

# Brain & Behavior

MAGAZINE

MARCH 2018



## RESEARCH FOR RECOVERY

ONE PERSON'S STORY OF  
RECOVERY FROM TREATMENT-  
RESISTANT DEPRESSION

## PARENTING

DIAGNOSING AND TREATING  
ANXIETY DISORDERS IN  
CHILDREN AND ADOLESCENTS

## TREAT EARLY AND FOLLOW THROUGH

A REVOLUTIONARY  
APPROACH IN ADDRESSING  
FIRST-EPISEDE PSYCHOSIS

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**Jeffrey Borenstein, M.D.**  
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As we embark on our 31<sup>st</sup> year of funding mental health research, we continue to be inspired by the investigators we support. Our grantees work at the cutting edge of science and strive each year to make discoveries and help patients in ways that outpace “business as usual” in the field. We help fuel their pace by investing the seed money so desperately needed, to nurture new ideas and new technologies that can have a significant impact on patients and their families for decades to come.

This issue marks the launch of two new columns that will showcase some of the inspiration that we receive from our researchers. “Pathways to the Future” stems from the thoughts and insights of our Outstanding Achievement Prizewinners from the past 30 years (see our November 2017 issue). Dr. Patrick McGorry’s success in treating psychosis early in Australian youth, through a comprehensive approach, offers our first look at how these visionary leaders continue to transform diagnoses and therapies (page 5).

Our second new column, “Research for Recovery,” focuses on a researcher and how his or her work is helping patients. It is thrilling to see how the research that we fund can spark discoveries with almost immediate effects on people living with these debilitating conditions, and in some cases offering new hope to those who have been seeking better treatment for years. The story of Dr. Lisa Pan and Bruce (page 9) shows the promise and hope of research.

With your help, we can continue to fund thoughtful and creative research that will drive the field of mental health forward and bring about better treatments, as well as cures and methods of prevention. Your role in this collaboration is crucial, and has an impact that goes far beyond 2018. Thank you for your support.

Sincerely,

A handwritten signature in black ink that reads "Jeffrey Borenstein". The signature is written in a cursive, flowing style.

Jeffrey Borenstein, M.D.

# Treating Psychosis Patients Early and Comprehensively Has Resulted in Improved Outcomes

By: Peter Tarr, Ph.D.



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

Columbia University  
Professor of Youth Mental Health  
University of Melbourne, Australia

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

2015 Lieber Prizewinner  
1998 Distinguished Investigator

**A** new approach to treating schizophrenia is based on a revamping of *the way* patients are treated, and when they are treated, relative to the onset of the illness. Spearheading much of the new and more optimistic research on treating schizophrenia is an Australian doctor, Patrick McGorry. In 2015, the Foundation awarded its prestigious Lieber Prize for Outstanding Achievement in Schizophrenia Research to Dr. McGorry for efforts that have “shifted the therapeutic paradigm for schizophrenia to early detection and intervention in young people.”

Early intervention has resulted in some eye-opening results in Dr. McGorry’s research that have given hope to many. To cite one example, in a trial involving 661 patients with first-episode psychosis, published last September in *Social Psychiatry and Psychiatric Epidemiology*, Dr. McGorry and colleagues reported that 63 percent reached “symptomatic remission” and 44 percent reached “functional remission.” (The former involves significant moderation or disappearance of symptoms; the latter signifies the ability to function in society, in a job, for instance). This was their status 18 months after receiving treatment for a first episode of psychosis, in centers for youth that Dr. McGorry and colleagues established to deliver this care,

which stress a comprehensive approach including social and vocational rehabilitation.

In order to detect and intervene early in young people who are at high risk of psychosis, have just had a first episode of psychosis, or have begun to experience symptoms associated with schizophrenia, there needs to be a system of care that is ready to receive them, and that young people know about and are not afraid to access. In a nutshell, this has been the focus of Dr. McGorry’s work and a cause he has been laser-focused on since the 1980s, and his efforts and political acumen have resulted in the creation in his native Australia of a system of mental health care geared to young people that might be considered revolutionary.

We asked him how he came to the idea that early intervention might change the course of schizophrenia, especially in light of the pervasive traditional view of the illness which stresses its incurability. “It started back in 1984, when I was still a trainee psychiatrist,” he said. “I had the opportunity, when I moved to Melbourne, to set up a research unit for schizophrenia, which was a new thing in those days in Australia. We didn’t have any research units focusing on that illness.”

