The Quarterly
Winter 2013

BRAIN & BEHAVIOR
RESEARCH FOUNDATION
Awarding NARSAD Grants

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FOCUS on STRESS

RESEARCH NEWS

FEATURE

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"The Brain & Behavior Research Foundation Scientific Council has grown to include 138 volunteer members, each of whom bring special skills and unique knowledge bases that cover every aspect of brain and behavior research. The reach of the Brain & Behavior Research Foundation support extends to the world's leading medical research and care facilities. Our effort knows no borders. The impact of our effort is not only in the development of promising scientists, but also in the focus it brings to the challenge and urgent need of bringing hope and better lives to all those living with mental illness."

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Jed Abrams and his dog, The General

Dear Members of Our Foundation Community,

I am honored to serve as the Acting President and CEO of the Brain & Behavior Research Foundation. As a practicing psychiatrist, I have witnessed first hand the critical role the Foundation plays in supporting research that has steadily advanced our understanding of mental illness and how to effectively treat it. As host of the public television program 'Healthy Minds,' for which our Foundation is a sponsor, I have been able to highlight a number of the scientists who have received support from the Foundation and share with our audience their exciting discoveries and advances.

Despite the importance of brain research, we face many obstacles. The budget of the National Institute of Health is under pressure due to federal budget constraints; pharmaceutical companies have significantly reduced their neuroscience and psychiatric research efforts; academic research programs are also under financial pressure to reduce their activities. Only 8% of private giving to charity is for health causes and institutions (*Giving USA,* 2011); a fraction of that is for mental health causes and even less is for brain research.

But together, we can overcome the obstacles facing mental health research. With the generous support of our donors, the Foundation has funded more than 4,000 grants totaling close to $300 million over 25 years. Our grants to Young Investigators not only fund important studies, but also serve as a springboard for the best and brightest scientists to focus on brain research.

The cover of *The Quarterly* has a picture of Jed Abrams with his dog, The General. Jed passed away as a result of his illness, which did not respond to conventional psychiatric intervention. Jed's parents, Jan and Stefan Abrams, are supporting research in order to find new treatments for others in the future. While we mourn the tragic loss of a loved one due to their condition, we should also be inspired by the generosity of spirit on the part of the Abrams Family to help avoid similar tragedies for other families.

I am very optimistic about the future. Until recently, medical science believed that 'old' brains could not grow new cells; research has shown that this is untrue. In this era of flourishing neuroscience, we are closer than ever to understanding the brain and how to treat, and even prevent and cure, its illnesses. I have had the opportunity to speak with a number of our donors; similar to the Abrams Family, their generosity and passion to relieve suffering by funding research is an inspiration. I look forward to meeting many more of our donors and others interested in the Foundation. With your help, the quest for answers can accelerate discovery and deliver hope—hope for healthy, productive and happy lives.

Sincerely,

Jeffrey Borenstein, M.D.
Acting President & CEO

A Sampling of NARSAD Grants at Work:

Ten Key Discoveries in 2012

Basic Research: Autism

Demonstrate improvements in symptoms of Fragile X Syndrome (the most common known genetic cause of autism) by increasing levels of endocannabinoids, natural chemicals in the brain.

Olivier Manzoni, Ph.D.
INSERM, France
2010 II

Daniele Piomelli, Ph.D.
University of California, Irvine
1988, 1990 YI, 1999 II, 2005, 2009 DI

Basic Research: Depression

Ronald S. Duman, Ph.D.
Yale University School of Medicine
Discovers a genetic switch that causes some parts of the brain to shrink in patients with major depression.

SC, 2002 Outstanding Achievement in Mood Disorders Research Prizewinner
1989 YI, 1997 II, 2005 DI

Diagnostic Tools/Early Intervention: Bipolar Disorder, Depression, Schizophrenia

Chiara Nosarti, Ph.D.
Institute of Psychiatry/King's College London
Led one of the largest studies investigating birth complications and later mental health, and found that premature birth heightens risk for multiple mental illnesses.

2008 YI

Diagnostic Tools/Early Intervention: Depression

Andrew Miller, M.D.
Emory University
Demonstrates that treating inflammation levels can improve symptoms of depression; a simple blood test can predict the antidepressant response.

1997 II

Diagnostic Tools/Early Intervention: Depression

Carlos Zarate, M.D.
National Institute of Mental Health
Discovers a brain signal—a potential biomarker—that identifies patients who respond to rapid-acting antidepressant (ketamine).

2011 Outstanding Achievement in Mood Disorders Research Prizewinner
1996 YI, 2005 II

Diagnostic Tools/Early Intervention: Schizophrenia

Anil Malhotra, M.D.
The Feinstein Institute for Medical Research
Identifies gene variant linked to antipsychotic-medication-induced weight gain.
SC Members Drs. James L. Kennedy, Jeffrey A. Lieberman and Herbert Y. Meltzer are co-authors.

SC, 1999 YI, 2001 and 2006 II

New Technologies: Schizophrenia

Paola Dazzan, M.D.
Institute of Psychiatry/King's College London
Devises a technology—support vector machine—that can predict outcomes, for the first time, after a first psychotic break.

2003, 2007 YI, 2009 II

Next Generation Therapies: Anxiety/Depression

Olivier Berton, Ph.D.
University of Pennsylvania
Links HDAC6 protein to natural resiliency in animal models, pointing to a new treatment possibility for stress-related disorders.

2005, 2008 YI

Next Generation Therapies: Depression

In separate research projects, investigators demonstrate the involvement of dopamine neurons in stress-caused depression, opening a new pathway for treatment possibilities.

Karl Deisseroth, M.D., Ph.D.
Stanford University
SC, 2005 YI

Eric Nestler, M.D., Ph.D.
Mount Sinai School of Medicine
SC, 2008 Outstanding Achievement in Cognitive Neuroscience Research Prizewinner, 2009 Outstanding Achievement in Mood Disorders Research Prizewinner, 1996 DI

Next Generation Therapies: Schizophrenia

Demonstrate in pilot study that computer 'brain training' improves cognitive function, such as the ability to distinguish experiences created internally from actual external events.

Karuna Subramaniam, Ph.D.
University of California, San Francisco
2010 YI

Sophia Vinogradov, M.D.
University of California, San Francisco
2000 II

Brain & Behavior Research Foundation
Scientific Council Member (SC)

NARSAD Grantees:
Young Investigator (YI)

Independent Investigator (II)

Distinguished Investigator (DI)

BASIC RESEARCH

Autism

New Understanding of Fragile X Syndrome Points to New Treatment Possibilities for Autism

Olivier J. Manzoni, Ph.D.
2010 NARSAD Independent Investigator Grant

Daniele Piomelli, Ph.D.
1988 and 1990 NARSAD Young Investigator Grants
1999 NARSAD Independent Investigator Grant
2005 and 2009 NARSAD Distinguished Investigator Grants

An international team of scientists has made critical new discoveries about which brain dysfunctions cause Fragile X Syndrome and how it may be possible to correct them. Fragile X Syndrome, the most commonly known genetic cause of autism, is caused by a genetic mutation (FMR-1).

This important study was co-led by **Olivier J. Manzoni, Ph.D.,** of INSERM (Institut National de la Santé et de la Recherche Médicale) in France and **Daniele Piomelli, Ph.D.,** of the University of California, Irvine. Their results were published in *Nature Communications* in September 2012.

Performing several sets of experiments in animal models, the Piomelli-Manzoni team discovered that the genetic FMR-1 mutation corresponds with the lack of a protein called Fragile X Mental Retardation Protein (FMRP). The lack of this protein causes Fragile X in humans. They also found that, together with the missing protein, a type of activity called long-term depression (LTD) was absent at synapses that link neurons in two critical parts of the brain—the ventral striatum and prefrontal cortex—and that this synaptic dysfunction affected the transmission of endocannabinoid signals in the brain. Without them, electrical signals at synapses are further compromised. And, indeed, in Fragile X Syndrome, problems in synaptic communication are known to be associated with cognitive and behavioral problems.

Drs. Piomelli, Manzoni and colleagues then sought to determine if they could artificially enhance or promote the impaired endocannabinoid-system signals. They found that pharmacological enhancement of such signaling normalizes the problem at excitatory synapses and corrects behavioral abnormalities in mice lacking the FMRP protein—a model for human Fragile X Syndrome.

A distinctly new path of research can now be pursued to uncover more details that could lead to the development of new treatments.

Depression

Discovery of a Genetic Switch That Can Cause the Brain to Shrink in Depression

Ronald S. Duman, Ph.D.
Scientific Council Member
2002 Outstanding Achievement in Mood Disorders Research Prizewinner
1989 NARSAD Young Investigator Grant
1997 NARSAD Independent Investigator Grant
2005 NARSAD Distinguished Investigator Grant

A major focus of research in laboratories around the world has been to find out why certain brain regions in people with severe depression are smaller and less dense than those of their healthy counterparts. A team of researchers, led by **Ronald S. Duman, Ph.D.,** Professor of Psychiatry at the Yale School of Medicine, has traced the genetic reason for this shrinkage and discovered a mechanism that causes it to occur.

Dr. Duman found that a single genetic switch known as a transcription factor represses the expression of several genes that are necessary for the formation of synaptic connections between brain cells. This in turn could contribute to loss of brain mass in the prefrontal cortex. The results were published in the August 12, 2012 issue of the journal *Nature Medicine.*

By testing the idea that stress causes a loss of brain synapses in humans, the team was able to show that circuits normally involved in emotion, as well as cognition, are disrupted when this single transcription factor is activated. In analyzing the tissue of depressed and non-depressed patients donated from a brain bank, the researchers found that the brains of patients who had been depressed exhibited lower levels of expression in genes that are required for the function and structure of brain synapses. They also discovered that at least five of these genes could be regulated by a single transcription factor called GATA1. When the transcription factor was activated, rodents exhibited depressive-like symptoms, suggesting GATA1 plays a role not only in the loss of connections between neurons, but also in symptoms of depression.

