Brain & Behavior Research Foundation

Quarterly

September 2015

2015 KLERMAN & FREEDMAN PRIZES

ALAN ANTICEVIC, PH.D.

CHADI G. ABDALLAH, M.D.

CARRIE J. MCADAMS, M.D., PH.D.

MICHAEL M. HALASSA, M.D., PH.D.

KRISTEN J. BRENNAND, PH.D.

NANDAKUMAR NARAYANAN, M.D., PH.D.

Understanding Addiction with **ERIC NESTLER, M.D., PH.D.**

Women Breaking the Silence About Mental Illness

Parenting Children with Anxiety Disorders with **DANIEL S. PINE, M.D.**

Scientific Council

150 Members

- **2** Nobel Prize Winners
- **4** Former Directors of the National Institute of Mental Health
- **4** Recipients of the National Medal of Science
- **13** Members of the National Academy of Sciences
- **21** Chairs of Psychiatry & Neuroscience Departments at Leading Medical Institutions
- **47** Members of the Institute of Medicine

PRESIDENT
Herbert Pardes, M.D.

VICE PRESIDENT EMERITUS
Floyd E. Bloom, M.D.

Anissa Abi-Dargham, M.D.
George K. Aghajanian, M.D.
Schahram Akbarian, M.D., Ph.D.
Huda Akil, Ph.D.
Susan G. Amara, Ph.D.
Stewart A. Anderson, M.D.
Nancy C. Andreasen, M.D., Ph.D.
Amy F.T. Arnsten, Ph.D.
Gary S. Aston-Jones, Ph.D.
Jay M. Baraban, M.D., Ph.D.
Jack D. Barchas, M.D.
Samuel H. Barondes, M.D.
Francine M. Benes, M.D., Ph.D.
Karen F. Berman, M.D.
Wade H. Berrettini, M.D., Ph.D.
Randy D. Blakely, Ph.D.
Pierre Blier, M.D., Ph.D.
Robert W. Buchanan, M.D.
Peter F. Buckley, M.D.
William E. Bunney, Jr., M.D.
Joseph D. Buxbaum, Ph.D.
William Byerley, M.D.
Marc G. Caron, Ph.D.
William T. Carpenter, Jr., M.D.
Cameron S. Carter, M.D.
BJ Casey, Ph.D.
Dennis S. Charney, M.D.
Bruce M. Cohen, M.D., Ph.D.
Jonathan D. Cohen, M.D., Ph.D.
Peter Jeffrey Conn, Ph.D.
Richard Coppola, D.Sc.
Joseph T. Coyle, M.D.
Jacqueline N. Crawley, Ph.D.
John G. Csernansky, M.D.
Karl Deisseroth, M.D., Ph.D.
J. Raymond DePaulo, Jr., M.D.
Ariel Y. Deutch, Ph.D.
Wayne C. Drevets, M.D.
Ronald S. Duman, Ph.D.
Jan A. Fawcett, M.D.
Stan B. Floresco, Ph.D.
Judith M. Ford, Ph.D.
Alan Frazer, Ph.D.
Robert R. Freedman, M.D.
Fred H. Gage, Ph.D.
Aurelio Galli, Ph.D.
Mark S. George, M.D.
Elliot S. Gershon, M.D.
Mark A. Geyer, Ph.D.
Jay N. Giedd, M.D.
Jay A. Gingrich, M.D., Ph.D.
David Goldman, M.D.
Frederick K. Goodwin, M.D.
Joshua A. Gordon, M.D., Ph.D.
Elizabeth Gould, Ph.D.
Anthony A. Grace, Ph.D.
Paul Greengard, Ph.D.
Suzanne N. Haber, Ph.D.
Philip D. Harvey, Ph.D.
Stephan Heckers, M.D.
Nathaniel Heintz, Ph.D.
René Hen, Ph.D.
Fritz A. Henn, M.D., Ph.D.
Robert M.A. Hirschfeld, M.D.
L. Elliot Hong, M.D.
Steven E. Hyman, M.D.
Robert B. Innis, M.D., Ph.D.
Jonathan A. Javitch, M.D., Ph.D.
Daniel C. Javitt, M.D., Ph.D.
Lewis L. Judd, M.D.
Peter W. Kalivas, Ph.D.
Eric R. Kandel, M.D.
Richard S.E. Keefe, Ph.D.
Samuel J. Keith, M.D.
Martin B. Keller, M.D.
John R. Kelsoe, M.D.
Kenneth S. Kendler, M.D.
James L. Kennedy, M.D.
Robert M. Kessler, M.D.
Kenneth K. Kidd, Ph.D.
Mary-Claire King, Ph.D.
Rachel G. Klein, Ph.D.
John H. Krystal, M.D.
James F. Leckman, M.D.
Francis S. Lee, M.D., Ph.D.
Ellen Leibenluft, M.D.
Robert H. Lenox, M.D.
Pat Levitt, Ph.D.
David A. Lewis, M.D.
Jeffrey A. Lieberman, M.D.
Irwin Lucki, Ph.D.
Robert C. Malenka, M.D., Ph.D.
Anil K. Malhotra, M.D.
Husseini K. Manji, M.D., FRCPC
J. John Mann, M.D.
John S. March, M.D., M.P.H.
Helen S. Mayberg, M.D.
Robert W. McCarley, M.D.
Bruce S. McEwen, Ph.D.
Ronald D.G. McKay, Ph.D.
James H. Meador-Woodruff, M.D.
Herbert Y. Meltzer, M.D.
Richard J. Miller, Ph.D.
Karoly Mirnics, M.D., Ph.D.
Bita Moghaddam, Ph.D.
Dennis L. Murphy, M.D.
Charles B. Nemeroff, M.D., Ph.D.
Eric J. Nestler, M.D., Ph.D.
Andrew A. Nierenberg, M.D.
Patricio O'Donnell, M.D., Ph.D.
Steven M. Paul, M.D.
Godfrey D. Pearlson, MBBS, M.D.
Daniel S. Pine, M.D.
Robert M. Post, M.D.
James B. Potash, M.D., M.P.H.
Steven G. Potkin, M.D.
Pasko Rakic, M.D., Ph.D.
Judith L. Rapoport, M.D.
Perry F. Renshaw, M.D., Ph.D., M.B.A.
Kerry J. Ressler, M.D., Ph.D.
Carolyn B. Robinowitz, M.D.
Bryan L. Roth, M.D., Ph.D.
John L.R. Rubenstein, M.D., Ph.D.
Bernardo Sabatini, M.D., Ph.D.
Akira Sawa, M.D., Ph.D.
Alan F. Schatzberg, M.D.
Nina R. Schooler, Ph.D.
Robert Schwarcz, Ph.D.
Philip Seeman, M.D., Ph.D.
Yvette I. Sheline, M.D.
Pamela Sklar, M.D., Ph.D.
Solomon H. Snyder, M.D., D.Sc., D.Phil. (Hon. Causa)
Murray Stein, M.D., M.P.H.
John S. Strauss, M.D.
J. David Sweatt, Ph.D.
John A. Talbott, M.D.
Carol A. Tamminga, M.D.
Laurence H. Tecott, M.D., Ph.D.
Ming T. Tsuang, M.D., Ph.D., D.Sc.
Leslie G. Ungerleider, Ph.D.
Rita J. Valentino, Ph.D.
Jim van Os, M.D., Ph.D., MRCPsych
Nora D. Volkow, M.D.
Mark von Zastrow, M.D., Ph.D.
Karen Dineen Wagner, M.D., Ph.D.
Daniel R. Weinberger, M.D.
Myrna M. Weissman, Ph.D.
Jon-Kar Zubieta, M.D., Ph.D.

Board of Directors

PUBLICATION CREDITS

Writers
Elena Gooray
Becky Ham
Jennifer Michalowski
Peter Tarr, Ph.D.

Editors
Lauren Duran
Randi Londer Gould

Design
Kim Howie

Contents

Cover Credit: Images courtesy of Chad Kraus, Eric Nestler, M.D., Ph.D., Daniel S. Pine, M.D., and the 2015 Klerman & Freedman Prizewinners.

PRESIDENT'S LETTER

Jeffrey Borenstein, M.D.

President & CEO
Brain & Behavior Research Foundation

Every one of us knows someone—a family member, friend, or other loved one—who has a psychiatric illness, chemical dependency, or both. In fact, mental illness and addiction often go hand in hand in what is referred to as a dual diagnosis. For example, compared with the general population, people addicted to drugs are roughly twice as likely to suffer from mood and anxiety disorders, with the reverse also being true. Approximately 50 percent of people diagnosed with severe mental illness are affected by substance abuse. Studies indicate that more than one-third of individuals with alcoholism and more than half of individuals with other drug addictions have at least one serious mental illness. A common question I am often asked is, "why do these disorders often co-occur?"

