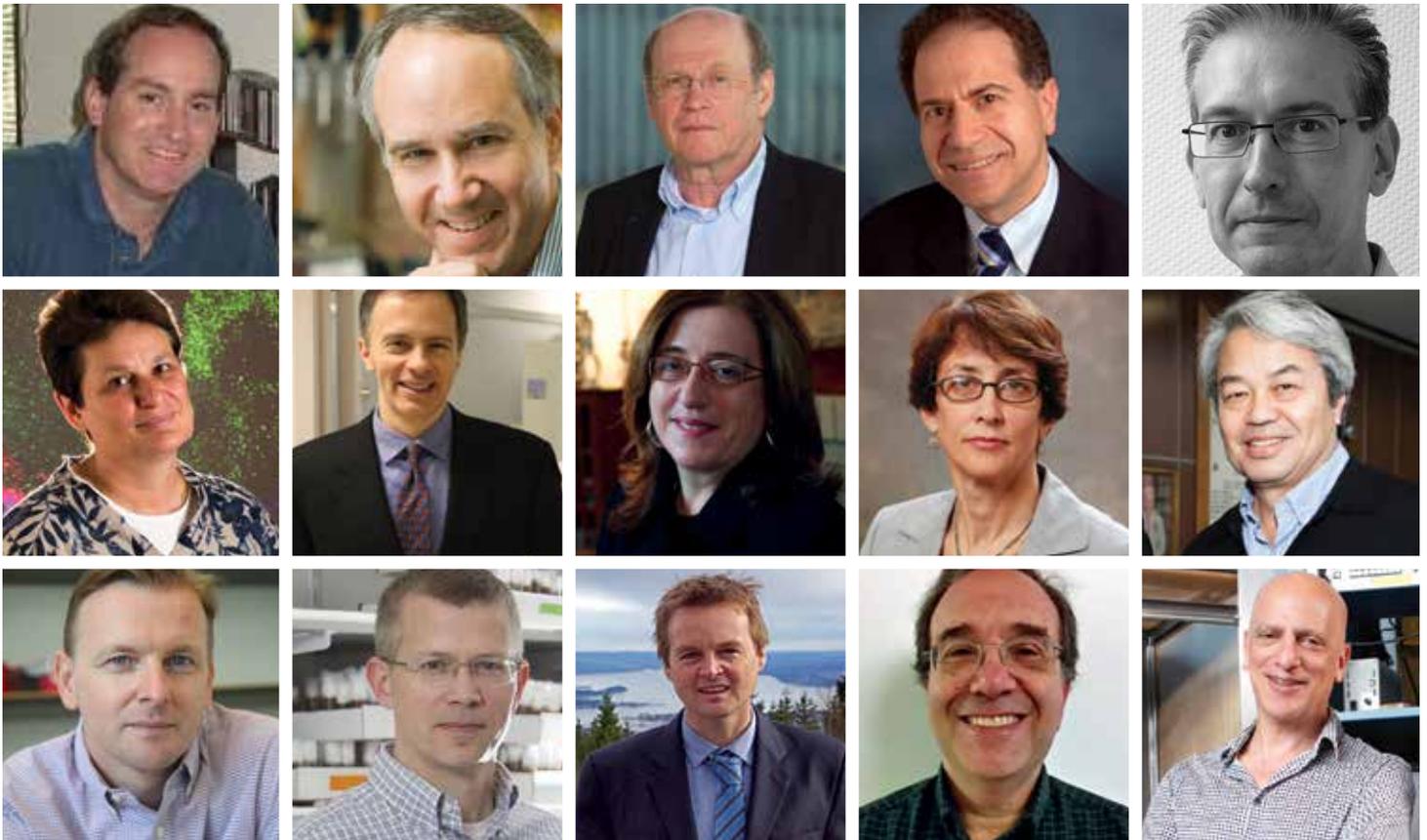


Brain & Behavior Research Foundation

Quarterly

January 2016



PRESENTING THE DISTINGUISHED INVESTIGATORS



Interview with a Researcher
HUDA AKIL, PH.D.



Advice on Caring for Bipolar Disorder
with **ROBERT M.A. HIRSCHFELD, M.D.**



A RECOVERY STORY:
From A Nightmare Childhood,
A Happy Path Forward

BY THE NUMBERS SINCE 1987

Awarded to Scientists



\$342 MILLION

Grants

5,000+

The breakdown of our grantees since 1987

- 3,888 Young Investigators
- 748 Independent Investigators
- 394 Distinguished Investigators



Universities & Medical Centers

529



Countries, Including the U.S.

34

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The group includes:

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PRESIDENT'S LETTER

Jeffrey Borenstein, M.D.

President & CEO
Brain & Behavior Research Foundation

I recently had the honor of representing the Brain & Behavior Research Foundation at an event at the U.S. Supreme Court honoring Judge Steven Leifman of Miami, Dade County, Florida. Judge Leifman, who received our Foundation's Productive Lives Award in 2012, received the William H. Rehnquist Award from Supreme Court Chief Justice John Roberts. This award is one of the nation's highest judicial honors and is presented to a state court judge "who exemplifies judicial excellence, integrity, fairness and professional ethics." Judge Leifman was honored for his "transformative work in the way people with mental illness are treated in the criminal justice system."

One of the saddest and most tragic aspects of mental illness is when a person becomes involved in the criminal justice system as a result of untreated or inadequately treated illness. Judge Leifman's work has served as a model to place people into treatment first, rather than prison.

In addition to improving our judicial system and access to treatment, research to improve our methods of treatment provides the key to solving the problem of people with mental illness being in the criminal justice system.

This issue of the Quarterly highlights the 15 exceptionally talented winners of our 2015 Distinguished Investigator Grants, which provide \$100,000 to senior scientists who have a cutting edge and innovative idea which requires seed money to gather data so as to gain additional funding. We offer advice on caring for people with bipolar disorder from preeminent psychiatrist and member of our Scientific Council, Dr. Robert Hirschfeld and feature an interview with Dr. Huda Akil, also a Scientific Council member and 2007 winner of the Goldman-Rakic Prize for Outstanding Achievement in Cognitive Neuroscience on the biology of emotions.

We also report on our Annual New York Mental Health Research Symposium and our Annual National Awards Dinner, including the presentation of the Pardes Humanitarian Prize in Mental Health. The scientific presentations offered a hopeful and exciting view of how supporting the Foundation can help fund scientists to pursue cutting-edge basic research and assist in translating these discoveries into treatments for those who live with these illnesses. We fund these innovative ideas because everyone has a family member or friend with a brain and behavior disorder, and we continue to work for the day when our loved ones will have the help they need to live full, productive and happy lives.

Sincerely,



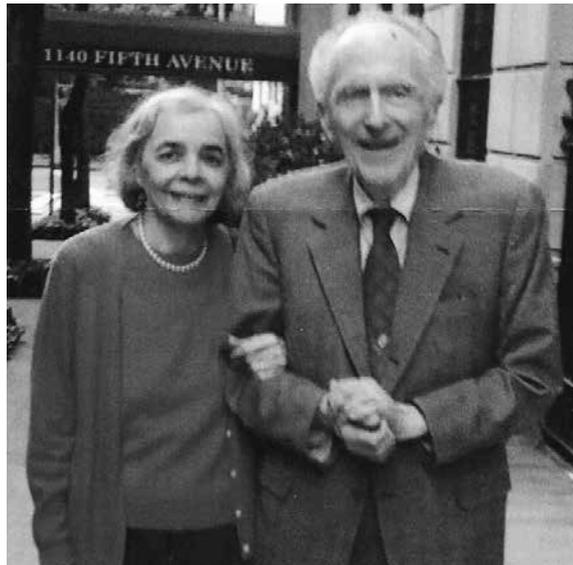
Jeffrey Borenstein, M.D.
President & CEO

Drs. Betty and David Hamburg Receive The Pardes Humanitarian Prize for Mental Health

Former First Lady Rosalynn Carter Receives Honorary Tribute



ABOVE: Former First Lady Rosalynn Carter



ABOVE: Drs. Betty and David Hamburg

On October 23, the Brain & Behavior Research Foundation hosted its 28th annual National Awards Dinner, honoring the year's Outstanding Achievement Prizewinners (see page 14) and the recipients of the Pardes Humanitarian Prize in Mental Health, at The Pierre in New York City.

This year's Pardes Prizewinners were Betty Hamburg, M.D. and David Hamburg, M.D., with an honorary tribute given to former First Lady Rosalynn Carter. "Together, the recipients embody the passionate and powerful work and international reach recognized by the Prize," said Jeffrey Borenstein, M.D., the Foundation's President and CEO.

The Pardes Prize, established in 2014, recognizes a physician, scientist or public citizen whose extraordinary contribution of humanitarian insight and service has made a profound and lasting impact by improving the lives of people suffering from mental illness and by advancing the understanding of mental health. The prize was named in honor of its first recipient, Dr. Herbert Pardes, M.D., who leads the Foundation's Scientific Council.

The Drs. Hamburg began their research studying human coping processes under severe stress, including physical stress, mental illness, poverty and war. Dr. David Hamburg established the first Mental Health Clinical Research Center at the National Institute of Mental Health, before becoming the Chair of an innovative and multidisciplinary Department of Psychiatry at Stanford University.

His negotiation skills during the 1975 kidnapping of four Stanford students in rural Congo brought him to international prominence, with a focus on health and science policy.

Dr. Hamburg served as the President of the Institute of Medicine (1975–1980), the President of the Carnegie Corporation (1982–1997), both institutions dealing with the most important humanitarian issues. In 1996 he received the Presidential Medal of Freedom, the highest civilian award in the United States.