He and his colleagues decided to focus on first-episode psychosis patients. Since psychosis occurs in several illnesses (including bipolar disorder and depression, although in a much smaller fraction of cases than in schizophrenia) this meant the focus was on “the psychotic break,” but not the specific diagnosis of the individual. This would be an important aspect of the model that would emerge from his experimental treatment program.

“We noticed three things pretty quickly,” Dr. McGorry recalls.

“First, our first-episode patients were young – teenagers or young adults, in the majority of cases. Second, they had long delays in getting treatment. It was usually something like a suicide attempt or an aggressive incident or some other kind of crisis that propelled them into treatment – often under traumatic and draconian circumstances, with police and handcuffs, coercive measures, involuntary treatment.

“The third thing we noticed was that they were terrified, because they were being brought into a mental hospital surrounded by people who were middle-aged, with the most severe, disabling illnesses. And psychiatrists were telling them things like, ‘this is a terrible, devastating illness; you’ll never get better; your life will now be very different.’”

At this early moment in his career, Dr. McGorry was stopped in his tracks. “All of those things were absolutely shocking to me – that such things could be happening! I had decided to train in psychiatry because I wanted to do something positive. And yet, I saw that there was so much harm being done to patients.”

As time passed, he noticed a fourth theme. In his view, patients “were being given 10 to 20 times as much antipsychotic medication as they really needed to get better.” At the same time, there was no real psychosocial treatment being offered. These observations provided the impetus for all that has followed in Dr. McGorry’s career. “We decided to try to turn all of this around – to basically challenge the idea that these people couldn’t get better.”

The new approach began with a decision “to try to limit the harm by using very low doses of medication,” but was accompanied by efforts to address the developmental and family needs of patients, “which were quite different from the needs of middle-aged chronic patients” receiving care in the hospital, he says.

At this early stage, the program was being run in a part of Royal Park Hospital, a chronic-care mental hospital in Melbourne. “But after a while we realized we needed to be based in the community, and using the hospital as a kind of backup system, rather than the other way around,” Dr. McGorry says. The result of moving into the community, to

treat young people where they lived, led to the development of a program called EPICC, which was extensively described in papers published by McGorry and colleagues in the 1990s. A major success that has been adopted in other nations in the intervening years, EPICC begins with the premise that psychosis causes acute distress in young people experiencing it for the first time, as well as among their family and friends, and that this distress needs to be attended to.

In retrospect, Dr. McGorry says, “what we have been trying to do is apply principles established in the care of heart disease and cancer, to psychiatry. Once we ‘found’ our patients, we didn’t discard them after initial treatments. Can you imagine doing that in cancer? With cancer, there’s a premium on early diagnosis; then you treat the patient as consistently and intensively as you can, or as is necessary, according to disease stage, until the patient gets better or dies. That has saved a lot of lives. It’s also lengthened the lives of many people who would have died more quickly. In other words, cancer treatment is disease-modifying. Whereas, in the way that serious psychiatric illness is treated, there is often revolving-door neglect.” Patients who lack insurance or the means to get first-rate care must access the public health system, where typically they “are patched up, episode to episode, but they are not maintained,” he said.

This situation, acknowledges Dr. McGorry, has a great deal to do with the failure of governments to effectively replace chronic long-term care in psychiatric hospitals with an effective community mental health system. Australia had very poor resources with which to deal with the psychiatric problems of the general population, and nothing that was geared to find and treat people in their late adolescence and early adulthood, the time in life when so many mental illnesses begin to manifest.

He has since received backing from various sectors, including Australia’s national government, to establish youth mental health centers nationwide. There are now over 110 such centers – called “headspace” clinics – and more are on the way. There is no publicly backed equivalent in the United States, although various localities in the U.S. and Europe have invited Dr. McGorry to help them design systems along the lines of the headspace centers he has established back home.

“I think what our experiment has shown is that when we do for first-episode psychosis patients what is done for those with serious physical illnesses, you get similar results,” he says. “We’ve shown this not only with early intervention for psychosis, but also in extending this idea to a broader youth mental-health paradigm, one that applies to all the emerging disorders in teenagers and young adults.”

