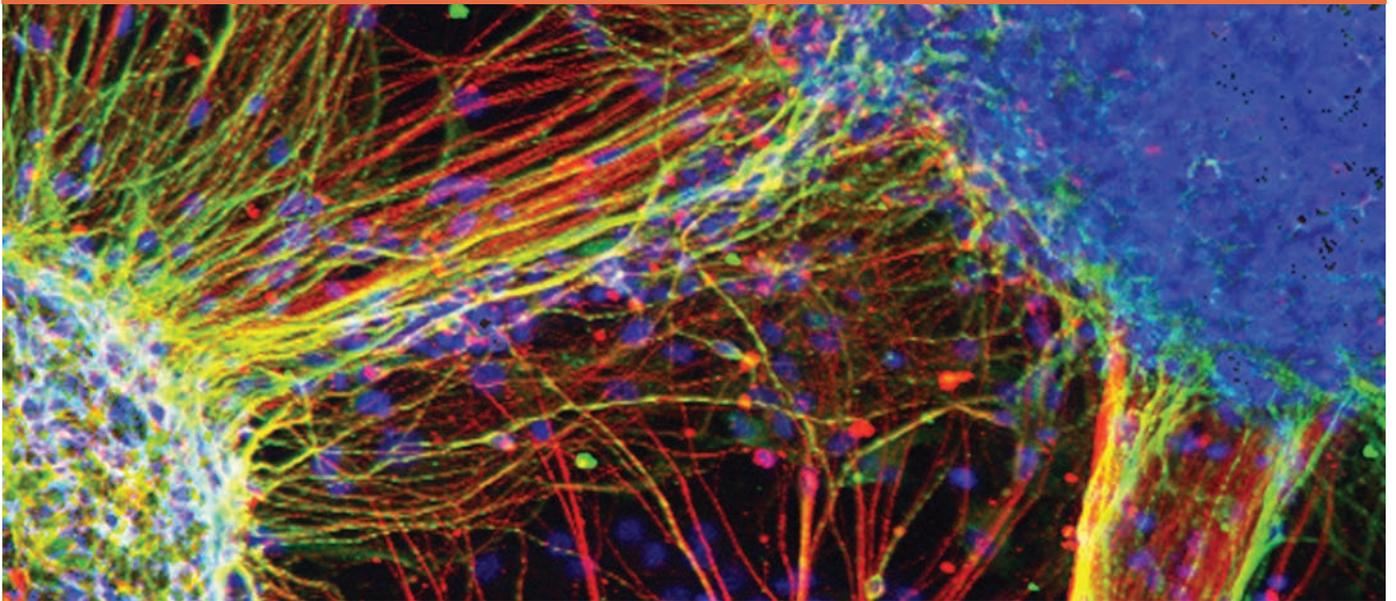




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Cover: Image of neurons, derived from schizophrenia patients, which were generated from hiPSCs. Neuronal marker III-tubulin (red), dendritic marker MAP2AB (green), nuclei (blue). Courtesy of Kristen Brennand, Ph.D., Gene/Research Trends (p.17)

Jeffrey Borenstein, M.D.

President & CEO
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One of the saddest aspects of mental illness is that it often strikes people at a very young age. Psychiatric conditions such as schizophrenia, bipolar disorder, depression, and chemical dependence all begin to surface in adolescence and young adulthood. A recent survey of more than 150,000 students nationwide, "*The American Freshman: National Norms Fall 2014*," found that 9.5 percent of respondents had frequently "felt depressed" during the past year, a significant rise over the 6.1 percent reported five years ago.

For the parents and siblings of young people diagnosed with psychiatric disorders, it can be frightening, bewildering, and frustrating. Where do they turn for help? Starting with this issue of *The Quarterly*, we're going to include, as part of our focus, information that can be of practical use to families coping with the diagnosis of a behavioral disorder or mental illness. (See page 24.)

Shaping behavior is a complex mix of genes, childhood experience, and the environment in which a young person reaches adolescence. Research is revealing how all these factors act in the context of a brain that is changing, with its own impact on behavior. The more we learn, the better we may be able to understand the abilities and vulnerabilities of teens, and the significance of this stage for life-long mental health. Understanding the changes taking place in the brain at this age presents an opportunity to intervene early in mental illnesses that manifest at this age.

Research shows that one in four people will experience a mental illness during their lifetime. Virtually every one of us has a loved one who has been affected. Treatment helps many people, but more effective treatment and new methods of treatment need to be developed. Now is the time to put more dollars toward prevention, early detection, and early-intervention brain research to find new and better ways to detect and treat mental illness.

The Brain & Behavior Research Foundation is the world's leading private funder of mental health research grants. The Foundation funds the most innovative ideas in neuroscience and psychiatry to better understand the causes and develop new ways to effectively treat brain and behavior disorders.

It is only through support for research that we can alleviate the pain and suffering mental illness can cause families, and find the advances and breakthroughs that will result in better treatments and hope for cures. Our research grants will pave the way for scientists to ultimately enable people to live full, happy, and productive lives.

Sincerely,


Jeffrey Borenstein, M.D.
President & CEO

Research Discoveries in the News

Finding the Way Forward Toward New Depression Treatments

In its November 13, 2014 issue, a section of which was devoted to depression, the prestigious journal *Nature* invited three researchers to suggest “the best way forward” in discovering new antidepressants. All three are past recipients of NARSAD Grant awards, and two are members of the Foundation’s Scientific Council. The suggestions they presented contrast markedly, and represent two powerful schools of opinion within the research community.

One approach was advocated by **Lisa Monteggia, Ph.D.**, of the University of Texas Southwestern Medical Center. She has twice received NARSAD Young Investigator Grants and in 2010 was an Independent Investigator Grantee. Dr. Monteggia, like the other scientists involved in the forum, acknowledged the problem: the absence of new antidepressants, including ones that might act more rapidly for urgent cases, as well as ones to help the large portion of depressed people whose depression does not respond to SSRIs—selective serotonin reuptake inhibitors* such as fluoxetine (Prozac).

Noting that many scientists are trying to study depression in rodents that “model” various depression symptoms such as loss of interest, the inability to experience pleasure, and susceptibility to anxiety, Dr. Monteggia instead recommends that we focus on better understanding drugs known to work in people. This approach has already been tried for SSRIs, but the answers have not been very helpful in figuring out how to make them work more rapidly. It often takes two to three months for SSRIs to show benefit.

Dr. Monteggia urges efforts to figure out how the fast-acting medication ketamine* exerts its often remarkable effects. Some people with recurring depression report

the lifting of symptoms in as little as one hour. Scientists know ketamine blocks NMDA receptors* in the brain for the neurotransmitter glutamate.

From this starting point, Dr. Monteggia argues, we should study how that blockade affects signaling in key brain networks. Such study might reveal powerful ways to make other drugs that act like ketamine, only better and with fewer side effects.

A second school of thought was represented in the *Nature* forum by **Robert Malenka, M.D., Ph.D.**, and **Karl Deisseroth, M.D., Ph.D.**, colleagues at Stanford University. Drs. Malenka and Deisseroth, both of whom are NARSAD Grant recipients and current Scientific Council members, think it makes more sense to stress research aimed at “a sophisticated understanding of the causes of illness [including, but not restricted to depression] at the level of neuronal circuits.”

Like lithium for bipolar disorder, ketamine for treatment-resistant depression can indeed be effective, Drs. Malenka and Deisseroth acknowledge, but these medications “affect neurons indiscriminately throughout the brain.” This makes it hard to figure out exactly how they benefit patients. Rather, the researchers argue, we should try to identify targets in malfunctioning brain circuits that, when manipulated using various advanced technologies, can actually repair the dysfunction.

Dr. Deisseroth and his colleagues are renowned for their invention, during the last decade, of a technology called optogenetics* that makes possible the manipulation of individual brain cells with colored laser light. Though experimental at this point, application of such methods to repair damaged circuits is a kind of “frontier approach” that contrasts with the “pharmaceutical approach” dominant until now. Both kinds of research—pharmaceutical-based and circuit-based—are certain to continue.



Lisa Monteggia, Ph.D.; Robert Malenka, M.D., Ph.D.; Karl Deisseroth, M.D., Ph.D.

TAKEAWAY: To improve treatment for depression, researchers advocate focusing on drugs known to work, and identifying malfunctioning brain circuits in an effort to repair them.

* Refer to glossary on page 28.

Targeting the D1 Dopamine Receptor to Improve Working Memory in Schizotypal Personality Disorder

For the first time, researchers have shown in a clinical trial that a chemical called a D1 agonist can reduce “working memory” impairments found in schizotypal personality disorder. Working memory is the ability to retain various pieces of information over short periods of time so that other parts of the brain can work with them. The scientists found that the D1 agonist increases activity at D1 receptors, which is important for memory. These receptors connect with dopamine, a neurotransmitter known to be involved in working memory disorders.

The research was conducted by a team that included seven past NARSAD Grantees and members of the Foundation’s Scientific Council.* They reported their findings in a paper that appeared online August 27, 2014 in *Neuropsychopharmacology*.

