The Brain & Behavior Magazine presents cutting edge research of BBRF grantees. This often includes newly published findings about part of the brain’s basic biology or a new approach to treatment. Sometimes it can also mean an in-depth look at how some of the field’s top researchers have built an important collection of essential knowledge through their decades of work.

Major research advancements create a paradigm shift in mental health, but more often these important changes come about through cumulative insights that eventually point the way to scientific and therapeutic breakthroughs. Ultimately, the goal is recovery for more people.

The high quality of the research we fund is made possible by the BBRF Scientific Council. This prestigious group of mental health researchers, led by its founding President, Dr. Herbert Pardes (page 12), reviews more than 1,200 grant applications each year and selects the most promising ideas with the greatest potential to lead to breakthroughs. The Scientific Council guides the Foundation to fund creative and impactful research relevant to the whole spectrum of mental health.

In this issue you can read about how two of our Scientific Council Members have spent their careers working on unraveling the mysteries behind bipolar disorder and disabling depression. Boris Birmaher, M.D. (page 26) discusses the findings from his long-term study of the children of parents with bipolar disorder, with an eye to predicting how the disease could develop for each individual. Similarly, Helen Mayberg, M.D. (page 9) who is in recovery from refractory depression because of treatment with deep brain stimulation.

As the scientists in this issue explain—and as so eloquently noted by Dr. Mayberg, “the needs of patients have driven the kinds of scientific questions I try to answer.”

Dr. Dolores Malaspina understands this point firsthand as both a researcher and as a family member, because her sister is a patient. In this issue (page 23), she shares how a diagnosis of a serious psychotic disorder like schizophrenia affects everyone in the family.

You can also read the astonishing story of Kathryn, a patient of Dr. Mayberg (page 9) who is in recovery from refractory depression because of treatment with deep brain stimulation.

I ask you to help us to accelerate the remarkable accomplishments of scientists such as these. It is only through support for research that we can alleviate the pain and suffering of mental illness, and find the advances and breakthroughs that will result in improved treatments, cures, and methods of prevention for psychiatric illness.

Sincerely,

Jeffrey Borenstein, M.D.

Contents

Pathways to the Future ..........................................................04
Research for Recovery ..........................................................09
A Pacemaker for Depression–and More
A Return To Life: One Patient’s Recovery After Receiving
Deep Brain Stimulation For Depression
The BBRF Scientific Council ................................................12
Interview with Dr. Herbert Pardes about the Scientific Council
Parenting ........................................................................23
Early Signs of Schizophrenia
Science in Progress .............................................................26
A New Understanding of Risk for Bipolar Disorder
Discovery to Recovery: Therapy Update ..............................30
Recent Research Discoveries .............................................32
Women Breaking the Silence About Mental Illness ..........36
Homelessness and Mental Illness .........................................40
Glossary ............................................................................42

100% of every dollar donated for research is invested in our research grants. Our operating expenses and this magazine are covered by separate foundation grants.
PATHWAYS TO THE FUTURE

A Pacemaker for Depression—and More

BY PETER TARR, PH.D.

Helen Mayberg, M.D.
Director
Center for Advanced Circuit Therapeutics at the Icahn School of Medicine at Mt. Sinai

Formally trained as a neurologist in the 1980s, by 1997 Dr. Mayberg had made use of brain imaging technologies to formulate what she termed “a working model of depression” that continues to be highly influential. The concept of depression that she advanced moved significantly beyond the model linked with antidepressant medications that tens of millions take daily. These medicines have long been assumed to address chemical imbalances involving message-carrying neurotransmitters and the molecules that transport them from cell to cell.

While not rejecting a role for these factors, Dr. Mayberg has championed an alternative, distinctly neurological view of depression, stressing circuits and networks in the brain that interact with one another in ways that change from moment to moment. Depression, she has suggested, arises when certain parts of the brain are out of sync.

Mayberg is most famous for her role in developing an experimental treatment for people with debilitating major depression who have not been helped by any available therapy. Called DBS, or deep-brain stimulation, it has worked spectacularly for some patients in small clinical trials, its impact described by those helped as a “lifting of the veil” and a “return to connectedness.” (page 7)

While continuing to learn from and improve DBS, Dr. Mayberg is deeply engaged with a range of research projects at her new post as Director of the Center for Advanced Circuit Therapeutics at the Icahn School of Medicine at Mount Sinai, where she is a professor in four departments. In this highly interdisciplinary environment, her most recent work on depression is devoted to learning how to predict which depressed patients will benefit from which forms of therapy, and just as important, who is not likely to benefit.

Talking in depth to Dr. Mayberg, one realizes that there is a consistent theme underlying all of her accomplishments. “Everything I’ve done reflects my training as a neurologist,” she says, meaning that she is a doctor who is also a scientist. From the beginning, she says, “the needs of patients have driven the kind of scientific questions I try to answer.” She is strongly motivated by a feeling that “the status quo” for patients is not adequate.

The scientist in Mayberg rules out working from intuitions or hunches. The brain is an organ of the body that in certain ways doesn’t work properly in depression and other mental illnesses. “The brain has regions that are connected to one another in pathways. Circuits, or subsystems, convey information for behaviors, actions, and thoughts in a very organized way,” she says. These networks have only begun to come into focus during the course of her career.

Mayberg the scientist is interested in evidence. When Sigmund Freud and other ancestors of modern neuroscience and psychiatry formed their ideas about mental illness, they had almost nothing to look at, beyond outward behaviors of their patients. “They couldn’t see depression” in the organ in which it is rooted, Mayberg reminds us.

Indeed, no one could claim to have seen depression until the era of neuroimaging, which took off when Mayberg was in training. In fact, Mayberg identifies with other intellectual precursors—the doctors and surgeons of the last century who performed exploratory operations and postmortems on people with brain injuries. They learned facts about brain function by correlating an injury in a particular brain area with the way that injury affected behavior and/or bodily functions.

Though deeply fascinated by the problem of how the brain works, Mayberg stresses that as a doctor who treats suffering patients, her quest is not merely intellectual or academic. “All the science is driven by clinical need. People want answers. They have sick family members,” she says. She became interested in the problem of depression when, as a neurologist, she began to ask why people with Parkinson’s disease are often depressed. It was generally assumed that the depression was “just a psychological reaction” to having this serious illness. But with the help of brain imaging she was able to suggest something dramatically different: that the physical degeneration of the brain that attends the disease impacts areas of the brain where dopamine, a neurotransmitter central in Parkinson’s pathology, has an impact on mood.

Having access to PET (positron emission tomography) scanning technology during her research fellowship training, which was fairly new at the time, Mayberg performed experiments that provided an example for future work. She used the scans to map glucose metabolism as well as dopamine, serotonin, and opioid receptors and their distribution in the brain, overlaying the chemistry on what then was a rudimentary understanding of brain areas and their functions.

“If you could map these things out in a living brain, you could then look at dynamic and not just static abnormalities,” she explains. The inspiration was that old yet fruitful approach of matching injuries in the brain to changes in the functioning of patients. Except now, one could watch these systems change their state over time. It was like the difference between having a still picture and movies.

This work “began to lay out the puzzle of where are the common places in the brain that, when damaged, cause someone to experience depression,” she says. In its earliest phases, this approach, with brain scans playing a key role, was denigrated by some as “blobology.” Mayberg and others were “trying to take the illuminated areas on the scans—bright or dim blobs—and imagine them within the structure in the brain where they live,” as she describes the approach. She had the clear idea...
of relating changing patterns of activity within known brain regions to the way those regions function.

Over the years she used data from patients to form theories about depression. “No complex behavior—no simple behavior, for that matter—is the exclusive domain of any one cell or region in the brain,” Mayberg says. The evidence from the scans led her to choose that depressed behavior, which affects many systems in the brain, might result when key brain regions that normally work together fail to synchronize properly.

This tended to corroborate the theory she first advanced in 1997, in which she suggested that depression was the result of a failure of two fundamental brain networks to coordinate properly—the limbic system, which is the seat of the emotions, and higher cortical areas associated with thought. This first sketch has proved remarkably robust as constantly improving imaging technologies have shed much more light on pathways and circuits of brain areas associated with these two basic brain functions.

It’s very important to Mayberg to make clear that this was not something she arrived at because it made sense in theory. She has arrived at all of her major insights by working backward from biological evidence. In the electronics industry this is called reverse engineering. She musts that the tools available “are becoming more and more sophisticated, which allows us to push the envelope in probing both how the brain is organized and how it breaks down in disease.” She looks forward to seeing how other scientists tackle these various complex problems including the secrets of consciousness. “For me, my hands are full studying depression.”

In repeated efforts to determine why certain depressed patients respond to a given treatment and others don’t, there were “straightforward experiments” she could readily perform that were very likely to shed light. “Our antidepressant treatments are evidence-based. Sometimes the effect in an individual patient is great, sometimes small, and sometimes there is no effect. We know that some people do recover. Our idea is to understand how any patient goes from sick to well.”

If the state of the individual’s brain can be observed in scans and through other measures to change over time while the treatment is being given, then valuable data is generated. Do this in many patients, with different reactions to different treatments, and a nuanced picture begins to emerge.

“If I can give people that I think suffer from the same problem the same treatments—and some get better and others don’t? Must there be an effect of treatment on the brain, irrespective of whether someone gets better or not. Something is happening in the brain. Can the [live-imaging] map show me?” she says. There are many variables to consider, which is why it is important to try to match comparable patients to try to compare apples with apples. Yet, depression may begin differently in different patients. If this is true, then it is possible they might respond differently to treatments, even if they report similar symptoms.