## Making Recovery Possible: Treatment That Begins Before Diagnosis

In their still-growing Australian network of over 110 “headspace” clinics for youth mental health, Dr. Patrick McGorry and his colleagues are putting into practice ideas at the cutting edge of psychiatry, ideas that he hopes will eventually replace “flawed conceptions from the age of steam.” This means two things above all, Dr. McGorry said last year in remarks written to help commemorate the 30th anniversary of the Foundation. One is shifting the focus to early diagnosis; the other, which is related, involves beginning treatment during the earliest stages of illness, and even before a diagnosis is possible to make, in many cases. This shift in focus “has shown that the course of illness is plastic and can be greatly improved if timely, evidence-based care is provided,” Dr. McGorry said.

One thing he and his colleagues have learned in their headspace clinics is that treatment is most effective when it is begun immediately after a troubled youth enters the clinic. The treatment he is talking about usually begins before a diagnosis is determined. This has a profound implication: in Dr. McGorry’s view, the diagnostic categories that we are familiar with are often not even needed to begin helping a young person at high risk for mental illness or in the first stages of illness, no matter what the diagnosis might turn out to be.

“We have a staging model for care that has been very important. Some people have tried to develop such models based on the traditional diagnostic ‘silos.’ But those, we find, miss the whole point of staging, at least in the period when an illness is just beginning to emerge,” he says. “We found consistently that our patients had a need for care – they were distressed, their functioning was definitely suffering.”

Critics have charged that this approach can lead to over-diagnosis and overtreatment. “It’s just the reverse,” Dr. McGorry insists. “We’re trying to provide care where it’s clearly needed, even when the patients have not reached the threshold to qualify for one of those more traditional diagnoses like schizophrenia or bipolar disorder, which can take years to become clear enough to actually make the diagnosis. And by that time, in our experience, the person already has been in need of care for months or years.” Perhaps the most valuable insight to emerge from his clinical experience is that damage is done – to the brain and to the person – if proper treatment is not begun at the very beginning of the disease process. This is the best time to intervene.

Headspace is a primary-care model, McGorry explains. It is not specialized to particular diagnoses, but rather reflects what he considers a 21st-century notion of treating the manifestations of mental ill-health while these are still plastic. These manifes-

tations – they could be symptoms, behaviors, genetic predispositions, or, in the period just ahead, biomarkers – combine in a person to generate what he calls “microphenotypes.” By this he means that youth who may ultimately receive a wide range of diagnoses may have some of these individual components of mental ill-health in common. The key point is to address the behaviors or symptoms as soon as they are manifest, and to treat them not only with medications, where appropriate, but importantly, with robust social, family, and developmental support, to the extent possible. This is the formula that has resulted in “symptomatic” recoveries of two first-episode psychosis patients out of every three within the first 18 months in the headspace clinics. Data on longer-term trajectories are being developed, McGorry says.

The headspace clinics are more like primary-care clinics than mental health centers by design. “We have built an entrance hall, the front rooms of the house that provide care across the lifespan,” says Dr. McGorry. “It is vital to get these vulnerable and suffering young people into care, and to stay with them. But we have not yet built the rest of the house, involving more specializations, for the later stages of illness.”

He believes one reason the clinics have succeeded so far is that “they are stigma-free. And they are popular because people don’t worry about all the arcane debates that we have in psychiatry about diagnostic boundaries, or criteria or labeling. Ordinary people, including politicians in Australia, understand that these young people are in trouble. We’re trying to help them, trying to make it easy for them to seek help. The entry into headspace is ‘soft.’ We are welcoming; there are no barriers, including financial ones. Young people just come in and talk to someone.

“We scale up the intensity of our response according to the needs the person has. Not just narrow medical needs. Medication can be part of it, but we’re also helping them get a job or finish their education or deal with substance abuse or relationships. These are young people in transition, trying to master developmental tasks, like identity. Many have sexual orientation issues. So it’s very holistic. We embed our psychiatric expertise within that kind of needs-based framework. Within that structure, we conduct [National Institute of Mental Health] NIMH-level research,” which has resulted in many publications and the start of a new journal to address this emerging field: *Early Intervention in Psychiatry*, published by John Wiley & Sons since 2007.

The RAISE clinical trial in the U.S., in which many researchers supported by the Foundation have participated, has pointed to the vital importance of treating psychosis early and comprehensively, in care that is integrated. The RAISE study (Recovery After an Initial Schizophrenia Episode), along with nine other

clinical trials, now shows that specialized first-episode programs produce better medium-term results, Dr. McGorry says. He adds: "They clearly have a much more potent effect if the delay in accessing treatment is not too long. Beyond a year or so of delay, they don't seem to be able to reverse the impact of the illness so well, which makes perfect sense clinically."