Dr. Betty Hamburg is a transformative researcher in child and adolescent psychiatry, credited with advancing the field of children's mental illness after decades of neglect. She developed the concept of peer counseling as Director of the Division of Child Psychiatry at Stanford, and worked to support child and adolescent health research as President of the William T. Grant Foundation (1991–1997), and as a member of the President's Commission on Mental Health under President Jimmy Carter. For the past 12 years, the Drs. Hamburg have worked on issues of genocide and international conflict, collaborating on the 2008 book *Preventing Genocide*.



ABOVE: Dr. Herbert Pardes presenting the Pardes Prize to Dr. David Hamburg

"The award recipients are people who have populated the leadership field in child and adolescent psychiatry and played roles in attacking global problems," Pardes noted in his remarks about the Hamburgs at the gala event. "How does one really promote peace? How does one interfere with the tendencies towards genocide? How does one reduce violence?"

As he accepted the award, Dr. David Hamburg praised the innovation and "brilliant track record" of the Brain & Behavior Research Foundation. "I feel so indebted to the Liebers who are great pioneers in support of psychiatric research and to interpret it broadly the responsibilities of the field," he said.

Rosalynn Carter was honored during the Pardes Prize presentation as one of the world's most prominent mental health advocates, particularly in battling the stigma associated with mental illness. Her compassionate stance and commitment to focusing national attention on mental health have helped to establish new partnerships among mental health organizations through the Rosalynn Carter Symposium on Mental Health Policy, and promoted public awareness through the Rosalynn Carter Fellowships for Mental Health Journalism. Among other accomplishments, Carter was recognized for her leadership as Honorary Chair of the President's Commission on Mental Health during the Carter Administration, and her role in the passage of the Mental Health Systems Act of 1980. In 2007, Carter successfully lobbied for national legislation requiring parity in health insurance coverage for treatment of mental illnesses. ■

The Biology of Emotions

“Emotions are among our tools for adapting to the world—anticipating it, coloring it, so that objects and events are memorable in a meaningful way, for future use.”

—DR. HUDA AKIL

Dr. Huda Akil is one of the world’s leading experts on what scientists call the neurobiology of emotions. She and her colleagues are now two decades into an investigation of what goes on in the brain when we experience emotions, with the objective of discovering new ways to target imbalances and biological abnormalities that contribute to depression, anxiety and substance abuse.

Huda Akil, Ph.D.

Co-Director and Research Professor
The Molecular & Behavioral Neuroscience Institute
University of Michigan

Foundation Scientific Council Member

2007 Goldman-Rakic Prize for Outstanding Achievement
in Cognitive Neuroscience



A member of the Foundation's Scientific Council, Dr. Akil co-directs the Molecular & Behavioral Neuroscience Institute at the University of Michigan, where she is a Distinguished University Professor. Born in Syria, she is the daughter of a father who introduced modern concepts of psychology to Arab culture; the sister of a psychiatrist; and mother of a son, Dr. Brendon Omar Watson of Weill Cornell Medical College who received a 2014 Young Investigator Grant to conduct brain research.

The constructive role that emotions play in our lives highlights what Dr. Akil and other scientists call their "adaptive" value. Scientists believe that emotions arose in higher organisms because they helped them survive. Problems with biological systems that regulate the emotions often have precisely the opposite effect: having major depression or chronic, acute anxiety makes daily survival that much more difficult.

"We simply can't live without emotions," Dr. Akil emphasizes. "If you experience something positive, you want to remember it in a certain way, perhaps so you can experience it again. The same with things that are negative—you want to remember them so as to avoid them in the future. It's when you get stuck or disconnected from reality that emotions become a problem."

Early in her career, Dr. Akil and colleagues discovered that endorphins, naturally occurring opioids in the human system, including the brain, are activated by stress and can relieve pain. Following this discovery, Dr. Akil gravitated to an even larger research question: whether, or how, individual temperament affects mood disorders.

"We all know from looking at people and how they react and suffer, that people are really different," she says. "We were especially interested [in this subject] because many genetic studies in psychiatric disorders hinted that temperament is really important, especially in determining who is prone to develop depression or anxiety disorders, or to become a substance abuser."

"I felt we didn't have a good way of studying differences in temperament in the lab," she says. That led Dr. Akil's team to develop rodent models of two fundamental behavioral types that she suspected—correctly—had much to do with individual susceptibility to depression, anxiety and substance abuse.

Genetically distinct rat lines were bred by Dr. Akil and her colleagues to be either "high reactivity" (HR) or "low reactivity" (LR). HR lab rats tend to be explorers of their space and are interested in social interactions with cage-mates. LR rats tend to find a corner and remain there, eschewing interaction with others. The team continued the breeding until they emerged with animals that reliably displayed one tendency or the other, in an extreme form. One thing this showed was that "this trait is very genetic—it breeds true," Dr. Akil says. "One set is very adventuresome and the other is very inhibited."

This became a solid platform for probing how animals with these two exaggerated temperaments differed from normal animals and from one another. Dr. Akil looked for differences in the way their genes were expressed, and in how the proteins they encode vary and influence emotional behavior in a range of tests. High-reactivity animals tended to be resilient to stress, resistant to depression, but at the same time were notable risk-takers and explorers. HR rats were inclined to experiment with cocaine when the drug was made available to them. It was the reverse with the "low-reactivity" animals. The LR rats tended to be prone to depression and anxiety; did not react well to stress; tended to isolate themselves; and were not especially interested in experimenting with drugs or very much else in their environment.

The accompanying story (on page 8) discusses some of the key molecules Dr. Akil discovered to be correlated with these models of temperament and emotion. Those findings were based partly on research with the rodent models. But they also derive in part from another major thrust of her research: postmortem investigations of the brains of people who suffered major depression and bipolar illness. Dr. Akil leads one of six groups in the international Pritzker Neuropsychiatric Research Consortium, which has assembled a collection of these very valuable brains, donated by families of deceased patients.

This work, "for which we owe so much to the families, has taught us a great deal," Dr. Akil says. "It has reframed my entire thinking about depression." The postmortem brains "enabled us to see a summary of everything that happened in that entire life" in terms of the brain—how the person's unique genetic inheritance played out, how the brain developed, the effects of aging and gender, and of course the effect of the illness on the brain.

This work, "for which we owe so much to the families, has taught us a great deal," Dr. Akil says. "It has reframed my entire thinking about depression."

The striking revelation: “When you look at the brains of chronically, severely depressed people, you realize it’s a whole-brain change. Almost every part of the brain is altered and touched by the illness. There is evidence of pervasive changes, in the number of genes that are affected, the number of brain regions affected,” Dr. Akil says.

Among the lessons Dr. Akil has learned from this is the importance of treating depression as early in life as possible, ideally when it first appears. Looking at the postmortem brains of people who were depressed for many years “makes you appreciate why depression can become ‘treatment-resistant,’” she says.

INTERVIEW WITH A RESEARCHER / SIDEBAR

Message of Hope: There Are Many Places To Attack Depression

About 10 years ago, Dr. Huda Akil and her colleagues in the Pritzker Consortium began scrutinizing the brains of deceased people who had suffered depression, using increasingly sensitive and powerful tools to measure gene activity in multiple brain regions. To their surprise, one set of molecules, called the FGF family, kept topping the lists they made of most-altered factors in these brains. FGF stands for fibroblast growth factor—one of various kinds of molecules that serve to stimulate and sometimes regulate the growth and activity of nerve cells in the brain.

FGFs were at first thought to play their main role early in the brain’s development. Dr. Akil’s team discovered that FGFs also played a role over the lifespan, helping to regulate emotions, specifically, on a moment-to-moment basis and over the long haul. “In rats, we can manipulate the FGF system and within minutes see a change in anxiety behavior,” she says. This makes certain members of the family—notably FGF2, levels of which decline in depression—targets for next-generation drugs.

The discovery that FGFs play two roles—helping to wire the brain and then, later, to help regulate and “bias” the emotions (for instance, to incline an individual to be more or less resilient to the impact of stress)—makes them even more attractive targets. Dr. Akil’s team has recently noted that

It’s as if the long-depressed brain is in a deep slumber, a kind of perpetual winter. “We need to get people rapidly out of their negative mood and deep depression early—and use every means available, whether fast-acting antidepressants, psychotherapy, physical activity, better eating, social support—to actively re-engage all the affected brain circuits,” she says. “Because by the time you have had multiple episodes and the person has become isolated, living in a socially stressful or impoverished state, is inactive, not sleeping or eating right...the brain does not look any longer like a normal brain. It will take so much more work to reverse that.”

FGFs are “interaction partners” with the “neurotransmitter systems we all know,” like serotonin, which is the target of SSRI antidepressants such as Prozac or Lexapro.

Dr. Akil noted, “We’ve shown that FGFs are important, but there are multiple players in multiple parts of the brain, acting in different registers at different times. We like FGFs because they have a wide playing field—lots of interacting molecular partners, at different times in life and throughout life. This makes them very attractive in our efforts to address some of those key changes that affect the whole brain in a disease like depression. Ours is a message of hope: there are a lot of places to attack depression and other emotional disorders, we have lots of options, lots of strategies we want to deploy. These will take time to test, but we will deploy them.” ■

Have A Question?

Send questions for Dr. Huda Akil to asktheresearcher@bbrfoundation.org.

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

Nora Volkow, M.D.

Director of the National Institute on Drug Abuse,
National Institutes of Health
Foundation Scientific Council Member



My father was a cocaine addict, and I'm worried that I might become an addict too. Are there tests that I can take to see if I've inherited any genes linked to addiction?

The short answer is no, at least not yet. However, if you recognize behavioral patterns or personality traits [in yourself] that hint at increased risk for substance use, there are things you can actually do to contain and counteract that risk, even if you don't know exactly where that risk comes from. In most cases, this vulnerability to drug use stems in part from some deficit deep inside the dopamine circuits that control things like reward, attention, emotion, motivation, and purpose. I think the secret to prevention is to find, as early as possible, the things in life that boost dopamine in the brain, but, unlike drugs, do so naturally. In other words, find your passion (whatever that might be) and run with it. In that way you'll be recruiting the idiosyncrasies of any liability genes toward a positive goal and you'll most likely be OK. Also, it could be helpful to think that your father left you not only genes but also life lessons that can be as, if not more, valuable than bits and pieces of DNA.