Targeting the D1 receptor represents a step forward in possible strategies for managing schizophrenia and other disorders. Antipsychotic medications are the common drug treatment for such disorders, but they do not improve symptoms for everyone who needs treatment. Because the antipsychotic drugs block D2 receptors, they work better at controlling psychosis, which is associated with excess D2 activity.

Because memory disorders are linked to reduced D1 activity, successfully targeting the D1 receptor to enhance its activity may expand possible treatment options for schizophrenia and other disorders and

perhaps avoid some of the more serious side effects caused by antipsychotics.

The team tested the effects of a compound called DAR-0100A, a type of a known dopamine agonist called DHX (dihydroxidine). The researchers found that compared to placebo,** DAR-0100A significantly improved the ability of patients with schizotypal personality disorder to add pairs of numbers, a task that requires working memory to keep track of the numbers as new pairs are continuously supplied.

Results were mixed for a second task that required sustained attention as well as visual memory and working memory. More research is needed to repeat the finding in a larger study and across a larger set of tasks, in order to demonstrate its robustness and its clinical significance, one of the study authors, **Anissa Abi-Dargham, M.D.**, notes. And although no significant side effects were observed in this study immediately after the tasks or during follow-up testing, more research is needed to test for possible side effects of D1 agonists.

To build on this work, the team says they are conducting a larger clinical trial to assess the effects of DAR-0100A on other cognitive functions besides working memory. They also suggest that better drugs need to be aimed at the D1 receptor in order to more fully test this target; the compound used in the research reported here, DAR-0100A, did not build up very well in the brain.



Margaret M. McClure, Ph.D.; Deanna M. Barch, Ph.D.; *Philip D. Harvey, Ph.D.; Ragy R. Girgis, M.D.



Erin A. Hazlett, Ph.D.; *Anissa Abi-Dargham, M.D.; *Jeffrey A. Lieberman, M.D.

TAKEAWAY: Medications called D1 agonists may offer a new way to treat a memory disorder in schizotypal personality disorder.

Ketamine Shown to Reduce Suicidal Thoughts

Rapid relief for people reporting suicidal thoughts or who are in a suicidal crisis may be on its way. The most talked-about drug to hit depression research in years is ketamine. This medication has been making waves for its ability to rapidly reduce depressive symptoms in some people, most importantly in those whose depression has not responded to other treatments. Now, a research team has found that ketamine can reduce suicidal thoughts (also called suicidal ideation), independent of its ability to reduce anxious and depressive symptoms.

Led by **Carlos Zarate, M.D.**, recipient of a 1996 NARSAD Young Investigator (YI) Grant and 2005 NARSAD Independent Investigator (II) Grant, the new findings on ketamine were published in the *Journal of Psychiatric Research* in November 2014 and discussed in the journal *Nature* January 8th in an article about expectations surrounding ketamine's clinical potential. The *Nature* story also mentioned research by 2010 YI Grantee **Kyle A.B. Lapidus, M.D., Ph.D.**, 2009 YI Grantee **James W. Murrough, M.D.**, 2001 Distinguished Investigator Grantee and Director of the National Institute of Mental Health **Thomas Insel, M.D.**, and 1998 II Grantee and member of the Foundation's Scientific Council, **Husseini K. Manji, M.D.**

Previous research has shown that ketamine can sharply reduce symptoms of depression within hours of being administered—quite an advantage over the most commonly used antidepressant drugs, selective serotonin reuptake inhibitors, which usually take one to three months to show full effects. The recent study led by Dr. Zarate is the first to show that, in addition to diminishing depression and anxiety, ketamine can separately and just as quickly reduce suicidal thoughts.

As discussed in the *Nature* article, the enthusiasm over ketamine's quick effects has somewhat obscured the uncertainty over how well the drug works in the long term, which will be important for determining its role in depression treatment. Though ketamine is only clinically approved as an anesthetic, many doctors are already prescribing it off-label for treatment-resistant depression, and drug companies are rushing to develop alternative versions of the drug that could avoid ketamine's serious side-effects, including hallucinations and "dissociation" * or detachment from reality.

Some argue that even if ketamine is not ultimately approved for long-term use, it could still be very beneficial as an emergency treatment for people in a suicidal state.

Ketamine works by reducing activity at NMDA (N-methyl-D-aspartate) receptors in the brain, which are implicated in the pathology of depression and act as a gate for the neurotransmitter glutamate. Other medications have been identified that regulate glutamate levels and have quick antidepressant effects, without causing hallucinations. But it is not yet known whether other glutamate regulators can reduce suicidal thoughts.

As noted in the *Nature* article, Dr. Zarate says that ketamine's fast action is particularly promising for suicide prevention. His research suggests that ketamine seems specifically to affect the desire to attempt suicide, whether a person is clinically depressed or not. In a trial now under way, Dr. Zarate and colleagues are using ketamine to treat around 50 people with depression, some of whom have suicidal thoughts, to study this in more detail.



Carlos Zarate, M.D.; Kyle A.B. Lapidus, M.D., Ph.D.



TAKEAWAY: Ketamine, known to rapidly reduce symptoms of anxiety and depression, has now also been shown to quickly reduce suicidal thoughts.

James W. Murrough, M.D.; Thomas Insel, M.D.; Husseini K. Manji, M.D.

* Refer to glossary on page 28.

Genetic Signals Emerging on Schizophrenia Risk

Bringing Scientists Together to Solve the Mystery of Schizophrenia's Causation



Patrick F. Sullivan, M.D., FRANZCP

Professor, Karolinska Institutet

M. Hayworth & Family Distinguished
Professor of Psychiatry
Professor of Genetics & Psychiatry
Director, Center for Psychiatric Genomics
University of North Carolina, Chapel Hill

2014 Lieber Prize for Outstanding
Achievement in Schizophrenia Research

NARSAD Grant:
Distinguished Investigator 2010

As a psychiatric geneticist, Dr. Sullivan works to decode the molecular and cellular consequences of the genetic variation underlying schizophrenia. He heads large, multinational projects across a range of disorders, dividing his time between Sweden, where he is a Professor at the Karolinska Institutet, and the University of North Carolina, where he is the M. Hayworth & Family Distinguished Professor of Psychiatry and UNC Professor of Genetics and Psychiatry, as well as the Director of the Center for Psychiatric Genomics.

“When people think about diseases with a genetic cause, they think about Tay-Sachs, Huntington’s disease, cystic fibrosis. These are situations where the genetic note from the orchestra is enormous—a loud, banging drum. If you have a particular genetic variation, you get the disease. If you don’t have it, you don’t get it.”

The speaker, Professor Patrick F. Sullivan, M.D., of the University of North Carolina and Sweden’s Karolinska Institutet, is setting up a contrast. What happens in schizophrenia, he says, could not be more different.

“In schizophrenia and other psychiatric illnesses, we haven’t found any loud, banging genetic notes—only far softer notes from many different parts of the genomic ‘orchestra.’ Schizophrenia is a highly complex disease, and while it has a strong heritable component, the genetic factors that contribute to risk are proving to be quite subtle.”

Dr. Sullivan, recipient of a NARSAD Distinguished Investigator Grant in 2010 and in 2014 the Foundation’s Lieber Prize (for schizophrenia research), is one of the leaders of an important movement in psychiatric

“Schizophrenia is a highly complex disease, and while it has a strong heritable component, the genetic factors that contribute to risk are proving to be quite subtle.”

genomics—the study of genes linked to mental disorders. He and a few colleagues co-founded the Psychiatric Genomics Consortium (PGC) in 2007. At last count, it included some 800 scientists from more than 90 research institutions in 25 countries who have published scientific papers on the genetics of many psychiatric illnesses, as well as genetic factors that several of the illnesses have in common.

“The neat story about the Consortium is that hundreds of investigators have decided to come together and work in a communal way,” Dr. Sullivan explains. “All the published papers are a sign that the Consortium is working, that we’re moving ahead, and really starting to deliver answers. But back in 2010 and 2011, lots of people in the field were saying that what we were doing was a very bad idea. We completely disagreed and stuck to our guns.”

Most of those who spoke out against the Consortium believed that the PGC scientists were too narrowly devoted to a particular method of probing the human genome called GWAS—genome-wide association study. In a GWAS, scientists look for single-letter variations called SNPs (“snips”) in the three-billion-letter human DNA code. SNPs occur frequently across vast swaths of the population. The idea behind the GWAS approach is that a common illness like schizophrenia (which affects about one person in 100, worldwide) most likely is caused by factors commonly shared, which should be seen repeatedly if the genomes of many affected people are scanned.

But while several years of GWASs on schizophrenia turned up hundreds of SNPs that occurred more often in patients than in healthy people, few scientists were convinced. There were two problems, Dr. Sullivan explains. One was that the SNPs found in one GWAS usually didn’t match the SNPs that turned up in the next study. This “reproducibility” problem was related to another problem: “We had always massively underestimated the number of people we would need to look at in these studies in order to get a clear signal from the genes,” he says. This problem of insufficient sample size spurred the formation of the Consortium. The hope was that by pooling many studies that involved large numbers of patients, reproducible genetic signals would emerge.