To Dr. McGorry, the RAISE results echo findings from his years of research dating back to the 1990s with first-episode patients. "If you do things properly for first-episode patients, from the earliest point of the illness – and the earlier the better, we have evidence of this – the better the outcome is liable to be. Our research shows that the best results come from identifying the patient in the first three months of development of sustained psychosis to really make a difference with early treatment programs like ours. So the timing (as well as specialized first-episode psychosis care) is very, very important. In 2012, the TIPS study (TIPS is an acronym for early detection and treatment) in Norway also showed in a population of 174 patients, 101 of whom received early treatment for first-episode psychosis, that if treatment delay is reduced to a few weeks, recovery rates are 'significantly' better 10 years later. And new research shows that you have to safeguard and build on those gains and not consign patients back to revolving-door care in traditional psychiatric services."

Data from the headspace clinics also support the importance of engaging and following up with so-called ultra-high risk individuals, those with genetic and behavioral warning signs that mark what doctors call the prodrome, the period leading to a psychotic episode. Only one person in three in this high-risk group progresses to psychosis. In a certain number of these people, Dr. McGorry hypothesizes, the condition may resemble – surprisingly – asthma. "Certain young people may have

a [biological] vulnerability, which they may grow out of," he says. Others may progress to psychosis, but if treated comprehensively in the very earliest stages, the damage may be limited and the impact of the illness either attenuated or perhaps postponed for some number of years.

This evidence seems to suggest there is a "critical period," says Dr. McGorry, which describes this first period of psychotic illness. "I've worked in the same place for 30 years," he says. "So I've looked after patients for very long periods of time." In his experience, young patients, when treated comprehensively and consistently followed up, improve over time, so the prognosis is better and more malleable than people have realized. Some fraction of patients, perhaps one in five, clearly deteriorate, he acknowledges. "These are the patients we have not learned how to help yet." Some young people at high risk of psychotic disorder seem to outgrow their vulnerability, while others do not. In some ways this pattern is reminiscent of childhood asthma, he says. Some of the latter become chronic patients, for reasons still not clear. Dr. McGorry suspects some portion of chronicity and the premature mortality that flows from physical illness and suicide "is built in by neglect, drugs, or just inactivity, as well as unemployment, social deprivation and poverty." One clear objective of the headspace clinics and the kind of early intervention he has inspired others to try to provide is "to prevent a lot of those co-morbidities, as best as we are able, given our resources."

He concludes: "There's a tremendous amount that can be done, if only the society and governments would actually commit the amounts of money and support for clinical care systems that are appropriate, and also to medical research, just as they do for cancer and HIV."

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# Research for Recovery

## Relief from Decades of Treatment-Resistant Depression Comes with Metabolite Replacement Therapy Trial

By: Fatima Bhojani

**B**ruce had tried everything. And yet, for three decades, he could not find any relief from his debilitating depression and suicidal thoughts.

Twenty medications. Electroconvulsive therapy. Countless hours of counseling and cognitive behavioral therapy. Nothing had worked.

Of the 15 million American adults diagnosed with major depression, 15 percent do not respond to any available treatments. They, like Bruce, have treatment-refractory depression. In many cases the illness poses significant risk of suicide.

Bruce's symptoms began early in his teens. As time went on, they became worse, slowly consuming all aspects of his life. He went from being a high-functioning professional, designing and repairing submarines for the Department of Defense, to someone who could barely muster enough willpower and cognitive capacity to shower, eat, and show up for work.

"But even this was becoming a tremendous struggle," Bruce recalls.

By the time Bruce turned 35, in 2000, his depression became so debilitating that he lost the ability to function day-to-day, and had to resign from his job. The realization that he was once successful and independent, but now on the verge of assisted living, caused him great anguish.

"How could that possibly be? With my career accomplishments, how could I now lack the capacity to even minimally function?" Bruce wondered.



Dr. Lisa Pan and her patient, Bruce.

Bruce turned into a "professional appointment keeper." His entire day was spent keeping up with doctor's appointments and managing his symptoms and the side effects from his medications.

Last year, at age 51, Bruce's current doctor referred him to Dr. Lisa Pan, who was leading research that offered great promise for those with untreatable depression.

Dr. Pan, a 2012 Brain & Behavior Research Foundation Young Investigator Grantee, had long worked with teens at risk for suicide. It was one such young person, under her care at the STAR (Services for Teens At Risk) Center at the University of Pittsburgh Medical Center's Western Psychiatric Institute, that led her to draw a connection between metabolism and depression.