Dr. Duman theorizes that genetic variations in GATA1 may one day help identify people at high risk for major depression or sensitivity to stress. He states, "We hope that by enhancing synaptic connections, either with novel medications or behavioral therapy, we can develop more effective antidepressant therapies."

DIAGNOSTIC TOOLS/EARLY INTERVENTION

Chiara Nosarti, Ph.D.
2008 NARSAD Young Investigator Grant

Bipolar Disorder, Depression, Schizophrenia

Premature Birth Heightens Risk for Mental Illness

According to the research of **Chiara Nosarti, Ph.D.,** senior lecturer in Mental Health Studies and Neuroimaging at the Institute of Psychiatry/ King's College London, babies born prematurely appear to have an increased risk for developing a broad range of severe brain and behavior disorders, including bipolar disorder, psychosis and depression.

Dr. Nosarti led a team from King's College London and Karolinska Institutet, Sweden, in one of the largest investigations to date, into the relationship between birth complications and mental health. They compared data from the Swedish Medical Birth Register on more than 1.3 million people born between 1973 and 1985, and the records of adult-onset psychiatric admissions (age 16 and over) from the Swedish National Board of Health and Welfare. Their findings were published in *Archives of General Psychiatry* in June 2012.

With a normal full gestation term being 37 to 41 weeks, Dr. Nosarti's examination revealed that babies born at 32 to 36 weeks' gestation were 1.6 times more likely than full term babies to develop psychosis, 1.3 times more likely to have depressive disorder and 2.7 times more likely to have bipolar disorder. Babies born at less than 32 weeks' gestation were 2.5 times more likely to later develop psychosis, 2.9 times more likely to have depression and a striking 7.4 times more likely to have bipolar disorder.

The team conducted other studies using functional MRI in young adults born very pre-term. These showed neuroanatomical alterations in brain networks also found to be disrupted in psychiatric populations.

Dr. Nosarti said, "We found a very strong link between premature birth and a range of psychiatric disorders. Since we considered only the most severe cases that resulted in hospitalization, it may be that, in real terms, this link is even stronger." She cautions that despite the increased risk, these disorders affect only a small percentage of babies born prematurely.

Andrew Miller, M.D.
1997 NARSAD Independent Investigator Grant

Depression

Treating Inflammation to Improve Resistant Depression—Simple Blood Test Predicts Effectiveness

Andrew Miller, M.D., Professor of Psychiatry and Behavioral Sciences at Emory University School of Medicine, is the senior author of a new study that demonstrates improvements in symptoms of depression in patients with high inflammation levels. The results were published in *Archives of General Psychiatry* in October 2012.

Inflammation and the release of immune-system chemicals called cytokines can get into the brain and induce depression: the higher the level of inflammation, the greater the severity of the depression. In the brain, cytokines act on growth factors like brain-derived neurotrophic factor (BDNF) that support the development of new neurons. They exert influence on neurotransmitters; for example, reducing levels of serotonin and dopamine, key players in depression, and increasing glutamate, a cytotoxic (i.e., cell-killing) neurotransmitter.

Study participants all had major depression and were moderately resistant to conventional antidepressant treatment. Each participant was assigned either to infliximab or placebo. (Infliximab is the active ingredient in the prescription drug Remicade®, one of the new biologic drugs used to treat autoimmune and inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.) While no significant differences were found in the improvement of depression symptoms between the drug and placebo groups, the subjects with high inflammation exhibited a much better response to infliximab than to placebo.

Inflammation in this study was measured using a simple blood test that is readily available in most clinics and hospitals. "The prediction of an antidepressant response using a simple blood test is one of the holy grails in psychiatry," says Dr. Miller. "This is especially important because the blood test not only measured what we think is at the root cause of depression in these patients, but also is the target of the drug."

Carlos Zarate, M.D.
2011 Outstanding Achievement in Mood Disorders Research Prizewinner
1996 NARSAD Young Investigator Grant
2005 NARSAD Independent Investigator Grant

Depression

Biological Marker Identified to Predict Responsiveness to Rapid-Acting Antidepressant

Carlos Zarate, M.D., Chief of Experimental Therapeutics and Pathophysiology Branch in the Intramural Program of the National Institute of Mental Health (NIMH), and team discovered a brain signal that may become a biomarker, or biological predictor, of which depressed patients will respond to the experimental, rapid-acting antidepressant, ketamine. The brain signal was identified through the use of noninvasive brain imaging and is also helping to identify how ketamine works to reduce the symptoms of depression within just a few hours. The findings of this study were reported in *Biological Psychiatry* in January 2012.

"We are investigating ketamine in multiple ways —studying genes, gene expression, synapses, cells, circuits and symptoms with neuroimaging, genetics, electrophysiological measures and other techniques," explained Zarate. "These studies hold hope for predicting the likelihood of response and for gaining insights into mechanisms of action."

Ketamine works through a different brain chemical system than conventional antidepressants. It initially blocks a protein on brain neurons, called the NMDA receptor, to which the chemical messenger glutamate binds. However, it is not known if the medication's rapid antidepressant effects are a direct result of this blockage or of downstream effects triggered by the blockage, as suggested by animal studies.

In this study, the NIMH team imaged depressed patients' brain electrical activity with magnetoencephalography (MEG). They monitored spontaneous activity while subjects were at rest, and activity evoked by gentle stimulation of a finger, before and 6.5 hours after an infusion of ketamine. Those who responded to ketamine showed an increased response to the finger stimulation, a greater excitability of the neurons in this part of the cortex.

Such a change in excitability is likely to result, not from the immediate effects of blocking the receptor, but from other processes downstream, say the researchers. "These clues help focus the search for the molecular targets of a future generation of medications that will lift depression within hours instead of weeks," explained Zarate. "The more precisely we understand how this mechanism works, the more narrowly treatment can be targeted to achieve rapid antidepressant effects and avoid undesirable side effects."

Anil K. Malhotra, M.D.
Scientific Council Member
1999 NARSAD Young Investigator Grant
2001 and 2006 NARSAD Independent Investigator Grants

Schizophrenia

Discovery of Genetic Links to Weight Gain From Antipsychotics Can Identify Those Most Vulnerable

'Second' generation antipsychotic medications are known as atypical antipsychotic drugs (AAPD). Among them are clozapine and olanzapine (Clozaril® and Zyprexa®). Although AAPDs have proven effective with positive symptoms in patients who were non-responsive to other treatments, their use has been associated with extreme weight gain and other metabolic effects. To date, there has been no way to predict which patients might be most vulnerable to weight gain induced by AAPDs.

Anil K. Malhotra, M.D., a professor of psychiatry at Hofstra North Shore-Long Island Jewish School of Medicine, led a study in which he and his team tracked 139 youths aged 4 to 19 who were undergoing their first exposure to the second-generation antipsychotic medications (aripiprazole, olanzapine, quetiapine, or risperidone). After 12 weeks of starting the medications, those taking aripiprazole, quetiapine, or risperidone gained comparable amounts of weight. Those taking olanzapine gained even more.

The research team was able to link 20 gene variants with weight gain—all of them located close to a gene on chromosome 18 that makes the melanocortin 4 receptor. They also found that one of the gene variants—rs489693—was significantly linked to weight gain in each of the samples, even when gender, race, initial body mass index, and the particular antipsychotic used were considered. The results of the study were published in September 2012 in the

Archives of General Psychiatry. Brain & Behavior Research Foundation Scientific Council Members James L. Kennedy, M.D., Ph.D.; Jeffrey A. Lieberman, M.D.; and Herbert Y. Meltzer, M.D., were co-authors of the study.

While there are currently no clinical tests available to identify specific gene variants, progress is being made quickly to improve access to individualized genomic mapping. When this type of testing becomes available and accessible, once specific genetic links have been identified, individuals found to be carrying the gene or gene variant can be offered alternative treatment strategies prior to commencing treatment.

NEW TECHNOLOGIES

Paolo Dazzan, M.D.
2003 and 2007 NARSAD Young Investigator Grants
2009 NARSAD Independent Investigator Grant

Schizophrenia

A New, Quick Approach to Predict Future Course of Psychosis

In recent years, the introduction of magnetic resonance imaging (MRI) has made it possible to visualize brain structure, but the neuroanatomical changes that occur in early psychosis are too subtle for standard MRI to be useful diagnostically. **Paola Dazzan, M.D.,** who leads early psychosis research at the Institute of Psychiatry/King's College London, has been seeking to find a reliable way to predict how psychotic illness will develop after a first psychotic break.

In a study reported in the May 2012 edition of *Psychological Medicine,* she and colleagues have provided preliminary evidence that an innovative technique to evaluate MRI, called support vector machine (SVM) MRI, can be used to predict the course of illness. She states that if validated in larger trials, their finding "could enable targeted clinical decisions based on imaging data."

The researchers began by making MRI scans of 100 patients at the time of their first psychotic episode and of 91 healthy controls. The patients were re-examined six years later and classified as having experienced a continuous, episodic or intermediate course of illness. The team then applied SVM to these MRI scans to study changes in brain structure, creating computer algorithms that could identify, at the time of this first scan, patients who would experience long periods of remission and those who would remain continuously unwell.

According to Dr. Dazzan, the technique she and her group have refined is easy to apply—a ten-minute test that could be incorporated into routine clinical investigations. "This is the first step towards being able to use brain imaging to provide tangible benefit to patients affected by psychosis," says Dr. Dazzan. "This could offer a fast and reliable way of predicting the outcome for an individual patient, allowing us to optimize treatments for those most in need, while avoiding long-term exposure to antipsychotic medications in those with mild forms."