These and many other variables have been carefully considered, even agonized over, by Mayberg and her colleagues. They have the aim, already partly fulfilled, of developing what doctors call “treatment algorithms” for depression. Also called “decision-trees,” these are widely used in other areas of medicine. Treatments given to people reporting trouble with their heart or who are found to have a cancerous tumor are based on a wealth of empirical evidence gathered in the clinic about how comparable patients have responded to available treatments.

The idea is to make a science of making treatment decisions—instead of following a hunch. That thought is the essence of Mayberg’s motivation as a doctor-researcher. She wants to take emotion and guessing out of the equation—because evidence-based facts, if they are available, are more likely to help the patient. It’s a way of removing the trial-and-error factor in psychiatric treatment.

“It is envisioned that in the future a psychiatrist making a decision to treat a patient with major depression will choose a pharmacological, psychotherapeutic, or somatic [bodily] intervention on the basis of objective measures of brain function in the context of known risk factors including genetics, comorbid conditions, psychosocial issues, and past history,” Mayberg wrote in the pages of Biological Psychiatry a decade ago.

Last spring, she and colleagues reported in the American Journal of Psychiatry that, on average, previously unmedicated patients with major depression who received medication experienced a similar reduction in symptoms over 12 weeks as did comparable patients who were assigned to receive cognitive behavioral therapy, a form of talk therapy. But that was not the key finding. By comparing individual outcomes with the brain scans of each participant taken before treatment began, the team identified patterns of brain activity that would help them predict who would respond well to each treatment approach, and for which patients each treatment was likely to fail.

“In my career it has always been a matter of: What is depression? How does it live in the brain? How does it change? What is its variability? All these questions feed into the big question: How does the brain go wrong and how do we fix it?” Hard evidence is leading at last to decision-trees for treatment that are likely to prevent or curtail an incalculable amount of human suffering—“a kind of suffering that has been part of the human condition in which small electric currents are passed through the brain, intentionally triggering a brief seizure that lifts depressed symptoms for a period of time that varies in different patients.” Mayberg’s lessons from the experience mostly concern the way a large clinical trial is designed and how its endpoints are selected. The experience, which was searing, has sent her back to her first research principles: scrutinizing the criteria by which potential candidates for DBS are selected; determining ways to improve implantation procedures to accommodate surgical teams less experienced with the procedure; improving methods of tweaking the device once implanted in a patient; and, most importantly, performing research to determine why DBS might not work in certain patients, and how to identify them before committing to surgery. The converse is also being studied: figuring out who is likely to be helped, and helped most rapidly, before the surgical procedure is performed.

The effectiveness of DBS in some depressed people makes for an interesting comparison with DBS as used in patients with Parkinson’s disease. Since the FDA approved DBS as treatment for Parkinson’s in 1997, it has been repeatedly observed that while correct “tuning” of the DBS electrodes (which are placed in a different part of the brain in Parkinson’s) causes Parkinsonian tremors to disappear, “it does nothing to the non-motor parts of the disorder,” Mayberg says. This suggests that circuits involved in Parkinsonian tremors are different from those causing depression in the same patients—or in any people suffering from depression.

When DBS works in depression, (so far the published studies report a response rate range of 40 to 80 percent after two years of continued treatment) research suggests that optimal response depends on the precise placement of the electrodes in the SCC region. Above this spot lies the immensely complex frontal cortical area, where thinking and consciousness reside; below it are circuits leading to the brain’s limbic system, which includes the amygdala, hippocampus, and other regions involved in emotional processing.

Last year, progress with DBS for depression came to a halt, at least temporarily. The largest clinical trial to date to test DBS, called BROADEN, was halted early by a medical device maker that had financed the trial. Small amounts of harm came to some patients.

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Prior to BROADEN, in which DBS was performed at many centers around the country, Mayberg led the research teams pioneering the procedure at the University of Toronto and at Emory University in Atlanta, and enjoys substantial relationships with many patients who have bravely volunteered to test the device as they are followed long-term as part of these experimental studies (see patient story, page 9). She has been deeply moved by both successes and failures, characteristically determined to learn from all outcomes. She has learned that even when DBS enables a patient to return to a life without debilitating depression, other facts of life impinge. “We can change your brain,” she says, “but we can’t change your life.”
She says that DBS seems to allow patients to tolerate stress differently once they have recovered, and the longer they continue with DBS. But it is those patients who have achieved a sustained remission after many years of disability who remind Mayberg that all of her efforts to optimize DBS and bring it safely to more people are more than worthwhile.

She is now exploring how certain patients evolve over time: those who transition from responding well to standard treat-ment to being treatment-resistant. The central thought in this hypothesis is that depression, perhaps like other illnesses such as multiple sclerosis, comes in a few different types. Some patients get very sick and never recover; some get sick, then recover, but then relapse. In depression, Mayberg speculates that some patients, over the course of the illness, pass a point at which a transition in the brain occurs, which she likens to a phase shift. Despite past success with treatment, a patient relapses and then can no longer respond even to treatments like ECT.

Researchers are testing the hypothesis that patients who respond only partly to depression therapy of any type—who continue to have symptoms even when their mood is gener-ally much better after treatment—may be at increased risk to eventually develop treatment resistance. “Residual” symptoms include anxiety or disturbed sleep or even moderately low mood, and diminished interest in life. Using data from imaging, Mayberg and colleagues are trying to test this concept, looking for evidence of progressive changes in brain circuits in patients over time, to see if such changes correlate with the develop-ment of treatment resistance.

“In certain people, the wrong treatment with only a partial effect may actually be putting you at risk of such a malignant transformation,” she proposes. It may be that DBS can bring a person who has gone past this point of transformation back into a phase where “tuning” communications between brain regions can restore the brain to health. But this is as yet unproven.

“The brain, even when it is well, is not stable,” Mayberg notes. “We have to characterize the steps of evolving resistance to treatment. Our trajectory of treatment may need to be differ-ent. This is why we have to work harder than ever to get at the origins of depression.”

For more information, please contact Dan Elwell, Senior Philanthropy Advisor at 646-681-4876 or delwell@bbrfoundation.org.

BBRF INITIATES FOUNDATION AFFILIATE PROGRAM

The Brain and Behavior Research Foundation welcomes the opportunity to collaborate with Foundations which fund mental health research.

The Affiliate Program offers foundations the expertise of our Scientific Council who select the most innovative and impactful research proposals along with the administrative support of BBRF. Our relationships with major research institutions allows funding for grants without overhead charges for early career researchers and minimal overhead charges for more senior scientists. 100% of every dollar donated by our Affiliate Partners go directly to research grants.

For more information, please contact Dan Elwell, Senior Philanthropy Advisor at 646-681-4876 or delwell@bbrfoundation.org.
“To live without hope is an extraordinarily difficult place to be,” she recalls.

When she read about Dr. Mayberg’s experimental testing of DBS, she felt a surge of hope that she had not felt in a long time. It was 2005, and she had reached her 39th year.

This is how Kathryn found herself in an operating room in Toronto later that year, with metal electrodes implanted deep in her brain through two small holes in her skull. A switch was flipped and it sent electric pulses that stimulated tissue in one tiny part of the brain called Area 25.

For what felt like many hours, the surgeons adjusted the settings, as Dr. Mayberg held Kathryn’s hand, asking her questions about how each new adjustment felt. The device will remain in Kathryn’s brain indefinitely, running on a battery.

For a while, it seemed as if the surgery didn’t work. Many of the study participants who responded showed an improvement within six months. But a year went by, and Kathryn’s depression didn’t improve. However, Dr. Mayberg’s team kept working with Kathryn, tweaking the settings at regular appointments. It was after one such tweak, more than two years later, that Kathryn walked out into that parking lot, and into a whole new world of sights, sounds, and smells.

“I didn’t expect it to last,” she admits.

Kathryn relates that she has been living without depression for “3,861 days,” pinpointing the number as she is able to do on any given day. That’s more than 10 years.

“I would walk down the street with the biggest smile on my face,” she said, recalling how her senses started coming back online, “even being able to feel the raindrops on my face was such an incredibly wonderful experience.”

Nowadays, Kathryn wakes up in the morning, excited for the day, no longer plagued by suicidal thoughts. She sleeps unmedicated, and is off all psychiatric medications.

Yet Kathryn makes clear that rebuilding her life was not easy. Finding the right DBS settings was just the first step.

“The stimulator can’t fix your life,” said Kathryn. “Recovery is a long, difficult process.”

When you’re as ill as Kathryn once was, she states that you are just focused on getting through each hour—“You’re not living, you’re existing.” And when suddenly “a veil of darkness is lifted,” where do you even start to rebuild your life?

It’s like waking up from a deep sleep and encountering a world that has profoundly changed.

“Nowadays, Kathryn wakes up in the morning, excited for the day, no longer plagued by suicidal thoughts. She sleeps unmedicated, and is off all psychiatric medications.”

“When I ‘checked out’ of grad school we were using WordPerfect as our word processor, and we weren’t using email. Suddenly, I come back to this world, and I go: ‘When did everything change to Word?’ And what is cut and paste? To me cut and paste is glue and scissors,” she says.

After years of not functioning, Kathryn had to learn how to live in the real world again. This is one of the reasons why the study team has continued to follow up with her regularly.

No aspect of Kathryn’s depression remains unresolved.

“It’s nothing short of a miracle to me, and to those who have watched the transformation,” she says.

