotic drugs if they are being taken. One side effect is called tardive dyskinesia, which manifests in lip, tongue, and cheek movements that are spontaneous. They are correlated with more rapid and severe cognitive impairment.

IN CASES WHERE THE PARENT KNOWS THEIR CHILD IS ON A DIFFERENT TRAJECTORY THAN NORMAL, WHAT ARE SOME OF THE STEPS THEY SHOULD TAKE?

If the course is really poor, have a frank discussion with the treating clinician and consider all the elements that might be contributing to it that might be modified. Avoid all drugs of abuse, minimize stress, consider a different drug treatment, consider cognitive remediation, evaluate whether some co-morbid medical condition might be occurring. Sometimes families do contribute to stress or other negative influences on outcome. Then, some type of alternative living arrangements might be worthwhile if a more supportive environment can be found.

IS THERE A WAY TO MINIMIZE COGNITIVE IMPAIRMENT?

In treating high-risk patients, one of my goals is to delay the onset of a full blown psychosis even if I cannot prevent it from occurring indefinitely. The later the age of onset, the better the prognosis. For example, instead of psychosis beginning at 19 during freshman year in college, if it happens at 24, following graduation, valuable skills and experiences should have been gained which will be helpful when the first episode has been treated.

WHAT KIND OF DRUGS SHOULD BE USED IN TREATING THOSE DIAGNOSED WITH SCHIZOPHRENIA?

As I mentioned above, I strongly urge people to not use first-generation drugs, also called typical antipsychotic drugs. Examples are haloperidol, perphenazine, thiorazine, thiori-

dazine, and fluphenazine. These drugs have been associated with greater loss of brain tissue in patients with schizophrenia. And as I mentioned, they increase the risk for motor side effects and tardive dyskinesia such as Parkinsonism and involuntary movements. They are associated with greater cognitive impairment. Second-generation, or “atypical” antipsychotic agents I mentioned previously have been shown to be less able to improve cognition in someone with tardive dyskinesia than someone without it.

IS IT TRUE THAT WHEN THE FIRST ATYPICAL ANTIPSYCHOTIC DRUG (CLOZAPINE) WAS APPROVED, IT WAS ORIGINALLY INDICATED ONLY FOR REFRACTORY [TREATMENT RESISTANT] CASES, AND THEN THAT WAS CHANGED?

There are other uses of clozapine, as I was first to show. The most important of these is to reduce the risk for suicide. Five percent of patients with schizophrenia and 15 percent of those with bipolar disorder commit suicide, and many more make attempts. Clozapine is very effective to reduce these rates. However, clozapine can produce a lot of side effects. Patients and doctors must work carefully to minimize these.

SHOULD SUICIDE BE A BIG CONCERN FOR PARENTS?

Although the risk of suicide is present throughout the illness, it is higher in the prodrome and first psychotic episode.

CAN YOU GIVE PARENTS SOME ADVICE ON HOW TO FIND THE BEST TREATMENT FOR THEIR CHILD?

Look for a clinician or clinical practice with experience in dealing with patients at high risk or with diagnoses of schizophrenia or bipolar disorder. The best around may be an academic medical center. Make sure the clinician is not biased against using medication. A mix of drug treatment and psychosocial programs is often the most effective approach. Academic medical centers and leading community mental health centers, on average, will be the best choice. I have found group and family therapy more useful than individual therapy for patients with schizophrenia. The support from other patients with the illness and their families has been very enlightening to new members of a group and their families.

HOW DO YOU MONITOR OR ENCOURAGE COMPLIANCE WITH MEDICATION?

As with all medication it's great to have the patient report to you on a regular basis that she or he is taking the medication. Everyone has a tendency to forget, so ask them if they remembered to take their pills. I'm also a very strong advocate of long-acting, injectable medication. They can be effective for anywhere from two weeks to three months. There are also experimental surgical implants that can last six to 12 months.

WHAT RECOMMENDATIONS DO YOU HAVE ABOUT ADJUSTING THE DOSING?

The answer is finding drugs with minimal side effects. You want to work with a clinician to find the lowest dose that is tolerable and effective. Don't be afraid to accept a recommendation from an experienced clinician to increase the dose of a drug if it is only partially effective at a tolerated dose. Raising the dose under supervision may achieve the desired level of improvement. Avoid polypharmacy (taking multiple drugs at once) in most instances—but I do not want to say it is never indicated. What I have seen is more problems from treating with multiple drugs than benefits.

WHEN SEEKING MEDICAL HELP, WHAT PROCESS SHOULD PARENTS FOLLOW?

It makes sense to start with a trusted physician who may have a referral network for specific types of patients with psychotic disorders. If there is no one, it might be best to go to an emergency room or to a walk-in clinic at a community mental health center.

LET'S SAY YOU KNOW YOUR ADOLESCENT IS IN THE PRODROME. DO YOU TELL ANYBODY?