“All the published papers are a sign that the Consortium is moving ahead and starting to deliver answers. But lots of people in the field were saying that what we were doing was a very bad idea. We stuck to our guns.”

That is what seems to be happening. (See “Following Up on Clues From Genes” on page 8.) Now, rather than conducting a GWAS comparing the genomes of 2,000 schizophrenia patients with 2,000 healthy people, the PGC is amassing samples of, say, 35,000 patients. By the end of the year, the number of schizophrenia patient samples should grow to 60,000 while the total number of samples across psychiatric illnesses could reach 400,000.

In addition to GWASs, which look for commonplace variations, members of the Consortium, including Dr.

Sullivan, also conduct studies on rare and ultra-rare variations of the genome. Most involve the abnormal multiplication or deletion of DNA segments at points along the genome. Prior research has shown that people with schizophrenia and autism, for example, have a much greater likelihood of having these rare types of mutations than healthy people. It’s hypothesized that when they occur in areas that contain genes involved in the early development of the brain, they have the potential to cause illness, even in the absence of other causal factors. In contrast, illness-associated SNPs, though commonplace, are thought to contribute a tiny amount to overall risk for becoming ill.

“Whether the genetic clues are rare, common, or both, the point is that we must use all available methods to find them,” Dr. Sullivan says. “As of now, the data are increasingly clear that schizophrenia is a common-variant disease, on average.” This means that in most patients, the portion of the illness traceable to genetic variation is probably due to large clusters of small-effect common variations that are only now becoming visible as vast numbers of patient samples are being brought together for study.

Following Up on Clues From Genes

In July 2014, members of the Schizophrenia Working Group of the Psychiatric Genomics Consortium published a landmark paper in the journal *Nature*. The many collaborating scientists included Lieber Prize winners Patrick Sullivan, M.D., Michael O'Donovan, M.D., Ph.D., and Michael J. Owen, M.D., Ph.D., as well as Foundation Scientific Council members Kenneth S. Kendler, M.D., and Daniel R. Weinberger, M.D. These senior authors and their colleagues revealed "biological insights" from a genome-wide association study of 37,000 schizophrenia patients, the largest-ever such study.

"That's the thing about schizophrenia genetics: it's an accumulation of small things. It seems each of us inherits some probability of having schizophrenia."

Common genetic variants—of which many more will likely be found—may, together, account for much of the total genetic portion of risk for schizophrenia.

As headline writers around the world noted, the Consortium had identified 108 loci, or locations along the 23 human chromosomes, where single-letter misspellings of the genetic code were thought to contribute to disease susceptibility. "Susceptibility" is the key word, Dr. Sullivan explains: "Each of the 108 variations increases risk by a little bit. That's the thing about schizophrenia genetics: it's an accumulation of small things. It seems each of us inherits some probability of having schizophrenia."

HAVE A QUESTION?

Send questions for Dr. Sullivan to asktheresearcher@bbrfoundation.org. Select questions and answers will be in the next issue of *The Quarterly*.

Please note that the researcher cannot give specific recommendations or advice about treatment; diagnosis and treatment are complex and highly individualized processes that require comprehensive face-to-face assessment.

Results of the study suggest to Dr. Sullivan that common genetic variants—of which many more will likely be found—may, together, account for much of the total genetic portion of risk for schizophrenia. At the same time, it is very likely that in a small percentage of cases—possibly as little as one percent of the total—single rare variations may be disruptive enough to cause illness without contributions from other genetic factors. In addition, the environment is always a factor that contributes in small or large part to risk in individual cases.

Going down the list of 108 newly identified common risk variants identified by the Consortium in July, one is immediately struck by a variation affecting one of the genes (called *DRD2*). This gene tells neurons how to make receptors, or docking ports, for the neurotransmitter dopamine. Dopamine signaling has been a suspect in schizophrenia for many years, in part because antipsychotic drugs are known to block dopamine receptors. Several genes involved in the transmission of the common signal-carrying molecule glutamate were also implicated.

Perhaps most intriguing, there were associations between some of the 108 risk variants and the expression of genes that play important roles in the immune system. Involvement of the immune system in schizophrenia and other neuropsychiatric illnesses has long been suggested. Some scientists have postulated that inflammation and/or infection is in some way related to heightened risk. GWAS findings draw attention to the major histocompatibility complex, a set of cell-surface markers encoded by a group of genes that controls several aspects of the immune response. An immune component of risk reflects the widely acknowledged "environmental" dimension of the total risk picture.

The study illustrates the importance of devoting more time and energy to fleshing out the biological pathways that could be involved in schizophrenia risk. Writing in *Nature*, two commentators call this effort "a tremendous advance, of the sort that rewrites textbooks."

Ask the Researcher



J. John Mann, M.D.

Paul Janssen Professor of Translational Neuroscience in Psychiatry and Radiology

Vice Chair for Research
Department of Psychiatry
Columbia University

Director of Research and Director of
Molecular Imaging and Neuropathology
Division
New York State Psychiatric Institute

2008 NARSAD Grantee

Foundation Scientific Council Member

“Our idea of doing an imaging study in real time of patients being given ketamine [to treat depression] would not have been funded without some pilot data. A NARSAD Distinguished Investigator Grant enabled me to get pilot data for this, and that led to a major NIH grant.”

J. John Mann, M.D.

In your interview you talked about the biological predisposition to suicide. I suffer from depression and worry that, because there has been a suicide in my family, I might be at risk. What should I do?

There is no risk if you are free from depression. But if you begin to experience a return of your depression or a worsening of symptoms, please get in touch with your doctor. If your depression has only partly responded to treatment, then work with your doctor to see if you can find further relief. Don't hesitate to get a second opinion. Some people worry that they will hurt their doctor's feelings if they see another physician. Any decent doctor should totally accept the need for such a request and a second opinion may shed new light on your treatment, or confirm that you are on the right track.

I know you are conducting clinical trials on ketamine, which are important to advance our knowledge about treatments. But I'm concerned about taking part in a study. What are the risks and benefits for me as an individual?

Every study is different and the staff will be happy to explain the risks and benefits and answer any and all of your questions. We have two types of studies and in both studies

you will get treated with ketamine even if you might get a placebo the first time around. One trial does brain imaging while you are getting the ketamine to measure its effect; the other clinical trial does not include brain imaging. The second study allows you to stay on your current medications. For more details, feel free to get in touch by calling 646-774-5788.

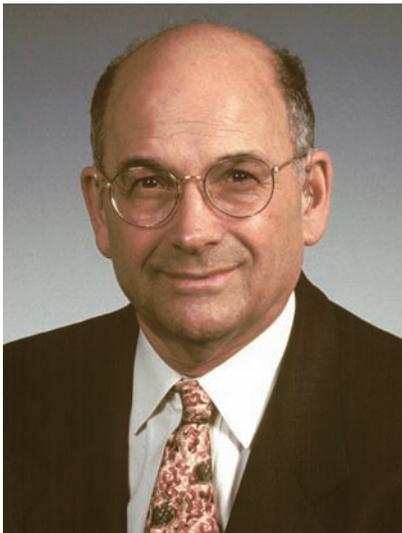
Our teenage daughter attempted suicide, but her injuries were not lethal. What can and should we do to help her and prevent another attempt that could be lethal?

It is a great relief that she survived and there is a chance to help her. The key thing to know is the type of psychiatric disorder that was associated with the suicide attempt. The most common type of mental illness that can lead to suicide is major depression. In that case, the goal is to treat the depression with the help of a psychiatrist so that the patient can feel better. The more effectively the depression is treated, the lower the risk for suicidal behavior. Other factors involved may include relationship problems or the use of drugs or alcohol. A therapist can often help in these types of cases. Any time a person attempts suicide or says he or she has thoughts about suicide, it should be taken seriously and help should be sought.

2015 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 project ideas.**

104
APPLICATIONS
▼
15
GRANTS AWARDED
▼
\$1.5M
TOTAL FUNDING



Jack D. Barchas, M.D.

Chair and Barklee McKee Henry
Professor of Psychiatry
Weill Cornell Medical College

Psychiatrist-in-Chief
Weill Cornell Medical Center
NewYork-Presbyterian Hospital
and Payne Whitney Clinic

Founding Member
Foundation Scientific Council

The current grantees were selected by members of the Foundation's Scientific Council, a volunteer group of 150 leaders in brain and behavior research. This year's 15 established investigators were selected from 104 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 collaborations of disciplines, while others took a deep look using a single discipline.

"The most striking conclusion is that a number of projects, although labeled in terms of one or another syndrome, actually have relevance for several," said Jack Barchas, M.D., of Weill Cornell Medical College, a Scientific Council member and Chair of the Distinguished Investigator Grant Selection Committee.

"The underlying fundamental neurobiology and psychobiology are beginning to come together in ways that suggest the emergence of a new integrative science for dealing with mental illness and addictive states. These proposals have relevance for conditions such as schizophrenia, depression, bipolar, anxiety and personality disorders, forms of substance abuse, and other conditions affecting individuals of all ages. While we cannot say when there will be progress, ultimately this work will help patients and their families. The result will be better understanding of mental disorders and more personalized care."