I want to quit smoking tobacco and replace my nicotine "fix" with e-cigarettes. I know e-cigarettes aren't perfect, but are they more dangerous to my health than smoking?

It is likely that e-cigarettes might be less dangerous than combustible tobacco. However, the safety of e-cigarettes has been questioned by the fact that although they do not produce tobacco smoke, e-cigarettes contain not just nicotine but other potentially harmful chemicals as well. Testing of some e-cigarette products found the vapor to

contain known carcinogens and toxic chemicals (such as formaldehyde and acetaldehyde), as well as potentially toxic metal nanoparticles from the vaporizing mechanism. The health consequences of repeated exposure to these chemicals are not yet clear. Clinical studies have not been done yet to assess the efficacy of e-cigarettes for smoking cessation. Until we learn more about the long-term impact of these chemicals, it would be advisable to stick with the known and approved nicotine replacement therapies.

I was curious about the therapeutic approaches you discussed (in the September Quarterly), especially the idea of strengthening executive function to achieve better self-control. If someone with an addiction does this, will he/she need to continue this therapy for the rest of their life to prevent a relapse?

The brain is an amazingly plastic organ: it can continue changing—for good and bad—until the bitter end. Here's what neurons do: they talk to each other in response to experience, and their contact points (synapses) become stronger or weaker as a function of their shared history. This is actually very reminiscent to an athlete whose performance gets better and better with practice. The more she practices the better she gets at a particular task or skill—up to a point, of course. What one could potentially accomplish by training his or her own brain can be equally amazing, with the positive results accumulating over time, thanks to synaptic plasticity. Therapeutic approaches for addiction, particularly cognitive training, can dramatically reduce and keep reducing the risk of relapse over time. ■

Large-Scale Analysis Links Two of 20 Candidate Genes to Panic Disorder

TAKEAWAY: An analysis of data pooled from 62 previous studies links variations in two genes to panic disorder among people with European ancestry, but also underscores the disorder's genetic complexity.

For people with panic disorder sudden attacks of fear can cause a range of symptoms including sweating, nausea and a feeling of being out of control. Worry about the next attack can be so intense that people avoid places where they have experienced panic in the past. Both genetic and environmental factors are thought to influence who develops the disorder, but researchers have struggled to tease out specific genetic variations related to increased risk.

Although no genes have been convincingly linked to risk for panic disorder, numerous studies have identified candidate genes that may be involved. In a massive meta-analysis study combining prior study results, published September 22 in the journal *Molecular Psychiatry*, researchers reconsidered the involvement of 20 candidate genes. The meta-analysis, which has greater statistical power than any single study, succeeded in linking variations in two genes with panic disorder among people with European ancestry.

The research team was led by 2008 Young Investigator Vincenzo De Luca, M.D., Ph.D., at the University of Toronto, and included 2006 Young Investigator Elisabeth B. Binder, M.D., Ph.D., at the Max Planck Institute of Psychiatry in Germany and 2002 and 2008 Young Investigator Jordan W. Smoller, M.D., at Massachusetts General Hospital. Dr. Aaron Howe of the University of Toronto was the first author of the paper reporting the team's results.

The research team was led by 2008 Young Investigator Vincenzo De Luca, M.D., Ph.D., at the University of Toronto, and included 2006 Young Investigator Elisabeth B. Binder, M.D., Ph.D., at the Max Planck Institute of Psychiatry in Germany and 2002 and 2008 Young Investigator Jordan W. Smoller, M.D., at Massachusetts General Hospital.

The team analyzed data from a total of 62 previous studies, plus additional data from their own research. The researchers found that among people of European descent, variations in genes called *TMEM132D* and *COMT* were more common among people with panic disorder than they were in unaffected people. The *COMT* gene tells nerve cells how to manufacture an enzyme involved in activating the message-carrying neurotransmitters dopamine, epinephrine and norepinephrine. Variations in *TMEM132D*, which produces a protein on the surface of certain brain cells, have been linked to increased anxiety in clinical and animal studies.

The meta-analysis revealed no significant genetic associations with panic disorder among people of Asian ancestry. The researchers also considered whether certain genetic variations might be linked to panic disorder only in men or women (women are twice as likely as men to experience the disorder). But they found no significant associations in those analyses. Likewise, no genetic associations were found in analyses that considered the effects of agoraphobia, a severe anxiety disorder that affects about one-third of people with panic disorder.

The researchers say a wide range of biological pathways likely influence individuals' susceptibility to panic disorder, and large-scale, genome-wide studies involving many people will be needed to better understand its complex genetics. ■



Vincenzo De Luca, M.D., Ph.D., 2008 YI
Elisabeth B. Binder, M.D., Ph.D., 2006 YI
Jordan W. Smoller, M.D., 2008, 2002 YI

Overactive Immune Cells Precede Schizophrenia Diagnosis

TAKEAWAY: New research finds overactive immune cells in the brains of individuals at high risk for schizophrenia, suggesting that inflammation may drive development of psychotic disorders in some people and that anti-inflammatory drugs may help treat them.

Evidence has been mounting that overactive immune cells in the brain may be among the causal factors in at least some cases of schizophrenia. Research reported in the October 15 issue of the *American Journal of Psychiatry* strengthens this case: According to the study, the activity of brain-protecting immune cells called microglia is ramped up not only in people who have been diagnosed with schizophrenia, but also in people considered to be at ultra-high risk for developing the disorder.

The team of scientists conducting this research included 2013 Independent Investigator Oliver D. Howes, M.D., Ph.D., at Imperial College London, and 2010 Distinguished Investigator Philip K. McGuire, M.D., Ph.D., at King's College London. Dr. Peter S. Bloomfield was listed as the paper's first author.

Microglia protect the brain from injury by engulfing and removing damaged or infected cells. But the inflammation this process causes can lead to neural degeneration and is suspected by some researchers of contributing to a variety of diseases, including Parkinson's disease, Alzheimer's disease, and multiple sclerosis.

Several lines of evidence have implicated microglia and inflammation in schizophrenia, including elevated levels of the cells found in brain tissue after patients' deaths. But Drs. Howes, McGuire and their colleagues wanted a clearer picture of how the immune cells behave earlier in life, when the disorder is still developing.

To find out, they used PET imaging to look for active microglia in the brains of three groups of people: 28 healthy controls, 14 people who had been diagnosed with

schizophrenia and 14 people who were considered to be at ultra-high risk for developing the disorder based on a clinical assessment. About 35 percent of people in this ultra-high risk category typically go on to develop schizophrenia or another disorder involving psychosis within two years.

Psychotic illnesses have in common symptoms that indicate a loss of contact with reality. Symptoms include delusions (false beliefs) and hallucinations (a perception of something [as a visual image or a sound] with no external cause).

The scientists administered to each study participant a dye that binds to a protein on the surface of activated microglia. This enabled them to visualize the cells with PET imaging. Their results indicated that microglial activity is elevated in schizophrenia patients and in those at very high risk of psychosis. Importantly, in those at high risk of psychosis, microglial activity was highest in those whose pre-psychotic symptoms were most severe.

The findings support the idea that inflammation is present in the brain during the development of psychotic disorders in at least some individuals, and suggest that chronic inflammation may in fact drive that development.

"A key issue for the field is whether microglial activation is secondary or primary [to schizophrenia] so our finding that microglial activation is seen in people showing at-risk symptoms is exciting, particularly as it was linked to more severe symptoms," says Dr. Howes. "The findings suggest that treatments to reduce microglial activation could be a new therapeutic approach to schizophrenia."

Monitoring microglial activity might also help clinicians predict which individuals are most likely to develop the disorder. ■

The team of scientists conducting this research included 2013 Independent Investigator Oliver D. Howes, M.D., Ph.D., at Imperial College London, and 2010 Distinguished Investigator Philip K. McGuire, M.D., Ph.D., at King's College London.



Oliver Howes, M.D., Ph.D., 2013 II
Philip K. McGuire, M.D., Ph.D., 2010 DI

Scientists Grow Brain “Organoids” To Study Autism Pathologies

TAKEAWAY: Researchers took skin cells sampled from autistic children and reprogrammed them as neurons, watching as the cells developed abnormalities. The work suggests the potential of this approach to understanding the causes of complex illnesses with a strong genetic component, from autism to schizophrenia, and in the efforts to find powerful new therapeutic targets.

Using an emerging technology that most scientists prior to the genome age would have considered impossible, three-time grantee Flora M. Vaccarino, M.D., and colleagues at Yale University have grown tiny clumps of human cells into structures that go through all of the stages that part of the developing fetal brain goes through, during the first trimester of pregnancy.

The point of Dr. Vaccarino’s experiments was to compare brain organoids grown from cells taken from unaffected fathers and from their autistic children. When they re-grew those cells as emerging brain cells, could any differences be seen?

In a paper published July 16 in the journal *Cell*, Dr. Vaccarino and her team described experiments suggesting how these developing structures, called brain organoids, provide a platform for scientists to study how the brain develops under normal conditions, and more importantly, how abnormalities in emerging brain structures may contribute to brain and behavior disorders.

Dr. Vaccarino’s team, which included 2013 Young Investigator Gianfilippo Coppola, Ph.D., and Jessica Mariani, Ph.D., focused on autism. Their starting point was to sample skin cells from fathers of four unrelated children with severe autism. The children all had abnormally enlarged heads, a condition called macrocephaly that correlates with severe symptoms of autism including intellectual disability and impairments in social communication.

Dr. Vaccarino’s team, which included
2013 Young Investigator
Gianfilippo Coppola, Ph.D., an
Jessica Mariani, Ph.D., focused on autism.