We're all aware of the stigma. We want to be cautious about who we tell. While initial assessments are going on, there is no need to share information with anyone other than members of the family, particularly siblings. Siblings have their own concerns such as “is it going to happen to me as well?” or that “it is also happening to me.” That sibling may want to have a psychiatric evaluation of their own. Identifying that someone is in the prodrome of a psychotic episode is important because intervention during that stage may yield great long term benefits.



Herbert Meltzer, M.D.

THE POWER OF A Research Partnership



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Eleonore Beurel, Ph.D.

Virginia Silver, a member of the Foundation's Board of Directors, and her husband, Mark Silver, M.D., have a research partnership with 2013 NARSAD Young Investigator Grantee Eleonore Beurel, Ph.D., of the University of Miami. Dr. Beurel is working to help usher in a new generation of better, more effective medications for the treatment of mood disorders.

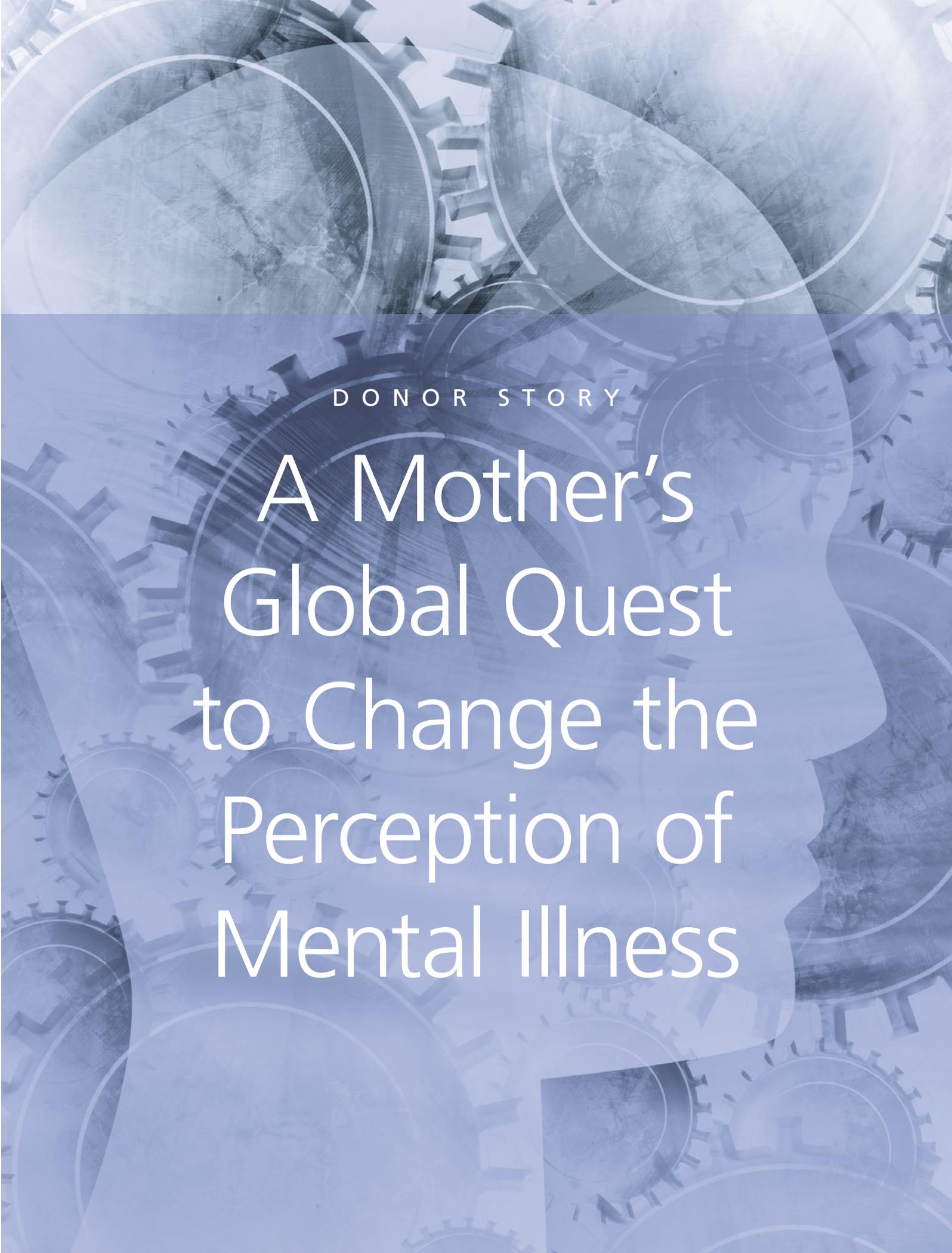
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"Our daughter was diagnosed five years ago with clinical depression and severe anxiety disorder. Although now stabilized and living a happy, productive life, I came to realize that if it weren't for research, she would not have had the medications that have worked for her. We were drawn to support the Brain & Behavior Research Foundation because we believe so strongly that research has to be supported for the sake of our children's children—and for all the generations down the road."

—Virginia Silver

For information on becoming a Research Partner or to support research in other ways, please call **800-829-8289** or visit our website at bbrfoundation.org/research-partner.