NEXT GENERATION THERAPIES

Olivier Berton, Ph.D.
2005 and 2008 NARSAD Young Investigator Grants

Anxiety, Depression

How to Limit the Negative Impact of Stress Hormones and Support Natural Resiliency

Elevated levels of glucocorticoid hormones mediates what we call 'stress,' creating various brain and behavior disorders. But an appropriate level of these hormones is essential to fine-tune immune responses and the systems through which cells manufacture and adjust their energy levels. It is not possible to simply try to 'turn them off' or reduce their level to treat stress-related disorders.

Olivier Berton, Ph.D., Assistant Professor of Psychiatry at the University of Pennsylvania, has discovered a potentially powerful strategy to overcome this obstacle and achieve blockade of the intracellular action of glucocorticoids more precisely in certain brain circuits critical for depression and anxiety. By studying mice exposed to the mouse-equivalent of bullying, Dr. Berton

and his team noticed that many of the mice developed behavioral problems, notably 'social defeat,' which takes the form of self-defeating social avoidance, but the team also noticed that a certain number of bullied mice were naturally resilient in that the bullying did not cause them to withdraw socially.

Subsequent studies identified one molecular 'signature' that confers this self-protective effect of resiliency: the action of a class of enzymes called histone deacetylases (HDACs). Further, Dr. Berton and his research team discovered that the natural reduction in the expression of HDAC6—one member of the HDAC family—was a hallmark of resilience in the animals that did not succumb to bullying and figured out a way to manipulate HDAC6 levels in neurons that mediate the neurotransmitter serotonin. Deleting HDAC6 in serotonin neurons in the mouse brain dramatically reduced social and anxiety symptoms in mice that were not naturally resilient. The results were published in *Journal of Neuroscience* in March 2012.

HDAC6 thus becomes a possible biomarker for, or predictor of, stress vulnerability. It also points toward the development of medications that can specifically inhibit the enzyme, thus minimizing the harmful impact of glucocorticoid signaling in serotonin neurons that results in symptoms of anxiety.

Depression

Identifying How Stress is Linked to Depression - Research Discoveries in the News, Page 9
Karl Deisseroth, M.D., Ph.D. and Eric Nestler, M.D., Ph.D.

Schizophrenia

Karuna Subramaniam, Ph.D.
2010 NARSAD Young Investigator Grant

Sophia Vinogradov, M.D.
2000 NARSAD Independent Investigator Grant

Computer Program Improves Behavioral Symptoms and Brain Activity in Schizophrenia

A hallmark symptom of schizophrenia is difficulty in distinguishing external reality from internal experiences ('reality monitoring'). Whether or not this impairment is irreversible has long been debated. Now, a pilot study at the University of California, San Francisco, led by **Sophia Vinogradov, M.D.,** has shown that targeted computer 'brain training' can improve reality monitoring in people with schizophrenia. NARSAD Young Investigator Grantee **Karuna Subramaniam, Ph.D.,** was the lead author of the research paper, published February 23, 2012 in the journal *Neuron.*

In the 16-week trial, 31 schizophrenia patients were randomly assigned to one of two groups: one group to receive 80 hours of active cognitive training, the other to serve as controls and spend the 80 hours of the trial period playing various commercial computer games. All the participants were assessed before and after the trial by means of behavioral performance tests and functional magnetic resonance imaging (fMRI) of brain activation patterns. Sixteen healthy comparison subjects were also studied for their brain activation patterns, but did not undergo training. In contrast to the control patients who showed no behavioral or neural improvements, the patients who received the training program demonstrated that they could perform a complex reality monitoring task, one that had not been part of their training exercises, and this improved ability correlated with increased medial prefrontal cortex (mPFC) activity.

Equally significant, tests showed that increased mPFC activity was associated with later improved social functioning. Another striking aspect of the research, the authors point out, is that the mean length of illness of the patients was 19 years, showing that even the chronically ill could benefit from this type of training.

"These findings," they state, "demonstrate that a serious behavioral deficit in schizophrenia, and its underlying neural dysfunction, can be improved by well-designed computer cognitive training, resulting in a better quality of life."

Research Discoveries *in the News*

photo by Jeff Miller, University of Wisconsin-Madison

Richard J. Davidson, Ph.D.
1995 and 2003 NARSAD Distinguished Investigator Grantee
Vilas Professor of Psychology and Psychiatry
Department of Psychology
Director, Lab for Affective Neuroscience
University of Wisconsin-Madison

Two-Decade Study Shows Girls More Susceptible to Early-Life Stress

How early in life does exposure to stress raise a child's likelihood to suffer anxiety, depression, or other stress-related disorders? If the child is a girl, the answer appears to be very early. This is one of the findings of a study performed by a team led by NARSAD Grant recipient Dr. Richard J. Davidson, Professor of Psychology and Psychiatry at the University of Wisconsin-Madison.

When a mother experiences high levels of stress during her female child's infancy, chances are good that the child will show differences in important brain functions and will experience anxiety symptoms by the time she is a teenager, relative to girls whose mothers were not stressed. Boys showed none of the same specific propensities, regardless of the mother's mental health status.

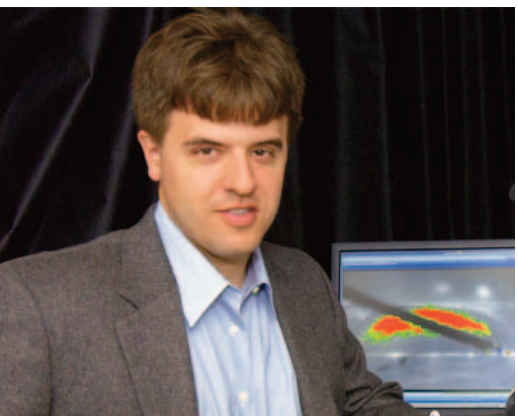
Merely being able to track such progressions is impressive. Extraordinary efforts to follow mothers and their children from the period of pregnancy through subsequent life have been made through the Wisconsin Study of Families and Work (WFSW), which was launched in 1991 with the registration of 570 children and their mothers. The study's initial aim was to gauge the impact of maternity leave, day care and other factors on family life. It is now providing insights into the elusive relationships between stress, illness, and gender—a highly complex subject, involving not only many of the body's biological systems, but also the problem of assessing individual differences, both in terms of biology and experience.

One of Dr. Davidson's colleagues, Dr. Rasmus Birn, developed a method of using a new type of functional MRI scan (called fcMRI) to assess a critical function in the 'resting' brain pertinent to the study—one involving the integrity of a circuit linking the brain's amygdala (its 'fear center') with a part of the prefrontal cortex that helps regulate the emotions. Using scans from 28 female and 29 male subjects now 21 or 22 years old, and followed from birth, the team found that girls with current weaker functional connections between the amygdala and prefrontal cortex had, as infants, lived in homes with stressed mothers. When tested as 4-year-olds, the same girls had above-average levels of the stress hormone cortisol.

> [The study] "raises important questions to help guide clinicians in preventive strategies…"

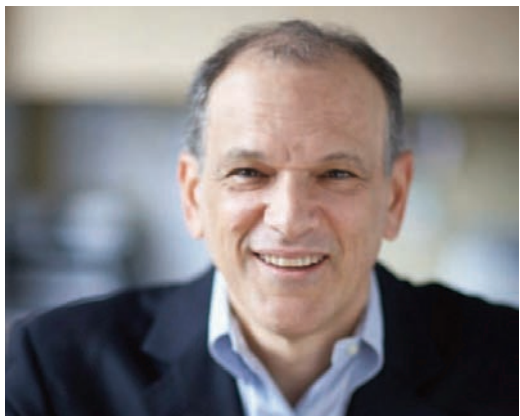
Dr. Davidson says the study, which appeared in December 2012 in *Nature Neuroscience,* "raises important questions to help guide clinicians in preventive strategies that could benefit all children by teaching them to propagate well-being and resilience."

As for differences in gender response to maternal stress, the team proposes that "females may be more sensitive to the effects of early-life stress" on the function of the neuroendocrine system, as well as prone to alteration of the pattern by which chemical groups mark DNA in cells, called epigenetic marking—a potential cause of changes in gene expression.❖



Karl Deisseroth, M.D., Ph.D.
Scientific Council Member
2005 NARSAD Young Investigator Grantee
Associate Professor of Bioengineering and Psychiatry
Stanford University

Identifying How Stress is Linked to Depression



Eric J. Nestler, M.D., Ph.D.
Scientific Council Member
1996 NARSAD Distinguished Investigator Grantee
Nash Family Professor of Neuroscience
Chair, Department of Neuroscience
Director, Friedman Brain Institute
Mount Sinai School of Medicine

Two research teams independently led by members of our Scientific Council have made important new discoveries about how stress impacts the circuitry in the brain and is linked to depression. The two teams, using some of the same advanced experimental techniques in mouse models of depression, obtained seemingly opposing results.

Yet, the results are complementary, and together appear to reveal more about the stress-depression relationship than either study does by itself. Dr. Karl Deisseroth of Stanford University led one team with NARSAD Young Investigator Grantees, Melissa R. Warden, Ph.D. and Kimberly R. Thompson, Ph.D. In a study published in *Nature* in December 2012, that team demonstrated for the first time how brain cells activated by the neurotransmitter dopamine are involved in depression.

The Stanford team used the new technology optogenetics, developed by Dr. Deisseroth with the support of a NARSAD Young Investigator Grant in 2005, that enables scientists to turn specific neurons on and off using beams of colored laser light. They did experiments with mice showing symptoms of depression after exposure to mild, chronic stress. Within seconds of switching off dopamine neurons in a part of the midbrain called the ventral tegmental area (VTA), the symptoms in the depressed mice vanished. When the same cells were switched on again, symptoms of depression returned.

At Mount Sinai School of Medicine in New York, a team led by Dr. Ming-Hu Han, a NARSAD Young Investigator Grantee, and Dr. Eric Nestler, was performing similar experiments, but with mice exposed to severe stress—a model Dr. Nestler calls 'social defeat.' After being bullied for ten days by much stronger mice, many of the 'defeated' mice showed several depression-like behavioral abnormalities. But some proved resilient and held up well under the repeated stress.