According to the National Institute on Drug Abuse, addiction is considered a mental illness because "addiction changes the brain in fundamental ways, disturbing a person's normal hierarchy of needs and desires and substituting new priorities connected with procuring and using the drug. The resulting compulsive behaviors that override the ability to control impulses despite the consequences are similar to hallmarks of other mental illnesses." While drug use disorders often occur with other mental illnesses, this does not mean that one caused the other, even if one appeared first. In fact, establishing which came first or why can often be difficult. According to the National Institutes of Health, research suggests the following possibilities for this common co-occurrence:

- *Drug abuse may bring about symptoms of another mental illness*. For example we now know that there is an increased risk of psychosis in vulnerable marijuana users which suggests this possibility.
- *Mental disorders can lead to drug abuse*, possibly as a means of "self-medication." People living with anxiety or depression may rely on alcohol, tobacco, and other drugs to temporarily alleviate their symptoms. These disorders may also be caused by shared risk factors, such as:
- *Overlapping genetic vulnerabilities*. Predisposing genetic factors may make a person susceptible to both addiction and other mental disorders or to having a greater risk of a second disorder once the first appears.
- *Overlapping environmental triggers*. Stress, trauma and early exposure to drugs are common environmental factors that can lead to addiction and other mental illnesses.
- *Involvement of similar brain regions*. Brain systems that respond to reward and stress, for example, are affected by drugs of abuse and may show abnormalities in patients with certain mental disorders.
- Drug use disorders and other mental illnesses are developmental disorders. That means they often begin in the teen years or even younger—periods when the brain experiences dramatic developmental changes. Early exposure to drugs of abuse may change the brain in ways that increase the risk for mental disorders. Also, early symptoms of a mental disorder may indicate an increased risk for later drug use.

Addiction and mental illness certainly have much in common. The most striking similarity however is the stigma associated with the illnesses. It is this very stigma that often prevents people from seeking and receiving help.

Research funding for all mental illness, including addiction is imperative. It is only through support for research that we can alleviate the pain and suffering mental illness can cause families, and find the advances and breakthroughs that will result in better treatments and hope for cures.

Sincerely,

Jeffrey Borenstein, M.D.
President & CEO

Gene Expression Analysis Points Toward Pathways Involved in Major Depression

Patrick Sullivan, M.D., 2014 Lieber Prize for Outstanding Achievement in Schizophrenia Research, 2010 DI

Dorret I. Boomsma, Ph.D., 2011 DI

Researchers have identified more than 100 genes whose activity differs significantly between people with major depressive disorder and people who have never experienced major depression. The differences, which could stem from inherited genetic factors or from environmental influences, help point scientists toward biological pathways likely to be involved in the disorder.

While there is good evidence that a person's genetics influence his or her likelihood of developing major depression, scientists have only just begun to uncover specific genetic variations that may increase risk. In a new study, published May 26th in the journal Molecular Psychiatry, scientists led by Patrick F. Sullivan, M.D., at the University of North Carolina School of Medicine honed in on relevant genes by measuring and comparing gene activity in the cells of more than 1,800 individuals. To date, this is the largest analysis of gene expression in people with major depression.

Dr. Sullivan is a 2010 NARSAD Distinguished Investigator and was the 2014 Lieber Prizewinner for Outstanding Achievement in Schizophrenia Research. Dorret I. Boomsma, Ph.D., a 2011 NARSAD Distinguished Investigator at the VU University Amsterdam, also took part in the research. The team's gene expression analysis is a complementary approach to genome-wide association studies (GWAS) being conducted by the Psychiatric Genomics Consortium that Dr. Sullivan co-leads. GWAS examine many common genetic variants in different people to find out whether any variant is linked with a trait. Dr. Sullivan has estimated that finding a genetic "signal" in a GWAS study of depression may require a sample size of 100,000 people, a goal that has not yet been reached.

Using blood samples collected as part of the Netherlands Study of Depression and Anxiety, Dr. Sullivan and his colleagues measured gene expression in the cells of 882 people with depression, 635 people who were not experiencing major depression at the time of the study but had in the past, as well as a control group of 331 people who reported no current or past depression.

They found 119 genes whose activity differed between the control group and people with current depression. Many of these, they found, were genes that affect immune function. This was consistent with other lines of research that have suggested a link between the immune system and mood disorders.

Changes seen in current depression patients were small but statistically significant. In contrast, gene expression patterns in people who been depressed in the past were not significantly different from—people in the study who never had depression.

Two years after their initial analysis, Dr. Sullivan and colleagues collected additional data from a subset of the people in their study. This enabled them to compare gene activity between those who had recovered from their depression and those whose depression had continued. Of the 119 depression-associated genes they had already identified, they found 19 genes whose activity also correlated with changes in depression—in these 19 genes, expression was more likely to have returned to normal among those who had recovered from their depression. ■

TAKEAWAY: In the largest study of its kind, researchers have found specific genetic variations that may increase risk for depression.

Stress-Induced DNA Changes May Be Biomarkers of Major Depression in Women



Gerome Breen, Ph.D., 2007 YI
Kenneth S. Kendler, M.D., 2000, 2010 DI and SC Member
Jonathan Flint, M.D., MRCPsych, 2007 DI

Women with major depression have physical alterations to their DNA that could be caused by stress, new research shows. In a study examining the genomes of more than 11,000 women, scientists have discovered two molecular signatures linked with major depression: a higher than usual amount of mitochondrial DNA (the subset of DNA that is contained in cells' tiny energy factories) and shorter-than-expected telomeres (protective structures that cap the ends of chromosomes). In experiments with mice, the researchers showed that such changes can result from stress.

The research is notable in part because of the urgency in finding biological markers of depression. The new study was conducted by a large international team led by 2007 NARSAD Distinguished Investigator Jonathan Flint, M.D., of the Wellcome Trust Centre for Human Genetics in the U.K. Among Dr. Flint's colleagues on the study are two-time (2000, 2010) Distinguished Investigator and Scientific Council member Kenneth Kendler, M.D., of Virginia Commonwealth University; and 2007 Young Investigator grantee Gerome Breen, Ph.D. Their report appeared May 4th in *Current Biology*.

The study provides clues that could help scientists understand the link between stress and major depression. It also suggests potential tools to help doctors better diagnose and monitor the disease.

As Dr. Flint and his colleagues analyzed the DNA of 5,864 women with recurrent major depression and 5,783 women without depression, they noticed that women with a history of depression had more mitochondrial DNA than the others. The telomere end-caps on their chromosomes were shortest in this group, as well. The DNA of women who had not experienced major depression did not share these features, even if those women had experienced childhood sexual abuse or other stressful life events.

According to the researchers, changes in the amount of mitochondrial DNA likely reflect changes to the function of mitochondria, which might be caused by metabolic changes in response to stress. Telomeres naturally shorten as we age, but some studies have found this process is accelerated in people with high levels of stress or anxiety.

The team designed laboratory experiments to test whether stressful conditions could trigger the kinds of molecular changes they had observed in the DNA of women with depression. Mice that experienced four weeks of stress did indeed develop shortened telomeres and greater amounts of mitochondrial DNA. However, normal telomere length and amounts of mitochondrial DNA amounts were restored after stressful conditions were eliminated.

There's no evidence that the molecular changes the team has uncovered actually cause depression, the scientists say. But these changes do represent a molecular signature of the illness that could help doctors diagnose the illness and monitor the effectiveness of its treatment. ■

TAKEAWAY: Molecular signatures of stress-caused changes to DNA found in women with major depression could help improve diagnosis and treatment of the illness.

Marker in Blood Has the Potential to Predict Who Will Benefit from a Treatment for Alcohol Dependence

Hyung Wook Nam, 2013 YI
Mark Andrew Frye, 2006 II

For people struggling to overcome an alcohol use disorder, there are a handful of medications that may help. One of these is acamprosate (sold as Campral), which seems to reduce cravings by modifying signaling in the brain. But the drug doesn't work for everybody, and while the U. S. Food and Drug Administration approved its use for treating alcohol dependence in 2004, it has not been widely prescribed.

Acamprosate might be used more often if health professionals could predict which patients would benefit from treatment. Encouragingly, new research reported August 18th in the journal *Translational Psychiatry* suggests the prospect of identifying those people who are likely to respond to acamprosate with a simple blood test.

Researchers found that alcohol-dependent people who had higher levels of glutamate in their blood were more likely to abstain from drinking during 12 weeks of acamprosate treatment than those with lower glutamate levels. The team of scientists was led by Doo-Sup Choi, Ph.D., at the Mayo Clinic College of Medicine and included 2013 NARSAD Young Investigator Hyung Wook Nam, Ph.D., as well as 2006 NARSAD Independent Investigator Mark Andrew Frye, M.D.