DONOR STORY

A Mother's Global Quest to Change the Perception of Mental Illness



“Early in the foundation’s infancy, we started receiving requests for help from all over the world,” explains Ms. Walker. “Throughout our growth, our mission has remained the same: to improve the understanding, diagnosis and treatment of bipolar disorder through research; support those affected by the condition; and destigmatize mental illness through education.”

Ms. Walker will tell you that the most difficult part of her family’s experience was the stigma. “It represents a huge barrier in health seeking behavior,” she says. “We shouldn’t separate mental from physical health—it’s all one body. And we’re trying to change that perception.”

The International Bipolar Foundation’s support of research is one way they aim to broaden current views toward mental illness. The foundation sees the potential research holds to better understand bipolar disorder and thereby lessen misconceptions.

They found an ideal partner at the Brain & Behavior Research Foundation through its Research Partners Program.

“What drew us to working with the Foundation is the caliber of scientists that they have in their cauldrons,” says Ms. Walker. “They have the resources to provide recommendations for the best scientists in their field.”

Through its partnership with the Brain & Behavior Research Foundation, the International Bipolar Foundation has access to the BBRF’s most innovative researchers. After reviewing several research proposals, the IBF selected 2016 Young Investigator Dr. Rupali Srivastava of *Johns Hopkins University* with a gift of \$30,000. Dr. Srivastava’s research work aims to understand the pathology of bipolar disorder. In directly supporting Dr. Srivastava, the IBF joined the BBRF’s Research Partners Program, an initiative that provides major donors

When Muffy Walker’s experience with mental illness became personal to her own family, she and her husband John C. Reed were desperate for resources and support, but found very little. Ms. Walker, who holds a Masters in psychiatric nursing, was determined to find answers and joined several mental health organization boards. She also began running support groups out of her home for caregivers, who like her, were struggling to navigate the mental health system. From that group, three other parents with children affected by bipolar disorder started the California Bipolar Foundation, while sitting around Ms. Walker’s kitchen table in 2007.

WHAT WILL YOUR LEGACY BE?

SUPPORT CUTTING EDGE
MENTAL HEALTH RESEARCH
AND ADVANCEMENTS

Name the **Brain & Behavior Research Foundation** as a beneficiary of your:

- Will or Trust
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Bequests and other planned gifts have a profound and lasting impact on the field of research. Your support enables scientists to pursue new, pioneering ideas to answer important questions or help identify new potentially game-changing targets for treatment in brain and behavior research.

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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with opportunities to directly fund scientists through specific interests including a particular illness, medical institution or region. This program enables donors to choose among the most unique mental illness research projects as selected by the BBRF's prestigious Scientific Council. Due to the generosity of two family foundations covering BBRF's operating expenses, 100% of the IBF's gift and all other donor contributions for research are invested directly in research grants.

For the nearly 5.7 million American adults affected by bipolar disorder in any given year, research may hold the key to identifying new diagnostic and treatment modalities. Committed to alleviating the suffering caused by mental illness, since 1987 the Brain & Behavior Research Foundation has awarded more than \$39 million to fund 556 grants to young investigators researching bipolar disorder.

"We don't yet have an effective means of diagnosis or treatment," says Ms. Walker. "But we have developed tools to help improve the quality of life for people with bipolar disorder, as a result of research findings."

Research has shown that those affected by a serious mental illness, which includes bipolar disorder, have a 10-25 year life expectancy reduction. The leading causes of this shortened lifespan are lifestyle choices, including poor diet, little exercise, and reluctance to seek medical care.

At the start of 2016, the International Bipolar Foundation launched a free online tool, called the Behavioral Health Quality of Life Questionnaire to help assess and improve the quality of life for those with mental illness. The answers generate treatment programs, and give people the option to be paired with a peer specialist to help them follow and stay on the healthy plans. Their free book, *Healthy Living with Bipolar Disorder*, which offers country specific chapters, has been translated into a variety of languages and is about to go into its 3rd edition with over 7,000 copies distributed.

By addressing a variety of audiences and ages, the International Bipolar Foundation tirelessly works to erase stigma and make transformational changes around the world, and looks forward to continuing a partnership with BBRF.

Together, both Foundations strive to improve the lives of the mentally ill through scientific discoveries and public education.

"We envision wellness, dignity and respect for people living with bipolar disorder," affirms Ms. Walker. "We need to keep opening doors, and through education, we can achieve that goal."

Recent Research Discoveries

Treating Metabolic Problems Improves Symptoms of Depression for Some Patients

TAKEAWAY: The majority of study participants with treatment-resistant depression improved when metabolic problems were diagnosed and treated.

Some people who suffer from major depression—including those who have failed to respond to medications, psychotherapy or electroconvulsive therapy (ECT)—have treatable metabolic deficiencies that may give rise to their symptoms, researchers have discovered. Metabolic deficiencies, which alter the body's ability to convert food to energy or generate vital biological compounds, can be detected by analyzing the complex mix of molecules in a person's blood, urine or spinal fluid.