When this resilient subset was exposed to optogenetic stimulation of dopamine neurons in the VTA—the same area stimulated in the Deisseroth experiments—they became more susceptible to the stress. Essentially the same stimulation to the same type of neurons in the same part of the brain instantly *lifted* the depression of the mice that were chronically, mildly stressed, but made the severely, socially stressed mice *more depressed*, or more likely to become depressed. These results were also published in *Nature* in December 2012. Dr. Nestler says of the results, "These studies highlight the complexity of microcircuits in the brain, the unique ability of optogenetic approaches to study circuits, and the importance of characterizing the function of those circuits in multiple animal models of mental illness."

Dr. Deisseroth's team also emphasized that the effects of stress on affected parts of the brain "are highly complex, as different stressors can cause very different responses from neurons." Simultaneously, depression and its treatment are "exceedingly complex," they said. These studies represent one more step forward in decoding this complexity—and point toward the development of more effective treatments for those suffering. ❖

Steven Laviolette, Ph.D.
2005 and 2007 NARSAD Young Investigator Grantee
Associate Professor
Department of Anatomy and Cell Biology
University of Western Ontario

Blocking the Recall of Memory for Treatment of Post-Traumatic Stress Disorder

NARSAD Grant recipient Dr. Steven R. Laviolette and members of his lab at the University of Western Ontario in Canada have accomplished an impressive feat. This past December they reported online in the journal *Neuropharmacology* that they had succeeded in blocking the kinds of memories known to activate symptoms of severe anxiety disorders such as post-traumatic stress disorder (PTSD), as well as substance abuse disorders such as morphine addiction.

Memories that doctors and scientists call 'associative'—terrifying memories of a traumatic episode or pleasurable memories of the 'high' obtained from psychoactive drugs—are understood to be activated and conveyed by the transmission of dopamine among nerve cells in the brain. Specifically, cells in the medial prefrontal cortex.

Dr. Laviolette and colleagues wanted to learn more about this process. Specifically, they wanted to pinpoint which of a variety of subtypes of dopamine receptors—molecular 'keyholes' on the surface of nerve cells into which dopamine molecules fit like 'keys'—are relevant in this process. They focused on the so-called 'D1' dopamine receptor type.

Importantly, they were also able to restore specific memories. This implied that blocking the memory did not destroy underlying memory traces.

By experimentally activating this receptor in the rat brain in behaviorally conditioned animals, the scientists found that both negative ('aversive') as well as rewarding associative memories could be temporarily blocked. Importantly, they were also able to restore specific memories (using prior addiction to morphine, and memory of its 'high,' as an example). This implied that blocking the memory did not destroy underlying memory traces.

"These findings are very important in disorders like PTSD or drug addiction," Dr. Laviolette comments. "One of the common problems associated with these disorders is the obtrusive recall of memories of fearful experiences in PTSD patients, and for people suffering from addiction, exposure to environmental cues that remind them of the rewarding effects of the drug. This can lead those in treatment to relapse."

Dr. Laviolette's team found that the same mechanism in the brain controls recall of both aversive and pleasurable memories. This mechanism not only involves the D1 dopamine receptor, but also, a kind of cellular signaling that depends on a molecule called cyclic AMP (c-AMP). Indeed, memories that were temporarily blocked were restored by administering an inhibitor of c-AMP signaling.

This research is directly relevant to the search for medications that will be able to provide relief for PTSD sufferers, for example, who might be experiencing a flashback. Such medications might also be used to help recovering addicts overcome sudden cravings for getting high. For this reason, Dr. Laviolette considers it important that the temporary memory blockages his team was able to induce didn't damage the delicate structures of the brain that actually 'hold' the stuff of memory. ❖

Interview

with

Dennis S. Charney, M.D.

Scientific Council Member
2007 NARSAD Distinguished Investigator Grantee
Anne and Joel Ehrenkranz Dean of Mount Sinai School of Medicine
Executive Vice President for Academic Affairs of the
Mount Sinai Medical Center

A Prescription for Resilience

World Expert Helps Explain What Can Make Us Stronger in the Face of Adversity

"I'm a big believer in mothers."

This is Dr. Dennis Charney speaking, and it is a remark that both charms and disarms the listener—so down to earth, yet coming from one of the most sophisticated and accomplished researchers in the field of brain research. Dr. Charney, a member of the Brain & Behavior Research Foundation Scientific Council, recipient of a NARSAD Distinguished Investigator Grant, former Chief of the Mood and Anxiety Disorder Research Program at the National Institute of Mental Health, and now Dean of the Mount Sinai School of Medicine in New York, has over 700 publications to his name—hundreds of scientific articles, dozens of scholarly books, chapters, and reviews—a list that continues to lengthen as his career moves forward.

Adapting to early stress

In this particular remark, not to be confused with a simple defense of motherhood, Dr. Charney is trying to place into proper context a remarkable recent research finding: "children, in particular, display remarkable resilience" when faced with sources of stress in their environment. A leading expert on resilience, Dr. Charney acknowledges the observation is true in the narrow sense that the brain of the young child is comparatively malleable. It is an organ still in the process of assuming its mature form—a process that will take the better part of two decades. It's an extraordinarily complicated process, involving the progressive unfolding of neural networks, shaped partly by individual experience, but also by the expression of hundreds of genes in each person's unique DNA.

Research shows that children are surprisingly good at adapting to stress. But only up to a point: for children most certainly need and depend upon parental protection. Some recent studies have shown that rodent pups subjected to early maternal separations later prove more resilient than pups that were not separated from their mothers. "But those are data from animal models of stress," Dr. Charney cautions. The applicability to humans remains ambiguous. A minimal experience of separation from 'mama' might be helpful in some cases when young people are involved, he allows, "as long as it is not that much." He adds that not only is he a big believer in mothers, but "in mothers who are very predictable and helpful."

But where is the tipping point in this, and other kinds of stress?

'Maybe we can learn from people who *have* been traumatized but who did *not* develop PTSD or depression or substance abuse problems.'

While many people exhibit remarkable resilience, there are many others, in response to stress, who go on to develop brain and behavior disorders, ranging from mood disorders such as depression, to anxiety disorders such as post-traumatic stress disorder (PTSD), to substance-abuse disorders like alcoholism and drug addiction.

Identifying the links between stress and illness

It is now widely known that there are biologically predisposing factors that make the onset of depression and other brain and behavior disorders more likely for some people than others. The development of the disorder in these cases may be triggered by adverse environmental circumstances or not.

The biology of depression and similar disorders has been linked to dysfunctions of the stress hormone system, and what physicians refer to as the HPA (hypothalamic-pituitary-adrenal) axis. The HPA axis is engaged with many key bodily systems, such as those regulating digestion and the immune response. There is also evidence of abnormal gene expression impacting the brain circuits and networks involved in the regulation of mood and the natural ability to respond to stress.

The Brain & Behavior Research Foundation funds much research to better understand what malfunctions and why, and importantly, how the dysfunctions can potentially be corrected. Of this support, Dr. Charney says, "The great thing is that the great majority of the grant money has gone to young people, early in their careers. They need a jump-start—to take the right ideas and test them. The Foundation has made a seminal contribution to the field."

What makes some people more resilient?

Dr. Charney, in trying to come to grips with possible and probable factors pertinent to the stress response, had an epiphany during his years at Yale. "In those years, along with fellow Foundation Scientific Council Members Drs. Eric Nestler and John Krystal and others, including Dr. Steven Southwick, I was studying PTSD and depression. We were doing a lot with military veterans, and ultimately we said, 'Maybe we can learn from people who *have* been traumatized but who did *not* develop PTSD, depression or substance abuse problems.'

"In the ensuing years, we have studied diverse populations of people who have demonstrated resilience. We studied POWs from Vietnam; men held in prison for 6 to 8 years; we studied the U.S. Special Forces; victims of hurricanes; victims of earthquakes in Pakistan; people who were raised in conditions of crime and poverty in inner-city Washington, D.C.

We began by saying, 'We want to learn from you. You tell us what enables you to show incredible courage and resilience to get through tough times.'"

This work has culminated in what Dr. Charney calls 'a prescription for resilience.' Again and again, he and his associates were told by people who were dealing successfully with trauma or stress that they called upon prior experiences in their lives that helped them get through the current challenge. Behavioral scientists call this form of coping 'stress inoculation:' exposure to the dangerous thing enables some people to learn how to cope with it.

"I've done this with my own children. You need to take them out of their confidence zone. You give them challenges they can manage, and therefore learn from."

"It has implications for how you might want to raise your children," Dr. Charney says. "If you grow up in a stress-free environment, you're not prepared for the inevitable stresses and strains that life presents. Everybody suffers the loss of loved ones. Everyone faces medical illness and meets with disappointment. The point is that you need to be prepared. I've done this with my own children. You need to take

Dr. Charney during Q&A Session at the Brain & Behavior Research Foundation Annual Mental Health Research Symposium in October, 2012

them out of their confidence zone. You give them challenges they can manage, and therefore learn from. And they develop a psychological toolbox they can call upon when faced with something difficult."

What he and his colleagues learned from veterans and victims of both natural calamities and physical and psychological abuse is that those who were resilient tended to be the ones who sought support from others. "If your house is burnt, you figure out ways to rebuild it; you don't wait for people to come to you. You engage the help of others to help you rebuild what has become broken."

Dr. Charney points out that it is perfectly normal to experience fear. It's an emotion and associated set of behaviors that evolution has preserved because it tends to promote our collective survival. "People who are courageous are not fearless," he notes. "Courage is all about overcoming fear—acting despite being afraid. Facing fears can increase your self-esteem," and thus enhance resilience.