Glutamate is involved in many metabolic processes in the body, and acts as the main excitatory neurotransmitter in the brain. Alcohol dependence is triggered partly by an imbalance in excitatory and inhibitory signaling in the brain. Acamprosate is thought to help restore balance by acting on excitatory signaling pathways that use glutamate as a neurotransmitter.

In their study, the researchers collected blood samples from 120 alcohol-dependent people before they had 12 weeks of treatment with acamprosate. A second blood sample was collected at the end of the 12 weeks. Seventy-one of the participants (59 percent) abstained from alcohol throughout the treatment period. Those who consumed any alcohol during the period were considered "non-responders."

The researchers performed tests to identify potential biomarkers that might gauge the effectiveness of acamprosate. They measured the levels of 36 substances in the blood called amino acid metabolites, comparing responders and non-responders. During the 12 weeks before treatment, glutamate was present in higher levels among responders than non-responders. As the treatment progressed, glutamate levels dropped in responders, although not in non-responders. ■

TAKEAWAY: Researcher have discovered that a simple test of glutamate levels in the blood has the potential to predict who will respond to treatment with acamprosate (Campral) for alcohol dependence.

A Scientific Discovery **Revolutionizes** Our View of Addiction

Few scientists, even famous ones, can pinpoint a day that changed not only their own life, but the entire direction of research in their field. One such scientist is Foundation Scientific Council member Nora Volkow, M.D. About 25 years ago, at her lab at Brookhaven National Laboratory on Long Island, she realized while examining images of people's brains that she was able to determine if a person was addicted to a drug.

Nora Volkow, M.D.

Director, National Institute on Drug Abuse

"The reason I could tell," explains Dr. Volkow, a psychiatrist who today is the Director of the National Institute on Drug Abuse, "was because I could see that in addicts, the frontal areas of the brain were impaired. They had increased activity in this area if they were studied while craving the drug, and markedly decreased activity when studied during withdrawal, but not experiencing drug craving."

This scientific surprise reverberated in medicine and society. As Dr. Volkow remembers, "no one at that time thought the frontal cortex was important in addiction—nobody!" At the time, leading theories linked the compulsion to take drugs with "the limbic brain"—structures outside the cortex usually associated with our "primitive urges." The frontal cortex is considered the home of higher-order processes such as thought, language, and executive decision-making.

The discovery about frontal cortical dysfunction in people with addictions was a crucial step in transforming how society views addiction. Rather than look at addicts as moral failures or weak-willed pleasure-seekers, informed people began to understand that they were people with an illness, a biological dysfunction that interfered with their ability to exert self-control.

"No one at that time thought the frontal cortex was important in addiction—nobody!"

Dr. Volkow, who was born in Mexico to the grandson of exiled Russian revolutionary Leon Trotsky, is therefore herself associated with a revolution. Perhaps more than anyone else, she is responsible for assembling the scientific evidence and, more recently as a government leader, in spreading the word about addiction as a brain disease. Although stigma persists, scientific knowledge is reducing it and making it possible to treat addiction more effectively than ever before.

The discovery of addiction's biological underpinnings is a superb example of the power of basic research (like that supported in many of the Foundation's NARSAD grants), to bring about major change in ways that can't be foreseen. At first, Dr. Volkow had been using PET scanning to look at limbic areas of the brain. The evidence of the scans focused her attention on the frontal cortex. "I always teach my students that you have to have the openness of mind to recognize the data the way it *is*, and to be prepared to admit it is not saying what you were initially expecting to find," she says.

To date, Dr. Volkow's research has been published in more than 600 scientific papers. It has taught us not only about the addicted brain, but also about how the healthy brain regulates itself. Her findings about addiction focused attention on the role of the chemical messenger dopamine, levels of which increase in the brain whenever we experience a reward. Dr. Volkow begins one paper with the simple statement: "Drugs of abuse (including alcohol) are inherently rewarding, which is why they are consumed." That is, such substances activate our built-in brain reward system.

It has become clear that all kinds of addictive substances, from alcohol to cocaine to methamphetamine to marijuana to nicotine, cause surges in dopamine in various brain areas. (In fact, an overlapping mechanism has been noted in morbidly obese people, who get their "high" from food.) But addiction has proven much more complicated than dopamine, and is now known to involve other neurotransmitters and other brain circuits as well.

Close observation by Dr. Volkow and others has shown that ingestion of an addictive drug—for example, cocaine—does not itself drive addictive behavior. Instead, cues associated with drug taking—whether place, time of day, simultaneous ingestion of another stimulant, etc.—are what cause dopamine to spike in addicts' brains. This makes the addict crave the next high. Surprisingly, then, it is the *anticipation* of the reward and not the drug itself, that, through behavioral conditioning, fuels the addict's irrational behavior.

How far will a person go to obtain a given reward? Only a fraction of people who try an addictive substance once become addicted—about one-third of those who try tobacco, 15 percent of those who try alcohol, and nine percent of those who try marijuana. By addiction, Dr. Volkow means people who "shift from controlled use to compulsive use, with loss of control over intake despite adverse consequences."

Who are these people? Can we identify them in advance? Recent research has shown that about 50 percent of addiction risk is genetic. "Some people are much more susceptible than others," Dr. Volkow says. "We don't know much, yet, about how to modify genetic risk, but we do know that if you have a genetic vulnerability, we can provide an environment that can strengthen you against it. This is where the big challenge is today: taking advantage of what we have learned, for example, to strengthen circuits in the brain that are involved in exerting self-control."

Worrisome Trends in Drug Use, But Optimism About New Treatments

As the leader of a government agency focusing on addiction, Dr. Nora Volkow constantly monitors the latest trends in how Americans are using and abusing addictive substances. She has written extensively on the danger of legalizing marijuana—in part because science shows that nine percent of all who ever try marijuana will become addicted. This figure rises to 17 percent if first use is during teen years. And like nicotine, marijuana has been shown to be a "gateway drug" in susceptible people. There is some evidence that when smoked in large quantities by young people at risk for psychosis and schizophrenia, marijuana can actually raise their risk and in some cases may trigger an early psychotic break. Although more research is needed, Dr. Volkow notes that one thing is certain: two addictive substances that are legal—nicotine and alcohol—already "cost us so much in terms of sickness and mortality" that there is reason to worry about legalizing yet another addictive substance.

Dr. Volkow is also very worried about addiction to opioids—painkillers that are overprescribed, and drugs like heroin, which in recent years has been making an unwelcome comeback. And she casts a wary eye on the phenomenon of e-cigarettes, in part because the delivery device can be adapted to provide not only nicotine in dangerously high concentrations, but other drugs as well—notably, THC, the active ingredient in marijuana.

"Marijuana with 12 to 20 percent THC is common nowadays, much stronger than in the past; but in e-cigarette cartridges, we have now seen concentrations greater than 90 percent," she says.

However, as a scientist and medical doctor, Dr. Volkow sees the other side of the coin. "I am actually optimistic," she says, "because we now recognize that poor executive function is a reason for drug taking, as it is for obesity, in certain instances. The fact is, executive function and self-control are malleable. There is a whole group of scientists developing strategies that use behavioral interventions, sometimes taking advantage of new tools like the web and social media. They are developing technologies to re-train the brain. We are also close to discovering reliable biomarkers to probe the function of circuits in the frontal cortex. Using these in combination with brain training technologies and software makes it possible for people to train themselves to improve their executive function."

Dr. Volkow also is encouraged by progress in developing medications designed to block craving. Another treatment approach (which can also help trauma victims) is to find ways of erasing memories that generate cravings.

In summary, Dr. Volkow noted that "right now three therapeutic approaches are not only feasible, but in practice and need to be brought to more people who can benefit from them: strengthening executive function to achieve better self-control; improving mood and decreasing sensitivity to stressful stimuli that often cause people to relapse; and providing alternative reinforcers—things a person enjoys doing that replace activities which used to provide the cues bound up with compulsive drug-taking. This protects against withdrawal symptoms and lessens the chance of relapsing into drug taking. ■

Have A Question?

Send questions for Nora Volkow, M.D. to **asktheresearcher@bbrfoundation.org.**

Select questions and answers will be in the next issue of the *Quarterly*.

ASK THE RESEARCHER

Myrna Weissman, Ph.D.

Diane Goldman Kemper Family Professor
of Epidemiology in Psychiatry
College of Physicians and Surgeons and
Mailman School of Public Health, Columbia University
Chief, Division of Epidemiology, New York State
Psychiatric Institute

Why does the incidence of depression go up after puberty? Is it because of hormones?