In a small study of people with treatment-resistant depression, reported August 13 in the *American Journal of Psychiatry*, nearly two-thirds of participants were found to have metabolic problems that impaired their bodies' ability to produce certain neurotransmitters. When these metabolic deficiencies were treated, patients' depression symptoms declined significantly. Some people even saw their depression go into remission when their metabolic problems were corrected.

A team of researchers led by 2012 Young Investigator Lisa A. Pan, M.D., at the University of Pittsburgh School of Medicine, undertook the study after seeing one 19-year-old man's unrelenting depression go away when he was treated for a metabolic abnormality. Dr. Pan had treated the patient for

years, trying every available treatment, but—as is the case for about 15 percent of people with major depression—his symptoms did not improve even with treatment.

Finally, she and her colleagues discovered abnormalities in the patient's cerebrospinal fluid (the fluid that circulates through the brain and spinal cord). This suggested that a cellular pathway needed to produce the neurotransmitters dopamine and serotonin was not working properly. A dietary supplement corrected the problem and the young man recovered quickly.

Dr. Pan and her colleagues, including 2001 Distinguished Investigator and 2006 Ruane Prizewinner David A. Brent, M.D., at the University of Pittsburgh Medical Center, wondered whether problems like these might be common among patients with treatment-resistant depression. In the current study, they looked for evidence of metabolic deficiencies in another 33 patients.

All of the depressed people in the study were between the ages of 14 and 40 and had failed to respond to at least three different antidepressant medications. Most had begun experiencing depressive episodes as children or adolescents.

No metabolic deficiencies were found among 16 healthy subjects included in the study to serve as controls, but 21 of the 33 study participants with depression (64 percent) were found to have metabolic deficiencies. The most common problem was a deficiency in cerebral folate, a condition that can be treated by adding folic acid to the diet. Twelve patients with treatment-resistant depression were found to have this condition, and all those who received folic acid treatment experienced reductions in their depression symptoms. Additional metabolic abnormalities were found in other study participants.

All of the metabolic deficiencies uncovered in the study were found by analyzing patients' cerebrospinal fluid, and could not be detected in blood or urine samples. The researchers note that since cerebrospinal fluid must be collected by inserting a needle between vertebrae in the lower back—a procedure called a lumbar puncture or "spinal tap"—routine clinical tests would not have identified the treatable source of their study participants' depression. Patients with depression whose physicians suspect may have metabolic disorders should be referred to a biochemical geneticist, the study authors say.



David A. Brent, M.D.

2006 Ruane Prizewinner
2001 Distinguished Investigator



Lisa A. Pan, M.D.

2012 Young Investigator

Calculator Offers Better, Individualized Predictions for People at High-Risk for Psychosis

TAKEAWAY: A new calculator lets clinicians determine the personal risk of psychosis for people whose symptoms indicate they are at high risk of having a first psychotic episode.

Psychotic disorders have early warning signs. Before people with schizophrenia or other such illnesses develop psychosis, they usually experience a decline in cognitive function (affecting learning and memory, executive function and sustained attention, among others) and important yet subtle disruptions or changes in their perceptions and beliefs. Still, most people who display these early warning signs never develop a psychotic disorder. Figuring out who will and who will not become psychotic has been a major objective of psychiatric researchers for decades. One reason is that early treatment often lessens the severity of subsequent illness.

People whose symptoms place them in a high-risk group for psychosis have typically been advised that about 30 percent of the people in this group progress to full psychosis within two years. Now, thanks to a diagnostic tool developed and tested by two teams of scientists, including more than a dozen NARSAD grantees, clinicians can offer their patients a more personalized assessment of their risks.

The researchers' aim was to develop a method of predicting psychosis comparable to the tools currently used to estimate individual risks for heart disease or certain cancers. Risk calculators can help guide patients and clinicians as they make treatment decisions, but until now have not been available for mental illness.

To determine which clinical, cognitive and demographic measures are the best indicators of whether someone will develop psychosis, a team led by 2006 and 1997 Distinguished Investigator Tyrone D. Cannon, Ph.D., at Yale University, followed 596 high-risk individuals between the ages of 12 and 35 for two years. Sixteen percent of the participants developed psychosis during the study period.

Focusing on factors that can be easily assessed in a clinical setting, Dr. Cannon's team identified five important indicators of risk. Those who were young when their warning symptoms began and who had more unusual thoughts and suspiciousness, lower verbal learning and memory, slower cognitive processing, and a greater decline in social functioning at the outset of the study were most likely to have progressed to full psychosis, the researchers found. These factors were incorporated into a risk calculator along with questions about family history of schizophrenia and past stressful or traumatic events, which, interestingly, the analysis revealed had a smaller impact.

Another team of scientists, led by 2012 Young Investigator Ricardo E. Carrión, Ph.D., at the Feinstein Institute for Medical Research, clinically validated the risk calculator in a separate group of 210 high-risk people. The calculator performed as well in this group as it had in the original study group. As the researchers had hoped, their tool achieved an accuracy reading comparable to that of existing risk calculators for cardiovascular disease and cancer.