BASIC RESEARCH

AUTISM SPECTRUM DISORDER



Karen Faith Berman, M.D., National Institute of Mental Health, will investigate the effect of genetic variation in autism spectrum disorder by comparing copy number variations (CNVs) in autism and Williams Syndrome, a rare developmental disorder. CNVs refer to alterations of the DNA. These alterations result

in the cell having an abnormal or, for certain genes, a normal variation in the number of copies of one or more sections of the DNA. Williams Syndrome and autism have differing CNVs in the same chromosomal region. The result in people with Williams Syndrome is hypersociability and language strength but visuospatial impairment—features exactly opposite those of autism. Using advanced brain imaging techniques to explore this contrast, Dr. Berman hopes to uncover basic information about the neurogenetic mechanisms of social behavior, cognitive disability, and brain plasticity during fetal development that may play a role in autism.

DEPRESSION

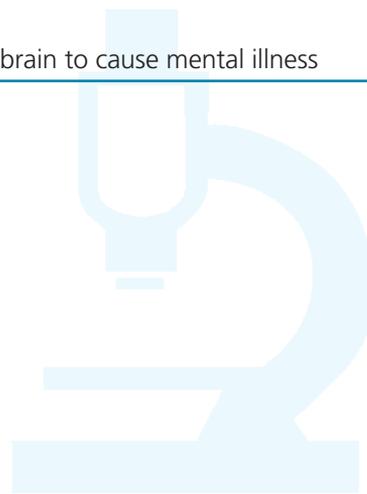


Gerard Sanacora, M.D., Ph.D., Yale University, will seek deeper understanding of the mechanisms underlying major depressive disorder by exploring the role of “glial-mediated glutamate clearance” in stress sensitivity. Glia are structural brain cells that support neurons; glutamate is the brain’s predominant

excitatory neurotransmitter. Based on previous studies, Dr. Sanacora hypothesizes that impaired glial function reduces glutamate uptake capacity and sensitizes susceptible components of the brain to the consequences of stress. The hope is that increasing or preserving glial glutamate “transporter function” will reverse or reduce the changes associated with stress commonly seen in the brains of patients with depression and that these studies will provide novel targets for future drug treatment development.

The support provided to my laboratory through the NARSAD Distinguished Investigator Grant will allow us to better understand the link between social and environmental stress and the changes in brain structure and function that are commonly observed in stress-related neuropsychiatric disorders.

Gerard Sanacora, M.D., Ph.D.



SCHIZOPHRENIA



Angelique Bordey, Ph.D., Yale University, hopes to gain insight into how brain circuits and networks are altered to give rise to psychiatric disorders, in particular schizophrenia, by focusing on the exchange of exosomes between neurons. Exosomes are a subtype of microvesicles—tiny membraneous sacs that transfer proteins, RNA, and

microRNA between cells. (MicroRNAs are short, non-coding RNAs that regulate gene expression.) Dr. Bordey’s working hypothesis is that exosomes released from diseased neurons act as disease carriers that spread and amplify cellular and molecular abnormalities across developing neuronal networks.



Jane R. Taylor, Ph.D., Yale University, will create rodent models to explore the cognitive impairments of schizophrenia, which are not understood and for which effective drug therapies are lacking. In addition to biological and genetic risk factors for schizophrenia, exposure to THC, the active ingredient in cannabis, can contribute to cognitive

dysfunction, and phencyclidine, popularly known as PCP or angel dust, causes schizophrenia-like symptoms in both humans and animals. Dr. Taylor will test several key hypotheses about the causes of the cognitive deficits of schizophrenia with rodent models of PCP- and THC-induced decision-making dysfunctions, combining PET molecular imaging with computational analysis.

This funding will allow us to fill a ‘translational gap’ by combining PET imaging with rodent models of decision-making dysfunction and apply a computational analysis that should promote advances in understanding the neurobiology of, and vulnerability to, psychiatric disorders such as schizophrenia.

Jane R. Taylor, Ph.D.

SCHIZOPHRENIA (cont.)



Suzanne Zukin, Ph.D., Yeshiva University, is seeking to identify mechanisms that affect N-methyl-D-aspartate receptors (NMDARs) during normal and abnormal brain development. NMDARs are proteins called ion channels that play a major role in the formation of synapses and neural circuitry and in higher cognitive functions. REST/NRSF is a factor expressed in stem cells and neural progenitors (cells that can differentiate into specific types of cells). This factor affects the NMDAR “subunit” GluN2B. Dr. Zukin and team recently discovered that maternal deprivation prevents REST activation and aberrantly elevates

GluN2B. The hypothesis driving this proposed project is that REST remodels and silences GluN2B during normal brain development and that dysregulation of REST and its target GluN2B contribute to the cognitive impairments associated with schizophrenia.

This NARSAD Grant will enable us to perform novel, paradigm-shifting research, forge collaborations with leading clinicians, and accelerate development of novel therapeutic strategies to ameliorate the cognitive deficits not only of schizophrenia, but of other mental diseases.

Suzanne Zukin, Ph.D.

MULTIPLE DISORDERS



Jill M. Goldstein, Ph.D., Harvard University, will explore why major depressive disorder appears to increase the risk for late-life cognitive decline and Alzheimer’s disease, with twice the risk for women. Dr. Goldstein will test the hypothesis that inflammation during fetal development disrupts the hypothalamic-pituitary-adrenal (HPA) axis development. HPA circuitry is central to stress response in both sexes, but affects women more intensely than men. Dr. Goldstein proposes to link immune pathway disruptions transmitted in utero with sex-dependent depression and later memory circuitry deficits using data

from a 50-year cohort of adults followed since gestation.

I am so grateful for this NARSAD Grant as it supports ideas that have the possibility of transforming how we think about disease from a sex-dependent point of view. Receiving the award helps validate this work and my career emphasis on sex differences in the brain.

Jill M. Goldstein, Ph.D.



Robert D. Hawkins, Ph.D., Columbia University, is studying synapse formation during long-term plasticity. Synaptic plasticity—a change in synaptic connections between neurons—is thought to underlie neural circuit formation and memory and to be disrupted in many psychiatric disorders, including schizophrenia, autism, ADHD, Rett syndrome, Alzheimer’s disease, and drug addiction. Long-term plasticity involves remodeling of existing synapses and growth of new synapses, which Dr. Hawkins and others have shown is accompanied by increases in clusters of pre- and post-synaptic proteins and structures, suggesting

that it involves a program of synapse assembly. Dr. Hawkins will explore that system to address questions about synapse formation during long-term plasticity in cells of the hippocampus, a brain memory center.

This funding makes it possible for me to pursue an exciting new research direction that seems to me to be of fundamental importance scientifically, and which should elucidate basic neuronal mechanisms that may be disturbed in a number of psychiatric disorders.

Robert D. Hawkins, Ph.D.



Tracey J. Shors, Ph.D., Rutgers University, aims to validate a novel animal model known as SCAR, which stands for Sexual Conspecific Aggressive Response. She will use the model to identify the necessary and sufficient brain processes and mechanisms that induce negative, long-lasting consequences on affect and cognition in women in response to early sexual trauma. SCAR produces persistent deficits in learning, neurogenesis, and maternal behavior in pubescent female rats exposed to sexually aggressive males. This model is designed to mimic responses that occur in the brains of women who were

sexually abused as pubescent children and young adults, resulting in trauma that leads to or exacerbates depression and other stress-related mental illnesses, including post-traumatic stress disorder.

It is a great honor to receive this NARSAD Grant, which will allow me to determine how sexual aggression during puberty may relate to symptoms of depression and post-traumatic stress disorder in women.

Tracey J. Shors, Ph.D.

MULTIPLE DISORDERS (cont.)



Claes Wahlestedt, M.D., Ph.D., University of Miami, will investigate the role of a microRNA, miR-134, in the epigenetic dysregulation in schizophrenia and depression. Earlier research by Dr. Wahlestedt found a dysregulated miR-132 in human schizophrenic subjects. EZH1 is an enzyme targeted by miR-132, and miR-132 and EZH1 are dysregulated in depression

when complicated by early life abuse. Dr. Wahlestedt has also found that miR-132 targets at least 34 other epigenetic enzymes and plans to conduct mouse studies to further characterize them. He will also expand his focus from microRNAs to epigenetic enzymes as possible targets for drug treatment of [schizophrenia](#) and [depression](#).

This prestigious award will allow our laboratory to further assess the importance of epigenetic mechanisms in mental disorders. We have already identified promising biomarkers and drug targets and will now be able to pursue further validation of their utility for the development of novel treatments.

Claes Wahlestedt, M.D., Ph.D.

OTHER DISORDERS:

FEAR-RELATED LEARNING AND MEMORY



Yi E. Sun, Ph.D., University of California, Los Angeles, is studying the differing roles of a microRNA, miR-9, in regulating fear-related learning and memory during development and in adulthood. Among her lab's recent findings, it was observed that disturbances

of miR-9 during dendritogenesis (the formation of dendrites) affected dendrite complexity, which in turn influenced fear learning and memory in adulthood. Dendrites are the structures on neurons that receive signals from other neurons. Having confirmed a developmental role of miR-9, Dr. Sun will investigate the molecular mechanisms underlying adult-onset miR-9 activity in the regulation of fear memory.