For years, Dr. Pan struggled to treat a teenager with debilitating, persistent depression, suicidal thoughts, and a history of multiple near-lethal suicide attempts.

Out of desperation and out of options, and recalling research from the 1980s that linked low levels of the neurotransmitter serotonin to suicide, Dr. Pan asked colleagues at the University of Pittsburgh, Dr. David Finegold, a professor of human genetics, and Dr. Jerry Vockley, a biochemical geneticist, if they could glean any clues by examining the young man's neurotransmitter profile. Our metabolism is responsible for manufacturing message-carrying chemicals called neurotransmitters, like serotonin and dopamine and norepinephrine, which help regulate our mood.

After running an extensive neurologic panel by analyzing the young man's cerebrospinal fluid (CSF), her colleagues found he was missing small molecules of tetrahydrobiopterin, or BH4, which helps synthesize neurotransmitters. The young man was given a synthetic BH4 replacement. Within weeks his symptoms greatly improved. The young man went off to college and was able to turn his life around.

Dr. Pan began analyzing the cerebrospinal fluid of other patients with treatment-refractory, life-threatening depression. The next three patients she tested all showed low levels of folate, an essential metabolite, in their cerebrospinal fluid, even though the levels in their blood were normal.

After being treated with folinic acid over a period of weeks, these patients began to show improvement.

Encouraged by these results, Dr. Pan, through her 2012 Young Investigator Grant from BBRF, conducted a small pilot study, the results of which were published in the *American Journal of Psychiatry* in August 2016.

Beginning in 2014, Dr. Pan and her team evaluated 33 patients with treatment-refractory depression. They found that 21 patients had metabolite abnormalities, with the majority suffering from cerebral folate deficiency.

Once treated, most patients showed a reduction in suicidal ideation and an improvement in their symptoms. In some cases, their depression disappeared altogether.

"The thing that is really exciting about these findings is that they suggest that we may have underlying metabolic abnormalities

that are contributing to psychiatric illness, particularly depression," says Dr. Pan.

Dr. Pan's best theory is that in most cases these patients' bodies cannot make the neurotransmitters the same way other people can. That would also explain why they don't respond to traditional psychiatric medications.

A common class of depression medications, called selective serotonin reuptake inhibitors (SSRIs), blocks the "re-uptake" of serotonin, which means that they stop neurons from reabsorbing serotonin after it has been released into the gap, or synapse, that separates communicating cells. However, if the body does not create enough serotonin to begin with, there is no "re-uptake" to block, she suggests.

Dr. Pan and her team are trying to fully understand the physiology behind the results to comprehend "why we are finding what we are finding," she says.

**"The thing that is really exciting about these findings is that they suggest that we may have underlying metabolic abnormalities that are contributing to psychiatric illness, particularly depression," says Dr. Pan.**

She has so far expanded her study to 140 participants. To qualify for the study, patients must have had three maximum dose anti-depressant trials for at least six weeks. However, Dr. Pan points out that most participants have undergone more treatments than that.

"Many have had multiple treatments trials, and so much therapy that they can almost teach it. Quite a few had suicidal behavior and ideation," she

says. "This is a chronically ill population, who is at risk for death. Their life is very hard. I admire these people more than anyone because they really fight every day."

Last fall, Bruce joined the study.

"Dr. Pan's staff have been incredibly engaging, and involved to a depth I have never experienced in the medical community," he remembers.

An analysis of Bruce's CSF revealed that he too, like the suicidal teenager earlier, had drastically low levels of BH4. He began oral BH4 replacement therapy in late April 2017. Within a few days, he knew "something was happening." Tackling his monthly bills had usually taken him a painfully long time, but by the first of May he was able to get them done in 15 minutes.

As time went on, the improvements kept coming. Before he had spent his whole day managing his condition, but now

Bruce found free-time in his day to actually “live.”

Almost two months into his treatment, Bruce cooked a barbecue dinner from scratch for his extended family on Father’s Day, after he spent five hours working on his car. This would have been impossible before he started treatment.

“I did not need one moment of time to manage my illness,” Bruce recalls.

Bruce’s cognitive functioning and willpower have improved so much that he is now contemplating a return to the professional scientific community.

This is “a remarkable contrast” to his life before, he says.

Bruce was one of the study participants who showed immediate and drastic improvement. Dr. Pan remembers Bruce as a very “slowed down” person.