Both research teams reported their results July 1 in the *American Journal of Psychiatry*, and made their risk calculator freely available to clinicians and researchers everywhere at <http://riskcalc.org:3838/napls>. Not only will the tool help clinicians offer better information to patients, it will also aid studies aimed at understanding which interventions work best for preventing psychosis in high-risk individuals, the study authors say.



Tyrone D. Cannon, Ph.D.

2006, 1997 Distinguished Investigator



Ricardo E. Carrión, Ph.D.

2012 Young Investigator

Newly Discovered Brain Circuit Helps Explain Why Antidepressants Sometimes Trigger Anxiety

TAKEAWAY: Increases in serotonin, such as those caused by certain antidepressant medications, activate a newly discovered anxiety-promoting circuit in the brains of mice.

People who are suffering from anxiety disorders are often prescribed a selective serotonin reuptake inhibitor (SSRI) such as Zoloft or Paxil, which are thought to improve mood by boosting the level of the neurotransmitter serotonin in the brain. These antidepressants can take weeks to have an effect, however, and many patients’ initial reaction to the medication is a distressing increase in anxiety and they stop taking the drugs before they see any benefit.

New research led by 2014 Independent Investigator and 2010 Young Investigator Thomas L. Kash, Ph.D., at the University of North Carolina, seems to explain this troubling side effect of SSRI treatment—and suggests a strategy for counteracting it. Dr. Kash and his colleagues reported September 1 in the journal *Nature* that they have identified a brain circuit in mice that heightens anxiety in response to serotonin. Giving mice the SSRI drug fluoxetine (Prozac) activates this circuit and provokes anxiety-like behaviors.

The research was conducted by a team of scientists that also included Scientific Council member and 2007 and 2005 Young Investigator Karl Deisseroth, M.D., Ph.D., at Stanford University; 2005 Young Investigator Andrew Holmes, Ph.D., at the National Institute on Alcohol Abuse and Alcoholism; and 1998 Young Investigator Lora K. Heisler, Ph.D., at the University of Aberdeen.

Dr. Kash and his colleagues began their study by scrutinizing a mood-regulating brain region called the dorsal raphe nucleus, which produces much of the brain’s serotonin. They found a small set of serotonin-producing neurons there that become active when an animal is reminded of a fearful situation, such as when it hears a sound that was previously accompanied a mild shock. Once activated, these cells use serotonin to signal to neurons elsewhere in the brain that trigger anxiety-like behaviors.

In experiments, direct activation of these serotonin-producing cells by the researchers was enough to trigger anxious behavior in the mice, even in the absence of a fear-inducing stimulus. What’s more, giving mice an SSRI was found to have the same effect on this brain circuit as putting the animals in a fearful situation: serotonin levels rise and anxiety-like behaviors increase.

The researchers found that they could prevent this serotonin-induced rise in anxiety by interfering with signaling from the cells in the circuit that receive the serotonin signal. Those cells produce a stress signal called corticotropin releasing factor (CRF). Chemically blocking CRF kept anxiety levels stable when animals were given an SSRI.

If a similar circuit also exists in the human brain—and that is quite possible, since the mouse brain and human brain are anatomically very similar—it may be possible to identify a CRF—blocker or other drug that prevents serotonin-induced anxiety, the researchers say. Such a drug might be given to a patient during the first few weeks of SSRI treatment to reduce early side effects.

Thomas L. Kash, Ph.D.

2014 Independent Investigator
2010 Young Investigator



Andrew Holmes, Ph.D.

2005 Young Investigator



Karl Deisseroth, M.D., Ph.D.

Scientific Council
2007, 2005 Young Investigator



Lora K. Heisler, Ph.D.

1998 Young Investigator



Ask the Researcher



Francisco Xavier Castellanos, M.D.

Director of Research
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Brooke and Daniel Neidich Professor of Child and Adolescent Psychiatry

Professor of Adolescent Psychiatry, Radiology, and Neuroscience
NYU School of Medicine

Research Psychiatrist
Nathan Kline Institute for Psychiatric Research

2015 Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research

2005 NARSAD Distinguished Investigator

MY SON HAS BEEN RECENTLY DIAGNOSED WITH ADHD. WOULD IT BE HELPFUL FOR HIM TO HAVE AN MRI AT SOME POINT, TO SEE EXACTLY WHAT PARTS OF HIS BRAIN MIGHT BE OUT OF SYNC?

Currently, the simple answer is no. The brain imaging community is still learning how to best use MRI to understand conditions such as ADHD, and our methods are not yet sufficiently precise or accurate for them to be of benefit to individuals. This is likely to change in the near future, because our methods are continuing to improve, but currently there are no situations in which an MRI scan will be helpful for someone with ADHD.

HAS ALL THE NEW INFORMATION FROM BRAIN IMAGING OF PEOPLE WITH ADHD LED TO ANY NEW MEDICATIONS TO TREAT ADHD (BEYOND THE STIMULANT CLASS AND MEDICINES LIKE STRATTERA AND INTUNIV)?