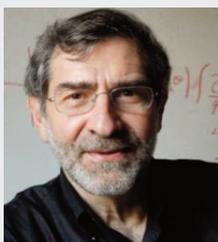
Please consider investing in a Research Partnership with any of our new Investigators.

For more information, visit: bbrfoundation.org/research-partner.

NARSAD Grants fund **New Technologies** to advance or create new ways of studying and understanding the brain

NEW TECHNOLOGIES

ADDICTION



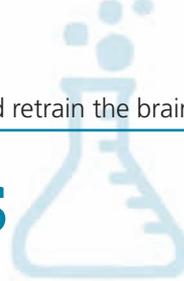
Henry A. Lester, Ph.D., California Institute of Technology, will lead a proof-of-principle project of a new tool developed by him and his colleagues for determining nicotine concentration in subcellular compartments in neurons, in order to better understand nicotine addiction. Early on the path to addiction, nicotinic acetylcholine receptors in neurons bind nicotine. In laboratory experiments, when nicotine is added to a solution containing neurons, the neuron's endoplasmic reticulum (ER), a network in cells involved in protein synthesis and transport, glows green. Using

this tool, Dr. Lester and his colleagues will measure how much and how quickly nicotine enters the ER and the effect of nicotine-receptor binding on the brain. The study will be augmented with X-ray crystallography to pinpoint chemical interactions between atoms of the nicotine and receptor molecules.

NARSAD support provides us with the resources to help pursue a project on the pharmacology of nicotine. Our hope is that this work will seed similar ideas about the mechanisms of anti-depressant and antipsychotic medications.

Henry A. Lester, Ph.D.

NEXT GENERATION THERAPIES



ANXIETY



David Eldon Clapham, M.D., Ph.D., Harvard University, is investigating the role of TRPC channels as novel regulators of fear and anxiety and as potential therapeutic targets. TRPC channels are a category of “pores” in cell membranes that allow ions such as sodium and potassium in and out of cells during metabolic processes. Based on his mouse studies, Dr. Clapham hypothesizes that distinct TRPC subunits differentially regulate fear and anxiety-related behaviors. He plans to identify these subtypes to improve knowledge of the neuronal microcircuits they affect and examine how genes influence these circuits in normal behavior and in anxiety-related disorders.

It's a difficult time in funding for science, so this grant enables us to continue our work. One of our goals is to identify drug targets for medications that treat anxiety disorders without causing sleepiness and involuntary muscle movements.

David E. Clapham, M.D., Ph.D.

DEPRESSION



Lee Stuart Cohen, M.D., Harvard University, will investigate the neurobehavioral effects of fetal exposure to maternal use of the widely prescribed selective serotonin reuptake inhibitor (SSRI) antidepressants. The research will involve assessment of neuropsychological and neurophysiological functioning in children ages four to 12 following fetal SSRI exposure, and a complementary laboratory study using a rodent model to delineate the effects on neural circuitry and to explore genomic factors that may modify risk for potential neural disruption. The outcomes will help inform the care of reproductive-age women

treated with psychiatric medications and the relative subsequent risks to their children of using these agents during pregnancy.

Receiving the 2014 Distinguished Investigator Grant provides an opportunity to explore a series of critical research questions that have implications for maternal and child health. The funds will help pave the way for a larger investigation of long-term behavioral outcomes after fetal exposure to antidepressants.

Lee Stuart Cohen, M.D.



Lisa M. Monteggia, Ph.D., University of Texas Southwestern Medical Center at Dallas, wants to learn how and where in the brain the antidepressant ketamine works. While remarkably faster and more effective for more patients than currently available antidepressants, ketamine's use has been limited due to problematic side effects. Working with mouse models, Dr. Monteggia will build on her findings of ketamine action in the hippocampus, a brain region implicated in the causes of depression and its treatment. An understanding of the cellular mechanisms and brain-region specificity of ketamine's efficacy

may yield critical information about what is needed to trigger a rapid antidepressant response that can then be applied to the development of future treatments.

I am thrilled to have received the 2014 Distinguished Investigator Grant. It will allow us to further delineate the underlying mechanisms of ketamine's action as an antidepressant, which we hope will translate into clinical advance.

Lisa M. Monteggia, Ph.D.

SCHIZOPHRENIA



Paul F. Worley, M.D., Johns Hopkins University, is investigating a possible new treatment target for schizophrenia. A gene called *Arc*, which encodes the Arc protein, is significantly linked to schizophrenia and is implicated in other diseases of cognition. The Worley lab has defined the structure of Arc, determined that a sub-domain of the protein called N-lobe binds to synaptic protein, and confirmed that mutation of the Arc gene selectively disrupts normal Arc N-lobe and synaptic activity, which is thought to contribute to schizophrenia pathogenesis. Dr. Worley hopes to identify in mice models those

molecules that can interrupt abnormal Arc N-lobe activity and ultimately be useful to treat schizophrenia and other disorders of cognitive dysfunction.

The NARSAD Distinguished Investigator Award provides recognition of the relevance of basic research into protein synthesis-dependent neural plasticity for understanding diseases of cognition.

Paul F. Worley, M.D.

Visit us at **bbrfoundation.org** to learn more about the research funded.

THE POWER OF A RESEARCH PARTNERSHIP



Kelley and Jack Scott

UNITING
DONORS
WITH
RESEARCHERS



Kazue Hashimoto-Torii, Ph.D.

The Scott-Gentle Foundation has a Research Partnership with 2013 NARSAD Young Investigator Grantee Kazue Hashimoto-Torii, Ph.D., of the Children's National Medical Center (Washington, DC). Dr. Hashimoto-Torii is investigating how genetic and prenatal environmental factors contribute to the pathogenesis of schizophrenia, a disorder in which the first episode is usually delayed until late adolescence or young adulthood.



LaVerne Gentle

Partner with a Researcher:

- Select a scientist in your area of interest, an institution or geographic area.
- Learn more about their work through personal communications and events.
- Receive progress reports that outline their research findings.
- Be recognized in published work resulting from the research.

"My aunt LaVerne Gentle had been seriously bullied by her sister who had schizophrenia. Her dying wish was to find a cure for this disease which destroys families. I promised her that I would use her estate to fund research to find a cure for schizophrenia. To me, curing schizophrenia would free the world of so much emotional pain. Dr. Hashimoto-Torii and her team share that vision. I encourage others to support the idea of a world without mental illness and help us make it a reality."

— Jack Scott

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.

To Better Understand Mental Disorders, Researchers Reverse Engineer Schizophrenia “in a Dish”

Foundation Support Helps Develop a Stunning New Technology

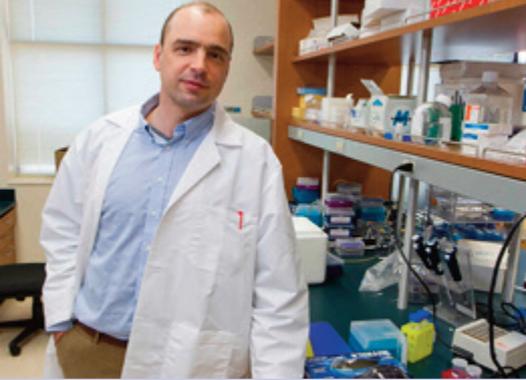
Imagine if it were possible to observe in real time the biological processes that contribute to schizophrenia or autism, as they occurred. Such magical technology has been under development since 2006, and the Foundation, through its NARSAD Grants, has funded many of the scientists involved in taking this idea from science fiction to research fact. The benefit to patients could be great.

“We now have the ability to study disorders of the nervous system in a new way—by rewinding the development of human neural cells,” says 2012 NARSAD Young Investigator Grantee **Alexander Urban, Ph.D.**, of Stanford University.

Using skin cells from people with schizophrenia, scientists have grown “iPS cells”—induced pluripotent stem cells*. All complex life forms begin with one major stem cell: a fertilized egg, explains **Fred Gage, Ph.D.**, of the Salk Institute, a prime mover in the emerging field, a 2013 NARSAD Distinguished Investigator, and Foundation Scientific Council member. “That one stem cell then divides and forms new cells that, in turn, also divide. Even though these cells are identical in the beginning, they become increasingly varied over time,” turning into nerves, muscles, and so on as the organs begin to organize and function together.

In an exciting breakthrough, neuroscientists learned that they could take ordinary human skin cells and induce them to go “back in time” to the primitive stem cell-like state that preceded their maturation. These cells in turn can be coaxed to re-mature, this time as neurons and astrocytes, the cells that in their billions populate the human brain. Early research in the field focused on figuring out whether the matured versions of neuronal iPS cells really took on the characteristic shapes and functions of adult human cells of the same types.