“Marla and I donate to the Brain & Behavior Research Foundation in support of science and the hope of finding better treatments for mental illness.

Better treatments came too late for my brother, Stewart, who lost his battle with schizophrenia, and too late for my father, Ken, who suffered from depression. But we believe that with ongoing research, it will not be too late for millions of other people thanks to BBRF. We know this because we have seen the scientific breakthroughs and results that have come from funding scientists. Marla and I are dedicated to helping people who live with mental illness and doing what we can to be a part of the solution by our continued giving to BBRF.”

—Ken Harrison, Board Member
Dr. Herbert Pardes Reflects on the Origins and Importance of the Foundation’s Scientific Council

BY PETER TARR, PH.D.

QUESTION: Dr. Pardes, as the founding President of the Foundation’s Scientific Council, your name above all others is associated with that body. So there is no one better suited than you to help us understand the vital role the Council has played in the Foundation’s history.

First, let’s provide a little context for our readers. The story begins in 1984, when, after serving for five and a half years under Presidents Carter and Reagan as Director of the National Institute of Mental Health (NIMH), you decided to return to academia, becoming Chair of Psychiatry at Columbia University and later the Dean of the Medical School and V.P. of Health Services at Columbia. But you also devoted time to related issues and causes. One of these is what you’ve called “citizen involvement” in the cause of mental health.

Dr. Pardes: That’s right. In my years in Washington, as we got the NIMH to focus more on research and clinical treatment of mental illness, I also felt strongly that we should work to develop collaborations with citizens. In 1979, I had been invited to a meeting in Madison, Wisconsin held by a group of parents of people with schizophrenia. They asked: “What if we had a family group that worked for mental illness causes?” I thought it was a great idea.

Dr. Pardes: Other citizen groups had been working for years on behalf of people with other illnesses, including muscular dystrophy, cancer and heart disease. There were no similarly powerful advocacy groups at that time for people with mental illness. Why? Well, most patients with severe mental illnesses aren’t able to advocate, either because of incapacity or a fear of being stigmatized. At the same time, most people who don’t suffer from a psychiatric illness figure they will never suffer from one—an attitude very few reasonable people have about cancer or heart disease, for instance. So I felt the time was ripe for a partnership between people in the psychiatric profession and the public.

I also thought we could make a serious dent in stigma by bringing families into the picture on a national scale. The group that emerged from that 1979 gathering in Madison did precisely that. It was called the National Alliance for the Mentally Ill, or NAMI. It continues to this day to be a highly influential citizen’s group on psychiatric illness.

Dr. Pardes: From the very beginning, the Council has been composed of a substantial number of people who are dedicated and very highly regarded leaders in their respective fields. These are people who have really understood how psychiatric research is funded, who have a deep knowledge of how things work.

Dr. Pardes: We’ve followed a number of principles that have stood the test of time. Number one: we agreed not to make elaborate or complicated bylaws. We were all volunteers (and continue to be). We were not out to establish a bureaucracy. Which leads to number two: we agreed that our emphasis was on excellence: It was our job to identify the very best people in need of funding for their research. We wanted our grants to reflect a broad spectrum of concerns in mental health and psychiatry, including basic research, translational research and also research on clinical care. Number three: we agreed that in inviting applicants, we would set as a priority the best people in need of funding for their research. We wanted our grants to reflect the fact that we have the very highest regard for the people who have invented and refined the frontiers of psychiatric knowledge.

Dr. Pardes: After NAMI was formed and stepped into the picture, the core group consisted of several leaders from NAMI and a group from Kentucky, Boston and other places, called the Schizophrenia Foundation. Together, under Gwill-Newman of Chicago, they formed an organization called NARSAD, the National Alliance for Research on Schizophrenia and Depression.

Dr. Pardes: The Scientific Council of NARSAD (and now BBRF) traces its origins to that same time, the year 1986, correct?

Dr. Pardes: Yes. The original members of our Scientific Council—about a dozen people—selected me as president at our first meeting in 1986. Little did I know then that the Council’s work would be one of the great professional and personal experiences of my life! For over 30 years, this group, which is now composed of over 172 leaders in all aspects of neurobiology, neuroscience, clinical care, psychology and psychiatry, has awarded thousands of grants worth more than $384 million to the very best scientists, many of them just starting out and in greatest need of external support. Having “a NARSAD” has become a mark of distinction, something academic researchers who receive such an award often boast about, in part because the grants are so thoughtfully awarded by experts in the field, who advise the Council.

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QUESTION: And the grants themselves, how does the Council go about finding the best people and the most important projects?

DR. PARDES: We decided in our earliest days that our focus was going to be Young Investigators. We thought it was essential to provide support for very bright people who were just beginning their careers. They have the special problem of trying to accumulate a body of data to support major, multi-year funding from the government. It takes time to formulate a hypothesis and perform experiments that generate the kind of data that’s needed. The Council, as it continued to add members, had members with a great diversity of expertise who could help in assessing the applications coming in from all over the world.

We settled on a system in which most members of the Council volunteer each year to assess a certain number of applications. Committees made up of several Council members coordinate and recommend to the entire group the final list of applicants which the full Council votes on. For many years we have been committed to annually awarding two-year grants to 200 Young Investigators. In this way we’ve helped seed an entire generation of researchers in diverse aspects of mental health, neuroscience and psychiatric research. I should add that I have never been involved in the review of any projects. It’s essential that there be no possibility of problematic conflict of interest. My feeling is, our scientists on the Council will tell us who the best and most deserving applicants are.

QUESTION: What about the other grant programs?

DR. PARDES: After establishing the Young Investigators program, we decided to invite people who have distinguished track records as investigators to apply for one-time $100,000 grants. The idea was to encourage brilliant people with known accomplishments to think outside the box—to propose projects that might not be funded by the federal government, which for understandable reasons is conservative in its approach. We felt our Distinguished Investigators, as we called them, had the potential to hit some home runs by proposing high-risk, high-reward ideas. All we ask at the beginning is a one-page description of a project they want to do. A committee of the Council narrows the list of several hundred each year to about 30 of the most interesting. Then we go back to those applicants and ask for more detailed proposals. About half of these are funded each year.

QUESTION: And what about the Independent Investigators?

DR. PARDES: It was obvious to us that there was another important gap to fill. For scientists who have already established themselves, but are not yet senior, it is crucial that funds be available to sustain their work as it matures. These are what we call the Independent Investigators, and for many years we have been able to award about 40 two-year grants annually. So when you consider all of our grant programs together, you can see how one can lead to the next, and how over a period of years, our Foundation can really have a major impact on the success of some of the most deserving brilliant minds who are leading the field forward. I am very proud of this, and I know the rest of the Council is.

QUESTION: Awarding grants is not the only part of the Council’s business that has had a big impact on the field, however. Tell us briefly about the Foundation’s Annual Awards.

DR. PARDES: Just as we set up committees to run each of the grant programs, we have groups of Council members who are responsible for giving awards to people who have done great research and have major accomplishments to their name. We realized, little by little, that the field could really benefit from awards program like this that would bring major recognition, both internally among colleagues and also from the general public. We began with an annual prize for excellence in schizophrenia research. Then we added a prize for affective disorders and then children’s disorders. We celebrate the prize winners at the Foundation’s annual symposium in October (the 26th of this year) and at the annual gala, held the same evening. These prizes are probably the most successful and important awards for psychiatric research given anywhere. They carry great prestige. We feel they bring well-deserved attention to researchers whose achievements often go unrecognized. Just as with our grant programs, the awards we give are continually helping to advance the field, and at the same time have brought great credit to the Foundation and its important mission to find better treatments for mental illness.

Each Year, The Scientific Council:
- Reviews more than 1,200 grant applications
- Recommends the best ideas from scientists around the world
- Mentors BBRF Young Investigator Grantees

In 30 years, the Scientific Council has reviewed more than 26,000 grant applications.
Our Scientific Council Members have spent their careers in the pursuit of treatments and cures for mental illnesses. They have all seen great progress in the past decades and know what we need to do next. The Scientific Council identifies proposals which demonstrate the most innovative and promising paths toward better understanding and treatment of brain and behavior disorders.

—Herbert Pardes, M.D.,
Chairman and Former President of the Scientific Council, Executive Vice Chairman of the Board of Trustees,
NewYork-Presbyterian Hospital
BBRF Grant Selection Committees

BBRF Young Investigator Grant

Helps researchers launch careers in neuroscience and psychiatry and gather pilot data to apply for larger federal and university grants.

Co-Chair of the Young Investigator Grant Selection Committee
Judy M. Ford, Ph.D.

“These grants to young investigators are the mother’s milk for launching a career in research. They come at a time when these young researchers are starting their own programs of research, and they need both the recognition and funding that these YI awards provide.”
—Judy M. Ford, Ph.D.

Co-Chair of the Young Investigator Grant Selection Committee
Suzanne N. Haber, Ph.D.

“It’s exciting to be able to help these young stars reach their goals.”
—Suzanne N. Haber, Ph.D.

BBRF Independent Investigator Grant

Supports mid-career scientists during the critical period between initiation of research and receipt of sustained funding.

Selection Committee Chair
Robert M. Post, M.D.

“It has been a great pleasure and honor to work with the Brain & Behavior Research Foundation, which is the most efficient research funding organization I have ever seen or could imagine.”

BBRF Distinguished Investigator Grant

Enables outstanding scientists to pursue new, cutting-edge ideas with the greatest potential for breakthroughs.

Selection Committee Chair
Jack. D. Barchas, M.D.