When he talks to non-scientists about stress and resilience, Dr. Charney finds that his audiences are "most interested in our finding that you can train yourself to be more resilient." He does not mean with the guidance of a psychoanalyst, and he is not talking here about those who are suffering from clinical depression (although the lessons do apply, he says, insofar as patients are able to apply them).

Optimism is strongly correlated with resilience. This is exemplified in what has been called 'the Stockdale paradox,' after one of the most famous of the Vietnam POWs, James Stockdale: "You know you are in deep trouble; so you face the brutal facts of the challenge you're facing. But at the same time you feel deeply that you will prevail."

Also, those who speak of having a strong set of core moral principles have been shown to be more apt to be resilient. So have those who seek models of successful coping behavior in others—whether a friend or relative or someone famous. Role models can help people hold up under stress, Dr. Charney reports.

"Depression is not the opposite condition of resilience. It's not as if people who suffer from depression are not resilient."

Having spent so much time studying clinically depressed people, Dr. Charney makes very clear that "depression is not the opposite condition of resilience. It's not as if people who suffer from depression are not resilient. You might be depressed because you are biologically predisposed. In such individuals, the illness must be treated in a 'precise and focused way,' with the help of professionals. Resilience, however, can separately help the depressed. So if you unfortunately suffer from depression because you are predisposed, working on some of the factors we've identified that promote resilience can help you deal with depression."❖

BRAIN & BEHAVIOR
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The Power of Partnership

A Personal Connection

Jed Abrams with his dog, The General

Uniting Donors with Researchers

Jennifer B. Wagner, Ph.D.
2010 NARSAD Young Investigator Grantee

"Raising and losing a very special child, whose issues did not respond to conventional psychiatric intervention, makes it all the more important for us and our community to support research that will alleviate these conditions for others in the future. We have great expectations for our young researcher, whom we sponsor through the Brain & Behavior Research Foundation." Jan Abrams
Jed's parents, Jan and Stefan Abrams, have a Research Partnership with Jennifer B. Wagner, Ph.D., of the College of Staten Island, City University of New York, a 2010 NARSAD Young Investigator Grantee.

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Answers to *Ask the Researcher*

from Robert C. Malenka, M.D., Ph.D.

Scientific Council Member
1990, 1992 and 2007 NARSAD Grantee
2010 Goldman-Rakic Prize for Outstanding Achievement in Cognitive Neuroscience
Pritzker Professor in Psychiatry and Behavorial Sciences
Stanford University School of Medicine

I thought the chemical imbalance theory of depression was a big step forward in treating depression as a bona fide illness. What are the implications of finding that it is out of date—and how long do you expect it to take to have new, more effective treatments?

There is no doubt that depression is a bona fide illness. Theories are made to be tested and revised as new scientific knowledge accrues. Even if eventually proven wrong, a theory stimulates research and is necessary for scientific advances. It is impossible to say when new, more effective treatments will be available. The causes of depression are still unknown and developing treatments for mental illnesses is an incredibly challenging task. The good news is that progress is being made using very exciting new approaches and techniques.

Our forty year-old son lives with bipolar disorder (manic depression) and takes 1,000 mg of Depakote® daily. It doesn't seem to be working; he remains unmotivated and very anxious. He feels no need to seek therapy—do you have any advice on how to get someone to visit a therapist?

Helping a friend or loved one understand that they will benefit greatly from seeing a therapist is often very difficult. In most cases, adults cannot be 'forced' to seek help even when it is obvious that they will benefit. The best you can do is to provide frequent, gentle reminders and examples of friends who have greatly benefited from therapy. However, this needs to be done in a supportive, non-confrontational manner.

Are there ways to alleviate stress before the damage is done to the melanocortin circuit you speak about?

There are many, many ways to alleviate stress but the particular approaches an individual takes can vary. It is important to identify and, as much as possible, understand the sources of the stress. Then, perhaps with the help of a professional therapist, take whatever steps are possible to eliminate or at least reduce these sources. Perhaps there are professional, relationship, or financial problems that can be addressed. Of course, it is frequently not possible to eliminate stress from our lives, and additional strategies are helpful such as exercise, meditation, or changes in lifestyle (e.g., making more time for enjoyable, relaxing activities, changing eating habits). It is important to remember that there is no simple solution to alleviating stress. It will take motivation and developing a multi-step plan.

Your work is fascinating. It is also a little frightening to think about neurotransmitters in the brain being manipulated to reduce or eliminate depressed behaviors. How do you foresee these malfunctions in brain circuitry and synaptic connections being treated?

The hope of all neuroscience researchers is that by defining the malfunctions in brain circuitry that underlie the symptoms of major mental illnesses we will open the door to very novel ways of developing new treatments. It would be wonderful if findings from this new type of research identifies a single target to which a medication could be made that reverses the circuit abnormalities. A single, new, effective medication would alleviate the suffering of millions of inadequately treated patients. However, the reality is that the brain and its circuits are incredibly complicated and it is unlikely that some 'magic bullet' will be found that can fix malfunctioning brain circuitry. It is much more likely that over the next decade or two we will learn how to use a combination of treatments (i.e., new medications, psychotherapy, perhaps direct manipulation of brain activity with magnetic waves) more effectively to reverse the abnormalities in brain circuitry that cause major symptoms.

Ask the Researcher

HAVE A QUESTION? E-mail **asktheresearcher@bbrfoundation.org** with questions for **Dr. Dennis Charney.** Select questions and answers will be published 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. This Q&A forum is not meant to serve as a substitute for that, but rather to share insights.

Frequently Asked Questions on Stress

Q

What is stress?

A

Stress is a normal physical response to events that make one feel threatened or that upset one's balance in some way. When the body senses danger—real or imagined—the body's defenses kick into high gear in a rapid, automatic process known as the 'fight-or-flight' reaction, or the stress response. The nervous system responds by releasing a flood of stress hormones, including adrenaline and cortisol, that rouse the body for emergency action.[1]

Q

What is the impact of stress?

A

Stress during development has often been regarded as a potentially disruptive force, capable of inducing disease states if overly prolonged or exceedingly intense. It can also, however, favor resiliency and adaptive processing that are crucial to navigating a human life. Countless studies have indicated that severe neglect during infancy, both in humans and in laboratory animals, results in long-term abnormal development of biological systems involved in the regulation of emotions, but the response to stress is also a key driver to individual development. The biological system responsible for physical reactions to a stressor not only coordinates immediate responses to external challenges but also functions as a tool that enables the characterization of an environment as favorable or threatening. Thus the stress response system promotes long-term adaptive processes that prepare the individual to cope with specific external challenges.[2]

Q A What are the main symptoms of stress in adults?

- Cognitive symptoms include memory problems; inability to concentrate; poor judgment; anxious or racing thoughts and constant worrying
- Emotional symptoms include moodiness; irritability or short temper; agitation; inability to relax; a feeling of overwhelm; a sense of loneliness and isolation
- Physical symptoms include aches and pains; diarrhea or constipation; nausea; dizziness; chest pain; rapid heartbeat
- Behavioral symptoms include eating more or less; sleeping too much or too little; isolating yourself from others; procrastinating or neglecting responsibilities; using alcohol, cigarettes, or drugs to relax; engaging in nervous habits (e.g., nail biting, pacing)[3]

Q A What are the symptoms of stress in children and teens?

Youth of all ages, but especially younger children, may find it difficult to recognize and verbalize when they are experiencing stress. For children, stress can manifest itself through changes in behavior. Common changes can include irritability, withdrawal from formerly pleasurable activities, routine expression of worries, excessive complaints about school, frequent crying, display of surprising fearful reactions, separation anxiety, sleeping too much or too little, or eating too much or too little. With teens, while spending more time with and confiding in peers is a normal part of growing up, significantly avoiding parents, abandoning long-time friendships for a new set of peers, or expressing excessive hostility toward family members may indicate that the teen is experiencing significant stress.[3]

Q A What is resilience?

In the physical sciences, materials and objects are termed resilient if they resume their original shape upon being bent or stretched. In people, resilience refers to the ability to 'bounce back' after encountering difficulty.[4]

Q A Are there coping factors to help deal effectively with stress?

In their 20 years of treating and studying trauma survivors, Drs. Charney and Southwick have identified ten common practices in people who have shown resilience in the face of extreme stress.

- Maintaining an optimistic but realistic outlook
- Facing fear (ability to confront one's fears)
- Reliance upon own inner, moral compass
- Turning to religious or spiritual practices
- Seeking and accepting social support
- Imitation of sturdy role models
- Staying physically fit
- Staying mentally sharp
- Cognitive and emotional flexibility (finding a way to accept that which cannot be changed)
- Looking for meaning and opportunity in the midst of adversity[4]

Sources:

1 National Institute of Mental Health
2 Simone Macri, Ph.D., NARSAD Young Investigator Grantee: bbrfoundation.org
3 American Psychological Association
4 Steven M. Southwick, M.D. and Dennis S. Charney, M.D.: *Resilience: The Science of Mastering Life's Greatest Challenges,* Cambridge University Press, 2012

Nothing to be Ashamed Of

From a family affected by mental illness, this man supports research to make a difference.

On February 29, 2000, Albert Bensimon, then in his early fifties, stepped into the waters off Laguna Beach, California, and kept on walking, not intending to stop. His recollection of the day is hazy, but he does remember getting "pretty far out until the water was up to my neck. I honestly don't know what stopped me."

Bensimon had been battling major depression for years. Whatever the immediate trigger that had tipped him over into near-suicide that day, what really underlay it was an accumulation of stressors over a period of decades. He remembers that, "It was everything in my life. I just didn't think I could cope with the stress and anxiety any longer."

The 'everything' encompassed a Job-like burden of family woes: an out-of-control sister with paranoid schizophrenia, a brother vanished and believed murdered, and, more recently, a father succumbing to Alzheimer's disease and a mother who tended to handle mental health issues with denial. Bensimon's constant task as the family's 'disaster control manager' had taken a heavy toll.