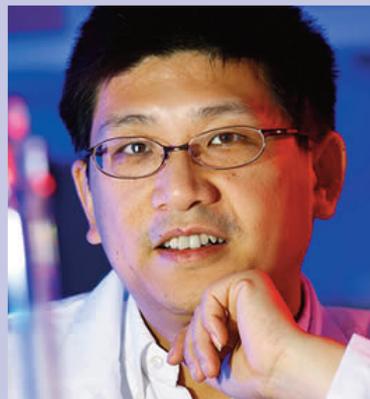
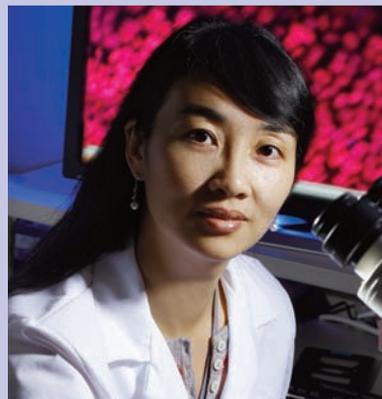
A landmark paper by Dr. Gage’s team published in *Nature* in May 2011 showed iPS cells were so much like the real thing, they could actually be used to test theories of how schizophrenia is caused. Most of the clues we have come from study of postmortem brain tissue donated by patients. But because this tissue is no longer alive, it’s different in important ways from tissue that exists in a living brain. Postmortem tissue can show



I-r:
Alexander Urban, Ph.D.
2012 Young Investigator

Fred Gage, Ph.D.
2013 Distinguished Investigator
Foundation Scientific Council
Member

Kristen Brennand, Ph.D.
2012 Young Investigator



I-r:
Vivian Hook, Ph.D.
2013 Distinguished Investigator

Guo-li Ming, M.D., Ph.D.
2010 Independent Investigator

Hongjun Song, Ph.D.
2008 Independent Investigator

“Neuroscientists could not have predicted a scenario in which patient-derived, live, functional neurons would be available for research.” – Dr. Gage

what the brain of a patient looks like after having the illness, perhaps for many years, and often after years of antipsychotic drug treatment. But if schizophrenia, like autism and other neuropsychiatric disorders, has roots in the early development of the brain, the postmortem brain may not be the best place to look for clues.

It would be ideal to be able to build a cellular “time machine” to observe the early brain biology of people with a mental disorder. In effect, that is what **Kristen Brennand, Ph.D.**, and her colleagues did, using iPS technology to provide a window into the past. Dr. Brennand, now at the Icahn School of Medicine at Mt. Sinai, was awarded a NARSAD Young Investigator Grant in 2012. She was first author on the 2011 *Nature* paper by Dr. Gage’s team, which used skin cells donated by living schizophrenia patients to grow iPS cells. The iPS cells were then reprogrammed as neurons to show the disease as it developed in real time, as the iPS cells matured.

Since then, many studies have followed. In 2014 alone, at least five studies conducted by teams led by or including Foundation-supported researchers reported new results on schizophrenia, based on iPS technology. In April, Drs. Brennand, Gage, and colleagues showed that aberrations in patient-derived cells gave rise, during maturation, to aberrant cell migration in the cortex and increased sensitivity to cellular stress caused by

oxidation. Previous research has linked unusual cell migration and sensitivity to cellular stress to the development of schizophrenia.

In October, Drs. Gage, Brennand, and **Vivian Hook, Ph.D.**, 2013 Distinguished Investigator, demonstrated that maturing iPS cells had the ability to secrete message-carrying neurotransmitters in response to stimuli. Prior research found that patient-derived iPS cells secreted too much dopamine, norepinephrine, and epinephrine, compared to cells from healthy controls. This was another sign that iPS cells can shed light on disease pathology.

In July and November 2014, researchers used iPS cells from schizophrenia patients to study suspected pathology as it developed in response to the deletion of a segment of chromosome 15 mutations in the DISC1 risk gene. These research teams were led by **Guo-li Ming, M.D., Ph.D.**, and **Hongjun Song, Ph.D.**, from Johns Hopkins University; they are 2010 and 2008 Independent Investigator Grantees, respectively.

Dr. Gage summarizes just how progressive this work is. “Neuroscientists in the past could not have predicted a scenario in which patient-derived, live, functional neurons would be readily available for research,” he says, “and researchers in the future will not be able to imagine a scenario without it.”

Battling the “Dragon” of Mental Illness

Instilling Hope in Others and in Themselves



Madelin Weiss

Madelin Weiss and Cory Gould have devoted their careers to helping people with mental illness. The two women have never met; their backgrounds and home towns are very different. But both have walked in the shoes of the people they serve. Since childhood, Madelin and Cory have dealt with harrowing mental illnesses that threatened to destroy any hope of a fulfilling future for either.

Today, Madelin, 64, holds a master's degree in social work. She is the Associate Executive Director of PIBLY Residential Programs, in the Bronx, New York, where she oversees rehabilitative and support services for several hundred people with mental illnesses. Cory, 58, has a master's degree in psychology and psychotherapy. She is the go-to mental health professional at Gifford Medical



Cory Gould

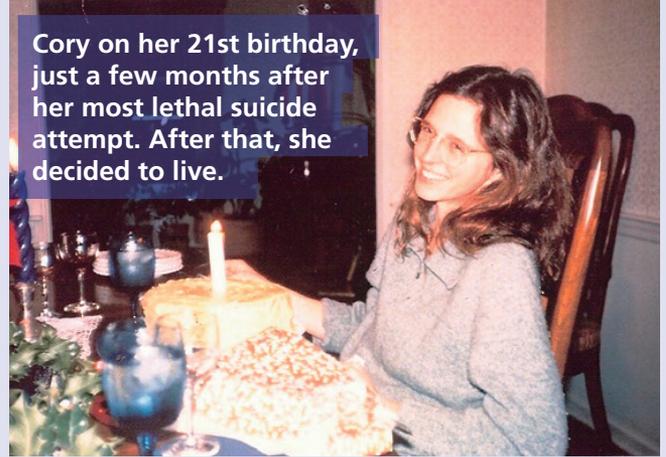
Center in Randolph, Vermont, and a co-founder of the Vermont chapter of the American Foundation for Suicide Prevention.

From the age of eight, Madelin experienced paralyzing anxiety and depression. Panic attacks made her fearful of going out, “afraid,” she says, “I wouldn’t be able to get back home.” Devastated by bipolar disorder from age 11, Cory had decided by the time she was 16 years old that she “didn’t belong on this planet.” She almost succeeded in removing herself from it.

In those not-so-long-ago days when little was known about mental illness in children, distraught parents had difficulty finding help. At first, Madelin was misdiagnosed with schizophrenia and given

“I support the Brain & Behavior Research Foundation because I believe that we will eventually discover the pathophysiology of psychiatric illness, and therein lies the 'cure.' Basic research will lead us to better treatments and will save lives, HAS saved lives.”

Cory Gould



Cory on her 21st birthday, just a few months after her most lethal suicide attempt. After that, she decided to live.

medications that didn't work. She barely made it through high school and failed twice to get through college. "I spent most of two years in bed," she says, "getting up only to go to therapy." There were hospitalizations, a suicide attempt, and in between, on "good days," sporadic attempts to find employment. "I looked for jobs like handing out flyers on the street, which was all I thought I could do. I couldn't foresee myself ever really functioning."

Then, she says, her luck changed. "I found a wonderful therapist and a psychiatrist who prescribed medications that actually helped." On her third try she graduated from college, with straight As. Instead of handing out flyers, she landed a job as a counselor at a mental health center in New Jersey where she worked for several years while completing her graduate degree.

Intellectually precocious, Cory had completed high school by age 16. But "my smarts didn't save me from depression," she says. Cory's suicide plan was tentative: She decided to leave home and think it over. Her farewell note was discovered before she had made her getaway. So Cory grit her teeth and went off to college. There, at age 20, a serious suicide attempt turned out to be a "life changer."

"I had swallowed three times the dose of phenobarbital that should have been lethal. But instead of dying, I woke up a couple of days later, itching all over. For the next couple of weeks, I stalked around campus thinking about how grossly incompetent I was; I couldn't even kill myself. Then I concluded that there must be mysteries in the universe, and decided to live."

For Madelin and Cory, mental illness is a life-long challenge. Cory pictures her illness as "this ugly

little dragon on a chain sleeping in a corner of my brain with little wisps of smoke coming out of its nostrils. Every once in a while, it pulls on the chain, the smoke gets darker and my vision clouds. I have to pay attention to the early warning signs. I've become expert at managing my illness, and that's what I teach my clients to do." As recently as two years ago, Madelin—who calls depression "an outside force from within"—suffered symptoms severe enough for her to have to stop work until her medications were adjusted.

Madelin believes, "We have progressed greatly in understanding mental illness and brain function. However there remains more that we don't know and don't understand. It is within research and evidence-based practice that the answers (and better treatment) lie."

But despite the setbacks and the constant vigilance, both women are grateful for the advances in research that have made it possible for them to live productive lives, and both are longtime supporters of the Brain & Behavior Research Foundation.

"I think the biggest thing I can give my patients," says Madelin, "is hope. I have to have hope, and the staff members I train have to have hope. Our patients are so sick it's often hard to see that little part of them that's still healthy, the part we have to ally with. Just seeing someone taking a shower who hasn't bathed in months is progress. Such little changes, and I go home at the end of the day feeling I've made a difference in someone's life."