“BBRF Grants are among the most competitive in biomedical research because of the great ability and career success of the applicants. Receiving a Distinguished Investigator Grant constitutes a great honor for the recipient.”

Each year more than 750 Applications
Approximately 200 Grants Awarded
Totaling $258+M Since 1987
Each year more than 300 Applications
Approximately 40 Grants Awarded
Totaling $81.8+M Since 1995
Each year more than 150 Applications
Approximately 15 Grants Awarded
Totaling $41+M Since 1988
BBRF OUTSTANDING ACHIEVEMENT PRIZES

The Selection Committees

These prizes are among the highest recognition possible for psychiatric and neuroscience researchers. Annually, since 1987, members of the Brain & Behavior Research Foundation Scientific Council have selected researchers for their outstanding lifetime achievements in brain and behavior science.

The Lieber Prize for Outstanding Achievement in Schizophrenia Research

The Lieber Prize has been awarded since 1987.

Chair
William E. Bunney, Jr., M.D.

Prize Selection Committee:
- Arvid Carlsson, M.D.
- Kenneth S. Kendler, M.D.
- Philip Seeman, M.D., Ph.D.
- Carol A. Tamminga, M.D.
- Daniel R. Weinberger, M.D.

The Colvin Prize for Outstanding Achievement in Mood Disorders Research

The Colvin Prize (formerly Bipolar Mood Disorder Prize, the Falcone Prize and the Selo Prize), has been awarded since 1993.

Chair
Robert M. Post, M.D.

Prize Selection Committee:
- Wade H. Berrettini, M.D., Ph.D.
- William E. Bunney, Jr., M.D.
- Jan A. Fawcett, M.D.
- Frederick K. Goodwin, M.D.
- Robert M.A. Hirschfeld, M.D.
- Husseini K. Manji, M.D.

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

The Ruane Prize was initiated in 2000.

Chair
Daniel S. Pine, M.D.

Prize Selection Committee:
- W. Joseph T. Coyle, M.D.
- Rachel G. Klein, Ph.D.
- James F. Leckman, M.D.
- Matthew State, M.D.
- Anita Thapar, F.R.C.Psych., Ph.D.
- Jeremy Veenstra-VanderWeele, M.D.

The Goldman-Rakic Prize for Outstanding Achievement in Cognitive Neuroscience Research

The Goldman-Rakic Prize was initiated in 2003 in honor of Patricia Goldman-Rakic, Ph.D.

Chair
Jack D. Barchas, M.D.

Prize Selection Committee:
- Huda Akil, Ph.D.
- Jonathan D. Cohen, M.D., Ph.D.
- Paul Greengard, Ph.D.
- Bruce S. McEwen, Ph.D.
- Michael I. Posner, Ph.D.
- Solomon H. Snyder, M.D.
- Leslie G. Ungerleider, Ph.D.

The Maltz Prize for Innovative and Promising Schizophrenia Research

Awards to a Young Investigator Grantee, and selected by the current year’s Lieber Prize winner. The Maltz Prize (formerly known as the Baer Prize) has been awarded since 2004.

Chair
W. Joseph T. Coyle, M.D.

Prize Selection Committee:
- W. Joseph T. Coyle, M.D.
- James F. Leckman, M.D.
- Matthew State, M.D.
- Anita Thapar, F.R.C.Psych., Ph.D.
- Jeremy Veenstra-VanderWeele, M.D.
Excep  tional Young Investigator Prize Selection Committees

The Foundation awards two annual prizes for Exceptional Research by a Young Investigator Grantee. Members of the Brain & Behavior Research Foundation Scientific Council select the winners each year.

The Klerman Prize for Exceptional Clinical Research by a Young Investigator

The Klerman Prize was established in 1994 by Myrna Weissman, Ph.D., in memory of her late husband, Gerald L. Klerman, M.D., who pioneered studies of psychotropic medications and developed and tested interpersonal psychotherapy, a treatment now used throughout the world.

Chair
Robert M.A. Hirschfeld, M.D.

Prize Selection Committee:
- Martin B. Keller, M.D.
- Rachel G. Klein, Ph.D.
- Nina R. Slochower, Ph.D.
- Karen Dineen Wagner, M.D., Ph.D.

The Freedman Prize for Exceptional Basic Research by a Young Investigator

The Foundation Board of Directors established the Freedman Prize in 1998 to honor the memory of a pioneer in biological psychiatry, Daniel X. Freedman, M.D.

Chair
Ariel Y. Deutch, Ph.D.

Prize Selection Committee:
- Joseph T. Coyle, M.D.
- Ronald S. Duman, Ph.D.
- Fritz A. Henn, M.D., Ph.D.
- Peter W. Kalivas, Ph.D.
- Husseini K. Manji, M.D.
- Eric J. Nestler, M.D., Ph.D.
- Bryan L. Roth, M.D., Ph.D.

Early Signs of Schizophrenia

BY PETER TARR, PH.D.

Dolores Malaspina, M.D., M.S., MSPH
Director, Psychosis Program
Icahn School of Medicine at Mount Sinai
2007 Distinguished Investigator Grant
2001 Independent Investigator Grant
1995, 1993 Young Investigator Grant

Dr. Dolores Malaspina applied to medical school with one aim—to understand the illness, schizophrenia, that afflicts her younger sister. Her research has found that about a quarter of all people living with schizophrenia may owe their symptoms to spontaneous mutations in paternal sperm—and the older the father, the more likely his sperm is to carry such mutations.

A practicing clinician with vast experience, Dr. Malaspina was part of the team that helped revise the 5th edition of the Diagnostic & Statistical Manual (DSM-V) used for the diagnosis of psychiatric and behavioral disorders. She and colleagues are now testing the relationship of bacteria in the gut—the microbiome—to inflammation in the brain that may cause or contribute to psychiatric disorders.

"What is unique and exciting about the Foundation is its unflagging support of novel ideas than can lead to changes in our ability to diagnose and treat serious psychiatric illness. I have had the opportunity to contribute to the Foundation's mission in many ways over the years, among them moderating the New York City symposium, which showcases the best of the Foundation's senior and young scientists."

—Robert M.A. Hirschfeld, M.D.
experiencing these symptoms need some treatment. Sometimes the prodrome leads to psychosis, other times it can mark the onset of another disorder, and sometimes the symptoms resolve themselves and the person does not become ill.

So the prodrome can foreshadow many things. This makes us curious to know, how do parents distinguish between normal adolescence, which can be rebellious and chaotic, and a real and serious problem?

Adolescent behavior can include a lot of acting out, a lot of bargaining, and difficulty with parents. It is a time of preparation for young adulthood. But I think a young person who continues to have good grades and an active social grouping should be reassuring to parents.

I think the concern is when there is a decline in interest in friends and academics, or when the young person has delusions, such as hearing voices. Young people may not have an endocrine disorder or an infectious disease. So the prodrome can foreshadow many things.

It’s important, first of all, for the child to have a full medical evaluation. Major medical centers that have departments of psychiatry are useful as well. But a pediatrician can often give a parent a sense of whether they are worrying too much.

What about medication?

Antipsychotic medications in my view are very over-prescribed to young people. These are very serious medicines that can help treat the delusions and hallucinations in people with psychosis, but they don’t usually cure a disease. Their use in the proper circumstances can be essential, but far too often, doctors are giving young people antipsychotic medicines without symptoms of psychosis.

Can general practitioners or pediatricians recommend antipsychotics?

Absolutely. And general practitioners are more likely, perhaps, to overprescribe them. But even some psychiatrists are of the mind that antipsychotics might help prevent psychosis in a young person at high risk. But there’s no good evidence, yet, that antipsychotics prevent the onset if there are no clear psychotic symptoms. Sometimes in the absence of psychotic symptoms, cognitive behavioral therapy (a kind of talk therapy), or treatments aimed at some depression symptoms would be far better. Also, antipsychotics come with risks, such as movement disorders and obesity for developing young people.

What are some risk factors for schizophrenia, which in some cases develops after a first psychotic episode?

One of the best-known risk factors for schizophrenia is having a family history. In reality, however, 80 percent of people with schizophrenia or bipolar disorder, particularly with psychosis, have no family history at all. Some of the important risk factors have been traced to different individual genes, although there’s no genetic test for schizophrenia yet.

But there are exposures which are much more common in people who develop a serious mental illness. One example is pre eclampsia or other severe pregnancy events in the mother. Another is a traumatic brain injury which may have happened during childhood. Another important risk factor is early childhood trauma, which will double or triple the risk for later psychiatric disease.

Early childhood trauma comes in many forms, for example separation from parents, abuse, neglect, and bullying. Additionally, cannabis abuse in the early teen years will triple the risk for later psychosis. That’s very significant. I’ve seen a number of parents who’ve told their children that they can smoke cannabis as long as they don’t drink alcohol. Cannabis has a particular action in the circuitry that connects the “thinking” part of the brain and the “emotional” part. Hence, in my view cannabis consumption should be discouraged. However, I would like people to understand that most people with these exposures are resilient. Even with the tripling of the risk for schizophrenia, 97 percent of people will be well.

What are ways to reduce risk?

A very nurturing family environment is protective. The brain has plasticity—the capacity to change in response to experiences. This applies to positive experiences just as much as to negative ones. Throughout childhood, later childhood, and even into the mid-twenties and later, brain cells are continuously being made. And you want to take advantage of that through nurturing, to help young people manage stress better. We don’t do enough of that. Too many parents have this idea that when someone turns 18, they no longer need nurture. Maybe that was true 40 years ago, but our brains are very different now. Young people need a longer period of high nurture, support, and of encouragement to not abuse substances. You should try to have a home that doesn’t involve a lot of screaming or a lot of fighting.