There are good population-based data showing that the onset of depression increases in women around periods of hormonal change. This would be during puberty, pregnancy, postpartum (after giving birth), and perimenopause (the period around menopause). The possible reasons for this are being studied by neuroscientists. Understanding the mechanisms behind the increase in the incidence of depression may lead to new treatments. For example, a group at the National Institute of Mental Health led by David Rubinow, M.D., is studying the effects of withdrawing estradiol (the main circulating estrogen) on mood in perimenopausal women. This is a large and interesting topic worthy of study in and of itself.

There is a history of depression in my family. But how do I know whether my teenage daughter is just moody (like lot of girls her age) or whether she's actually depressed?

Here we need to differentiate between population science and individual care. On a population level it is clear that teenage girls have high rates of transient (short-term) mood changes. Whether an individual girl has crossed the boundary between normal behavior and depressed behavior requires a personal evaluation with a clinician who is an expert in adolescent mental health. A family history of depression should make that consultation more urgent, whether or not the young woman's symptoms have impaired her schoolwork, friendships, and/or family relationships. If she is not willing to go with you to see someone, seek advice about her behavior yourself with someone who can evaluate the seriousness of her symptoms.

I've dealt with depression all my life and I'm worried that my young children may be affected. Is there a test they can take to find out whether they're at risk?

I know of no tests that are better than a good clinical evaluation. While the odds are increased that your children may have depression if there is a family history, many family members often do not develop this mental illness. Scientists are looking for biomarkers in their extensive ongoing research using diagnostic tools like MRI, EEG, and genetic studies.

How can I explain my depression to my third-grader? I don't want to hurt his chances of having good mental health if he knows I'm struggling.

The evidence is quite strong that if you can keep yourself in remission, which may require continual available treatment, your children are less affected; again, this is the case when we look at populations as a whole. On an individual level you might explain that you understand that he/she sees you looking sad but you are taking care of this problem. You might say, "it's a grownup problem called depression and Mommy is getting help for it." If you are still concerned, consider having a consultation with a clinical expert who specializes in working with children. A therapist can talk with you about the things that worry you and suggest ways you can engage your child in a discussion. ■

Answers are based on research in populations and not intended as advice to specific individuals.

FEATURE

On a Quest to Understand and Alter Abnormally Expressed Genes That Promote Addiction

Eric Nestler, M.D., Ph.D.

Professor and Director of the Friedman Brain Institute at the Icahn School of Medicine of Mount Sinai Hospital

What happens when an addictive drug enters your system, as you swallow it, smoke it, or shoot it into your veins? What happens when you are compelled to take that drug repeatedly, to the point where getting the next dose becomes a central preoccupation?

These are very different but related questions; together they describe the concerns that have driven more than 30 years of research by 1996 NARSAD Distinguished Investigator and long-time Foundation Scientific Council member Eric Nestler, M.D., Ph.D., Nash Family Professor and Director of the Friedman Brain Institute at the Icahn School of Medicine of Mount Sinai Hospital.

Within 10 years of the founding of his first lab in 1987, Dr. Nestler and a colleague had published a paper in *Science* that would energize the field of addiction studies. Titled "Molecular and Cellular Basis of Addiction," it reflected the growing ability of neuroscience to explore the biological underpinnings of outward behaviors. Doctors had been observing addicted people for many years. But the question remained: What happened at the level of the cells and circuits of the brain and nervous system in such people to make them "high," and also addicted—dependent on obtaining the next dose.

When any drug—alcohol, nicotine, marijuana, cocaine, methamphetamine, heroin—is ingested, it disturbs naturally occurring activity at synapses, the tiny spaces between neurons where messages are relayed from one cell to the next. Different types of drugs affect different kinds of neuronal receptors and neurotransmitters. Eons before the first person smoked tobacco or became addicted to pain pills, the brain of mammals already had naturally occurring nicotinic and opioid receptors.

What's interesting about addiction is what happens, not just at these receptors, but "downstream," inside and among neurons, as drugs unnaturally occupy these docking ports and can induce changes to entire circuits in the brain.

In other words, the brain of the addicted person molds itself in response to a new and powerful environmental factor, the regular taking of addictive drugs. It's an adaptation, but more precisely, it's a "maladaptation," as the brain's marvelous natural plasticity is harnessed to an unhealthy purpose. That's one of the things that makes addiction so vexing.

In 1998, Dr. Nestler and colleagues made a notable finding. They conducted experiments in mice addicted to cocaine. "We discovered that by manipulating the reward pathway in these mice, we were not only able to prevent the rewarding effects of cocaine, but surprisingly, we could push these animals to a point where they were anhedonic—unable to experience pleasure." This frequent symptom of depression alerted Dr. Nester to the importance of the brain's reward system in both addiction and depression.

The ways in which addictive drugs engage the reward centers and circuits of the brain have been charted by leaders in the field including Dr. Nora Volkow [see *Interview with a Researcher,* pages 6–8]. Dr. Nestler has pioneered exploration of the ways in which drug activation of reward circuits alters gene activity, inside the nucleus of individual brain cells. It's complicated, but the idea behind this research is not. "Ultimately, the ability of environmental stimuli to influence an organism requires changes in gene expression," he says.

Dr. Nestler's 1998 revelation—that there is a continuum in rewards from drug-induced ecstasy to depression-like inability to feel any pleasure—calls attention to what chronic stress and chronic drug-taking have in common. "The ability of chronic stress, on the one hand, or a drug of abuse on the other, to produce long-lasting changes in behavior requires changes in gene expression in specific brain regions," he says. "Certain genes are expressed more, others less."

But which genes? What are the mechanisms that control their expression? And how can we intervene to reduce or reverse the changes? This, in brief, has occupied Dr. Nestler's lab for the past 15 years. "To mediate the constant interplay between our genes and stimuli from the environment in which we live, including stress and drugs, there are mechanisms we call epigenetic," he explains. These are a variety of naturally occurring molecular processes that evolution has devised to change the way genes are expressed. Rather than change the DNA sequence of the gene, epigenetic mechanisms change the cell's ability to physically access the gene and switch it on or off, or increase or lower its activity.

Numerous papers from Dr. Nestler's lab have described in intricate detail how different epigenetic mechanisms are involved when a person is addicted. One way to sum up the cumulative wisdom from this body of work is to say that when the brain re-molds itself to accommodate the regular taking of, say, cocaine—an abnormal input from the environment—the cell can respond in various ways, most of them maladaptive. Consider the epigenetic mechanisms called methylation and acetylation. Inside the cell nucleus, at the DNA sequence of a gene involved in, say, the reward response, a cell might add or subtract chemical "tags" consisting of methyl or acetyl molecules. These chemical tags actually enable or prevent the cell's gene-activating machines from accessing such genes. Alternatively, these tags can attach to bundles of tightly coiled DNA called chromatin, changing the bundle's shape and in that way altering gene activity.

Yet another way addictive drugs (and chronic stress) change the way genes are expressed is by altering the activity of proteins called transcription factors (TFs). When a TF such as ΔFosB is blocked or degraded inside the cell nucleus, it cannot attach to DNA to initiate the expression of a given gene.

Hundreds of factors can alter gene activity in response to drugs. At least in principle, many of them are reversible. Recent work in the Nestler lab has provided vivid examples of how, by targeting epigenetic mechanisms known to change in addiction, it may be possible to weaken or abolish the grip of both craving and withdrawal. There are, for example, specialized enzymes called methyltransferases and acetyltransferases that carry methyl and acetyl "tags" to DNA and chromatin, causing gene activity to change. Another set of enzymes removes these chemical tags. Future pharmaceutical treatments might involve inhibitors or promoters of these epigenetic modifiers of gene activity, applied selectively in parts of the brain where addiction circuits converge.

There is a powerful rationale to continue vigorous basic research on such potential treatments, not only to help people who are addicted, but their children as well. We now know that certain harmful epigenetic changes may be inherited across generations. Research can help find a way to prevent the children of people who are addicted from being "primed" for addiction— from the moment of their birth, or even before birth, while still in the womb of their mother. ■

FEATURE

Women Breaking the Silence About Mental Illness

A Luncheon Discussion Focuses on the Importance of Removing the Stigma From Mental Illness

ABOVE: *Back Row:* Haley Barrows, Carole Mallement, Harvey Mallement, Margaret Flanagan, Ellen Levine, Dr. Richard Levine, Melinda Fager, *Front Row:* John Golden, Suzanne Golden, Caroline Hirsch, Lee Woodruff

ABOVE: Ellen Levine, Lee Woodruff

Photography courtesy of Chad Kraus

ABOVE: Faith Rothblatt, Lillian Clagett, Renée Steinberg, Jeffrey Borenstein, M.D., Carole Mallement, Suzanne Golden, Jill Sirulnick, Beth Elliott, Lilian Sicular

ABOVE: Ellen Levine, Suzanne Golden, Jacqueline Rofe, Carole Mallement, Lee Woodruff

On June 15th, the Brain & Behavior Research Foundation hosted its second "Women Breaking the Silence About Mental Illness" Luncheon. The event featured a lively and moving discussion between Hearst Magazine's Editorial Director Ellen Levine and advocate, author, and philanthropist Lee Woodruff. Their topic: depression, anxiety, and the importance of removing the stigma from mental illness. The luncheon, held at the Metropolitan Club in Midtown Manhattan, attracted 300 people who raised close to $150,000 for brain and behavior research.