New York Mental Health Research Symposium

KAUFMAN CENTER

On Friday, October 24, 2014, the Brain & Behavior Research Foundation held its 26th Annual New York Mental Health Research Symposium at The Kaufman Music Center in New York City. Eight 2014 Brain & Behavior Research Foundation Outstanding Achievement Prizewinners and two especially promising NARSAD Young Investigator Grantees reported on recent innovations and insights that are revolutionizing the ability of neuroscientists to explore the brain and apply new information to prevent or reverse the course of mental illness. The following summaries are from three of the Outstanding Achievement Prizewinners who presented.



David L. Braff, M.D.

Distinguished Professor of Psychiatry
University of California, San Diego

**2014 Lieber Prize for Outstanding
Achievement in Schizophrenia Research**

NARSAD Grant:
Distinguished Investigator 2007

Deconstructing and Overcoming Schizophrenia: Genes, Neural Circuits and Improving Outcomes

Dr. Braff has pursued and extended our understanding of the neurobiology, genomic architecture, and treatment of schizophrenia via a number of major research projects. These projects include a long-standing National Institute of Mental Health (NIMH) and NARSAD Grant-funded translational research program which has been continuously funded for over 30 years. In addition, Dr Braff, a NARSAD Distinguished Investigator Grantee, is the Director of the NIMH Consortium on the Genetics of Schizophrenia (COGS), working with many distinguished colleagues at over 10 sites to identify the behavioral (endophenotype) and genomic deficits associated with schizophrenia.

Endophenotypes are quantitative and heritable neurocognitive and neurophysiological biomarkers that show laboratory-based deficits in schizophrenia patients. These neuroscience-based neurophysiological and neurocognitive behavioral measures are analyzed via cutting edge techniques including genotyping; gene expression; gene sequencing; stem cell research identifying genetic deficits and then repairing or “rescuing” these deficits using state-of-the-art techniques; and other promising neuroscience methods. Cumulatively, the COGS and UCSD translational research cohort of over 5,000 subjects represents probably the largest neuroscience-based behavioral and genomically studied schizophrenia cohort available to researchers who want to use emerging methods to fully understand the molecular, biological, and genomic, as well as the functional and outcome deficits, in schizophrenia.

Dr. Braff and COGS colleagues have conducted detailed genomic studies of the neurocognitive and neurophysiological deficits as well as clinical features and outcomes of patients and families with schizophrenia. One advantage of this strategy that merges neuroscience measures with genomics is that each patient is extensively studied using state-of-the-art neurophysiological and neurocognitive techniques to fully characterize them behaviorally. This means that when a genomic abnormality is identified, there is an informatics basis to understand how the genes are expressed behaviorally and in real-world function. The driving concept is that while we have a rapidly increasing base of facts about schizophrenia, integrating these facts is a major challenge and one that is necessary to integrate our research findings into better patient care.

The quantifiable schizophrenia-related neurophysiological and neurocognitive endophenotypes are heritable, and along with genomic information can open unique pathways to understanding the origins of schizophrenia. In a complementary manner, the relationship of endophenotype and related genomic deficits to real-world functional deficits offers targets for development of new treatments designed to reverse and ultimately detect and prevent the neurocognitive and functional disabilities of schizophrenia.

A 1970 graduate of the Perelman School of Medicine at the University of Pennsylvania, Dr. Braff completed psychiatric and research training at Yale University and the University of California, San Francisco.

Neuroimaging of Bipolar Disorder Reveals Abnormalities of Brain Structure and Function: Implications for Novel Therapeutics

Dr. Drevets discussed how the biological basis of bipolar disorder is being elucidated progressively by converging evidence from studies of brain function and structure, and of genetic and other types of molecular biomarkers.

One of the technologies that enabled these endeavors involved biomedical imaging tools, such as positron emission tomography (PET) and magnetic resonance imaging (MRI), which provided the means to noninvasively investigate brain function, structure and chemistry in patients suffering from bipolar disorder. These technologies also facilitated complementary research in healthy individuals aimed at characterizing the brain circuits that normally regulate the cognitive-behavioral domains affected in bipolar disorder, such as emotional experience, mood regulation and social processing.

Taken together, the findings from research conducted using these technologies has shown that the brain circuits that function normally to modulate emotional behavior, stress responses and reward processing are altered profoundly in patients with bipolar disorder relative to healthy controls. Notably, the abnormal patterns of functional activity and tissue volume loss in these circuits in patients with bipolar disorder are impacted variably by drugs that produce mood stabilizing or antidepressant actions. The effects of these medications on brain imaging measures and molecular assays from patients with bipolar disorder, as well as on experimental animals subjected to repeated stress, are beginning to guide the discovery of new drugs, which potentially will more effectively maintain symptom remission and promote illness recovery.

Dr. Drevets received his M.D. from the University of Kansas School of Medicine, completed residency in psychiatry and a fellowship at the



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Young Investigator 1996,
Independent Investigator 1999

Prizes:
2000 Freedman Prize Honorable Mention
for Exceptional Basic Research by a Young
Investigator

Washington University School of Medicine in St. Louis. He served on the faculties of Washington University and the University of Pittsburgh and as Chief of the Section on Neuroimaging in Mood and Anxiety Disorders of the National Institute of Mental Health Intramural Research Program. Before moving to Janssen, he held the Oxley Foundation Chair in Neuroscience Research at the University of Oklahoma, where he was founding President and Scientific Director of the Laureate Institute for Brain Research.

New Ideas for the Design of an Effective Antidepressant

Depression is one of the leading health problems in the world, causing more disability than any other class of illness including heart disease or cancer. Dr. Henn's approach to study depression—what causes it and how to better treat it—was to attempt to develop an animal model that mirrored the disease and included a stress component and a genetic component, as major depressive illness does.

Dr. Henn approached this by adding genetic vulnerability to the learned helplessness model of depression in animal models. Looking at how the brain of the "helpless" and "non-helpless" (or resilient) animals differed, Dr. Henn and his colleagues found that activating the lateral habenula, a small structure above the thalamus in the brain, caused depressive symptoms. Activation of the habenula was also seen in depressed human patients.

The lateral habenula controls reward perception and directly controls the monoamines, dopamine, serotonin and norepinephrine, which appear to play a role in depression. An overactive habenula inhibits reward perception and serotonin activation, and blocking this activity with deep brain stimulation reversed it in animals and people.

Dr. Henn found that over-activity of the lateral habenula is due to increased glutamate activity at nerve endings. This increased glutamate also destroys nerve endings in the cortex. One approach to new antidepressants is to increase the reuptake of glutamate and Dr. Henn and his group are currently attempting to do this in a medication trial with patients.

Finally, what is the molecular basis of the habenular activation? Using proteomics, Dr. Henn found one protein responsible and showed that down-regulating this protein led to the immediate loss of depressive symptoms, thus providing another target for a truly effective antidepressant.

Dr. Henn earned a Ph.D. in biochemistry and biophysics at Johns Hopkins University and completed his M.D. and residency in psychiatry at Washington University School of Medicine. After returning from research posts in Germany, for which he received the Federal Cross of Merit awarded by the President of Germany, he served briefly as Associate Director of Brookhaven National Laboratory before joining Cold Spring Harbor Laboratory in 2007.



Fritz A. Henn, M.D., Ph.D.

Professor
Cold Spring Harbor Laboratory

Professor of Psychiatry
Icahn School of Medicine at Mount Sinai

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Child and Adolescent Anxiety: Psychopathology and Neuroscience

WITH:

Daniel S. Pine, M.D.
National Institute of Mental Health



MODERATOR:

Jeffrey Borenstein, M.D.

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Parenting

Advice for Parents of Children with Behavioral and Psychiatric Disorders



Judith L. Rapoport, M.D.

Chief, Child Psychiatry Branch
National Institute of Mental Health
Foundation Scientific Council Member

Since 1984, Foundation Scientific Council member Judith L. Rapoport, M.D., has been Chief of the Child Psychiatry Branch at the National Institute of Mental Health. We asked her what advice she could offer parents and siblings of children affected by behavioral and mental health disorders. Our conversation ranged widely and included discussion of attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), learning disorders, anxiety, phobias, depression, and the fallout from divorce. Dr. Rapoport also addressed ways to help children with autism, bipolar disorder, and schizophrenia.

If a child appears to be having a psychological or behavioral problem, what course of action should a conscientious parent take?

There's an important rule of thumb: there is no "disorder" until a problem begins to significantly interfere with a child's quality of life. Children have all sorts of experiences that can worry a parent. For example, they might be in the

“Parents should know that they are not locked in to any one approach. If, after a few months, a treatment isn’t working, you and your child’s doctor should reconsider and be open to trying a different approach.”

back seat during a car accident and may now be fearful of getting into a car. That’s normal, and the way you handle it is to have them get back in the car—that is, don’t accommodate their fear. Or, many children feel sad, but for good reason, such as when they lose a pet. But when fear or sadness or an inability to concentrate takes over and starts to interfere with the child’s life, either at home or at school, that’s when you should take action.