At one point, it was believed that bad parenting caused schizophrenia.

Sadly that was the case, and of course it is entirely untrue. Many years ago, you couldn’t put the recognition that most people with schizophrenia had no family history of the illness, so it was a way of explaining what happened. But that led to a very sad time in American psychiatry, where mothers were blamed. And I, myself, experienced that perspective when my sister was ill, and my family had to go to family therapy that was particularly confronting towards my mother.

As someone who has been through this, tell us about the experience of your family during the period when your sister began to experience symptoms of psychosis.

My experience, and that of my parents, was first of all, denial. You just can’t believe what you’re seeing, and you don’t pay attention to it, or you tell someone to get on with things. Often family members experience post-traumatic stress disorder (PTSD), and there is the constant desire to see a difficult time, for example a particularly rough phase or the disorder, as “behind” you. And that leads to a lot of families being on a roller coater. Whereas, a better understanding would be that, like all other conditions, it may ebb and flow. And that would be helpful for families.

For parents, the goal is to love the child, where they are, and to understand their uniqueness.

How should families react to a loved one with a diagnosis?

We know that one factor in the course and outcome of these diseases is the way emotions are expressed within the family. This field was pioneered 30 years ago, and we saw at that time that families who had a lot of negative observations, hostile comments, and other negative interactions toward those diagnosed had a much worse outcome. You could even predict how quickly someone would be re-hospitalized or how well they would do, based on this negative emotional expression of a family. As, part of treatment, work is now done with the family to help them understand the nature of the illness, and help them understand other ways of communicating and not criticizing. The reduction of hostile communication really can lead to a great improvement in the diagnosed person.

And the way to achieve this understanding is for the family, as a whole, to go to therapy?

There is a family-wide intervention called psycho-education, often involving social workers who are experts in helping families deal with emotional expression. There might be a family therapy that accompanies the onset of a disorder. Of course, some people will develop psychosis and recover remarkably, but for other families, there can be a grieving: someone with a disorder may have a successful life, but not the one that you had imagined. And helping families cope with that, first of all, gives them hope for their loved ones, but also knowledge that their life needs to go on as well; that this diagnosis shouldn’t end happiness for the whole family.

Any final words of hope and wisdom for parents going through this difficult time?

For parents, the goal is to love the child, where they are, and to understand their uniqueness. This is not easy to do. Your child is a dear and a whole human being. And to accept and reinvest in the person they are becoming, apart from your expecta-

ions, is what gives joy back to a family.

For parents, the goal is to love the child, where they are, and to understand their uniqueness.
Bipolar disorder (BD) can be a difficult condition to diagnose because its signature symptoms—episodes of abnormal, often persistent, highs and lows—are related to one another in different ways in different people. We often think of highs and lows as mutually exclusive opposites. Yet in BD they are not opposites but are sometimes “mixed” in varying degrees of intensity.

One can be depressed, for instance, and yet for brief intervals—say, a couple of days—display certain features of mania, or a less severe form of mania called hypomania (for example, elation, increased energy, decreased need for sleep, rapid speech, irritability, a tendency toward risky behavior). It’s also possible to experience milder or “subthreshold” symptoms that aren’t classified as either manic or depressive. In some patients, depression may be the dominant mood; in others, there will be distinct periods of mania and depression of varying duration, and in others very rapid changes in mood. A fairly new term, bipolar spectrum disorder (BPSD), covers the full range—from the one period of mania or hypomania, but also subthreshold depressive and/or manic mood symptoms. BPSD is an umbrella term that emphasizes that the manifestations of BD exist in a continuum.

Identifying patterns—in moods, behaviors, brain activity, gene activation, even the body’s metabolism—can distinguish different sub-groups of patients, and is a major objective of research being conducted by many of the Foundation’s grantees. Describing these patterns and determining their prevalence in a growing range of illnesses from psychosis and schizophrenia to depression and suicidality is now leading to the development of the first tools to predict risk, as well as the course a disorder will take in specific individuals, a major achievement that is decades in the making.

At the University of Pittsburgh’s School of Medicine and Western Psychiatric Clinic, Scientific Council Member Boris Birmaher, M.D., Ph.D., and 2008 Young Investigator Dara Sakolsky, M.D., Ph.D., who are also at the University of Pittsburgh.

First BIOS Results

In 2009, the BIOS study generated its first headlines. Six years after contacting over 1,600 people living within 200 miles of Pittsburgh, they assembled an initial study cohort of 388 children of 233 parents with BD, plus 251 children of 143 families in which both parents had BD. BIOS showed the risk to be 14 times higher.

Before BIOS, various experts estimated that children of BD parents aged six to 17 would have anywhere from two to seven times the risk of developing BD symptoms as compared with children of parents without BD. BIOS showed the risk to be 14 times higher.

It also revealed a two- to three-fold greater incidence in these high-risk children of developing any mood or anxiety disorder. Families in which both parents had BD generally had more offspring with BD spectrum disorders than families with one affected parent. And a very important finding from the study revealed that in children of affected parents who developed BD, episodes began during childhood, usually before age 12, most often manifesting with sub-threshold manic symptoms, and to a lesser degree, depression. Fully 85 percent of the children who developed BD had comorbid conditions—usually anxiety disorders, disruptive behavior and/or ADHD—that typically preceded the onset of BD.

The study made clear that children of parents with bipolar illness were indeed at very high risk of developing the disorder...
toms before the onset of mania drew from results across the
antipsychotic medications.
prelude to mania and BD. Those with the diagnosis are usually
opposed to depression. Among other things, antidepressants
people will ever experience mania or hypomania and therefore
treated with mood stabilizers including lithium, anti-seizure and
BD. The risk of developing AD\(HD\) was calculated to be eight times that of a matched
control sample consisting of 102 children of 65 parents.
Children of parents with BD also had six times the risk of
having two or more other psychiatric disorders.
Again, there was a ray of hope generated by these worry-
ing results. At the time of the report, only three of the 121
preschool children of bipolar-diagnosed parents had developed
mild depressions, and none had developed BD. The remainder,
particularly those with AD\(HD\), were much more likely than chil-
dren of control parents to have subclinical manic and depressive
symptoms. “We believe there is a window of opportunity for
prevention in the high-risk group of kids,” Dr. Birmaher said at
the time of the study’s release.
Another report from the BIOS team appeared in 2016. In the
pages of the American Journal of Psychiatry, Drs. Halfman and
Birmaher and the BIOS team now were able to measure the risk
that children of bipolar parents would show warning signs,
sometimes called a “prodrome” period by doctors. Children
of BD parents with symptoms of depression, anxiety, unstable
mood, and subclinical manic symptoms were at high risk to
develop BD. The risk of developing BD increased to almost 50
percent in children with these symptoms whose parents had
developed BD before age 21.
A Calculator to Measure Risk
This result highlighted a familiar problem. A major depressive
episode is known to be a warning sign of risk for conversion
to bipolar disorder. But only a minority of depressed young
people will ever experience mania or hypomania and therefore
receive a BD diagnosis and treatments specific to BD, as
opposed to depression. Among other things, antidepressants
may not help a young person whose depression is just the
prelude to mania and BD. Those with the diagnosis are usually
treated with mood stabilizers including lithium, anti-seizure and
antipsychotic medications.
The BIOS team’s 2016 paper that identified prodromal symp-
toms before the onset of mania drew from results across the
study cohort as a whole, but did not identify the individual risk
for specific children. To address this issue, a paper published
by the BIOS team in August 2017 in JAMA Psychiatry brought
hopeful news.
Based on a study cohort that now numbered 412 children of
parents with BD–of whom 54 had themselves developed BD
during the follow-up period of the study–the team was now
able to construct a risk calculator. Based on established criteria
for assessing risk for BD–mood and anxiety symptoms, general
psychosocial functioning, and age of one’s parent when she
or he began to suffer from a mood disorder–the risk calculator
was tested in the BIOS study population, where the researchers
had observed some of the high-risk young people initially en-
rolled actually develop the illness over the course of the study.
Estimating the preliminary or prodrome period for BD at
anywhere from two to 10 years, depending on the individual,
the team noted that all of the early warning signs were not in
themselves specific to BD. One could be anxious or habitually
defy authority or be irritable or have sleep disturbances or be
depressed–and not go on to develop mania and BD.
Yet such symptoms as factored into the risk calculator
tested by the team succeeded with a 70 percent accuracy of
“predicting” which of the high-risk young people in the BIOS
study did go on to receive a BD diagnosis within five years of
their “check-in” assessment. The accuracy was by no means
perfect, but it was almost exactly equal to that used in risk
assessments for heart disease and colorectal cancer that are
widely adopted in medicine.
Dr. Birmaher and colleagues caution that the risk calculator
is not yet ready for clinical use because it needs to be tested in
sample populations not involved in the BIOS study. Yet the
tool does give a sense, finally, of what doctors should look for in
trying to assess whether a specific young patient is at high risk
developing BD within the next five years.
Preventive interventions can be undertaken in those whose risk
is found to be high. The tool is equally valuable for researchers,
who now can pay particularly close attention to those thought
to be likely to develop the illness but who have not yet done
so. These are ideal candidates for state-of-the-art brain imaging
and other monitoring tools, which have a good chance of
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Ar T Bo the Numbers Since 1987

AWARDED TO SCIENTISTS

GRANTS

5,700+)

The breakdown of our grantees since 1987
5,700+

Young Investigators
828

Independent Investigators
426

Distinguished Investigators

UNIVERSITIES & MEDICAL CENTERS

557

COUNTRIES, INCLUDING THE U.S.