The troubles had come seemingly without warning. Born in 1947, the oldest of the family's three children, Bensimon recalls a mostly happy childhood in an ordinary middle-class family in New Jersey. The unraveling began when, in her late teens, Al's sister, Michele, two years his junior, started

Al with his mom and dad, Easter 2007

Al at home on his deck (p.18) and on his patio (above)

....it is critical "to be brutally candid with oneself and others, to not try to mask, hide or diminish the fact that you—or they—need help."

hearing voices coming from the backyard trees. Not long after, she dropped out of college and set off on a decades-long, near-fatal roller-coaster ride.

By contrast, Al Bensimon was determined to forge a productive life. In 1970, shortly after graduating college, he married Patricia, a registered nurse. They had two children. Over a span of 30 years, Al worked for large and medium-sized corporations, travelling extensively. While he proved himself smart and versatile and steadily took on more responsibility, he acknowledges having been a mostly absent parent.

In 2006, Al and Pat made the decision to make a disruptive move from Orange County, California to Florida to assist Al's ailing parents. Al's mother, still insisting that his father was just having "minor memory issues," fought efforts to move them into an assisted living facility, a move ultimately made in 2008.

Al credits the right mix of talk therapy and medication with helping him re-engage in life after his suicide attempt. "But what helped me the most," he says, "was my wife's consistent support and medical knowledge. It was she who forcefully suggested I see a psychiatrist, and it was she who found the right one. He was the one to whom I turned when feeling suicidal."

Along with his wife's wise counsel, Al says that a lifelong habit of turning to books for insights and information also proved very helpful. He has amassed a library on depression to help him gain broader understanding. Prominent among them and close to Al's heart is the French writer and philosopher Albert Camus, who ultimately rejected suicide. "The better I understand myself, the more I learn, the more I find I can help others to understand how important it is to not give up—to keep on keeping on."

Today, Al and Pat live in Georgia to be close to their daughter, now married and a successful corporate lawyer. Their first grandchild was born last August. Their son and family live in southwest Florida. And, Al says that life is great.

Al Bensimon believes strongly, on the evidence of his own life, that for people suffering with a mental illness, and for their loved ones, it is critical "to be brutally candid with oneself and others, to not try to mask, hide or diminish the fact that you—or they—need help. One of the reasons I'm doing this interview is to try to make more people aware that mental illness is not something to be ashamed of. And that suicide is not the answer."

"I make donations to the Brain & Behavior Research Foundation my number one gift each year. I believe that research will change what it means to have a mental illness."

Albert Bensimon has been a Brain & Behavior Research Foundation supporter for over two decades and views the foundation's mission as "very personal." "I make donations to the Brain & Behavior Research Foundation my number one gift each year. I believe that research will change what it means to have a mental illness."

"I've researched enough to know that the Brain & Behavior Research Foundation does excellent work, and that all of the dollars I donate go directly to research. My wife, with her medical background, understands the science more, but I understand enough to know it's making a difference. And if I can help make that difference, I'm going to keep on doing it."❖

NARSAD Distinguished Investigator Grantees in 2012

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NARSAD Distinguished Investigator Grants enable outstanding scientists to pursue new, cutting-edge ideas with the greatest potential for breakthroughs. The fifteen established investigators, selected from 225 applicants, will receive one-year grants of up to $100,000 to pursue innovative research ideas for disorders including depression, bipolar disorder, schizophrenia, autism and anxiety disorders such as obsessive-compulsive and post-traumatic stress disorders.

Dr. Barchas, Chair of Psychiatry at Weill Cornell Medical College said: "The portfolio of awards is exciting and impressive in its depth and possibilities for important and transforming discoveries. We could easily justify funding a far greater number."

Jack D. Barchas, M.D.
Scientific Council Member
Chair, NARSAD Distinguished Investigator Grant Selection Committee

BASIC RESEARCH

"This NARSAD Distinguished Investigator Grant will allow me to explore one of the most exciting leads I have uncovered in my career—a new gene and possible mechanism for bipolar disorder. It will make it possible for this novel exciting work to move forward."

John R. Kelsoe, M.D.

Autism, Schizophrenia

Gary Bassell, Ph.D.
Emory University School of Medicine

Dr. Bassell will explore synaptic dysfunction in brain and behavior disorders, including autism and schizophrenia. The synapse is the site where information is transmitted from cell to cell in the brain. This research will center on a signaling pathway, important in synapse development and plasticity, and, thus, in learning and memory, that influences the function of dendrites —tiny spines on nerve cells where brain messages are received.

"I am so excited to receive this NARSAD Grant and grateful to the Brain & Behavior Research Foundation for this support. This Grant will allow me to explore a new theory about the shared neurobiology and critical differences between two disease models, and to validate potential new therapeutic strategies."

Gary Bassell, Ph.D.

Bipolar Disorder

John R. Kelsoe, M.D.
University of California, San Diego

Dr. Kelsoe will investigate the role in bipolar disorder of the neurotrophin system of neuronal growth factors. Neurotrophins are proteins of the nervous system that regulate the growth and survival of neurons. One of the neurotrophins is called brain-derived neurotrophic factor (BDNF). Both lithium, the leading treatment for bipolar disorder, and selective serotonin reuptake inhibitor (SSRI) antidepressants stimulate BDNF expression. The study, in collaboration with Dr. Fred Gage, of the Salk Institute (and Brain & Behavior Research Foundation Scientific Council Member), will explore the relationships between neurotrophins and other factors in bipolar disorder. Dr. Gage's landmark finding that the brain can grow new neurons offers the possibility of replacing diseased cells.

Schizophrenia

Bonnie L. Firestein, Ph.D.
Rutgers University

Dr. Firestein is interested in a schizophrenia susceptibility gene that may be implicated in the striking changes in dendrites observed in schizophrenia patients. Dendrites are the spine-like projections on nerve cells that receive brain messages. There is strong evidence that changes in dendrite formation can influence neuronal function. The study will attempt to show that dendrite defects can be reproduced in genetically variant cells from people with schizophrenia.

DIAGNOSTIC TOOLS/EARLY INTERVENTION

Bipolar Disorder

Lars Vedel Kessing, M.D., D.M.Sc.

University of Copenhagen

Dr. Kessing hopes to help resolve the critical question of how to predict which bipolar disorder patients will benefit from lithium treatment. He has assembled the world's largest cohort of bipolar disorder patients, among whom 500 have shown a therapeutic response to lithium and 3,500 have not. The study will examine the genetic differences underlying this disparity in order to identify the genetic characteristics causing a beneficial response.

Schizophrenia

Schahram Akbarian, M.D., Ph.D.

Mount Sinai School of Medicine

Dr. Akbarian will examine changes in the brain's prefrontal cortex that may be relevant to changes observed in people with schizophrenia. The study will build upon an earlier finding by Dr. Akbarian, supported by a NARSAD Young Investigator Grant, of activity by a key enzyme in the prefrontal cortex, which, when it malfunctions, may be critically involved in psychosis.

> With support from this NARSAD Distinguished Investigator Grant we will once again push the frontier in human brain research, as we did more than 15 years ago with the support of a NARSAD Young Investigator Grant.
>
> Schahram Akbarian, M.D., Ph.D.

NEW TECHNOLOGIES

General Mental Illness

Brian Litt, M.D.

University of Pennsylvania School of Medicine

Dr. Litt will apply his background in neurology and bioengineering to investigate the use of nanodevices to deliver specifically targeted treatments for brain and behavior disorders. Recognizing that these diseases involve specific nerve cells and circuits, the goal of the project is to develop devices with a therapeutic payload that reach only the targeted tissues, thus avoiding potentially harmful impact on uninvolved areas of the brain.

Schizophrenia

Rafael Yuste, M.D., Ph.D.

Columbia University

Dr. Yuste will examine the role in schizophrenia of chandelier cells. The study is based on the hypothesis that these neurons act as switches controlling cortical activity and could alter the balance between internal brain processes and external sensory stimulation. This would imply that damaged chandelier cells could cause cognitive disorders. Chandelier cell function will be examined in mice using advanced imaging approaches, including efforts to optically manipulate the firing of the cells with photon lasers.

NEXT GENERATION THERAPIES

> The NARSAD Distinguished Investigator Grant will enable our laboratory to apply our expertise, in the field of presynaptic biology, to an important societal need by identifying novel therapeutic targets for rapid treatment of depressive symptoms in patients.
>
> Ege T. Kavalali, Ph.D.

Depression

Ege T. Kavalali, Ph.D.

University of Texas Southwestern Medical Center

Dr. Kavalali wants to improve the usefulness of the drug ketamine as a fast and powerful new treatment for depression. While ketamine can reverse depressive symptoms within hours, as opposed to many weeks needed for currently available antidepressants, it has serious side effects. Having previously determined that ketamine influences the brain growth factor, brain-derived neurotrophic factor (BDNF), Dr. Kavalali will now explore ketamine-BDNF interactions to find ways to combat the drug's negative effects.

Psychosis

Sohee Park, Ph.D.

Vanderbilt University

Dr. Park, an earlier NARSAD Young Investigator Grantee, studies the social impairments caused by psychotic disorders and the real-life consequences for patients. In this study, tests and treatments will be designed to specifically target the social brain network through virtual reality and robotics technology that adjusts to the patient's monitored affective state. The aim is to increase the level of engagement in individualized social training for such real-life activities as job interviews.

General Mental Illness

Nenad Sestan, M.D., Ph.D.

Yale School of Medicine

Dr. Sestan studies mechanisms underlying development and dysfunction in the cortex, the seat of higher brain function. These processes may be important in the severe cognitive impairment in Fragile X Syndrome, but understanding them could have broad implications for other mental illnesses. This investigation will examine human and animal cortical tissue at the mid-fetal period, infancy, adolescence, and adulthood to obtain insights that may yield targets for new treatments for diseases of cortical impairment.