Skin cells sampled from the fathers of the four children and from the children were grown separately, after reprogramming by Dr. Vaccarino’s team. The reprogramming method is called iPSC, an acronym for induced pluripotent stem cell technology. iPSC restores or “resets” cells to a much earlier state in their development, when they were stem cells. Stem cells can take many different developmental paths, transformed by genetic programs into any one of a number of mature cell types. In this way, scientists can harmlessly gather ordinary skin cells and then take them back to a stem cell-like state, at which point they induce the stem-like cells to mature as neurons.

The team found several marked differences. In organoids grown from autistic children, too many GABA cells—which inhibit nerve signals—emerged from the stem cell precursors. This led to an imbalance in the ratio of inhibitory and excitatory nerve cells that is required for normal brain function. In addition to over-proliferation of GABA cells, there were also too many connections, or synapses, between neurons. These observations meshed with several prior theories about the causes of autism.

The researchers linked the excessive numbers of inhibitory neurons at least partly to the overactivity of a gene called *FOXG1*. When they grew organoids again using cells from the same autistic children—but this time artificially decreasing the expression of the *FOXG1* gene—some of the key developmental defects did not appear. Perhaps most importantly, the normal balance of excitatory and inhibitory neurons was restored. ■



Flora M. Vaccarino, M.D., 2011 DI, 2003 & 2000 II, 1994 & 1990 YI

Highlights from the 2015 New York Mental Health Research Symposium

On October 23, 2015, the Brain & Behavior Research Foundation held its 27th annual New York Mental Health Research Symposium, with presentations by top researchers in the field of mental illness. The symposium at the Kaufmann Music Center in New York City featured research talks by nine of the foundation's 2015 Outstanding Achievement Prizewinners, along with two promising Young Investigator grantees.

The Prizewinners are selected by special committees of the Foundation's Scientific Council, a volunteer group of 165 preeminent mental health professionals in brain and behavior research.



ABOVE: Robert R. Freedman, M.D.



ABOVE: Patrick McGorry, M.D., Ph.D.

2015 Lieber Prize for Outstanding Achievement in Schizophrenia Research



Robert R. Freedman, M.D.

Professor and Chairman,
Department of Psychology
*University of Colorado School
of Medicine*

Scientific Council Member

Distinguished Investigator
2006, 1999



**Patrick McGorry, M.D.,
Ph.D.**

Professor of Youth Mental Health
University of Melbourne, Australia

Executive Director,
Orygen, the National Centre of
Excellence in Youth Mental Health

Distinguished Investigator 1998

Dr. Freedman, a leading researcher in the neurobiology of schizophrenia, discussed his work on genetic variants that affect the risk for schizophrenia and bipolar disorder. In particular, he noted the progress that has been made by his research group and others on understanding and preventing genetic abnormalities in early brain development that may lead to mental illnesses later in life. Dr. Freedman's current work focuses on deficits in the *CHRNA7* gene, which increase the risk for schizophrenia, autism spectrum disorders and attention deficit hyperactivity disorder. The gene produces receptors on nerve cells that are activated normally by the nutrient choline in the amniotic fluid surrounding a fetus. This activation fails to occur fully in the illnesses mentioned above. Dr. Freedman and his colleagues hypothesized that increasing choline activation of these critical receptors during pregnancy would help prevent later mental illness, and are studying the impact of choline supplementation during pregnancy. (Choline is a normal component of meat, eggs and soybeans.)

Dr. Freedman's clinical trials have shown that dietary supplementation in the second and third trimesters of pregnancy can improve newborn neuronal function, and at around age four, these children have fewer problems with their attention and social interaction. These investigations have led to new treatments currently in FDA-approved trials for the treatment of schizophrenia in adults and for administration to pregnant women and their newborn children.

"This work and each innovative stage of it would not have been possible without The Brain & Behavior Research Foundation," Dr. Freedman said at the symposium. "Although the National Institute of Mental Health funds most mental health research, generally it doesn't fund things that are as new and innovative as the Brain & Behavior Research Foundation does. So it is really the catalyst to move mental health research forward."

Dr. McGorry, also a 2015 Lieber Prizewinner, is a world-renowned researcher in early intervention services for youth with emerging mental disorders, most notably psychotic and severe mood disorders. In his commendation for Dr. McGorry, Dr. William Bunney, M.D., the award chairperson, said that the Australian researcher has "shifted the therapeutic paradigm for schizophrenia to early detection and intervention, and led the major international development of evidence-based therapies with controlled trials that demonstrate significant reduction in progression to full psychosis in clinical high-risk subjects."

In his symposium presentation, Dr. McGorry noted the "inconvenient truths" of diagnosis for mental disorders, which often do not fit into discretely defined disease categories. As a result, he said, diagnoses can sometimes be controversial and drug therapies are not always as specific as the FDA and the pharmaceutical industry suggest.

Dr. McGorry's own research indicates the need for greater staging of mental illnesses, which would allow clinicians to refine treatments and avoid over- and under-treatments. Staging could also help clinicians and researchers better identify a disorder's underlying genetic, neurobiological and psychosocial mechanisms—which may span traditional diagnostic boundaries—and allow for a more personalized treatment strategy for individual patients.

2015 Colvin Prize for Outstanding Achievement in Mood Disorders Research

Drs. Berk and Young discussed their work on the role that oxidative stress on cells, poor energy metabolism, and inflammation may play in the development of neuropsychiatric disorders, including bipolar disorder.



Michael Berk, Ph.D.

Alfred Deakin
Professor of Psychiatry
Deakin University, Australia

National Health and Medical Research Council
Senior Principal Research Fellow

Dr. Berk noted new research suggesting that repurposed medications such as statins and anti-inflammatory agents such as NSAIDs and aspirin may have therapeutic potential in treating these elements of psychiatric disorders. Dr. Berk discussed his research on looking for immune biomarkers that may be targets for psychiatric therapy, along with studies of many of the psychiatric uses of N-acetylcysteine (sometimes known as NAC), a medication with anti-inflammatory properties. NAC has been used to treat the negative symptoms of schizophrenia (including problems with motivation, speech and social interactions) and to treat addiction in cannabis users. NAC has also been tested as a treatment to improve the quality of life in patients with bipolar disorder, which has increasingly been seen as a disease of cellular energy imbalance. Berk noted the rise in studies showing that there are elevated levels of inflammation in the body prior to the onset of many mental illnesses such as major depression. This insight has led to research on the use of repurposed medications such as statins and anti-inflammatory agents such as NSAIDs and aspirin which may have therapeutic potential in treating these elements of psychiatric disorders. He urged his fellow researchers to work across disciplinary lines to collaborate on treatments for mental illness, in the same way that cancer researchers have begun to approach that disease.



L. Trevor Young, Ph.D., M.D.

Dean, Faculty of Medicine and Vice Provost, Relations with Health Care Institutions
University of Toronto, Canada

Scientific Council Member

Independent Investigator 1995, Young Investigator 1989

Dr. Young shared data from his extensive work analyzing the oxidative damage in brain tissue taken from autopsies of patients with bipolar disorder. In his studies, he and his colleagues have documented evidence of increased oxidative damage in regions of the brain's frontal cortex that appear to correspond with bipolar disorder. This damage appears to be different in brains with bipolar disorder compared to those brains with depression and schizophrenia. Young has also uncovered evidence of oxidative damage in blood cells and in the lipid component of the brain's white matter (which serves as insulation for the brain's neural connections) in brains with bipolar disorder and schizophrenia. Changes in the extent and pattern of this damage, he suggests, might someday be used as a marker to assess the progression of these diseases as well as a guide to how well certain therapies are working in a patient.



TOP: Michael Berk, Ph.D.

BOTTOM: L. Trevor Young, Ph.D., M.D.

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

Drs. Casey and Castellanos are leaders in the innovative use of neuroimaging to study the critical stages of brain development in children and adolescents, with an eye to earlier intervention in mental illnesses.



Francisco Xavier Castellanos, M.D.

Brooke and Daniel Neidich Professor of Child and Adolescent Psychiatry

Professor of Radiology and Neuroscience, *NYU Langone Medical Center, New York*

Director of Child and Adolescent Psychiatry Research, *Nathan Kline Institute for Psychiatric Research*

Distinguished Investigator 2005

At the symposium, Dr. Castellanos spoke about his work on understanding the neurobiology of attention-deficit hyperactivity disorder, using neuroimaging and genetics-based approaches. His lab has focused on visualizing the synchronized fluctuations in neural activity in the brain, and developing a set of principles that helps to explain how this “functional connectome” draws together seemingly disparate parts of the brain into specific behaviors. He and his colleagues have looked how the functional connectome operates (or falls short) in diseases such as ADHD, autism spectrum disorders, schizophrenia, dyslexia and normal aging. Other researchers, he said, have been using the functional connectome approach to better understand the circuitry involved in addiction. He noted that the pace of progress in understanding conditions such as ADHD has been enhanced by the open sharing of neuroimaging data among researchers, through efforts such as the Functional Connectomes Project and the International Neuroimaging Data-sharing Initiative—both of which Castellanos helped to establish.



BJ Casey, Ph.D.

Director and The Sackler Professor, *The Sackler Institute for Developmental Psychobiology*

Professor of Psychology, Psychiatry and of Neuroscience

Brain and Mind Research Institute, Weill Cornell Medical College

Scientific Council Member

Dr. Casey discussed her research in characterizing adolescence’s sensitive period of brain development, and how environmental and genetic factors may alter this development to contribute to the risk of mental illnesses in young people. Adolescence is the peak age of emergence for many mental illnesses, she noted. Anxiety disorders in particular are common among adolescents, in which they are mostly treated with cognitive behavioral therapy. However, about only half of adolescent patients respond to this therapy, and researchers would like to know more about why some patients do not respond and if there are other ways to improve the therapy to increase its success. Dr. Casey’s studies have involved brain imaging and genetic approaches that show that adolescent brain circuitry may not be able to regulate fear as well as in younger and older ages. This imbalance in fear regulation is a result of normal changes in the brain’s prefrontal cortex during this age that are important for emotion regulation. Casey is using her research to help fine-tune cognitive behavioral therapy for adolescents with anxiety disorders in a way that acknowledges their differences in fear regulation.