35

The group includes:

52 Members of the National Academy of Medicine
25 Chairs of Psychiatry & Neuroscience Departments
13 Members of the National Academy of Sciences
4 Recipients of the National Medal of Science
2 Former Directors of the National Institute of Mental Health
2 Nobel Prize Winners

The all-volunteer Foundation Scientific Council is composed of leading experts
cross disciplines in brain & behavior research who review grant applications
and recommend the most promising ideas to

As of August 2018

$394+ MILLION

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Brain Scans Identified People Most Likely to Benefit from Exposure Therapy for Trauma

Exposure therapy, which involves using a safe setting to accu- mulate an individual to things, people, or places associated with a past trauma, is the most effective treatment for post-trau- matic stress disorder (PTSD). Yet it only works for about half of patients. A new study suggests individual differences in how the brain responds to emotional cues may explain differences in the therapy’s outcome.

The study included 66 people with PTSD whose brain activity was monitored by fMRI brain scanning as they completed tasks requiring them to process and regulate their emotions. After the brain scans, half of the participants started a 12-session course of exposure therapy and the rest joined a waiting list. The team found people with the best response to therapy and the largest reduction of symptoms had already shown signs of less emotional reactivity and stronger regulation of emotions in their initial brain scan before the trial began. They were better able to spontaneously engage emotion-regulating regions in the prefrontal cortex and showed less activation in the amygdala in response to fearful stimuli.

The new findings suggest it may be possible to predict who responds to exposure therapy before patients and their doc- tors invest time and effort. The research also suggests that non-responders might benefit from methods such as tran- scranial magnetic stimulation, or TMS, to boost the activity of emotion-regulating brain areas. So far, this idea has not been tested, however.

The study was published in The American Journal of Psychiatry. The study team was led by Amit Etkin, M.D., Ph.D., a 2012 Young Investigator at Stanford University and included Barbara Olof Rothbaum, Ph.D., a 2012 Distinguished Investigator at Emory University, Desmond Jay Oathes, Ph.D., a 2016 Young Investigator at the University of Pennsylvania, and Steven E. Lindley, M.D., Ph.D., a 1995 Young Investigator at Stanford University.

In Small Study, “NAC” Medication Improved Memory in Patients with Schizophrenia and Bipolar Disorder

For people with schizophrenia and bipolar disorder with symp- toms of psychosis, depression, and mania can be debilitating. Ill patients may also suffer from memory and learning prob- lems. These are not relieved by antidepressant medications and can significantly contribute to difficulty in functioning. Now, new research finds that adding N-acetylcysteine (NAC) medica- tion to the treatment regimen may help address this problem.

NAC is an already-approved medication, often used to treat acetaminophen overdose and to loosen mucus in pulmonary diseases. But it may also have neuroprotective effects, possibly preventing the result of its impact on the neurotransmitter glutamate. Glutamate is the most prevalent excitatory signal-carrying chemical in the brain, crucial for synaptic plasticity—the ability of connections between neurons to change in strength. This is the very basis of memory and learning. NAC is also an antioxidant and may help reduce oxidative damage in critical brain regions.

The new study is a small one, involving 58 patients diagnosed with either schizophrenia or bipolar disorder. Twenty-seven participants received two grams of NAC a day. After six months of treatment, the patients scored significantly higher on tests of working memory than 31 similar patients who had received a placebo.

The findings add to other recent studies that have suggested NAC may be a promising supplement treatment for psychotic disorders as well as various other conditions, such as depression, obsessive-compulsive disorder, and Alzheimer’s disease. The team is conducting another study with first-episode psy- chosis patients to determine whether NAC might delay or even prevent the start of cognitive deterioration in these disorders.

The findings were published in Psychological Medicine. The study team was led by Marta Rapado-Castro, Ph.D., a 2016 Independent Investigator at the Universidad Complutense Madrid (Spain), and included Michael Berk, Ph.D., MBbch, MMed, FFPsych, SA, FRANZCP, a 2015 Colvin Prizewinner, and Olivia May Dean, Ph.D., a 2013 Young Investigator at McLean Hospital.

Vagus Nerve Stimulation Improved Treatment-Resistant Depression Over Extended Period

Adding vagus nerve stimulation (VNS) to the usual treatment for depression may lead to better long-term outcomes, a five- year study suggests.

Running from the brainstem down to the chest and abdomen, the vagus nerve governs involuntary functions of the heart, lung, and digestive tract. It is often thought of as the main connection between the brain and the “gut.” Vagus nerve stimulation (VNS), performed via an electrical implant in the chest, is approved by the U.S. Food and Drug Administration for treating depression and epilepsy in people who have not benefited from other treatments.

The new findings come from a five-year study conducted to track the efficacy of the treatment after the FDA approved its use. The study included 795 people with depression who had not responded to four or more anti-depression treatments. Of these patients, 494 received VNS in addition to their usual care, which included medications and psychotherapy, and 301 patients received usual care without VNS.

Among the patients in the VNS group, 67.6 percent experi- enced a reduction of their depressive symptoms by half or more. In comparison, 40.9 percent of patients in the usual care group saw a similar drop in symptom severity. More than 43 percent of those who received VNS were in remission and no longer considered to need treatment for depression, compared to 25.7 percent of the usual-care patients. The findings are published in the American Journal of Psychiatry.


Two-Coil Array for Transcranial Magnetic Stimulation Appears Safe and Effective for Resistant Depression

In recent years, non-invasive brain stimulation has shown great promise in treating people with resistant depression, i.e., those who have not been helped by multiple courses of antidepressant therapies. Currently, stimulation is performed using a transcranial magnetic stimulation (TMS) device, an electromagnetic coil that is placed over the scalp which sends pulses to a targeted brain region to alter neuronal activity. New research now suggests that an upgraded TMS device that includes two magnetic coils and allows operators to access deeper areas of the brain is safe and effective.

Cools used in conventional TMS devices provide focused stim- ulation but can only penetrate two centimeters (three-fourths of an inch) beneath the skull. Some of the structures involved in major depression, however, lie deeper in the brain. Using larger coils could help reach those areas but may also stimulate adjacent regions and cause side effects.

This explains the decision to test multiple small coils. The idea is that they might deliver combined electromagnetic fields that converge to provide precise stimulation to deeper regions. To assess the safety and effectiveness of this approach, re- searchers treated 38 patients with resistant depression with a two-coil TMS device. After 20 daily sessions, 55.3 percent of the patients experienced a reduction in the severity of their depression of at least 50 percent. In comparison, 32.4 percent of 37 controls who had received a “sham” TMS treatment showed a similar improvement. When tested a month after treatments ended, the TMS group still appeared to show a bet- ter response than the control group, but the difference was no longer statistically significant, perhaps due to the small number of participants, the researchers said.

The treatment did not cause adverse effects, other than headaches and jaw pain.

The findings were published in the journal Brain Stimulation.

The study team was led by Linda L. Carpenter, M.D., a 2005 Independent Investigator and 1997 Young Investigator at Butler Hospital, and included Paul E. Holsheimer, M.D., a 2016 Independent Investigator and 2007 Young Investigator at the Dartmouth-Hitchcock Medical Center, and William M. McDonald, M.D., a 1999 Independent Investigator at Emory University School of Medicine.

Abstract: https://www.sciencedirect.com/science/article/pii/ S1935661X17308343

DISCOVERY TO RECOVERY

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

BY BAHAR GHOLIPOUR

Brain Stimulation

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Two-Coil Array for Transcranial Magnetic Stimulation Appears Safe and Effective for Resistant Depression

In recent years, non-invasive brain stimulation has shown great promise in treating people with resistant depression, i.e., those who have not been helped by multiple courses of antidepressant therapies. Currently, stimulation is performed using a transcranial magnetic stimulation (TMS) device, an electromagnetic coil that is placed over the scalp which sends pulses to a targeted brain region to alter neuronal activity. New research now suggests that an upgraded TMS device that includes two magnetic coils and allows operators to access deeper areas of the brain is safe and effective.

Cools used in conventional TMS devices provide focused stim- ulation but can only penetrate two centimeters (three-fourths of an inch) beneath the skull. Some of the structures involved in major depression, however, lie deeper in the brain. Using larger coils could help reach those areas but may also stimulate adjacent regions and cause side effects.

This explains the decision to test multiple small coils. The idea is that they might deliver combined electromagnetic fields that converge to provide precise stimulation to deeper regions. To assess the safety and effectiveness of this approach, researchers treated 38 patients with resistant depression with a two-coil TMS device. After 20 daily sessions, 55.3 percent of the patients experienced a reduction in the severity of their depression of at least 50 percent. In comparison, 32.4 percent of 37 controls who had received a “sham” TMS treatment showed a similar improvement. When tested a month after treatments ended, the TMS group still appeared to show a bet- ter response than the control group, but the difference was no longer statistically significant, perhaps due to the small number of participants, the researchers said.

The treatment did not cause adverse effects, other than headaches and jaw pain.

The findings were published in the journal Brain Stimulation.