Schizophrenia

Stephen Traynelis, Ph.D.

Emory University

Dr. Traynelis will explore an approach to treating schizophrenia based on altering the function of the neuroregulator glutamine in a chain of events that involves glutamine receptors called NMDA (N-Methyl-D-aspartic acid). There is evidence that boosting the activity of NMDA receptors in the prefrontal cortex may be therapeutic. Dr. Traynelis' previous research identified six classes of receptor potentiators that interact with the NMDA receptor, which he now plans to evaluate in animal models of schizophrenia.

NARSAD Distinguished Investigator Grantees in 2012 with a focus on Stress-Related Disorders

DIAGNOSTIC TOOLS/EARLY INTERVENTION

Barbara O. Rothbaum, Ph.D.
Emory University School of Medicine

Dr. Rothbaum is striving to identify the optimal timing for early intervention aimed at preventing the development of post-traumatic stress disorder (PTSD). Unlike some other brain and behavior disorders, the precipitating triggers for PTSD are clearly known, which thus allows for immediate intervention. However, most efforts to date have been focused on treating chronic PTSD, well after the traumatic event, often with limited effect.

Recent research led by Dr. Rothbaum suggests that therapy administered soon after trauma can significantly reduce the onset of PTSD and the depression that frequently accompanies it. The key question is how soon after the trauma must treatment be given. Will it work as well after a week as compared to hours afterward? To answer this question, the investigation will be conducted in the real-world environment of an emergency room. Among the team members who will be collaborating with Dr. Rothbaum in the study is Emory University colleague and Brain & Behavior Research Foundation Scientific Council Member Kerry J. Ressler, M.D., Ph.D., one of the world's leading experts in the study of PTSD and the biological mechanisms of fear.

The hope is that this trial will pave the way toward development of novel, inexpensive and immediate measures to stop PTSD in its tracks before it becomes a long-term debilitating condition. The implications, just in terms of the many thousands of recent combat veterans, are significant.

NEW TECHNOLOGIES

Susan M. Dymecki, M.D., Ph.D.
Harvard Medical School

Dr. Dymecki will study neurons of the serotonin neuroregulatory system to better understand their behaviors, including their response to serotonin selective reuptake inhibitors (SSRIs), the most widely prescribed antidepressant medications. In addition to depression, the neurotransmitter serotonin is associated with many disorders, including sleep problems and post-traumatic stress disorder. Different behaviors may be involved with different aspects of serotonin signaling and the networks of serotonin-containing neurons in the brain, pointing to a need for much deeper knowledge and understanding of the various microsystems involved.

Dr. Dymecki is widely recognized for groundbreaking work in developmental neuroscience and brain-mapping technologies, delineating cell fate and function and the parameters of brain circuits. To conduct her new study, she will add electrophysiology to her background in bioengineering, molecular biology and genetics. Using these multiple approaches, she and her team will work to define the molecular heterogeneity of serotonin-system neurons. They will develop maps of serotonin subtypes and determine their relation to behavior. Finally, they will investigate the responses ' of varying serotonin subtypes to different medications.

The ability to characterize the processes of serotonin signaling in multiple ways and untangle serotonin actions should provide the kind of information that could lead to new approaches to the development of more specifically targeted treatments for serotonin-related disorders.

NEW TECHNOLOGIES

Luis de Lecea, Ph.D.
Stanford University School of Medicine

Dr. de Lecea will explore the possible role of nerve cells called noradrenergic A2 neurons in stress-related disorders, including anxiety, depression and post-traumatic stress disorder. Stress-related circuits in the brain include the norepinephrine systems, of which the area called locus coeruleus constitutes about 90 percent and is involved in wakefulness, arousal and attention. The other 10 percent, about which much less is known, is made up of the norepinephrine neurons A1 and A2. Until now it has been difficult to assign roles to these two different systems.

Dr. de Lecea is a leader in research into the role of neuroregulators, a particular category of neurotransmitters that influence cognition, emotion and behavior. Among his achievements, he and his colleagues have uncovered previously unknown neuroregulators involved in sleep processes. In this new investigation into A2 neurons he will make use of optogenetics, a revolutionary technology combining genetics and optics that makes it possible to control and study behavior in animal models with a precision not before possible. A previous collaboration with Karl Deisseroth, M.D., Ph.D., Brain & Behavior Research Foundation Scientific Council Member and the developer of optogenetics, led to the first millisecond-scale optogenetic manipulation of genetically identified neurons in lab mice.

Optogenetic methods that permit manipulation of neuronal activity with high specificity should make it possible to determine whether activity in A2 neurons leads to anxiety and depression. It should also provide the means to compare A2 and locus coeruleus activity.

NEXT GENERATION THERAPIES

Barbara Milrod, M.D.
Weill Cornell Medical College

Dr. Milrod, an expert in the psychotherapeutic treatment of patients with anxiety disorders, will use her NARSAD Grant to study separation anxiety, specifically as it occurs in people who do not respond to currently available anti-anxiety treatments. Separation anxiety precedes most cases of adult anxiety and is a risk factor for treatment failure for many people with anxiety disorders and depression.

There is a dearth of treatments for separation anxiety, the most frequently used being fear extinction, in which the patient is repeatedly exposed to a fear cue in the absence of the actual fearful event. Instead, Dr. Milrod will use a form of psychodynamic psychotherapy that she has been refining and for which she has received considerable recognition in the psychiatric community. Psychodynamic psychotherapy focuses on the psychological roots of emotional distress. The goal of psychodynamic psychotherapy is to develop a patient's self-awareness and understanding of the influence of past experiences on present behavior and pathology.

Dr. Milrod will conduct a trial of panic-focused psychodynamic psychotherapy as a treatment for separation anxiety for patients with depression and/or anxiety who have not responded to other forms of treatments. The objectives of this investigation will be to determine the contribution of separation anxiety to the overall burden of illness, the response to the separation-anxiety targeted treatment, and, ultimately, the neurobiological signatures of separation anxiety.

> "What an honor! I am extremely grateful to the Brain & Behavior Research Foundation for this NARSAD Grant. Personally, for me, as an investigator, this Grant will enable me to branch out from my past work into another area that can potentially provide links to current translational anxiety research.
>
> Barbara Milrod, M.D.

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New Treatments

Leading Work in Designing More Effective Medications

Bryan L. Roth, M.D., Ph.D., Brain & Behavior Research Foundation Scientific Council Member and NARSAD Grantee, is among leaders of a team that has successfully tested an automated process to develop new medications, including those with promise to be effective in treating brain and behavior disorders. The team seeks to find new compounds to 'hit' multiple specific targets in the brain ('therapeutic targets'), designated in advance, while avoiding other unintended targets that cause side effects. According to Dr. Roth, one of the compounds the team identified showed efficacy in a mouse model of attention-deficit hyperactivity disorder.
Source: Nature

Functional MRI (fMRI) Used to Predict Success of Talk Therapy

A team of researchers, including NARSAD Grantees Stefan G. Hoffman, Ph.D., and Frida E. Polli, Ph.D., set out to determine if study participants with social anxiety disorders were likely to respond to cognitive behavioral therapy (CBT). The researchers first used functional magnetic resonance imaging (fMRI) to measure the response of 39 patients to neutral faces versus angry faces and emotional scenes versus neutral scenes—and then measured again after they were treated with CBT. They found that the measured brain response to the images prior to treatment provided a substantially greater means of predicting outcomes of CBT than traditional clinical measures alone.
Source: JAMA Psychiatry

Supplement Shows Promise for Preventing Schizophrenia

NARSAD Grantees Robert Freedman, M.D., Randal G. Ross, M.D., Sherry Leonard, Ph.D., Karen E. Stevens, Ph.D., and team found that choline, an essential nutrient, may lower a physiological risk associated with schizophrenia. A 'healthy brain' will inhibit a response to a second clicking sound immediately following a first ('sensory filtering'), while response is not inhibited in patients with schizophrenia. With prenatal dietary supplements of choline in the last two trimesters of pregnancy in addition to postnatal supplements, 86% of babies having received choline had the 'healthy brain' response as opposed to only 43% of unexposed babies.
Source: The American Journal of Psychiatry (AJP)

Women's Mental Health Conference: The Art & Science of Caring

On September 14, 2012 the Brain & Behavior Research Foundation hosted a Women's Mental Health Conference: The Art & Science of Caring in New York City. The event included a panel discussion on Early Intervention, Rehabilitation and Reintegration; small group discussions with leading researchers across mental illnesses; and a final panel discussion on overcoming stigma and the future of public policy and research. The following pages contain highlights of some of the presentations. Full transcripts of the talks are available at **bbrfoundation.org/2012-WMHC**.

Recovery Interventions that Promote Productive Lives

Tiffany Herlands, Psy.D.

Tiffany Herlands, Psy.D.
Director of Rehabilitation Psychology,
Department of Psychiatry,
Columbia Presbyterian Eastside
Assistant Professor of Psychiatry,
Columbia University Medical Center

Currently available medications can often provide relief from the so-called positive symptoms of schizophrenia—psychotic delusions and hallucinations — but they do not help much with the negative symptoms—decrease in motivation, lack of attention and affect, memory loss and social withdrawal. The so-called negative symptoms are often the most pervasive and ultimately destructive symptoms of the illness. Eighty-five percent of patients with schizophrenia also have some level of cognitive impairment, in verbal learning, problem-solving and the mental flexibility necessary for negotiating unpredictable circumstances.

In Columbia University's Lieber Recovery Clinic, Dr. Herlands and colleagues use a variety of behavioral interventions to help people with schizophrenia improve their functioning in these critical areas of deficit. The interventions are intended to promote functional recovery and to provide patients with the skills to help them regain autonomy so that they believe they can live fulfilling, productive lives.