TOP: Francisco Xavier Castellanos, M.D.

BOTTOM: BJ Casey, Ph.D.

2015 Goldman-Rakic Prize for Outstanding Achievement in Cognitive Neuroscience

Dr. Arnsten is continuing the pioneering work of the prize's namesake, in her exploration of the molecular foundations of the brain's center for abstract thought.



Amy F.T. Arnsten

Professor of Neurobiology
Yale Medical School, Yale University

Scientific Council Member

Distinguished Investigator 2008, Independent Investigator 1998

Dr. Arnsten studies the brain's prefrontal cortex, which is critical to higher-level brain processes such as abstract reasoning, decision making and regulating behavior and attention. In her symposium presentation, she discussed her work on the molecular mechanisms behind prefrontal circuitry, and how these circuits generate the mental representations that are critical to higher thought. Following in the footsteps of her mentor Patricia Goldman-Rakic, Arnsten is studying the factors that make these circuits so vulnerable in mental illness. In particular, her research demonstrates how the fine-tuned molecular maintenance of these circuits is also affected by stress, sometimes leading the circuits to “disconnect” when there is too much stress. The molecules that would rein in the stress response and keep the prefrontal cortex connections strong, she said, are some of the same molecules that are linked to an increased risk of schizophrenia when they are genetically damaged or altered.

Her findings have led her and her colleagues to develop a treatment called guanfacine (Intuitiv) to address deficits in prefrontal circuits in a variety of prefrontal disorders, beyond schizophrenia. These illnesses include ADHD, Tourette's syndrome and autism spectrum disorders. Arnsten said the drug has also proved to be especially helpful in treating children who have been abused or traumatized, and that the medication is now in trials as a therapy for mild traumatic brain injury and substance abuse.

The Goldman-Rakic prize was created in memory of Patricia Goldman-Rakic, Ph.D., a distinguished neuroscientist renowned for discoveries about the brain's frontal lobe, after her tragic death in an automobile accident in 2003.



Keith O'Neil

Former NFL Super Bowl Champion

The day's presenters also included Keith O'Neil, a former NFL Super Bowl champion who gave a keynote speech about his personal experience of living with bipolar disorder.



TOP: Amy F.T. Arnsten

BOTTOM: Keynote presentation *Living with Bipolar Disorder* by Keith O'Neil, former NFL Super Bowl Champion

2015 Sidney R. Baer Prize for Outstanding Achievement in Innovating & Promising Research

Drs. Hoffman and Nelson study the earliest stages in the development of mental illness, from the time in the womb to young adulthood.



M. Camille Hoffman, M.D.

Assistant Professor of Maternal Fetal Medicine

University of Colorado School of Medicine and Denver Health Medical Center

In her symposium presentation, Dr. Hoffman discussed her research on assessing fetal brain development, with an eye to assessing stresses experienced by the fetus during pregnancy, and in determining whether there are prenatal interventions that could decrease the incidence of mental illness. Previous studies have shown that children of preterm birth (earlier than 37 weeks gestation), low birth weight, and those born to mothers with prenatal or postnatal mood disorders are at a higher risk of behavioral and developmental delays and autism spectrum disorders. Later in life, these children may have a higher risk of schizophrenia and mood disorders, and even chronic neurodegenerative disorders such as Parkinson's disease. These findings confirm that prenatal care may have multigenerational benefits when it comes to mental illness, Hoffman says. She has investigated the time period in utero where nature and nurture influences on a growing fetus begin to intersect, finding a critical period within the second trimester. Her research uses noninvasive therapies that compare hair from a mother and her newborn, each of which captures a time-sensitive record of hormones and other neurological proteins involved in fetal brain development. The studies show that psychosocial stress in the mother during the second trimester may produce more stress hormones in the fetus, which can sometimes lead to preterm birth. She is also using 3D ultrasounds to track similarities and differences in fetal brain development in children who go on to develop mental illness.



Barnaby Nelson, Ph.D.

Associate Professor

Orygen, The National Centre of Excellence in Youth Mental Health

Independent Investigator 2015, Young Investigator 2008

Dr. Nelson presented his work on a long-term study of young patients at ultra-high risk for schizophrenia and other psychotic disorders, including an examination of the clinical, neurobiological, cognitive and genetic predictors of the disease outcome in these patients. He discussed one of his studies conducted at Orygen on the long-term follow up (on average, 7.5 years after arriving at the clinic for pre-schizophrenia symptoms) of 400 patients deemed ultra-high risk for schizophrenia, hoping to retrospectively identify behavioral and biological markers that would help predict the transition to full-blown disease. The study, one of the first of its kind internationally, found that 35 percent of the patients did transition to schizophrenia, most within one to two years of their first arrival at the clinic. Some of the predictors of this transition, Nelson said, include poorer patient functioning, a longer duration of symptoms and a history of childhood sexual abuse. Nelson is now studying the phenomenon of "self-disturbance," in which patients lose a sense of themselves as cognitive, social and bodily individuals. Disturbance of this basic self may help to predict transition to schizophrenia in high-risk individuals, according to Dr. Nelson.



TOP: M. Camille Hoffman, M.D.

BOTTOM: Barnaby Nelson, Ph.D.

2015 Young Investigator Presentations

With increasingly focused tools and diagnostics, Drs. Zhang and Landry show how the treatment of mental illnesses may soon be refined to the level of the single cell and the individual patient.



Jianping Zhang, M.D., Ph.D.

Attending Psychiatrist
Zucker Hillside Hospital, North Shore-LIJ Health System

Assistant Investigator
Feinstein Institute for Medical Research

Young Investigator 2014, 2010

Dr. Zhang presented his recent findings in the field of pharmacogenomics, which aims to use genetic variations in patients to predict which therapies would be most effective in treating their symptoms while minimizing side effects. The guiding principle of this field, as Dr. Zhang noted, is “delivering the right drug for the right patient at the right time.” In schizophrenia patients, for example, up to 30 or 40 percent of patients do not respond to their first prescribed antipsychotic medications. The answer to why this might be could lie in subtle genetic differences between patients, he said. Dr. Zhang works with others to probe massive databases of genetic variants to pair specific variants with responses to drugs such as the antipsychotics aripiprazole and clozapine. His current work involves genetic variations in the DRD2 dopamine receptor gene and brain-derived neurotrophic factor (BDNF) protein, both of which may affect how patients respond to certain antipsychotic drugs.



Markita Patricia Landry, Ph.D.

Assistant Professor of Chemical and Biomolecular Engineering
University of California, Berkeley

Young Investigator 2014

Dr. Landry presented her work on detecting and observing how neurotransmitters, the brain’s chemical communicators, operate at the level of the single cell. The ultimate goal, she notes, is to visualize in real time how brain cells interact with each other. Her background in physics and chemical engineering has led her to develop a carbon nanotube-based nanosensor that can detect chemicals such as nitric oxide (produced in inflammation), hormones and potentially neurotransmitters such as dopamine that are often altered in mental illness. She will soon test these optical nanosensors in devices that detect the release of neurotransmitters in the rodent brain. She is also exploring the use of two-photon microscopy—an imaging technique that is beginning to make significant inroads in the neurosciences after use in other disciplines—to combine with her nanosensors to provide a more complete look at neurons in the living brain.



TOP: Jianping Zhang, M.D., Ph.D.

BOTTOM: Markita Patricia Landry, Ph.D.



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

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

2015 Distinguished Investigator Grants

181 Applications

15 Grants Awarded

\$1.5 Million Total Funding

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

The grantees were selected by members of the Foundation's Scientific Council, a prestigious group of 165 leaders in brain and behavior research. This year's 15 Distinguished Investigators were selected from 181 applicants. Their projects demonstrate the variety of ways in which our knowledge about mental illness and brain and behavior disorders is advancing. Some of these studies represent multi-disciplinary collaborations, while others take a deep look using a single discipline.

"We received a large number of outstanding proposals. Some deal with a specific research problem in one area of mental illness; many are relevant for a number of illnesses; some involve basic research that will serve as the basis of clinical or translational research; and others start from a translational or clinical foundation. We are able to see the growth of the field and the manifestations of the enhanced power of research related to mental illness that have come about with the remarkable support of the Brain & Behavior Research Foundation"

JACK D. BARCHAS, M.D.

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

Psychiatrist-in-Chief
Weill Cornell Medical College, NewYork-Presbyterian Hospital and
Paine Whitney Clinic

Chair, Scientific Council Distinguished Investigator Selection Committee



Jack D. Barchas, M.D.

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

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

Founding Member of the
Foundation's Scientific Council

Recipients of the 2015 Distinguished Investigator Grants

Addiction



YAVIN SHAHAM, PH.D., of the National Institute on Drug Abuse has created a rat model to investigate the mechanisms underlying voluntary abstinence from methamphetamines following addiction. Past research suggests that both humans and rats experience stronger methamphetamine cravings the longer they choose to abstain from the drug. In this study, Dr. Shaham's team will test

how those increased cravings are driven by particular connections within the brain. Those connections emanate from a region of the brain called the insula, which contributes to diverse functions from survival instincts to self-awareness, and are traced to the central part of the amygdala, the brain's emotion center. Better understanding of this circuit's impact on drug cravings, the team hopes, will improve approaches to preventing relapse among methamphetamine users.

Autism Spectrum Disorder



DANIEL H. GESCHWIND, M.D., PH.D., of the University of California, Los Angeles, seeks to understand the genetic basis of social and communication deficits in autism spectrum disorders. Some of these deficits can be reduced in animal models with infusions of the hormone oxytocin into the nervous system, which promotes context-dependent social

behaviors. Dr. Geschwind's team will explore the genetic and molecular mechanisms driving oxytocin's effects in autism. To do so, they will study a gene expressed in oxytocin-producing neurons that encodes a protein called *Cntnap2* (for contactin-associated protein-like 2). The team will test whether the *CNTNAP2* gene contributes to social deficits in autism by regulating the structure of, and signaling from, oxytocin-producing neurons.