Once again, the humbling reality is that brain imaging has not yet produced insights that have impacted how we provide care for patients with ADHD. However, the history of science suggests that we can be optimistic in the long run, especially as we learn more from brain imaging studies and the brain mechanisms behind ADHD.

DOES EVERYONE EXPERIENCE MIND WANDERING AND IS IT WORSE IN PEOPLE WITH ADHD?

Yes, the emergence of spontaneous thoughts (sometimes called “task-unrelated thoughts,” also referred to as “mind-wandering”) is a general phenomenon. Some studies have

documented that up to half of all reported thoughts are of this type. This suggests that spontaneous thinking is likely valuable, at least in some contexts. It is true that we have developed cultural expectations in which focused concentration is required—often for extensive periods. I do not know of completed studies in which persons with and without ADHD have been compared on the frequency of such spontaneous thoughts, but some studies are likely in process.

DO YOU THINK YOUR BRAIN IMAGING WORK IS GOING TO EVENTUALLY LEAD TO PEOPLE BEING DIAGNOSED WITH SEVERAL DIFFERENT TYPES OF ADHD?

This is precisely the principal objective of conducting brain imaging studies. We certainly do not need them to diagnose ADHD. Taking a history (asking questions about behavior) is still the gold-standard, and much less expensive than a brain scan. However, subjective reports and even descriptions of hyperactivity, impulsivity and inattention cannot distinguish whether these occur for the same or different types of brain mechanisms. The expectation is that as our methods improve in reliability and precision, that we will be able to document different types of ADHD on the basis of distinct brain mechanisms. A few such approaches have already been published using a variety of methods, including brain imaging. These are preliminary results, but if they are found to be replicable in larger samples, they may well serve as the basis for a new way of distinguishing among the types of ADHD—based on brain biology, instead of on global descriptions such as inattention or impulsivity. The major unknown is how long this will take.

Discovery to Recovery: Therapy Update

Recent News on Treatments for Psychiatric and Related Brain and Behavior Conditions

IN CHILDREN WITH AUTISM, METFORMIN MAY REDUCE WEIGHT GAIN SIDE EFFECT OF RISPERDAL AND ABILIFY

Children with autism spectrum disorders (ASD) who take newer generations of antipsychotic medications like risperidone (Risperdal) and aripiprazole (Abilify) to help reduce agitation and irritability may experience weight gain—a troublesome side effect especially for children who begin the medications early on and stay on them long-term. But a new study published August 24 in *JAMA Psychiatry* suggests that this side effect can be alleviated with metformin, a drug most commonly used to control blood sugar in patients with diabetes.

The new study, which focused on children with ASD, adds to previous research in other populations finding that metformin can reduce weight gain that occurs as a side effect of antipsychotics.

The study involved 60 children, between the ages of six and 17, who had been taking a second-generation antipsychotic medication for at least one month and had gained weight during that time. Over 16 weeks, half of the participants were given metformin, and the other half received a placebo. To track changes in weight gain, the researchers used body mass index (BMI) and took into account age and sex-specific norms. Those children who took metformin gained significantly less weight than those who took a placebo. Study participants tolerated the metformin well, with few side effects. The study was led by 2006 Young Investigator Evdokia Anagnostou, M.D., at the Bloorview Research Institute in Toronto, and the team included 2010 Young Investigator Jeremy M. Veenstra-VanderWeele, M.D., at Vanderbilt University School of Medicine.

FULL TEXT: <http://jamanetwork.com/journals/jamapsychiatry/article—abstract/2546510>

COMBINING ECT WITH ANTIDEPRESSANTS MAY BE A FAST, EFFECTIVE TREATMENT OPTION IN DEPRESSED OLDER ADULTS

Results of a recent clinical trial show that adding electroconvulsive therapy (ECT) to treatment with antidepressant medication improves the success rate of the treatment in older adults with major depression. What's more, patients who continued with this combined treatment after remission had a lower risk of relapse.

In a study titled "Prolonging Remission in Depressed Elderly (PRIDE)," researchers tested a treatment involving the antidepressant venlafaxine (Effexor) plus right unilateral ultrabrief ECT, a type of ECT designed to minimize cognitive side effects such as memory problems.

Two hundred and forty patients aged 60 to 89 participated in the study. In Phase 1 of the study, about 60 percent of the patients responded to treatment within four weeks and saw their symptoms remit, according to the findings reported July 15 in the *American Journal of Psychiatry* (AJP).

One hundred and twenty participants whose depression was in remission after completing Phase 1 entered the second phase of the study, to determine the effects of additional ECT in preventing relapse.

After 24 weeks, patients in the ECT-plus-medication group showed fewer symptoms than those who received medication alone, according to a second paper in the AJP. Adding ECT to the post-remission treatment resulted in prolonged remissions and fewer relapses. At the end of the trial, patients in the ECT-plus-medication group were about five times more likely than their peers in the medication-only group to be considered depression free.