The clinic's treatments are personalized to take into account each individual patient's cognitive and social functioning, family history and living skills, and their ability to adhere to treatment and manage symptoms. A program is then customized to create the motivational context for learning, which is done through different approaches that present a variety of choices:

- Computer-based software helps to train attentiveness. Through computer games, patients learn how to pay attention in such real-life situations as navigating city streets.
- Cognitive behavioral therapy (CBT) and dialectical behavioral therapy (DBT), both forms of 'talk therapy', are used to address negative thinking and counterproductive behavior patterns.
- Patients may also be helped by a recovery coach, someone who goes out into the world with them to help them practice the skills they are learning.

Providing multiple contexts helps patients to generalize outcomes to everyday situations. For example, someone who is learning with CBT to mitigate anxiety may do fine in the clinic, but not so well when out alone in the subway. The concept of generalization refers to the ability to transfer clinical learning to everyday needs. As patients start to achieve their goals, they reduce their time at the clinic. Dr. Herlands reported that to date the clinic has had a high rate of success with almost all patients achieving, partially if not completely, the goals they have set for themselves.

Myrna M. Weissman, Ph.D.
1991, 2000 and 2005 NARSAD Distinguished Investigator Grantee
Professor of Epidemiology and Psychiatry
Columbia University College of Physicians and Surgeons

Depression in Families: Treating Mothers, Helping Children

Myrna M. Weissman, Ph.D.

Depression appears to run in families. To examine this tendency and its significance for preventing and treating depression, Dr. Weissman and her colleagues have been conducting a long-term study of parents, mostly mothers, with moderate to severe depression, and the effect of their illness on their children and grandchildren. The major finding of this 30-year investigation, now extending into the third and even fourth generations, is that offspring of depressed parents have a two- to six-fold greater risk of developing depression and anxiety disorders than the offspring of non-depressed parents.

A more recent phase of research that Dr. Weissman led is the children's portion of a study conducted at 7 sites across the country exploring the question of whether children of depressed mothers benefit from a remission of the mother's depression. Not surprisingly, when this research was initiated, it was observed that a third of the children of the families participating in the study were actively ill with a brain and behavior disorder at the time of recruitment and half had a lifetime history of mental illness.

All the mothers in the study were treated with the antidepressant citalopram (trade name Celexa®). After three months, about a third of them experienced at least a 50 percent reduction in symptoms, and when the mothers remitted, there was an 11 percent overall decrease in the children's diagnoses. Children of the mothers who did not get better had an 8 percent overall increase in illness. Of the children who were ill at the time of entry in the study, 33 percent got better if their mothers got better, but only 12 percent of those children whose mothers did not remit got better. All the children without a diagnosis at baseline remained well if their mothers got better, but 17 percent got ill if their mothers did not improve. A follow-up study using three different antidepressants yielded the same results.

While depression is generally believed to have a genetic base, the genes involved are as yet unknown. However, as Dr. Weissman's findings have helped to demonstrate, environment is critically important in triggering symptoms. The research she and her group conduct is providing clinical data for identifying the offspring of depressed parents as a particularly vulnerable population. The research also provides the encouraging information that if a family can be kept in remission, its offspring have a better chance of staying well.

Current Progress in Developing More Effective Treatments for Bipolar Disorder

Wayne Drevets, M.D.

Wayne Drevets, M.D.
Brain & Behavior Research Foundation
Scientific Council Member
1996 NARSAD Young Investigator Grantee
1999 NARSAD Independent Investigator
Grantee
Vice President
Mood Disease Area Leader,
Neuroscience Therapeutic Area
Janssen Research and Development

The goal of research by Dr. Drevets and his colleagues is to learn what current treatments for bipolar disorder actually do inside the brain, and how this information can lead to more effective treatments. He outlines some of the critical brain functions known to be impeded in bipolar disorder and explains how researchers are working to target these areas with new treatments.

Brain function is controlled by a process called neurotransmission through which nerve cells, or neurons, communicate via chemicals called neurotransmitters. The neurotransmitter glutamate, which controls glucose metabolism, is responsible for 80 percent of the brain's neurotransmission. Too much glutamate transmission and a corresponding overproduction of glucose adversely affect neuron health and are critically involved in bipolar disorder.

The neurotransmitter sent by a signaling neuron is apprehended by molecules of structures, called dendrites, on the neuron receiving the message. Glucose overproduction destroys dendrites, leading to a reduction in brain-tissue volume. Animal studies have shown that the areas affected by this abnormal neurotransmission are those associated with emotion regulation. Studies have also shown that some of the successful treatments for bipolar disorder, principally lithium, restore normal emotional function by restoring dendrite development.

Two proteins involved in dendritic restoration are brain-derived neurotrophic factor (BDNF) and Bcl-2. In bipolar disorder there is evidence of reduced BDNF, impeding the creation of new neurons. While lithium and valproic acid, another treatment for bipolar disorder, reverse this negative BDNF effect, these drugs do not restore functioning of Bcl-2. Dr. Drevets is exploring new drug developments to restore Bcl-2 function.

A significant finding of Dr. Drevets' research has been the decrease of glial cells in patients with mood disorders. Glial cells are brain cells that support the functioning of neurons—and also take up excess glutamate. Dr. Drevets and colleagues found that glial decrease leads to dendritic decrease; he and his team are currently exploring ways to reverse loss of glial function.

Another avenue being explored by Dr. Drevets and many mood disorder researchers is the rapid-acting antidepressant effect of ketamine. Ketamine can induce antidepressant effects in a few hours, as opposed to the weeks needed for conventional antidepressants to work. The downside is that ketamine's benefits last only a few days. A major line of research now underway is to discover how to prolong ketamine's beneficial effects and to reduce the occurrence of any adverse side effects.

Go to **bbrfoundation.org/2012-WMHC** to read the full transcripts of presentations made at the Women's Mental Health Conference.

Glossary

Helpful definitions of terms used in this issue

Bcl-2 (p. 27): A regulatory brain protein involved in the process of programmed cell death, or apoptosis.

brain-derived neurotrophic factor (BDNF) (p. 4, 20, 21, 27): A brain protein important in the growth, function and survival of nerve cells.

c-AMP (p. 10): Cyclic adenosine monophosphate relays signals from receptors on the cell surface to target molecules inside the cell. c-AMP affects the function of higher-order thinking in the brain's prefrontal cortex via its regulation of the ion channels that allow charged atoms to enter and exit nerve cells.

cortisol (also known as hydrocortisone) (p. 8, 16): A type of steroid hormone called a glucocorticoid, produced by the adrenal gland and released in response to stress; raises blood sugar levels and suppresses the immune system.

D1 dopamine receptor (p. 10): One of five known variants of the 'keyhole' cell-surface protein into which molecules of the neurotransmitter dopamine fit.

fcMRI (p. 8): Functional connectivity magnetic resonance imaging; A variant of magnetic resonance imaging which enables researchers to make key measurements of activity and function in the resting brain.

glutamate (p. 4, 5, 27): The most abundant excitatory neurotransmitter in the nervous system; it controls glucose metabolism.

HPA (hypothalamic-pituitary-adrenal) axis (p. 12): A key portion of the body's hormonal system, in which interactions among the hypothalamus, the pituitary and the adrenal glands participate in the reaction to stress and regulate various processes including digestion, the immune system, mood and emotion, as well as energy storage and expenditure.

locus coeruleus (p. 23): A small area in the forebrain involved in the release of noradrenaline in the response to stress and important in attention, emotion, motivation, decision making, learning and memory.

neuroregulators (p. 23): Chemicals that modulate the activity of neurons.

neurotransmission (p. 27): A chain of events through which nerve cells, or neurons, exchange information in the brain. Signaling cells release a chemical neurotransmitter across the synapse, the gap between neurons, which is caught by the receiving cells.

NMDA receptors (p. 5, 21): N-Methyl-D-aspartate receptors; a class of keyhole-like features on the surface of nerve cells in the brain, into which molecules of the excitatory neurotransmitter glutamate fit in "key-like" fashion.

noradrenergic A2 neurons (p. 23): Nerve cells of the brain associated with the neurotransmitter norepinephrine and believed to be involved in stress-related responses.

norepinephrine (p. 23): A chemical that plays roles as both a stress-related hormone and a neurotransmitter.

optogenetics (p. 9, 23): A technology using light to switch 'on' and 'off' individual neurons in the brain, and making possible a new generation of experiments aimed at identifying specific circuits involved in brain and behavior disorders. Karl Deisseroth, M.D., Ph.D., of Stanford University invented the new technology with the support of a NARSAD Young Investigator Grant in 2005.

prefrontal cortex (p. 3, 7, 8, 10, 21): The region in the brain responsible for higher cognitive functioning, such as the ability to differentiate among conflicting thoughts.

VTA (p. 9): ventral tegmental area, a section of the midbrain involved in cognition and motivation.

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Moderated by:
Jeffrey Borenstein, M.D.
Acting President & CEO
Brain & Behavior Research Foundation

Tuesday, February 12
2:00 p.m. — 3:00 p.m. EST
"Depression in Families"
Myrna Weissman, Ph.D.
NARSAD Distinguished Investigator Grantee
Professor, Departments of Epidemiology and Psychiatry
Columbia University College of Physicians and Surgeons

Tuesday, March 12
2:00 p.m. — 3:00 p.m. EST
"Research Discoveries in Schizophrenia"
Daniel R. Weinberger, M.D.
Brain & Behavior Research Foundation
Scientific Council Member
Director and CEO
Lieber Institute for Brain Development

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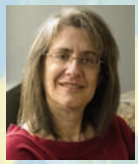

Elyn R. Saks, Esq., Ph.D.
Best-selling author of *The Center Cannot Hold: My Journey through Madness,* Professor of Law

Moderator:

Jeffrey Borenstein, M.D.
Acting President & CEO
Brain & Behavior Research Foundation

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9:00 a.m. — 2:00 p.m.
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