NAHUM SONENBERG, PH.D., of McGill University, will explore the activity of a protein that helps regulate gene expression, and specifically the process by which other proteins are generated, in many parts of the brain, with implications for treating autism spectrum disorder. The protein, called eIF4E, has already been linked to autism-like deficits in animal models. Using human cells,

Dr. Sonenberg's team will create different mutations affecting eIF4E. They will then track which genes show altered expression as a result of the mutations. Since eIF4E-controlled gene expression is already FDA-approved as a target for drug compounds, this work aims to bring researchers one step closer to exploiting eIF4E to treat disorders on the autism spectrum.

Bipolar Disorder



ALAN STEWART BROWN, M.D., M.P.H., of Columbia University, hopes to more clearly identify which prenatal risk factors can increase a child's likelihood of developing bipolar disorder (BD). His work will focus on a cohort of 19,000 individuals born between 1959 and 1967 whose data were used to find prenatal risks for schizophrenia. Building on those findings, Dr. Brown and col-

leagues will investigate the effects of a mother's immune system, smoking habits and levels of thyroid hormone on children's later development of bipolar disorder. They will also study how these effects differ by sex and family history of psychiatric disorders. The findings may help inform public health interventions that improve prenatal care to reduce the risk of bipolar disorder.

Depression



MICHEL BARROT, PH.D., of the University Pierre & Marie Curie, will investigate the imprint of depression on part of the brain crucial for the dopamine system. Dopamine, a chemical in the brain, plays a role in a range of neurological and psychiatric disorders. The dopamine-rich region Dr. Barrot will study is the tail of the ventral tegmental area, or the tVTA. Looking at a

rat population, Dr. Barrot's team will try to identify genes with high rates of expression in the tVTA, as possible drug targets for regulating dopamine activity. Then, they will induce depression in rats to examine what the disorder looks like in the tVTA. By examining these aspects of the tVTA, the team hopes to broaden our understanding of the region's role in mood and other disorders.



CATHERINE G. DULAC, PH.D., of Harvard University, will explore how different patterns of connections in the brain contribute to behaviors that define postpartum depression. Affecting about 10 percent of mothers and five percent of fathers in the U.S., postpartum depression describes prolonged emotional disruptions in parents after childbirth that can

interfere with parent-child bonding. Using mouse models that parallel the biology and behavior of human parenting, Dr. Dulac's team will study connections to parenting-associated brain cells that may mediate postpartum depression. These cells are in the medial preoptic area of the hormone-producing hypothalamus. By examining these cells' neural connections, gene expression, and effects on parental behavior, the team hopes to shed light on the pathology of postpartum depression and identify possible chemical targets for treatment.

Yavin Shaham, Ph.D.,

"We hope that our results will inspire translational studies using noninvasive brain stimulation approaches to prevent drug relapse in meth users."

Alan Stewart Brown, M.D.

"This [data] will allow us to conduct the most comprehensive and rigorous study to date on prenatal exposures and BD, and evaluate their relationships with family history of psychiatric illness and with phenotypic outcomes."

Michel Barrot, Ph.D.

"The elucidation of a new brain structure is a relatively rare event in the present age of neuroscience. Such discoveries have the potential to rapidly advance our knowledge, as evidenced by the speed with which new data have emerged regarding the tVTA."

Catherine G. Dulac, Ph.D.

"Despite the heavy societal impact of postpartum depression, and the recognition that the sudden changes in the levels of circulating hormones and neuropeptides around childbirth lay the groundwork for the high vulnerability of young mothers to PPD, relatively little is known about postpartum depression's biological basis."

Bernice Ann Pescosolido, Ph.D.,

The proposed [survey] couples experienced and emerging leaders in this area of mental health research, and promises to provide critical information for those with interest in translational science and personalized medicine."

Moses V. Chao, Ph.D.

"We will follow a hypothesis-driven approach that leverages crucial mutations identified in sporadic cases to identify high impact cell signaling pathways that are disrupted."

Anthony John Koleske, Ph.D.,

"Our goal is to identify therapeutic strategies aimed at preventing or reversing this loss of neuronal connectivity [in schizophrenia]."



JEFFREY H. MEYER, M.D., PH.D., FRCP(C), of the University of Toronto, hopes to shed light on periods of major depressive disorder that have been linked to abnormalities in the immune system. Some people do not get relief from depression while taking commonly prescribed SSRI-class antidepressant medication like Prozac. Dr. Meyer and colleagues recently found

that in certain brain regions of some treatment-resistant patients, there are signs of increased inflammation, which reflects immune system activity. Continuing this work, Dr. Meyer's team will give such patients an anti-inflammatory drug. The team expects that among these patients, high levels of inflammation in the brain will predict strong relief from depression symptoms in response to the drug. Confirming this prediction would advance attempts to personalize depression treatment by targeting immune response in certain patients who do not respond well to current antidepressant options.

Mental Illness



BERNICE ANN PESCOSOLIDO, PH.D., of Indiana University, will repeat and reinvent the largest U.S. survey examining persistent stigma toward mental illness. Past surveys of attitudes toward mental illness have found that many Americans do harbor prejudices about mental illness, ironically, even as more people accept neurobiological explanations for the most

prevalent disorders. Dr. Pescosolido will examine whether that trend has changed in the past decade and will expand the research to other factors, including what it is like to experience mental illness-based discrimination and respondents' amount of contact with mental health diagnoses. With this research, her team aims to help reduce the health burden of stigma, which has negative effects on important recovery factors ranging from self-esteem to willingness to seek help.

Post-Traumatic Stress Disorder



ISMENE L. PETRAKIS, M.D., of Yale University, hopes to lay the groundwork for the pharmacological treatment of overlapping post-traumatic stress disorder (PTSD) and alcohol abuse disorder. Although it is common for people to suffer from both conditions, current pharmacological treatments only target one or the other. With this study, Dr. Petrakis will investigate

the hormone progesterone as a treatment option. Best known for its role in the female reproductive cycle, progesterone can also promote healthy brain activity. It has been shown to reduce alcohol withdrawal symptoms and soften physiological responses to mental stress. Among people diagnosed with both PTSD and alcohol abuse disorder, Dr. Petrakis' team will test progesterone's effects on alcohol consumption, stress responses to trauma, mood, cognition and motor coordination (while controlling for women's internal progesterone levels).

Schizophrenia



MOSES V. CHAO, PH.D., of New York University, will study proteins in the brain that have previously been associated with aggressive behavior in schizophrenia. In particular, his team will expand on their previous work examining genes that encode proteins called neurotrophins. Neurotrophins support the development and function of brain cells. Dr. Chao's team hopes to

identify rare mutations in neurotrophin-encoding genes linked to aggression in schizophrenia, and explore how those mutations affect signaling between brain cells. They hope to shed light on the pathology underlying aggression, which is significantly more common among people with schizophrenia and other conditions that involve distorted experiences of reality.



PAUL J. KENNY, PH.D., of the Icahn School of Medicine at Mount Sinai, will study genetic mechanisms that may give rise to behavioral deficits in schizophrenia. Specifically he will study microRNAs, or miRNAs. These brief messages copied from DNA do not, like much longer RNA molecules, contain the code for manufacturing proteins. Rather, they appear to play

regulatory roles. Some miRNAs are thought to help regulate structure, function and plasticity of neurons in the brain. One particular miRNA, miR-206, has been linked in schizophrenia to low amounts of the brain chemical GABA—crucial for tamping down, and thus helping to control, communication activity among neurons. It has also been linked to symptoms of psychosis, or distorted perceptions of reality. Studying a mouse population, Dr. Kenny's team will disrupt miR-206 in certain brain cells known as interneurons, which play key modulating roles in communication networks. The team expects these disruptions to create schizophrenia-like behavioral deficits in the mice, shedding light on the miRNA's role in the disorder.



ANTHONY JOHN KOLESKE, PH.D., of Yale University, seeks to uncover potential drug targets to reverse the loss of connections between brain cells seen in schizophrenia. These connection deficits appear in the form of reduced dendrite structures, the branching thread-like filaments that connect neurons. Reduced dendrite structures are believed to be associated

with disruptions in perception, cognition, emotional expression and motor skills among people with schizophrenia. One type of protein that may contribute to dendritic deficits is the Trio family. Dr. Koleske plans to expand his past work on Trio proteins by studying the proteins—and genes that encode them—in greater detail. The findings, he hopes, will point toward Trio as a promising target for new schizophrenia drugs.



EDWIN S. LEVITAN, PH.D., of the University of Pittsburgh, will explore the precise effects of antipsychotic drugs on transmission of the brain chemical dopamine. Often used to treat schizophrenia and bipolar disorder, antipsychotics work by blocking activity at docking ports for dopamine that are located on the surface of nerve cells. These drugs can also enter

the structures within neurons, called vesicles, that store and release dopamine. Dr. Levitan and colleagues will investigate how the buildup and release of dopamine in vesicles alters the effects of antipsychotic drugs when those drugs are also released from vesicles. Their findings may influence the design of antipsychotics and other drugs whose ingredients can get trapped in brain chemical storage sites.



JONATHAN S. MILL, PH.D., of the University of Exeter, will continue to investigate genetic patterns that build a foundation for schizophrenia. Known to have a strong genetic component, schizophrenia also has been tied to epigenetic variation—chemical groups attaching to genes that affect gene activity. People with schizophrenia have shown unique epigenetic markers

within genes that direct brain development in the fetal stage. In this study, Dr. Mill plans to study a specific epigenetic modification and how that modification changes during fetal development. This work aims to sharpen our picture of the neurodevelopmental trajectory underlying schizophrenia.