The study was co-led by Charles H. Kellner, M.D. at the Icahn School of Medicine at Mt. Sinai, and Sarah H. Lisanby, M.D., the head of translational research at the National Institute of

Mental Health. Lisanby is a 1996 Young Investigator, 2003 Independent Investigator, 2010 Distinguished Investigator, and a 2001 recipient of the Klerman Prize. The team included 2008 Young Investigator Shawn M. McClintock, Ph.D., at the University of Texas Southwestern Medical Center; 2009 Independent Investigator Joan Prudic, M.D., at Columbia University Medical Center; and 1996 and 2010 Young Investigator, 2003 Independent Investigator, 2010 Distinguished Investigator, and 2001 Klerman Prizewinner Styliani Christos Kaliora, M.D., at the Feinstein Institute for Medical Research.

FULL TEXT: <http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2016.15081101>

FULL TEXT: <http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2016.16010118>

IN OLDER PATIENTS WITH BIPOLAR DISORDER, LURASIDONE MAY REDUCE DEPRESSION WHEN USED AS A STAND-ALONE DRUG

Do all psychiatric drugs work the same for people of all ages? Sometimes that is difficult to know for sure. Older adults with bipolar depression, for example, make up an overlooked age bracket when it comes to treatment research. In a new study, researchers focused specifically on the portion of data from older adults in previous research to examine the effects of the antipsychotic medication lurasidone (Latuda) in this age group.

Lurasidone has been previously shown to reduce patients' depressive symptoms both when it is used as a stand-alone medication and when it is added to a mood stabilizer. To assess these two methods in older patients, a new analysis, published in the *Journal of Clinical Psychiatry* in August, gathered data from 140 people aged 55 and older, who had participated in the previous trials.

Those patients who took lurasidone alone showed an improvement of depressive symptoms similar to that of participants of other ages, and significantly more than their peers who received a placebo.

However, the analysis suggested that using lurasidone as an add-on to mood stabilizers may not work as well. Those older adults who received a combined treatment had a similar outcome to those who had a placebo added to their mood stabilizer. It is possible that the number of participants was too low to see an effect. It is also possible that long-term use of mood stabilizers in older adults reduces the effects of lurasidone, the researchers said.

The study was led by Martha Sajatovic, M.D. at University Hospitals Case Medical Center in Cleveland, and the team included Brent P. Forester, M.D. at Harvard Medical School, a Young Investigator grantee in 2004 and 2008.

FULL TEXT: <http://www.psychiatrist.com/jcpl/article/Pages/2016/v77n10/v77n1017.aspx>

ESTROGEN DRUG MAY EASE SYMPTOMS IN OLDER WOMEN WITH SCHIZOPHRENIA

Many older women with schizophrenia continue to experience symptoms despite treatment with antipsychotic medications. It is thought that declining estrogen levels, which occur after menopause, may contribute to the severity of symptoms. Raloxifene, a drug that targets the cellular receptor, or docking port, for estrogen, may help reduce the symptoms when taken in addition to antipsychotics, according to results from a new clinical trial published September 1 in *JAMA Psychiatry*.

Raloxifene is often used to treat or prevent osteoporosis in postmenopausal women. It has been shown to increase estrogen levels in the brain and a study last year found the drug can improve memory in men and women with schizophrenia.

In the new study, 56 women aged 40 to 70 with treatment-resistant schizophrenia received either raloxifene or a placebo for 12 weeks. In addition, the participants continued with their antipsychotic treatment. After 12 weeks, women in the raloxifene group showed a significant reduction in their symptoms, judged by their score on the Positive and Negative Syndrome Scale, compared with those in the placebo group.

Raloxifene mainly worked to improve general symptoms such as anxiety, depression, impulse control and social avoidance, the researchers found. The drug did not seem to significantly affect schizophrenia's positive and negative symptoms. Positive symptoms include altered perception of reality such as hallucinations and delusions, while negative symptoms include apathy and blunting of affect.

Overall, raloxifene was well tolerated and reduced the severity of illness, showing potential for being used in clinical practice, the researchers said.

The study was authored by Jayashri Kulkarni, MBBS, Ph.D. of Monash Alfred Psychiatry Research Centre, Monash University, Melbourne, an Independent Investigator grantee in 2000.

FULL TEXT: <http://jamanetwork.com/journals/jamapsychiatry/article—abstract/2535242>

The Importance of Funding Young Investigators

Q
A

AT WHAT AGE DO MOST U.S. BIOMEDICAL SCIENTISTS RECEIVE THEIR FIRST MAJOR NATIONAL INSTITUTES OF HEALTH (NIH) GRANT?

According to a recent study conducted by Johns Hopkins University president Ronald J. Daniels, the average age at which an investigator with a medical degree receives his or her first major NIH grant is 45 years old.¹ The number of principal investigators 36 years old and younger who have received R01 grants (NIH's main research grant) has fallen from 18 percent in 1983 to 3 percent in 2010.

The NARSAD Young Investigator Grant program aims to bring more support to younger scientists who are increasingly left out of early career funding from government sources. The Foundation's Young Investigator research grant program was initiated in 1987 to help researchers launch careers in neuroscience and psychiatry.