The study team was led by Linda L. Carpenter, M.D., a 2005 Independent Investigator and 1997 Young Investigator at Butler Hospital, and included Paul E. Holsheimer, M.D., a 2016 Independent Investigator and 2007 Young Investigator at the Dartmouth-Hitchcock Medical Center, and William M. McDonald, M.D., a 1999 Independent Investigator at Emory University School of Medicine. Abstract: https://www.sciencedirect.com/science/article/pii/S1935661X17308343
Thoughts in Patients with Severe Depression

The study, led by BBRF Scientific Council Members Husseini Manji, M.D., Wayne Drevets, M.D., and Gerard Sanacora, M.D., Ph.D., was conducted at 11 treatment facilities throughout the United States. Dr. Sanacora is at Yale School of Medicine, and Drs. Manji and Drevets, as well as the paper’s lead author, Carla M. Canuso, M.D., 1998 Young Investigator, are all at Janssen, the pharmaceutical company that makes esketamine. Larger clinical trials will be needed to evaluate esketamine’s safety and effectiveness, but the researchers are hopeful that it could be a valuable treatment for patients in urgent need, bridging the gap until traditional antidepressant medications can take effect.

The authors wrote, “the results of this proof-of-concept study support the hypothesis that intranasal esketamine may be an efficacious treatment for rapid reduction of depressive symptoms, including suicidal ideation, in patients assessed to be at imminent risk for suicide. These findings may reflect a promising breakthrough in the clinical management of a potentially lethal condition for which there are no approved pharmacotherapies.”

Brain Scans of Thousands of Patients with OCD Offer Clues to Disorder’s Roots

An analysis of thousands of brain scans reveals subtle structural abnormalities in the cortex associated with obsessive-compulsive disorder.

Millions of people—one in 40 adults and one in 100 children—have obsessive-compulsive disorder (OCD). This sometimes-disabling disorder causes recurring, uncontrollable thoughts and behaviors. Medications and psychotherapy help relieve these symptoms for some patients, but to find ways to more effectively treat the disorder, researchers need a deeper understanding of its causes.

Progress has been limited in part because studies about OCD have been small. Now, however, researchers around the world have come together to share data about the disorder and look for answers. In the May 8 issue of the American Journal of Psychiatry, an international team led by 2009 Young Investigator Odile A. van den Heuvel, M.D., Ph.D., at VU University Medical Center in Amsterdam, Netherlands, reported on the largest analysis to date of the structure of the brain’s cortex in people with OCD.

The cortex, the outermost layer of the brain, performs its most complex functions, giving rise to memory, attention, perception, cognition, thought, language, and emotion. By analyzing MRI scans of the brains of thousands of people, including 1,905 people with OCD and over 1,700 who are unaffected, Dr. van den Heuvel and her colleagues identified several structural abnormalities associated with the disorder. The findings point researchers toward regions where brain function appears to be disrupted.

Both children and adults participated in the study. The research team—the ENIGMA-OCD consortium—used MRI scans collected at 27 sites worldwide to create detailed maps of each participant’s cortex, then compared the maps of people with and without OCD. The study’s unprecedented size is what enabled the team to say with confidence that the subtle structural differences that they found to be associated with the disorder are statistically significant. In the past, studies have been too small to generate such findings.

The ENIGMA analysis revealed several areas of the cortex that were thinner and had less surface area in people with OCD than they did in control subjects, pointing researchers to specific brain systems for further study.

In particular, the researchers noted that a region called the parietal lobe was thinner in people with OCD. This part of the brain is thought to be involved in attention, planning, and response inhibition—functions that are often impaired in people with OCD. Abnormalities in the parietal lobe, which the team observed in both children and adults, might contribute to the recurring thoughts and repetitive behaviors associated with the disorder, the researchers say.

The researchers also observed abnormalities that occurred only in subsets of patients. Some areas of the cortex were thinnest in adult patients who were taking medication to control their OCD, whereas the surface area of other regions was smallest in children who were taking OCD medications. However, the researchers did not have enough information to determine whether medications were the cause of these differences. This will be the subject of future studies, they say.

Recent Research Discoveries

Important Advances by Foundation Grantees that are Moving the Field Forward

Esketamine Rapidly Reduced Suicidal Thoughts in Patients with Severe Depression

The experimental drug esketamine could be used in emergency settings to rapidly reduce suicide risk before currently approved antidepressant medications take effect.

Patients who are admitted to the hospital because they are at imminent risk for suicide need treatment fast. FDA-approved antidepressant medications, however, can take weeks to have an effect. Ketamine and the related drug esketamine, in contrast, can relieve symptoms of depression within hours, a number of studies over the last several years have demonstrated.

A clinical trial, reported on April 16 in the American Journal of Psychiatry involving 68 patients aged 19 to 64 with severe depression, all of whom were considered at imminent risk of suicide, found that adding esketamine to standard-of-care antidepressant medications caused patients’ suicidal thoughts to subside much more quickly.

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Carla M. Canuso, M.D.
1998 Young Investigator

Wayne Drevets, M.D.
Scientific Council Member
2014 Calvin Prize for Outstanding Achievement in Mood Disorders Research
1999 Independent Investigator
1996 Young Investigator

Husseini Manji, M.D.
Scientific Council Member
1999 Falcone Prize for Outstanding Achievement in Affective Disorders Research
1998 Independent Investigator

Gerard Sanacora, M.D., Ph.D.
Scientific Council Member
2014 Distinguished Investigator
2001, 1999 Young Investigator

Odile A. van den Heuvel, M.D., Ph.D.
2009 Young Investigator

 Recent Research Discoveries
Super Close-Up Image of Drug and its Receptor Suggests Design for Safer Antipsychotic Medications

Researchers have determined the precise structure of a key brain receptor as it interacts with the antipsychotic medicine risperidone, which may allow for fine-tuning of the drug’s effects on the brain.

Researchers who want to design safer, more effective antipsychotic medications now have a better roadmap, thanks to new insights from highly detailed structural images of a key brain receptor. The new images are the work of a team led by BBRF Scientific Council Member Bryan L. Roth, M.D., Ph.D. and his colleagues.

Dr. Roth is a pharmacologist at the University of North Carolina Chapel Hill Medical School. In the March 8 issue of the journal Nature, his team reported that they have determined the precise molecular structure of the antipsychotic medication risperidone (Risperdal) interacting with a D2 dopamine receptor, the drug’s target inside the brain.

By blocking D2 dopamine receptors, risperidone can prevent hallucinations and delusions in people with schizophrenia, bipolar disorder, and other illnesses that cause psychosis. In fact, all existing antipsychotic medications work by suppressing signaling from these same receptors. But they don’t do a good job of singling out their targets. The D2 receptor is one of five types of dopamine receptors in the brain, which have similar structures but distinct functions. D2-targeting drugs tend to bind to many of these, as well as other types of receptors in the brain. These unwanted interactions lead to a number of side effects, including movement problems, dizziness, weight gain, and other metabolic problems.

While scientists have known for nearly 30 years that antipsychotic medications target the D2 dopamine receptor, no one had been able to determine the detailed structure of a D2 receptor interacting with a drug. And without knowing how existing antipsychotics latch on to the D2 receptor, researchers had few clues as to how to modify those drugs to fine-tune their effects on the brain.

Generating a high-resolution image of the D2 receptor physically bound to one of these drugs was a decade-long effort for Dr. Roth’s lab. Now that they have obtained it, researchers can visualize the molecular interaction with detail approaching that of individual atoms. The Roth team’s new three-dimensional picture reveals several surprising features of the risperidone-receptor complex, including key structural distinctions between the D2 receptor and other dopamine receptors whose structures have already been determined. That gives scientists important clues about how to design next-generation drugs that bind more specifically to their targets without interfering with signaling elsewhere in the brain.
Over 300 people gathered in New York City on Tuesday, May 15th, in support of psychiatric research and eliminating the stigma of mental illness at the Brain & Behavior Research Foundation’s fourth annual Women’s Luncheon, Women Breaking the Silence About Mental Illness.

The event, co-chaired by BBRF Board Members Carole Mallement and Virginia Silver, and also by Beth Elliot and Sheila Scharfman, featured a conversation between Anne Ford, noted author, advocate and philanthropist, Ellen Levine, an advisor and consultant at Hearst, and Dr. Jeffrey Borenstein, President & CEO of BBRF.

During the event Anne Ford spoke candidly about her personal experience associated with raising a child with severe learning disabilities. When Anne, the great-granddaughter of Henry Ford, learned that her daughter Allegra’s “differences” were the result of severe learning disabilities, she faced a challenge that neither money nor social position could help ease. Desperate for answers, she sought out doctors, teachers, and counselors, who could help build a support network for herself and her daughter, while fighting common myths associated with raising children with brain and behavior disorders.

The luncheon’s conversation revolved around many of the challenges Allegra and Anne faced, including stigma. Anne also discussed her own feelings of worry and uncertainty about her child and what it was like raising and continually advocating for a child with severe learning disabilities.

The Brain & Behavior Research Foundation Women’s Luncheon honors women (often the primary caregivers), who are willing to speak openly about brain and behavior disorders and inspire others to speak out against the stigma surrounding psychiatric illness. Funds raised from the luncheons support scientists at leading universities who are conducting research into disorders such as post-traumatic stress disorder (PTSD), schizophrenia, ADHD, depression and bipolar disorder.

“Our luncheon shows how everyone is touched by these conditions,” said Dr. Borenstein, who noted that 100 percent of every dollar raised for research—all from private donations—goes to support research grants. “There is still so much we are learning about the brain, how it functions and how to properly treat and cure its illnesses. We depend on the generosity of our donors to support the researchers who are working to develop the breakthroughs we need for our loved ones. As a result of research, more people living with mental illness will go on to live full, productive and happy lives.”