DAVID L. SULZER, PH.D., of Columbia University, will study brain chemicals linked to schizophrenia at the molecular level, aiming for a better understanding of the chemical processes driving the illness. Antipsychotic medications commonly used to treat schizophrenia target docking ports for the chemical dopamine, which can in turn promote the production of the chemical

norepinephrine. Looking at mice, Dr. Sulzer will examine the release of dopamine and norepinephrine in response to the drug amphetamine. Amphetamine has previously been used to identify abnormalities in the dopamine systems of people with schizophrenia. His team will also look at dopamine and norepinephrine release during working memory tasks, which are impaired in schizophrenia. They hope to use this work to identify genetic factors and communication points in the brain that alter dopamine release in schizophrenia.

Depression

Q Does Depression Last For A Lifetime?

A Depression is a highly recurrent disease, meaning that most people who live with it have more than one occurrence of it in their lifetimes. Half of those who have recovered from one depression episode are likely to have at least one relapse, and those who have recovered from two episodes have an 80 percent chance of the depression returning. On average, people with major depression will have five to nine episodes during their lifetimes.¹

Q What kinds of “next-generation” depression treatments are scientists pursuing?

A Several research teams, including those led by Young Investigator grantee James W. Murrough, M.D., of the Icahn School of Medicine at Mount Sinai, Scientific Council member J. John Mann, M.D. of Columbia University Medical Center and Independent Investigator grantee Carlos Zarate, M.D. of George Washington University have recently found that intravenous doses of the drug ketamine can reduce the symptoms of depression and suicidal behavior within hours, instead of weeks as is usually the case with standard antidepressants.^{2,3} Scientists are planning clinical trials to find out more about ketamine’s long-term usefulness and safety, and to test whether oral or nasal versions of the drug might also be effective.

Other scientists are looking for ways to target the neural circuitry that is altered in depression. Foundation Scientific Council member Fritz Henn, M.D., Ph.D. of Cold Spring Harbor Laboratory is studying the effects of electrically “silencing” a small portion of the brain called the habenula to reduce depression symptoms in humans and mice.⁴ Scientists are looking toward therapies based in a technology called optogenetics, which would use light-sensitive proteins to control neural circuits related to depression.⁵

Q What is treatment-resistant depression?

A Treatment-resistant depression is depression that does not respond to standard treatments such as antidepressant drugs or psychotherapy. These therapies may not ease the symptoms of depression at all, or they may only work sporadically in a patient. Patients who appear to have treatment-resistant depression may benefit from trying a variety of antidepressant or different forms of psychotherapy. Several therapies that stimulate nerve cells electrically are effective in treating some patients with treatment-resistant depression, including electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) and vagus nerve stimulation (VNS).⁶

Q Can a person be too old to develop depression?

A Depression is a common diagnosis among older adults: a 2007 study estimated that there were about seven million U.S. adults aged 65 or older who were affected by depression.⁷ Depression in these adults may be caused by the same genetic and environmental factors that contribute to depression in younger people. Some older adults with no family history of depression also may develop “vascular depression,” which occurs when aging blood vessels stiffen and reduce the flow of blood to the brain, leading to depression symptoms.⁸

Q What is the difference between grief and depression?

A Grief and depression can sometimes be difficult to distinguish, since they can share many of the same symptoms such as intense sadness, sleep disorders, loss of pleasure and difficulty concentrating. But there are some key differences that help to separate the two. People with depression often suffer a drop in self-esteem and a feeling of isolation and disconnection from others, while these symptoms are less common in people with grief. Grieving people are usually able to carry on with most daily functions within two to three weeks of their loss, while people with depression may not be able to function for weeks or months at a time.⁹

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Parenting: Advice on Caring for Bipolar Disorder



Robert M.A. Hirschfeld, M.D.

Robert M.A. Hirschfeld, M.D., is a professor of clinical psychiatry at Weill Cornell Medical College. Prior to joining Weill Cornell in April 2015, he served for nearly 25 years as Professor and Chair of the Department of Psychiatry at the University of Texas Medical Branch in Galveston; and for 18 years at the National Institute of Mental Health as Chief of the Mood, Anxiety, and Personality Disorders Research Branch. He is a founding member of the Foundation's Scientific Council, a 2002 Distinguished Investigator grantee, and winner of the Falcone Prize for Outstanding Achievement in Affective Disorders Research (renamed the Colvin Prize in 2012).

Dr. Hirschfeld is world renowned for his research on the diagnosis and treatment of bipolar disorder and depression. He developed the Mood Disorder Questionnaire (MDQ) in 2000, the most widely used screening instrument for bipolar disorder in the world. He served as chair of the original and the revised American Psychiatric Association Guidelines for Treatment of Patients with Bipolar Disorders.

There are lots of misconceptions about bipolar disorder. Can you define the disorder and explain the relation between its “manic” and “depressive” phases?

Bipolar illness was once referred to as “manic-depressive” illness. It’s usually a lifelong disorder, characterized by episodes of abnormal, often persistent, highs, and abnormal, often persistent, lows. The highs are characterized by a “too-good” mood, irritability, increased energy, increased interest in activities, decreased need for sleep, and sometimes, delusions—some people who are manic actually believe they can fly or believe they have super powers.

Sometimes, people who are in the “manic” phase of bipolar disorder make rash decisions, do things that get them into trouble, such as spending way too much money, or getting involved in sexual promiscuity—this would be in people who would never, when not manic, be promiscuous—and it’s all part of the illness. Of course, behaviors of this kind can ruin lives, families, and relationships.

The other half of the illness involves depression, which is almost the polar opposite of mania. You have decreased energy, lower mood, you’re sad—you feel empty, depressed. You’re very pessimistic—you only see the negative side of things. And, of course, there is always a possibility of suicide, when people are depressed in this way.

I want to make sure I understand the relation between the two phases, manic and depressive. If I hear you right, they’re both features of bipolar illness, but the “high” itself has nothing to do with a crash that must follow next. The up and down phases don’t cause one another or necessarily follow in sequence.

That’s mostly correct. You don’t need the depression to make the diagnosis; you do need at least one manic or hypomanic [a less severe form of mania] episode. But in general I would characterize bipolar disorder as an illness usually involving episodes of both highs and lows.

Is it hard to determine if a person has bipolar disorder, since we all have highs and lows? Statistics show that only about three percent of us have bipolar disorder.

It’s true that everyone on the planet, or almost everyone, has times when they’re feeling good, when they have a lot of energy, like when new projects are coming up, that kind of thing. But it’s different in those with bipolar disorder. Their ups are different from those that healthy people have. One symptom that’s characteristic is that the need for sleep decreases substantially in people with mania. People who normally sleep eight hours a night to feel rested are sleeping four or five hours, and are waking up in the morning with complete energy. People in the depressed phase of the illness can sleep for 12 hours, and still have no energy. Those lows are different than the usual lows that virtually everyone has.

In fact, the latest edition of the manual that doctors use to diagnose psychiatric disorders, the DSM-5, has made a major change in how we conceptualize and diagnose bipolar disorder, one that I think is very helpful—and that is to include not just the mood disturbance that we’ve been talking about, but also the disturbance in energy, and in activation. We’ve always seen this as part of the illness. But now it’s understood as a necessary part—if you simply have the mood disturbance and no change in energy, you do not get a diagnosis of bipolar disorder.

What is the difference between the two major types of bipolar disorder, called “Bipolar I” and “Bipolar II?”

Bipolar I is the more classic form of the disorder which requires at least one episode of mania. People with Bipolar I can have episodes of less severe hypomania (see below), but must have at least one manic episode.

Bipolar II involves at least one episode of hypomania. Hypomania is less severe than mania and does not require hospitalization or include delusions. But let me stress that Bipolar II is not necessarily a less severe *illness*, because the depressions that can occur in both types—Bipolar I and II—can be equally severe. Hence, there is an elevated suicide risk in both types.

The rate of suicide is quite elevated in people who have the diagnosis, compared with the rate in the overall population.

True. The most frequent cause of suicide is depression, and depression is fundamental to bipolar disorder. The elevated suicide rate among people with the illness is almost exclusively related to the “depressive” phase, not the manic.

We sometimes hear of “rapid cycling” or the “rate of cycling.” What does this mean?

Rapid cycling refers to having frequent episodes—four or more in a year. It’s more common to have one or two episodes in a year. Those who have frequent episodes are often more difficult to treat. In fact, there are people who cycle even more rapidly, on a two- to three-day cycle. There is disagreement about how to classify such patients, but I certainly treat people who have cycles as short as a single day in length. They are clearly hypomanic for that day, and then depressed the next day.

When you say “episodes,” do you mean both the “up” and “down” phases—together they make one episode?

No. Either one is an episode. You can have manic-only cycles or depressed-only cycles. You don’t have to cycle back and forth. Some people will become manic for a very short period of time, then they return to normal mood; and their next episode could again be manic, or it could be depressive.

When someone is depressed, how do you know if they are “just” depressed—what doctors call “unipolar depression”—or perhaps they are in the depressive phase of bipolar disorder?

The issue of missing bipolar disorder is one that I’ve done a lot of research on and have been concerned about for my entire professional life. The problem is that most bipolar patients first come in depressed. About about one in five depressions we see—20 percent—are people who in fact have bipolar disorder. That’s a lot.

One problem is that people don’t think about the possibility of bipolar illness. The patient coming in with depression may not even remember that they’ve had hypomanic or manic episodes, and they don’t bring it up. The family isn’t thinking about it. And if the healthcare provider doesn’t ask, it’s missed. I’ve done a number of studies on this. It’s really easy to miss. Someone comes in, and they’re so low that they almost crawl into your office—you can’t *imagine* this person being high, being manic. But they may have been, and so if you don’t ask about it, you’re not going to find out about it. I like to have a family member come in with the patient on the first visit because they can often bring very useful information that the patient him or herself is just not able to get in touch with.