Where, and to whom, should a parent turn for help?

A good place to start is the nearest medical school or teaching hospital, even if it’s a considerable drive from home. You want to ask who at the school or hospital, or within its department of psychiatry, sees children. Find out who in particular specializes in the kind of problem your child may be facing. Once you are presented with the name of a doctor or therapist, it’s smart to ask how much experience that person has had with other children like yours, and what approaches to treatment he or she might take. Often, you’ll find therapists who can offer several different approaches, who will want to match the approach to the specifics of your child’s case.

What are the various therapy options and who will be recommending them?

Parents will find that some of the experts in these institutions may be psychologists or psychiatric social workers. This reflects an important development over recent decades in which there have been many advances in psychological and behavioral treatments that don’t involve the use of medications. There are many forms of therapy, depending on the disorder. The type of psychotherapy I strongly believe is effective for childhood depression is not the same

therapy that would be used for children with phobias, or OCD. For anxiety, a behavioral treatment might take the form of relaxation therapy or even biofeedback.* There’s a broad spectrum of approaches and impressive advances that have been made across these areas.

When are medications appropriate for children?

There is no blanket approach. Some medications are clearly useful in children, and some studies have shown that it can be useful to give drug therapy and psychotherapy together, at least in the beginning of treatment. I’m often asked by behavioral therapists to consult as a psychopharmacologist*. They may want to add a medication to help a child stick with a behavioral therapy. In ADHD, many times a pediatrician will prescribe a stimulant such as Ritalin, and that will solve the problem by itself. However, parents should know that they are not locked in to any one approach. If, a few months after you begin a therapy, it doesn’t seem that you are getting anywhere, you should reconsider and be open to trying a different approach.

Are Ritalin and other stimulant treatments for ADHD over-prescribed?

About 70 percent of youngsters in the U.S. with ADHD are given a stimulant; it is probably the treatment of choice. Stimulants make people more alert and focused. Does your child need such treatment? Parents need to judge how much the problem is interfering with their child’s life. In school, has the child responded to logical first steps, such as sitting in the first row of the classroom, or getting very clear instructions and regular feedback from the teacher? Such approaches can be very helpful in mild cases. You have to go with

* Refer to glossary on page 28.

“Getting the right professional consultation is key, especially if the disorder is significantly affecting the child’s quality of life.”

what produces substantial benefit, in terms of normalizing the child’s life.

Are stimulants addictive?

Parents can take some comfort in knowing that Ritalin and similar drugs are not addictive in children. A child’s mood is not elevated by stimulants. And epidemiologic studies have shown that children with ADHD who take these medications do not have a greater tendency to abuse drugs later on.

Turning to another topic: depression. How can a parent tell the difference between a child who is sad and one who is depressed?

Children do become sad, and this could be due to so many possible triggers. There’s chronic demoralization—you often see this in children with learning disabilities, especially in families in which the parents are high achievers and have trouble accepting the child’s difficulties. Often, children are sad in response to a particular event—like the loss of pet, as mentioned before. But it could easily be other, broader disappointments. For example, when peers become a very important part of a child’s life, something that intensifies in the teen years, and a child has problems trusting or relating well to peers, this can lead to sadness. If parents are getting divorced—a very common situation—a child may be having a hard time. One or both parents may be putting the child

in a difficult position that he or she doesn’t know how to handle. There are also children and adolescents with chronic depression for which there does not appear to be any specific trigger. Getting the right professional consultation is key, especially if the depression is significantly affecting the child’s quality of life.

Let’s discuss what to do in the most serious cases—when a child is thought to show signs of bipolar disorder or schizophrenia or psychosis.

Childhood-onset schizophrenia is very rare, and when this seems a possibility, getting a consultation from a really experienced mental health professional is critical. Psychosis—hallucinations, hearing voices—is a symptom of schizophrenia in many adults. However, in children, a broad array of disorders may cause them to report having psychotic experiences. For example, sometimes a seriously depressed child reports hearing a voice saying “you’re a bad person.” The literature indicates that, at some point, about 5 percent of all children talk about delusional things. Yet only 1 percent end up with a schizophrenia diagnosis, which, when it occurs, usually doesn’t start generating symptoms until the late teens or the twenties.

There has been some confusion about bipolar disorder and ADHD. It turns out that some portion of children with ADHD, even when they respond to

“Following a diagnosis, the first thing parents need to do is make sure that everyone in the family understands the situation. Sometimes, meeting with a family therapist can help—not necessarily on regular basis, but for orientation purposes and during times when the child’s condition creates family problems.”

treatment, have remaining “mood dysregulation” problems. This diagnosis now appears in the latest edition of the Diagnostic and Statistical Manual (the “DSM-5” handbook for clinicians). Bipolar disorder in childhood is very rare.

What advice can you offer parents and siblings living with children who are already diagnosed with serious disorders, from bipolar disorder to schizophrenia and autism?

Following a diagnosis, the first thing parents need to do is make sure that everyone in the family gets on the same page. Sometimes, meeting with a family therapist can help—not necessarily on a regular basis, but for orientation purposes and during times when the child’s condition creates family problems. For example, sometimes siblings will feel that the situation at home is too unpleasant, and they can’t bring friends to the house. The basic rule is: everybody has to feel safe at home. Whether or not you have guidance from outside, it helps to have family meetings in which you talk about what’s going on and what siblings’ roles should and should not be. It’s important for parents to agree on a consistent approach when coping with a child who is ill. It’s also important for parents, if they can, to find a skilled caretaker they trust to look after their child so they can have some time away once in a while, on weekends.

There are many things families can do to help children with psychological disorders. The isolated child with a disorder, who has some interest or talent, may be helped by taking part in a special class or art camp. If a child is interested in computers, he or she could be enrolled in a program that might be an entrée to new friendships.

We’ve seen parents do some amazing things with children who are autistic—very moving examples



of children who, because of their parents’ efforts, were able to take part in mainstream education. Sometimes the child’s teacher can educate the class about the child’s problem. In the case of one very sick child I know, this happened and the child’s memories of school went from being very miserable to feeling very good about it. It was remarkable. Of course, you can only think of trying such things in school districts prepared to accommodate children with special needs.

Finally, one of the major changes in the last 30 years is the advent of patient support groups. Such groups exist for most common disorders. There’s a Tourette’s group in just about every city—support groups for children and their parents to meet others in the same situation. The public is now very conscious, too, of a condition like autism. Those who are affected need not be isolated or alone. They should be able to say, “I’m not the only one who has this problem.”

Going forward, what are the prospects for affected families?

I am upbeat. There has been so much useful research on diagnosis, prognosis, and the different types of treatments that are available. Parents will benefit enormously from seeking out good information, and from connecting with the many good support groups. Regarding treatments, many of the medications we have are good. Without question, they have made a tremendous difference for children and for their parents. And with continuing research, we are going to see important new treatments, over time.

Glossary

biofeedback: A method that trains people to control their stress, blood pressure, or heart rate, for example. A therapist can measure skin temperature, muscle tension, or brain wave activity to monitor how well the patient is doing with this training.

dissociation: A state in which the perceptions of sight and sound are distorted and a feeling of detachment—dissociation—is experienced. Sometimes described as an out-of-body experience, dissociative symptoms can be induced by medications such as ketamine but they are also among the symptoms reported by some people with PTSD—post-traumatic stress disorder.

induced Pluripotent Stem Cells (iPSCs): Adult cells that have been genetically reprogrammed to an embryonic stem cell–like state. It is not known if iPSCs and embryonic stem cells differ in clinically significant ways. And although more research is needed, iPSCs are already useful tools for drug development and modeling of diseases.

ketamine: A molecule that is an antagonist of the NMDA class of nerve-cell receptors. It has been used primarily for inducing and maintaining general anesthesia, along with sedatives. It has also been used to treat depression in patients diagnosed with bipolar disorder who have not responded to other antidepressants. It has been used experimentally, too, in treatment of refractory major depression, producing therapeutic effects in a matter of hours. Ketamine is controversial because of its side effects, which include hallucinations and a raising of blood pressure, among others.

NMDA (N-methyl-D-aspartate) receptors: Nerve-cell receptors or docking ports located on the surface membrane of a class of neurons in the brain that are sensitive to excitatory neurotransmitters, mainly glutamate. NMDA receptor dysfunction may be linked to impaired brain plasticity, memory formation and the negative symptoms of 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.

placebo: A look-alike, but inactive treatment. In clinical trials, a placebo may be given to one group of participants instead of the active drug or treatment in order to find out whether the active treatment is actually effective.

psychopharmacologist: A psychiatrist who specializes in managing the medication(s) prescribed to treat mental disorders. Psychopharmacologists monitor “pharmacokinetics” (what the body does to medication) and pharmacodynamics (what the medications do to the body).

selective serotonin reuptake inhibitors (SSRIs): Currently the most popularly prescribed class of antidepressant medications. SSRIs keep the neurotransmitter serotonin in the synaptic gaps between nerve cells in the brain by preventing their rapid reabsorption into the neurons that release them, thus promoting signaling between cells. These medications are effective for some patients, but usually not until some weeks following the first time they are taken.



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