The conversation between these two remarkable women focused on how life can change dramatically in a single moment. Lee experienced firsthand the feelings of depression, anxiety, and even despair after her husband, ABC News journalist Bob Woodruff, was injured in a roadside bomb while reporting from Iraq.

Lee spoke about how the experience motivated her to share her own family's history of depression and mental illness. "Stigma and the fear of being labeled prevents many people from finding the help they need," said Ms. Woodruff. "Speaking openly about mental disorders helps people understand they are not alone and encourages support for the kind of research that will lead to more effective treatments."

The luncheon's topic directly addressed stigma and how to deal with mental illness without fear of judgement. "As a noted author and public figure, Lee Woodruff's willingness to share her experiences goes a long way toward eliminating the shame and embarrassment that keeps mental illness in the shadows," said Ms. Levine.

Ellen Levine made publishing history in October 1994 as the first woman to be named editor-in-chief of *Good Housekeeping* since the magazine was founded in 1885. During her tenure, she was instrumental in launching new titles at Hearst Magazines, including *O, The Oprah Magazine*, the most successful magazine launch ever. In May 2006, Ms. Levine was appointed editorial director at Hearst Magazines. In addition to many other awards, she received the first annual Media Award by the American College of Neuropsychopharmacology for the numerous articles on mental illness she published in *Good Housekeeping*.

Lee Woodruff is the author of three books, including "In An Instant," a New York Times bestseller that also garnered critical acclaim for its compelling and humorous chronicle of her family's journey to recovery following her husband's injury in Iraq. She serves as co-founder of the Bob Woodruff Foundation, which has raised more than $20 million to help veterans successfully reintegrate into their communities and receive critically needed long-term care.

At the Foundation's first women's luncheon in November of 2013, Swanee Hunt—former Ambassador to Austria and Harvard University's Eleanor Roosevelt Lecturer in Public Policy—discussed her struggles to get her daughter help for bipolar disorder.

The Women's Luncheon series is designed to pay tribute to the brave women who are willing to speak candidly and personally about mental illness and use it as an inspiration to speak out and remove the stigma from brain and behavior disorders. "By engaging in this important conversation about depression, anxiety, and recovery, Ellen and Lee are educating the public, raising awareness and, most importantly, helping eliminate the stigma around mental illness that keeps so many people suffering in silence instead of seeking help," said Foundation President and CEO Jeffrey Borenstein, M.D. "We are grateful for their candor." ■

2015 Klerman & Freedman Prizes for Exceptional Research By NARSAD Young Investigator Grantees

Six Young Investigators received the Annual Klerman & Freedman Prizes on Friday, July 24th in New York City, in recognition of their exceptional research.

These two prizes pay tribute to Gerald L. Klerman, M.D., and Daniel X. Freedman, M.D., whose legacies as researchers, teachers, physicians, and administrators have indelibly influenced neuropsychiatry. These prizes recognize exceptional clinical and basic research by young scientists who have been supported with NARSAD Young Investigator Grants—our hallmark program, which enables aspiring young scientists with innovative ideas to garner the pilot data needed for their research. Once they have "proof of concept" for their work, they often go on to receive further funding.

The prizewinners are selected by committees of the Foundation's Scientific Council, an all-volunteer group of 150 distinguished scientists across brain and behavior research disciplines. This early recognition of their work by the Scientific Council serves as a precursor to further accomplishments, awards, and prizes as well as to their establishment as Independent Investigators at their institutions.

The Klerman Prize Selection Committee

CHAIR:
Robert M.A. Hirschfeld, M.D.
Weill Cornell Medical College, Cornell University

MEMBERS:
Martin B. Keller, M.D.
Brown University

Rachel G. Klein, Ph.D.
New York University

Nina R. Schooler, Ph.D.
State University of New York, Downstate

Karen Dineen Wagner, M.D., Ph.D.
University of Texas Medical Branch at Galveston

The Freedman Prize Selection Committee

CHAIR:
Ariel Y. Deutch, Ph.D.
Vanderbilt University

MEMBERS:
Joseph T. Coyle, M.D.
McLean Hospital, Harvard Medical School Affiliate

Ronald S. Duman, Ph.D.
Yale University

Fritz A. Henn, M.D., Ph.D.
Cold Spring Harbor Laboratory
Icahn School of Medicine at Mount Sinai

Peter W. Kalivas, Ph.D.
Medical University of South Carolina

Husseini K. Manji, M.D., FRCPC
Johnson & Johnson PRD
Visiting Professor at Duke University

Eric J. Nestler, M.D., Ph.D.
Icahn School of Medicine at Mount Sinai

Bryan L. Roth, M.D., Ph.D.
University of North Carolina School of Medicine

2015 Klerman Prizewinner for Exceptional Clinical Research

The Klerman Prize was established in 1994 by Myrna Weissman, Ph.D., in memory of her late husband, Gerald Klerman, M.D.

"Receiving the NARSAD Young Investigator Award was nothing short of transformative for our group, generating vital momentum for establishing a broader research program focused on computational psychiatry. The Brain & Behavior Research Foundation has played an instrumental role in supporting our lab to pursue a high-risk/high-reward question that in turn provided the basis for programmatically extending this work into an innovative yet neurobiologically-grounded computational and experimental platform designed to characterize cognitive deficits in schizophrenia. We are deeply thankful for the Foundation's invaluable support and its scientific vision to help improve the lives of people suffering from severe mental illness."

Alan Anticevic, Ph.D.

Alan Anticevic, Ph.D., Co-Director Neurocognition, Neurocomputation, and Neurogenetics (N3) Division and Assistant Professor and Principal Investigator, Anticevic Lab, Department of Psychiatry at Yale University is being honored for his work looking at cognitive function—brain processes associated with thought and their related behavior—in schizophrenia.

Schizophrenia is characterized in part by cognitive deficits such as impairments to working memory (the short-term memory that allows us to retain new chunks of information like phone numbers). Researchers have tried to understand the cognitive aspects of schizophrenia in different ways: at the level of individual brain cells, using mathematical models to represent cell activity underlying cognition; by the level of brain circuits connecting cells, identified by neuroimaging; and at the behavioral level, looking at how individuals with the disorder show cognitive deficits in a range of tasks.

For his 2012 NARSAD Young Investigator grant project, Dr. Anticevic's team connected these different levels of cognitive dysfunction associated with schizophrenia via mathematical models of the brain. They developed computational models that effectively predicted brain activity and behavioral performance, reflecting cognitive errors made by patients. In particular, the team looked at the balance of excitatory connections in the brain, which promote communication between cells, with inhibitory connections that reduce communication between cells. They found that disrupting the balance between excitatory and inhibitory connections can lead to specific patterns of cognitive deficits. The mathematical models used in this study may help track and predict the development of cognitive dysfunction among people with schizophrenia. Future studies will expand the models to examine larger networks in the brain associated with schizophrenia-related cognitive dysfunction. A better understanding of these networks will aid our ability to identify and treat schizophrenia in a neurobiologically grounded way.

With his work, Dr. Anticevic broadly aims to mechanistically characterize brain circuits involved in cognition and their interaction with circuits that direct emotional processing by combining neuroimaging, pharmacology, and computational modeling. His team also aims to understand how to harness state-of-the-art neuroimaging to develop better diagnostic markers for severe neuropsychiatric illness. He hopes to continue shedding light on how the interactions between these different circuits are upset in cases of severe neuropsychiatric illness, such as schizophrenia, bipolar disorder, and substance abuse.

Dr. Anticevic earned his Ph.D. in clinical psychology at Washington University in St. Louis and then served as an associate research scientist at Yale's Center for the Translational Neuroscience of Alcoholism, before joining the Yale faculty in 2013.

2015 Klerman Prize Honorable Mentions

Chadi G. Abdallah, M.D.

Chadi G. Abdallah, M.D., is an Assistant Professor of Psychiatry at Yale University, where he is also Director of Neuroimaging and Clinical Trials at the Clinical Neuroscience Division of the National Center for Posttraumatic Stress Disorder. He is being honored for his NARSAD grant work looking at the effects of ketamine on the brain.