At Hearst, Ellen Levine works across corporate divisions, from newspapers, to television to entertainment, to develop new projects and to foster ideas and collaboration. From 2006 to 2016, she was the editorial director of Hearst Magazines. During her tenure, she was instrumental in launching new titles, including O, The Oprah Magazine, followed by Food Network Magazine, HGTV Magazine, Dr. Oz The Good Life and most recently The Pioneer Woman Magazine. She made publishing history in October 1994 as the first woman to be named editor-in-chief of Good Housekeeping magazine. Throughout her career in publishing, she has been recognized many times for outstanding achievements. Among Ellen’s awards is the first annual media award by the American College of Neuropsychopharmacology for the numerous articles on mental illness she published in Good Housekeeping.

Anne Ford served as chairman of the board of the National Center for Learning Disabilities from 1989 to 2001. Anne has received many honors for her advocacy work for people with learning disabilities. She has co-authored five books with John-Richard Thompson. Their first book Laughing Allegra: The Inspiring Story of a Mother’s Struggle and Triumph Raising a Daughter with Learning Disabilities told Anne and Allegra’s story in a deeply moving and personal way. Their other books include On Their Own: Creating an Independent Future for your Adult Child with LD and ADHD, A Special Mother: Getting Through the Early Days of a Child’s Diagnosis of Learning Disabilities and Related Disorders, and The Forgotten Child: “If She is Special, What am I?”. When Learning Disabilities Cause Tension in the Home, Anna’s most recent book is The Stigmatized Child: Helping Parents Overcome the Stigma Attached to Learning Disabilities, ADHD, and Lack of Social Skills was given to all luncheon attendees.
At the Foundation’s first women’s luncheon in November of 2013, Swanee Hunt, former Ambassador to Austria and Harvard University’s Eleanor Roosevelt Lecturer in Public Policy, discussed her struggles to get her daughter help for bipolar disorder. In 2015, at the second luncheon, philanthropist and activist Lee Woodruff discussed how her life changed dramatically in a single moment after her husband, ABC News journalist Bob Woodruff, was injured in a roadside bomb while reporting from Iraq and how she experienced firsthand the feelings of depression, anxiety, and even despair. The 2016 women’s luncheon featured presentations and conversation with pioneering mental health researchers Dolores Malaspina, M.D. on schizophrenia and Myrna Weissman, Ph.D. on mood and anxiety disorders.

The New York Women’s Committee selected four Young Investigators to fund from a pool of hundreds of early career researchers in BBRF’s major donor Research Partners Program. This unique program provides donors with an opportunity to personally select and support scientists based on various criteria, including, but not limited to, illness specialty area, specific institutions, or a combination of criteria. The Women’s Committee chose four scientists with diverse areas of expertise including Lynette Astrid Averill, Ph.D. of Yale University who is researching PTSD, Estefania Pilar Bello, Ph.D. of the University of Buenos Aires, Argentina who is studying schizophrenia, Laura K. Fonken, Ph.D. of the University of Colorado Denver who is looking at late-life depression, and James J. Prisciandaro, Ph.D. of the Medical University of South Carolina who is researching substance misuse and bipolar disorder.

The Women’s Luncheon series is designed to pay tribute to the brave women who are willing to speak candidly and personally about mental illness and use them as an inspiration to galvanize all of the necessary resources needed to speak out, remove stigma, and break the silence about brain and behavior disorders.
Homelessness and Mental Illness: A Challenge to Our Society

WHAT IS THE PREVALENCE OF MENTAL ILLNESS AMONG PEOPLE EXPERIENCING HOMELESSNESS IN THE U.S.?

According to a 2015 assessment by the U.S. Department of Housing and Urban Development, 564,708 people were homeless on a given night in the United States. At a minimum, 140,000 or 25 percent of these people were seriously mentally ill, and 250,000 or 45 percent had any mental illness. By comparison, a 2016 study found that 4.2 percent of U.S. adults have been diagnosed with a serious mental illness.

WHAT ARE THE MOST COMMON TYPES OF MENTAL ILLNESS AMONG PEOPLE EXPERIENCING HOMELESSNESS?

Affective disorders such as depression and bipolar disorder, schizophrenia, anxiety disorders and substance use disorders are among the most common types of mental illness in the homeless population.

HOW ARE HOMELESSNESS AND MENTAL ILLNESS CONNECTED?

Most researchers agree that the connection between homelessness and mental illness is a complicated, two-way relationship. An individual’s mental illness may lead to cognitive and behavioral problems that make it difficult to earn a stable income or to carry out daily activities in ways that encourage stable housing. Several studies have shown, however, that individuals with mental illnesses often find themselves homeless primarily as a result of poverty and a lack of low-income housing. The combination of mental illness and homelessness can also lead to other factors such as increased levels of alcohol and drug abuse and violent victimization that reinforce the connection between health and homelessness.

CAN HOMELESSNESS EXACERBATE AN EXISTING MENTAL ILLNESS?

Studies do show that homelessness can be a traumatic event that influences a person’s symptoms of mental illness. Having ever been homeless and the time spent homeless can be related to higher levels of psychiatric distress, higher levels of alcohol use and lower levels of perceived recovery in people with previous mental illness.

HOW Do HOMELESSNESS AND MENTAL ILLNESS INFLUENCE A PERSON’S INTERACTIONS WITH POLICE AND THE JUSTICE SYSTEM?

In general, homelessness among people with mental illness can lead to more encounters with police and the courts. For instance, rates of contact with the criminal justice system and victimization among homeless adults with severe symptoms such as psychosis, are higher than among housed adults with severe mental illness. Homeless adults with mental illness who experienced abuse or neglect in childhood are more likely to be arrested for a crime or be the victim of crime.

HOW DOES HOMELESSNESS AFFECT MENTAL ILLNESS WITHIN FAMILIES?

One of the biggest impacts of homelessness on mental illness comes through its effect on the mothers of families. For instance, mothers who experience postpartum depression during the first year after birth are at higher risk for homelessness or factors leading to homelessness such as evictions or frequent moves in the two to three years after the postpartum year. One of the largest studies of children and homelessness (17,000 children in Denmark) found a higher incidence of psychiatric disorders, including substance abuse, among adolescents with a mother or both parents with a history of homelessness.

WHAT KINDS OF INTERVENTIONS HELP PEOPLE WITH MENTAL ILLNESS EXPERIENCING HOMELESSNESS?

Programs that provide long-term (a year or longer) stable housing for people with mental illnesses can help to improve mental health outcomes, including reducing the number of visits to inpatient psychiatric hospitals. A 2015 study concluded that services that deliver cognitive and social skill training, particularly in developing and maintaining relationships, would be useful in helping people with mental illnesses and homelessness regain housing.

A Free Monthly Discussion | Learn about the latest research from international experts in the field of brain and behavior research including addiction, ADHD, anxiety, autism, bipolar disorder, borderline personality disorder, depression, eating disorders, OCD, PTSD and schizophrenia.

- **Bright Light Therapy for Mood Disorders including Bipolar Depression**
  Tuesday, September 18th, 2:00PM EST
  **Dorothy Sit, M.D.**
  Northwestern University

- **Nicotine Receptors in the Brain: Implications for Addiction and Depression**
  Tuesday, October 9th, 2:00PM EST
  **Marina Picciotto, Ph.D.**
  Yale University School of Medicine

- **Pathways to New Treatments in Autism Spectrum Disorder**
  Tuesday, November 13th, 2:00PM EST
  **Jeremy M. Veenstra-Vanderweele, M.D.**
  Columbia University

- **Neuroimaging Inflammation in Depression and Obsessive Compulsive Disorder**
  Tuesday, December 4th, 2:00PM EST
  **Jeffrey Meyer, M.D., Ph.D.**
  Centre for Addiction and Mental Health, Canada

**MODERATOR**

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

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**Glossary**

**Deep-brain stimulation:** A “next generation therapy” for intractable depression in which an electrode inserted into the brain stimulates an area called the subcallosal cingulate or “Brodmann Area 25.”

**Dopamine and dopamine neurons:** Dopamine is a neurotransmitter in the brain that can activate five types of dopamine receptors (D1, D2, D3, D4, D5) located on neurons (dopamine neurons) that are specifically activated by dopamine. It is a key element of the brain's reward system and is also believed to play a central role in the learning of new motor skills. Reduced dopamine concentrations in the prefrontal cortex are thought to contribute to ADHD and some symptoms of schizophrenia.

**Esketamine:** a chemical “cousin” of the general anesthetic drug ketamine that is being tested in nasal spray form for use as a fast-acting (within hours) antidepressant. Also called S(+)-ketamine or (S)-ketamine.

**PET (positive emission tomography):** A brain-scanning technology that produces a three-dimensional image of brain processes.

**Prodrome/prodromal period:** Refers to the early stage of a brain and behavior disorder, a period just before an illness fully manifests. Researchers are particularly interested in studying the prodromal period of psychosis with the hopes of developing early intervention techniques that can prevent the damage of a psychotic break and greatly improve the chances for recovery.
Research for Recovery

30 years

For the past 30 years the Brain & Behavior Research Foundation has fostered new research pathways and transformative breakthroughs.

60k+ donors

Our 60,000 donors have joined together in the great challenge of modern medical science—overcoming mental illness.

$394M awarded

Since 1987 the Foundation has awarded more than $394 million to fund more than 5,700 grants.

4,700 researchers

Grants have been given to more than 4,700 leading scientists around the world.

100% of every dollar donated for research is invested in our research grants. Our operating expenses are covered by separate foundation grants.

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