How many bipolar patients lack insight about their condition, for instance, have no self-awareness of having been manic?

In Bipolar I, it’s probably 40 to 50 percent—a substantial number. In Bipolar II, [it’s] substantially less. In general, those with Bipolar II don’t have the devastation to family, career, and education in the same kind of way. But they do have terrible problems with productivity, lost jobs and so on, because they have been depressed and they can’t deliver on things one is expected to do in life.

In Bipolar I, the most common variety, it usually takes several manic episodes, having devastating consequence, before people with the disorder recognize they actually have an illness and they’re going to have to deal with it for the rest of their life. They will deny, deny, deny—and it’s very sad. I often see people in their 30s who are finally coming to terms with it and they have lost a decade of their life to the illness.

Is there any way to prevent this tumult?

The problem of self-awareness is real and is one of the reasons we developed the MDQ—the Mood Disorder Questionnaire. It's a 13-question “yes/no” questionnaire, asking things about whether you've ever had times when you spent too much money, times when you had an abnormally high mood—it goes through a number of the symptoms of mania, and it takes about five minutes to fill out. You can score it, or a health professional can. It's available on the Internet if you do a Google search. You can also get it in many doctors' offices, and certainly from advocacy organizations. (The MDQ is available at www.dbsalliance.org/pdfs/MDQ.pdf)

What should you do after you complete the MDQ?

Let me state again that the MDQ is a screening instrument. If you screen positively, it does not mean you have bipolar disorder. It means that you're likely to have it and that you should be more comprehensively evaluated. If you score it yourself and are “positive,” then you should discuss the results with your primary care provider, or better, a psychiatrist or another mental health professional.

Can the MDQ help in those situations where, let's say, a mother and daughter disagree on whether the daughter has had manic symptoms?

Yes. A version of the MDQ we recently tested specifically addresses this sort of problem, when children and their parents don't agree on symptoms. A study in which I was involved, led by my colleague Dr. Karen Dineen Wagner (Foundation Scientific Council Member and 2012 Colvin Prizewinner for Outstanding Achievement in Mood Disorders Research), gave the adolescent version of the MDQ to parents about the child; but we also gave it to the adolescent him or herself, and also asked the child to fill it out again, this second time “pretending you are your best friend or someone who knows you well—from the point of view of what you think they would say about your behavior?”

Which of the three versions proved to be most accurate?

By far it was the form filled out by the parent. It was clear that the parents were much more able to accurately describe things that the doctors ended up strongly believing were correct in terms of symptoms.

I've heard in the past that there is a particular danger when someone with bipolar disorder is misdiagnosed as having only unipolar depression and is prescribed antidepressants. Can you explain?

We used to think that giving an antidepressant medication without a mood stabilizer to a patient with bipolar disorder would serve to destabilize the illness—in other words, make more cycles, more rapidly, and even might precipitate a manic episode. That was based on experience mainly with the “tricyclic” class of antidepressants, for example Tofranil (imipramine). These are medications that we use very rarely these days. It turns out that these issues are usually moot when a doctor prescribes one of the modern class of antidepressants—SSRIs like Prozac, Paxil, Zoloft. It doesn't seem that they destabilize bipolar disorder. But for reasons we don't understand, they don't seem to work as well as antidepressants in people with bipolar illness.

Much more generally, what advice can you offer to anyone who is curious about bipolar disorder, who may be wondering if they or a loved one is affected? What should they do?

I would ask people to recognize that bipolar disorder is a serious brain disorder and there's a huge amount we can do to help people with this illness to manage it, to reduce or prevent episodes. I would also strongly encourage those who are concerned that they, or a loved one or friend, might have bipolar disorder, go online, find the MDQ, and if the score is positive, or if there is any question as to the result, contact a doctor or mental health professional for a thorough evaluation. ■

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“Supporting research is essential in order to advance our knowledge as to how the brain works and what can go wrong to cause mental illness. Focused research is certain to lead to relief and comfort for the millions who struggle daily with these illnesses. Our participation for over 20 years with the Foundation, and as Research Partners for the past 13 years, gives us the opportunity to support and motivate the endeavors of the Young Investigators who are focused on these complex issues.”

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A Recovery Story: From A Nightmare Childhood, a Happy Path Forward

After reclaiming her life from bipolar disorder, a volunteer gives back.



It was in eighth grade that Maureen Gillespie began feeling like she was no longer herself.

She experienced hallucinations and unexplained bursts of anger. She started acting out. One time she saw John and Bobby Kennedy in her bedroom. Another time, she wandered out of school for recess and didn't come back.

"I was turning into another person," she recalls.

In 1964, she had a visit with psychiatrist Dr. Raul Zaldivar in her hometown of Chicago. She remained under his care for 20 years, until his death. "Dr. Zaldivar became my savior," who was as diligent as he was compassionate, Maureen says. Despite all his efforts, Maureen's symptoms continued throughout her teens. At 16, she was diagnosed with bipolar disorder.

During her junior year of high school, her parents reluctantly gave her permission to go on a class trip to visit New York and Washington, D.C. Maureen did not have any close friends; no one wanted to be her roommate. During the trip she was in an acute state of mania—not sleeping, talking constantly.

"It was a nightmare," she put it simply.

She found herself in Washington University Hospital, where she remembers being on a gurney in the hallway of a crowded emergency room. Then she was in St. Elizabeth's Hospital—heavily medicated, lying on a mat, in a padded cell; people drifting in and out, holding her down, giving her a shot. She would repeatedly ask if her parents knew where she was and if she could go home; she would never get a straight answer. Scared, alone, weaving in and out of consciousness, Maureen has no idea how long she was in that room.

She missed most of her junior year of high school, returning on the last day to say goodbye to the seniors that she knew. It was a wonderful day, but the warm feeling soon dissipated. In a fog of depression, she spent hours in the basement watching TV, rarely stepping outside. Her depression was punctuated by fits of rage; she threw her dad against the wall; she smashed her fist through the glass coffee table.

In her parents' eyes, she could see their pain, their helplessness. It haunts her to this day.

Dr. Zaldivar got Maureen to join a test group of patients who would be put on lithium—a year before the drug was available in pharmacies. "I was lucky to be under the care of a doctor who was on the cutting edge, and parents who believed in him," she says.

The lithium enabled Maureen to reclaim her life. Returning to school for her senior year, she went to her prom, homecoming and graduation. After college, she went into a career in management and customer service. She was never hospitalized again.

"I have never let my mental illness define me," Maureen says. "It's just like having an illness, like diabetes." She has never viewed her mental illness as a stigma.

After 44 years of taking lithium, Maureen changed her medication due to its side effects. In early 2010, she was prescribed Lamictal (lamotrigine), which worked well, but gave her a rash. In April, Dr. Steven Resis in Schaumburg, Illinois changed medications and prescribed her divalproex sodium. It took her a little time to adjust to this medication and her mania returned.

Maureen left work in April 2010 for 12 weeks, and started therapy. She met with "an extraordinarily gifted psychologist," Dr. Kimberly Kerley, also in Schaumburg, who to this day continues to give Maureen the tools to help her manage her life.

Dr. Kerley would say to her, "Your medication controls the big swings. I'm here to help you with the small bumps on the road." After a tough year, she was able to come through to a life "now filled with much promise and happiness," she says.

Maureen is a supporter of the Brain & Behavior Research Foundation because she strongly believes that "there is hope through brain research above all else because the brain is the control center for so many bodily functions," she says. "The more we unlock the mystery of the brain, the more we will know about humankind."

Maureen has joined her local chapter of the National Alliance on Mental Illness and serves as a volunteer board member. In early 2013, she shifted to a career in health care, working with patients with Alzheimer's disease and other neurological disorders. She believes her illness has made her a perfect fit for this type of work, gifting her with tremendous patience and empathy.

"I can identify with mentally ill people with chemical imbalance issues because I have been there," she says. "I understand their feelings, struggles, disconnection, and overall disorientation."

Today, 64-year-old Maureen is living a very happy life in the suburbs of Chicago with her two little dogs. "I believe I am the best I have ever been in my life—right now," she says. She retired in 2015, but continues to volunteer with older adults. "My life was built to end up doing this," she says. ■

Glossary

Choline: A nutrient that is part of the B vitamin complex. Neuroscientists interested in the causes of autism spectrum disorders and ADHD are studying the role choline plays in activating fetal nerve cells.

Dentate Gyrus: A part of the brain's hippocampus (involved in learning, memory and mood) where new hippocampal cells form.

Guanfacine: A drug used to treat ADHD, sold in the United States under the brand name Intuniv. The drug is thought to strengthen parts of the brain's prefrontal cortex that regulate attention and impulse control.

Hypomania: a mood state in which a person with bipolar disorder may feel elated, irritable or hyperactive, but to a lesser degree than mania (see below).

Mania: a mood state in which a person with bipolar disorder feels abnormally energetic, elated, or irritable. If severe enough, mania may involve psychosis.

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Life Elevated: Examining Altitude-Related Effects on Mental Illness

Perry F. Renshaw, M.D., Ph.D.

Professor of Psychiatry at the *University of Utah School of Medicine*



TUESDAY, FEBRUARY 9, 2PM EST

Depression

Deanna M. Barch, Ph.D.

Professor and Chair in the Department of Psychology
Washington University School of Medicine



TUESDAY, MARCH 15, 2PM EST

Child and Adolescent Bipolar Disorder

David J. Miklowitz, Ph.D.

Professor of Psychiatry in the Division of Child and Adolescent Psychiatry
UCLA Semel Institute



TUESDAY, APRIL 12, 2PM EST

Schizophrenia

Marc G. Caron, Ph.D.

James B. Duke Professor in the Department of Cell Biology
Duke University Medical Center



MODERATOR:

Jeffrey Borenstein, M.D.

President & CEO, Brain & Behavior Research Foundation
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