Ketamine is a medication sometimes used as a human and animal anesthetic that has also been a drug of abuse, with psychedelic and dissociative side effects in some users. In recent years, researchers have shown ketamine produces rapid and profound antidepressant effects, especially for people with depression that resists typical treatments such as psychotherapy and common SSRI-class antidepressants. With his 2012 and 2014 NARSAD Young Investigator grants, Dr. Abdallah used novel brain imaging technology to investigate ketamine's effects on energy and glutamate production in the brain—glutamate being an excitatory neurotransmitter that drives much brain activity. The findings from this study may clarify the role of glutamate production in ketamine's rapid antidepressant effects, which can be noted in some patients in hours or even minutes. The results may also help determine optimal doses of ketamine for treating depression, as well as ketamine's interaction with other antidepressant medications. Dr. Abdallah hopes to apply this work to understanding the abnormally low glutamate signaling associated with schizophrenia, as well as the use of antipsychotic drugs in treating glutamate impairments.

Dr. Abdallah earned his M.D. at Lebanese University in Beirut. He completed his residency at SUNY Downstate, Brooklyn and a traineeship at Cornell University before joining Yale University in 2011 as a neuroimaging fellow.

"While many invest in research, NARSAD invests in researchers—launching and nurturing numerous careers, fostering streams of innovation, and endless successes. Three years ago, the NARSAD grant funded my first research project, which was critical in helping me establish a research program that is currently funded by the National Institute of Mental Health, the Veterans Administration, Department of Defense, and several research foundations."

Carrie J. McAdams, M.D., Ph.D.

Carrie J. McAdams, M.D., Ph.D., Assistant Professor of Psychiatry at the University of Texas (UT) Southwestern Medical Center at Dallas, is being honored for her work examining brain activity related to social behavior in anorexia nervosa.

In previous work, Dr. McAdams found that brain activity during social tasks differed in adults recovering from anorexia nervosa compared to healthy adult women. Her NARSAD grant allowed her to expand this work to adolescents, a crucial population, as most eating disorders develop during adolescence and young adulthood. The research team compared specific brain circuit activity among young women in early stages of anorexia treatment with the activity in the same circuits among women who do not have anorexia. They found young women with anorexia had different activity in only some of the brain regions previously identified.

These findings suggest that differences in certain brain regions may affect social behavior in ways that promote the development of anorexia, whereas differences in other brain regions may change later, after the disorder has advanced. This work helps identify which brain regions and related social behaviors may be early indicators of anorexia, as well as possible targets for intervention.

Dr. McAdams earned her Ph.D. and M.D. at the Baylor College of Medicine. She completed a postdoctoral research fellowship in neurobiology at Harvard University before beginning psychiatric residency at UT Southwestern, where she joined the faculty in 2012.

"The NARSAD Grant allowed me to examine whether biological differences in social neurocircuitry were present in adolescents with anorexia nervosa. By linking this data with our earlier studies in adults, we found that some neural differences were present in the younger subjects but others were only seen in adults. This award allowed me to expand my work into this patient population, improved our understanding of neurocircuit dysfunction in anorexia nervosa, and may eventually lead to more individualized, neuroscience-based treatments of this serious mental illness."

2015 Freedman Prizewinner for Exceptional Basic Research

The Freedman Prize was established in 1998 in honor of the late Daniel X. Freedman, M.D., a founding member of the Foundation's Scientific Council.

"The NARSAD Young Investigator Award came at a critical time in my career and allowed me to take risks that have continued to generate tremendous returns. Rather than going after the 'next obvious question,' I was able to develop the necessary tools for asking how thalamic inhibition fundamentally worked. These tools are now revealing how thalamic inhibitory circuits can go awry in neurodevelopmental disorders and how targeting thalamic circuits can provide unique therapeutic benefits."

Michael M. Halassa, M.D., Ph.D.

Michael M. Halassa, M.D., Ph.D., Assistant Professor at the New York University Neuroscience Institute with appointments in Neuroscience and Physiology, Psychiatry and the Center for Neural Science, is being honored for his work examining the regulation of sensory information in the brain. This work has possible implications for treating disorders such as schizophrenia, autism, and attention deficit hyperactivity disorder, all of which involve disruptions to the flow of sensory information both to and within the brain.

With his 2012 NARSAD Young Investigator grant, Dr. Halassa and colleagues investigated the role of the thalamus in attention towards appropriate sensory inputs amid the overwhelming amount of sensory information we experience in our environments. Located near the center of the brain, the thalamus has been identified as a possible gatekeeper for attention because it relays sensory information to the cortex for fine-tuned processing. In particular, researchers have suggested that sensory attention is directed by the thalamic reticular nucleus (TRN), a group of neurons that inhibit communication within the brain and can therefore increase attention toward sensory input by reducing their own inhibitory activity.

To understand TRN activity, Dr. Halassa's team recorded TRN neuron firing in mice during sleep as well as a visual attention task. They found that TRN neurons that communicated with visual processing regions of the brain reduced their activity—thus reducing inhibition—during the visual task, but increased their activity during sleep. That means the TRN neurons allowed for greater sensory relay to visual brain regions during the visual task, helping to focus attention based on what was relevant to behavior.

In a similar vein, the team found uniquely decreased activity during sleep among TRN neurons that help promote memory consolidation, and neutral activity levels for these same neurons during the visual attention task. Thus, TRN neurons again increased the flow of sensory information based on what was behaviorally relevant—in this case, the need to consolidate memory during sleep. These findings indicate that TRN neurons help regulate the flow of attention in task-specific ways. Disruptions to the activity of TRN neurons may contribute to disorders where the flow of attention is not properly regulated.

Dr. Halassa earned his M.D. at the University of Jordan and Ph.D. in neuroscience from the University of Pennsylvania. He completed a residency in psychiatry at Massachusetts General Hospital and a postdoctoral fellowship with Dr. Matthew Wilson at Massachusetts Institute of Technology before joining New York University in 2014.

2015 Freedman Prize Honorable Mentions

Kristen Brennand, Ph.D.

Kristen Brennand, Ph.D., Assistant Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai, is being honored for her work pinpointing irregularities in brain cells associated with schizophrenia.

Brain cells in people with schizophrenia are known to show different properties compared to neurons in those without the disorder. Yet it is not well understood which cell types are most affected by the disorder, nor which genetic mechanisms produce these differences. To address these questions, Dr. Brennand's NARSAD grant project is looking at skin cells from people with schizophrenia. These mature cells are genetically reprogrammed to revert to their stem-cell origins, and are then directed to develop into different kinds of neurons.

By comparing the features and activity of these neuron subtypes, Dr. Brennand aims to reveal how and why brain cells differ for people living with schizophrenia. A better understanding of these cellular differences may contribute to the creation of a screening platform for new interventions that treat—and possibly even prevent—schizophrenia by targeting cellular irregularities.

The findings of this study will provide clues into the nature of the disease at the cellular level. Ultimately, Dr. Brennand hopes, these clues will help researchers identify the genetic basis of schizophrenia.

Dr. Brennand earned her Ph.D. in developmental and stem cell biology at Harvard University and completed postdoctoral work at the Salk Institute for Biological Studies before joining the Icahn faculty in 2012.

"This NARSAD grant was the very first grant I obtained as an independent investigator. Their support not only provided the funding to support my laboratory's earliest experiments, but it gave me the freedom and ability to focus on conducting key preliminary observations that proved critical to my success in obtaining additional funding from the National Institute of Mental Health and the New York Stem Cell Foundation. The support of NARSAD, one of the most influential organizations in schizophrenia research, signaled to other researchers that my research approach had been vetted and showed promise, greatly facilitating the development of a number of important collaborations with clinical and laboratory researchers.

Nandakumar Narayanan, M.D., Ph.D.

Nandakumar Narayanan, M.D., Ph.D., Assistant Professor of Neurology at the University of Iowa Carver College of Medicine, is being honored for his studies of the brain circuits that underpin our thought processes. These circuits are dysfunctional in mental illness as well as neurodegenerative disease, giving rise to a wide range of cognitive deficits. Dr. Narayanan works to understand where and how these circuits go wrong in order to find new targets for the treatment of cognitive symptoms in neurological disorders.

With his NARSAD grant, Dr. Narayanan and colleagues have extended their work to explore specific circuits in animal models. Their results so far suggest that it is possible to identify problematic activity in brain circuits as that activity occurs in real time. According to the researchers, it may be possible to correct problems with brain circuitry in real time. These findings point toward potential new strategies for treating cognitive symptoms, which are common in mental illnesses such as schizophrenia, obsessive-compulsive disorder and attention-deficit hyperactivity disorder.