Q
A

WHO RECEIVES MORE NIH R01 AWARDS—OLDER OR YOUNGER INVESTIGATORS?

As of 2014, principal investigators who were 65 years and older received more than twice as many R01s as investigators who were 36 years old and younger. This is different than the early 1980s when more of the younger investigators received R01 awards.²

Q
A

DO YOUNGER INVESTIGATORS CONDUCT DIFFERENT TYPES OF RESEARCH THAN OLDER INVESTIGATORS?

Yes. One of the key reasons the Foundation supports young investigators is that they do often pursue research that is different from that of older peers. The Young Investigator program is unique in that it is intended to facilitate innovative research opportunities and supports basic, translational and clinical researchers. The program helps young researchers expedite the gathering of crucial pilot data necessary for future federal and university grant funding. Research published by early-career scientists tends to draw from newer research concepts, technologies and discoveries than research published by older investigators, according to a study that reviewed more than 20 million biomedical papers published in the past 70 years.³



DOES OVERALL GOVERNMENT SCIENCE SPENDING AFFECT THE AMOUNT OF SUPPORT AWARDED TO YOUNGER INVESTIGATORS?

Several studies suggest that NIH and other U.S. science agencies, faced with annual budgets that are reduced or do not keep pace with inflation, tend to become more conservative in awarding grants to younger investigators.^{4,5} That is, they tend to award grants to researchers who have established themselves in their fields, and they fund research that makes incremental contributions to an established field of study rather than fund more innovative and more “risky” research questions. The NARSAD Young Investigator Grants are specifically designed to support younger scientists and their innovative ideas, before the “proof of concept” stage that would make it more likely that the research is funded by the NIH.



HOW DO EARLY-CAREER GRANTS HELP YOUNG INVESTIGATORS WITH THEIR RESEARCH AND PROFESSIONAL PATHS?

Young scientists say early-career grants help them in several ways. The support allows them to pursue innovative ideas at the start of their careers, rather than waiting to accumulate decades’ worth of data.⁶ With support like the NARSAD Young Investigator grant, researchers can build on preliminary data that moves larger studies forward, says Scientific Council member John H. Krystal, M.D. of the Yale University School of Medicine.⁷ Grants to young researchers also keep them working as scientists, instead of turning to an alternative career.⁸

1. RJ Daniels, “A generation at risk: Young investigators and the future of the biomedical workforce,” *Proceedings of the National Academy of Sciences*, Volume 112, Pages 313—318, January 2015.
2. S Rockey, “Age Distribution of NIH Principal Investigators and Medical School Faculty (National Institutes of Health, Bethesda, MD,” <https://nexus.od.nih.gov/all/2012/02/13/age—distributionof—nih—principal—investigators—and—medical—school—faculty>.
3. M Packalen and J Bhattacharya, “Age and the trying out of new ideas,” *National Bureau of Economic Research Working Paper Series*, <http://www.nber.org/papers/w20920.pdf>.
4. JM Nicholson and JPA Ioannidis, “Research grants: Conform and be funded,” *Nature*, Volume 492, Pages 34—36, December 2012.
5. FC Fang and A Casadevall, “NIH peer review reform—change we need, or lipstick on a pig?” *Infection and Immunity*, Volume 77, Pages 929—931, March 2009.
6. A broken pipeline?: Flat funding of the NIH puts a generation of science at risk, <http://www.harvard.edu/sites/default/files/content/Broken—Pipeline.pdf>.
7. “Dr. Krystal on the vital role of NARSAD grants,” <https://bbrfoundation.org/brain—matters/dr—krystal—on—the—vital—role—of—narsad—grants>.
8. JQ Taylor et al., “Point of view: Avoiding a lost generation of scientists,” *eLife*, Volume 5, Page: e17393, 2016.

CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE): a progressive degenerative disease of the brain, found in people who have had a severe blow or repeated blows to the head.

ELECTROENCEPHALOGRAPHY (EEG): a method for recording electrical activity in the brain.

fMRI: a variant of magnetic resonance imaging, which enables researchers to make key measurements of activity and function in the resting brain.

GWAS: short for genome-wide association study, an examination of a genome-wide set of genetic variants in different individuals to see if any genetic variant is linked to a specific trait or disease.

MENTALIZATION: the ability to understand the mental state, of oneself or others, that underlies a person's behavior. This ability is often impaired in people with schizophrenia.

OPTOGENETICS: a new technology developed with the early support of a NARSAD Grant by Dr. Karl Deisseroth and colleagues that enables research scientists to use colored laser light to switch "on" and "off" individual neurons in the brain. This technology makes possible a new generation of experiments aimed at identifying specific circuits involved in brain and behavior disorders.

PRODROME/PRODROMAL PERIOD: refers to the early stage of a brain and behavior disorder, a period just before an illness fully manifests.

TRANSCRANIAL DIRECT CURRENT STIMULATION: a form of brain stimulation which uses constant, low electric current delivered using electrodes placed on the scalp, used most often as a treatment for depression.

WORKING MEMORY: temporary memory needed for a short time to complete a momentary task such as dialing a phone number.

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