Dr. Narayanan received both his M.D. and Ph.D. in neuroscience at Yale University, where he also completed his internship and residency before joining the University of Iowa in 2012.

"The NARSAD Young Investigator grant enables promising investigators to either extend research fellowship training or to begin careers as independent research faculty. My NARSAD award did both. It provided me with funding to perform crucial experiments that established my independence. I have been able to leverage this key data to transition from a harried neurology resident to an independent investigator running a National Institute of Health-funded laboratory of five scientists at the University of Iowa. We have translated key findings from this work to humans, and will soon explore these findings in mental illness. We are optimistic that these efforts will lead to new insights about cognitive function and could help alleviate suffering in mental illness." ■

WITH A WILL…
THERE'S A WAY TO HELP

A GIFT TO THE FOUNDATION SUPPORTS CUTTING-EDGE MENTAL HEALTH RESEARCH AND FUTURE BREAKTHROUGHS

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

- Will or Trust
- IRA or other retirement plan
- Life income or other planned gift
  Charitable Gift Annuity, Charitable Remainder Trust, Charitable Lead Trust or Remainder Interest in a personal residence.

MAKING A BEQUEST

Bequests and other planned gifts have a profound and lasting impact on the field of research by funding Young, Independent and distinguished Investigators around the world.

100% of dollars raised for research are invested in grants leading to advances and breakthroughs in brain and behavior research.

FOR MORE INFO, PLEASE VISIT BBRFOUNDATION.ORG/PLANNEDGIVING OR CALL 800.829.8289

BRAIN & BEHAVIOR
RESEARCH FOUNDATION
Awarding **NARSAD** Grants

Drug Addiction

Q What are some of the risk factors for addiction?

A Scientists say no single factor can predict whether a person might become addicted to drugs. But they think about half of the risk of addiction may come from a person's biology and the other half from his or her environment. Some of the environmental factors that could make addiction more likely, especially among teens, include a lack of family involvement, the availability of drugs at school or in the home, or spending time with friends or family who use drugs. Smoking or injecting a drug also increases the risk of addiction, possibly because these methods have the quickest impact on the brain and body. The earlier a person begins using a drug, the more likely he or she is to become addicted.[1] People with anxiety, depression or other mental health disorders such as attention-deficit /hyperactivity disorder and post-traumatic stress disorder also have a higher risk of drug addiction.[2]

More recently, researchers have identified specific genes that influence a person's risk of addiction. For instance, Scientific Council member Wade Berrettini of the University of Pennsylvania led a research team in 2014 that uncovered rare variations of a gene that reduced the risk of heroin and cocaine addiction among some people.[3]

Q Can drug addiction lead to other mental health disorders?

A It's not uncommon for a person with a drug addiction to have another mental illness, but scientists say it's difficult to know whether addiction is the cause of the mental illness, or whether people with mental illnesses turn to drug use to "self-medicate." It's also likely that some of the same genes and brain regions involved in addiction are also involved in other brain and behavior disorders, such as schizophrenia and depression.[4]

Several studies show that in some cases marijuana can produce psychotic symptoms similar to those experienced by people with schizophrenia.

Q The legal use of marijuana is spreading in the United States. Does that mean marijuana isn't addictive?

A No. Although marijuana is not as addictive as alcohol or nicotine, nine percent of those who have tried marijuana at least once will become addicted to the drug. Researchers who analyzed 20 years' worth of marijuana studies concluded that one in ten people worldwide who try the drug will become addicted.[5] Marijuana was the illicit drug with the largest number of persons with past-year dependence or abuse in 2013, followed by pain relievers and cocaine. Of the almost seven million persons aged 12 or older who were classified with illicit drug dependence or abuse in 2013, more than four million had marijuana dependence or abuse (representing 1.6 percent of the total population aged 12 or older).[6]

Q What do new studies tell us about treating addiction?

A The past 15 years of imaging studies have shown that there are more types of brain circuitry involved in addiction than researchers previously thought. For instance, these studies have shown that drugs such as cocaine can impair parts of the brain involved in problem solving, reasoning, and planning. As a result, scientists have looked for ways to strengthen these circuits in people at risk for addiction—for instance, through behavioral methods aimed at improving executive function and decision-making.[7] Imaging studies also show that some of the brain circuits involved in addiction are impaired in mental illnesses such as depression and schizophrenia. Saleem M. Nicola, Ph.D., of Albert Einstein College of Medicine, a NARSAD Young Investigator Grantee, and NARSAD Independent Investigator Alan I. Green, M.D., of Dartmouth Medical School are among the researchers using this information to explore whether medications used to treat these mental illnesses could aid the development of new treatments for addiction.[8, 9]

SOURCES:

1 National Institute on Drug Abuse, Drugs, Brains and Behavior: The Science of Addiction, http://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction

2 Mayo Clinic, Drug addiction risk factors, http://www.mayoclinic.org/diseases-conditions/drug-addiction/basics/risk-factors/con-20020970

3 Low frequency genetic variants in the mu-opioid receptor (*OPRMI*) affect risk for addiction to heroin and cocaine *Neurosei Lett*. 2013 May 10: 542: 71–75.

4 National Institute on Drug Abuse, Comorbidity: Addiction and Other Mental Illnesses, http://www.drugabuse.gov/publications/comorbidity-addiction-other-mental-illnesses

5 W. Hall, "What has research over the past two decades revealed about the adverse health effects of recreational cannabis use?" Addiction, Volume 110, Pages 19–35, January 2015.

6 U.S. Dept. of Health and Human Services, "2013 National Survey on Drug Use and Health" Sec. 7.1

7 A. Diamond and K. Lee, "Interventions shown to aid executive function development in children 4–12 years old," Science, Volume 33, Pages 959-964, August 19 2011.

8 V.B. McGinty *et al.*, Invigoration of reward seeking by cue and proximity encoding in the nucleus accumbens," Neuron, Volume 78, Pages 910–922, June 5 2013.

9 A.I. Green et al., "Substance abuse and schizophrenia: pharmacotherapeutic intervention," Journal of Substance Abuse Treatment, Volume 34, Pages 61–71, January 2008.

FEATURE

Parenting:
Advice for Parents of Children with Anxiety Disorders

Daniel S. Pine, M.D.

Chief of the Section on Development and Affective Neuroscience in the National Institute of Mental Health Intramural Research Program

Daniel S. Pine, M.D., a member of the Foundation's Scientific Council, is the chief of the Section on Development and Affective Neuroscience in the National Institute of Mental Health Intramural Research Program. His research focus is pediatric mental illnesses, including the biology and drug treatment of mood, anxiety, and behavioral disorders in children. Dr. Pine has also served as the chair of the Psychopharmacologic Drug Advisory Committee for the Food and Drug Administration and chair of the Child and Adolescent Diagnosis Group for the DSM-5 Task Force. (The task force is composed of scientists and doctors who oversee and update the DSM—the *Diagnostic and Statistical Manual of Mental Disorders*. This important handbook is used by health care professionals in the United States and much of the world as the authoritative guide to the diagnosis of mental disorders).

We asked Dr. Pine what advice he could offer parents concerned about a child with a possible anxiety disorder. We also talked with him about what the latest basic science research says about the causes and possible treatments for anxiety.

How can you tell if a child's anxiety is normal or a part of an anxiety disorder?

There are three things that we usually look at to tell the difference between abnormal anxiety that is part of an anxiety disorder, and the anxiety that children, or really anybody, experiences as a normal part of life. The first and probably the most important thing we look at is whether there is impairment—anxiety that interferes with a person's ability to function and leads to avoidance. Most people feel anxious when they're in a new social setting, or when they're starting out a new job. But someone with an anxiety disorder may miss work because they're so nervous, or they'll refuse to go to school or attend a party, for example.

A second thing we look at is what we call extreme distress—whether a person is experiencing distress beyond what is typical. There is some amount of clinical or subjective judgment in determining whether stress is extreme.

The third thing we look at is whether abnormal anxiety goes on for many weeks or months. A person with abnormal anxiety is persistently worried or afraid of the same thing over and over again.

Are anxiety disorders on the rise among children?

These are very difficult things to track, because diagnosis is heavily based on what people tell us. As the stigma attached to mental disorders goes down and our understanding of these conditions improves, people are more willing to talk about them and they're easier to identify. There is some evidence that anxiety disorders are on the rise, but there's also evidence that suggests we are better at identifying or targeting these problems. There's no convincing evidence that rates of anxiety disorders are increasing.

Is a pediatrician the first person a parent should consult if they think their child has an anxiety disorder?

Pediatricians are usually a wonderful place to start. They vary in how much they know, and in how comfortable they are in talking about these types of problems. But they may be able to refer their patient to a knowledgeable therapist. Schools are often very familiar with local therapists experienced in cogitative behavioral therapy (CBT). Another place to find a therapist trained in CBT is an advocacy organization such as the Anxiety and Depression Association of America or The American Academy of Child and Adolescent Psychiatry.

What are the most common treatments for children and adolescents with anxiety disorders?

There are generally two types of treatments that seem to be equally effective: cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitor (SSRI) medications. The best study that compared them directly in kids found one is no better than the other, and that combining the two works better than using one or the other alone. Cognitive behavioral therapy is a really wonderful treatment, but the therapist has to have some experience delivering it. Specific techniques need to be followed. There are not that many therapists in the United States who are readily available to apply those methods.

In situations where a family doesn't have access to a well-trained therapist, CBT wouldn't be the first choice. It would be better to use an SSRI rather than try to do CBT with a therapist who isn't well-trained and experienced. Pediatricians are often comfortable prescribing SSRIs, but we don't completely understand how these medications help children with anxiety disorders. Because of this, I think some parents are uncomfortable using them.

Are there any connections between substance abuse and addiction, and anxiety disorders in children?

There is a whole range of mental health problems in children that accompany substance abuse. It's quite common to see substance abuse in anxiety, but it's also quite common to see it connected to other kinds of mental health problems. We are not sure about why substance abuse problems occur with anxiety. Some adolescents may have problems with anxiety, and find that when they use illicit substances they feel that their anxiety gets better. They're engaging in behavior that some people call self-medicating. But there are other adolescents who have no problem with anxiety and they begin using an illicit substance and then they develop anxiety that follows directly from the illicit drug use. It's really hard to say why this happens. Right now we don't have any firmly established mechanisms that link the two in most cases. Some adolescents have problems with substance use and problems with anxiety that are completely unrelated.

If someone has an anxiety disorder in childhood, will he or she continue to have the disorder as an adult?

For any mental disorder, we really do not have the ability to confidently state which are going to go on and change very little, which are going to get somewhat better, and which are going to completely disappear. Some disorders like autism, for instance, tend to be more persistent. Many children with autism will have at least some level of problem throughout their lives. But the story is very different with anxiety. A large group of children with anxiety will do completely fine when we follow them over time. And we really do not have a very good ability to predict which children will do better, although there are some things that we think can help us predict this.

What do doctors and scientists look for when they try to assess a child's prognosis?

The kinds of things that do help us are by and large clinical observations, which are more useful, at least right now, than measures of brain function, hormones, or physiology. For instance, kids with more extreme anxiety problems tend to do worse over time than kids with relatively mild problems, although that's not an absolute. Another factor is the level of avoidance. Kids who tend to avoid things tend to have more persistent anxiety, compared to kids who are anxious but will not avoid the situations that make them afraid. A third factor has to do with the behavior of parents. When parents are particularly encouraging, their kids tend to do better.

What kind of encouragement do these parents give their children?

These are parents who can help their kids face the situations that make their children most afraid, and encourage their kids to not avoid the things they're afraid of. They are parents who look for situations and circumstances and experiences where kids are going to have to deal with their anxiety. Those kids tend to do better with their anxiety compared to kids whose parents are doing absolutely everything they can to prevent their kids from ever getting anxious.

What has basic science research revealed about the possible causes or treatments for anxiety?

One thing concerns something we just talked about: facing fears. There's an idea called extinction that people think a lot about in basic science research on anxiety. Extinction is a process that we study where organisms such as rodents and non-human primates learn how to overcome their anxiety. One of the things we know about extinction is that it's an active process; to extinguish a fear, organisms have to be exposed to the fear. Beyond just learning how to cope, maybe one of the reasons why kids who face their fears do better over time is that they have opportunities to develop extinction. Research on extinction is starting to be helpful because people are coming up with new ideas about how treatments like CBT might be adjusted to increase extinction learning.

Another avenue that's been promising in neuroscience is that we now understand a lot about "information processing biases" in anxiety. We've learned that people with anxiety tend to pay undue attention to threats in their environment. This has led to novel ideas about how to treat anxiety, including using things like video games to train attention. This is something we've tested with combat veterans who have post-traumatic stress disorder (PTSD).

Are these kinds of extinction and attention bias treatments available to patients yet?

This kind of basic science research has had relatively little impact on how we treat individual patients. Right now, these are just new ideas, and while they're promising, the most exciting ideas are not yet ready for prime time, they're not routine treatments that can be applied in all patients just yet. For instance, in our PTSD study, it's not clear how robust the findings are. There's some concern that if the training is not done in the right way, it could make symptoms worse. We don't understand those kinds of things well enough.

However, I think one of the nice things about basic research on fear and anxiety is that there's tremendous "cross-species conservation." What that means is that the relationship between brain and behavior in anxiety is very similar in rodents, non-human primates and people. Because of those similarities, which occur more so in anxiety than in other mental health problems, I think we are getting closer to finding novel treatments for anxiety than we may be in other disorders. ■

Glossary

Biomarkers or Biological Markers: A characteristic or biological factor that can be objectively measured, which indicates whether a person has or does not have a specific illness or an elevated risk for developing that illness.

Cognitive Behavioral Therapy (CBT): A short-term, goal-oriented psychotherapy treatment that takes a hands-on, practical approach to problem-solving. Its goal is to change patterns of thinking or behavior that are behind people's difficulties, and change the way they feel.

Computational Psychiatry: Mathematical models of the brain, developed with the aid of computers, designed to predict brain activity and behavioral performance. Can be used to study patterns of cognitive errors made by patients with schizophrenia and other disorders in which normal cognitive processes are impaired.

Epigenetics: Groups of molecules that attach to the double helix of DNA, "marking" or "tagging" it and helping determine whether a given gene is switched "on" or "off," or the degree to which a gene that is switched on "expresses" itself (by giving a cell instructions to make more or less of a specific protein).

Neurotransmitter: A chemical that relays information across the gap (synapse) between one neuron (nerve cell) and a nearby neuron or a non-neuron cell.

Pharmacology: A branch of medicine concerned with the uses, effects, and modes of action of drugs. A subset of pharmacology is neuropsychopharmacology: the study of mechanisms in the nervous system that drugs act upon to influence the brain and behavior.

Population-Based Data: Information drawn from people in the general population who share a common characteristic such as age, sex, or health condition. This group may be studied for different reasons, such as their response to a medication or risk of getting a disease.

Psychomotor Speed: The speed at which the brain is able to translate between perception, thought, and action—for example, how quickly someone can perform a task after receiving spoken instructions.

Receptor: A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific effect in the cell.

Remission: A period during which no signs or symptoms of a given disease appear to be present.

Self-Medicate: The term "self-medicate" often refers to a person's use (or abuse) of alcohol or illegal drugs to ease or mask symptoms.

Save The Date

Friday October 23, 2015

Day:

27th Annual

NEW YORK MENTAL HEALTH RESEARCH SYMPOSIUM

Outstanding Achievement Prizewinners and select Young Investigators will present updates on leading research discoveries across brain & behavior disorders.

Evening:

28th Annual

NATIONAL AWARDS DINNER

Pardes Humanitarian Prize and Outstanding Achievement Awards will be presented.

FOR MORE INFORMATION

events@bbrfoundation.org

800.829.8289

BRAIN & BEHAVIOR RESEARCH FOUNDATION

Awarding **NARSAD** Grants

BRAIN & BEHAVIOR
RESEARCH FOUNDATION
Awarding NARSAD Grants

90 Park Avenue, 16th floor, New York, NY 10016–1301
646.681.4888 | 800.829.8289
bbrfoundation.org

Investing in Breakthroughs To Find a Cure

OUR MISSION:

The Brain & Behavior Research Foundation is committed to alleviating the suffering caused by mental illness by awarding grants that will lead to advances and breakthroughs in scientific research.

OUR VISION:

To bring the joy of living to those affected by mental illness—those who are ill and their loved ones.

HOW WE DO IT:

100% of our donor contributions for research are invested in NARSAD Grants leading to innovative ideas in neuroscience and psychiatry to better understand what causes and how to effectively treat brain and behavior disorders. These disorders include depression, bipolar disorder, schizophrenia, autism, attention-deficit hyperactivity disorder, anxiety, borderline personality disorder, chemical dependency, obsessive-compulsive disorder and post-traumatic stress disorders.

OUR CREDENTIALS

For more than a quarter of a century, we have awarded more than $340 million to fund more than 5,000 grants to more than 4,000 scientists around the world.

SIGN UP FOR ENEWS
bbrfoundation.org/signup

FIND BBRFOUNDATION ON