“He moved slowly, spoke slowly. And now we have a very energetic and excited person, who is motivated,” she says.

In her larger sample of patients, Dr. Pan’s initial findings stand. More than 50 percent of those tested have a treatable metabolic disorder.

So far, Dr. Pan’s team has found seven disorders, most commonly cerebral folate deficiency and BH4 deficiency. There are also patients for whom the team has yet to find a known metabolic disorder.

The study requires patients to come back for a follow-up visit six months after beginning treatment, and Dr. Pan says most are showing improvements in their symptoms.

“We see everything from a really startling change [such as with Bruce] which is very impressive, to a gradual improvement over time,” says Dr. Pan.

Every day, Dr. Pan receives calls and emails from fraught patients and family members across the country.

“I really hope that Dr. Pan’s diagnostic technology is made available to as many doctors throughout the U.S. and the world, because depression is a true biological, medical condition that can be diagnosed under a microscope,” says Bruce. “It is not a moral or character flaw.”

Depression by itself is difficult, if not disabling. “But to have a depression that has been going on for years, or even decades, without any relief is an incredible burden to bear,” says Dr. Pan.

And Dr. Pan’s research could change the way we treat those who bear that burden.

“The promise of that, even though it’s very early, is very exciting,” says Dr. Pan.



From running in a marathon to hosting a golf outing or bake sale, support the Brain & Behavior Research Foundation and let your talents, interests, and creative ideas lead to your own fundraising endeavor and Team Up for Research.

Learn more at [bbrfoundation.org/teamup](https://bbrfoundation.org/teamup) and request a Team Up for Research Fundraising Guide.

Questions? Contact Special Events at 800-829-8289 or [events@bbrfoundation.org](mailto:events@bbrfoundation.org).

# The 2017 Pardes Humanitarian Prize in Mental Health

**O**n October 27, 2017 the Brain & Behavior Research Foundation hosted its 30<sup>th</sup> annual International Awards Dinner, honoring the year's Outstanding Achievement Prizewinners (featured in the Symposium story on page 29), as well as the recipients of the Pardes Humanitarian Prize in Mental Health, at the Pierre Hotel in New York City.

This year's Pardes Prize recipient was Doctors Without Borders/ Médecins Sans Frontières (MSF) for providing vital psychiatric and psychological care to people ravaged by man-made or natural disaster for more than 20 years. The organization currently has mental health related programs in 41 countries across five continents treating adults and children.

An Honorary Prize was given to the late Constance E. Lieber, the Foundation's President from 1989 to 2007 and President Emerita until 2016, for a lifetime of extraordinary advocacy and support for psychiatric research of schizophrenia, depression, and other mental illnesses.

The international Pardes Humanitarian Prize in Mental Health is awarded annually to recognize a physician, scientist, organization, or person whose extraordinary contribution has made a profound and lasting impact by improving the lives of people suffering from mental illness and by advancing the understanding of mental illness. The Prize focuses

public attention on the burden of mental illness on individuals and society. It also recognizes the urgent need to expand and enhance mental health services in both the developed world and developing countries. Established in 2014, the Prize is named in honor of Herbert Pardes, M.D., who leads the Foundation's Scientific Council.

Dr. Pardes said the Prize was established "to honor individuals who comprehensively care, teach, investigate, work, and passionately advocate for improving the mental health of society, and who have had a powerful impact on reducing the pain inflicted by psychiatric illness."



Dr. Jeffrey Borenstein, Steven Lieber, Dr. Herbert Pardes, Jason Cone

Doctors Without Borders/Médecins Sans Frontières provides emergency medical aid and mental health care in response to armed conflicts, natural disasters, famines, and epidemics. Violence, armed conflict, disease outbreaks, natural disasters, sexual violence, and neglect can be profoundly traumatic for individuals who live through them and can lead to severe mental health issues both in the moment and beyond. Depression and anxiety can immobilize people at just the time when they need to take action for themselves and their families. MSF intervenes where there is a lack of mental health services in areas afflicted by disasters, and as a support to other medical activities.

The first MSF mental health interventions were in Armenia in 1990 after a major earthquake in the country. In the 1990s, MSF initiated mental health programs in Gaza, the Balkans, and in Eastern Europe, and in 1998, MSF formally recognized the need to implement mental health and psychosocial interventions as part of their emergency work. Since then, the scope of interventions originally tailored towards survivors of disasters has been broadened to include more and more integrated activities within medical programs. Today, MSF considers providing mental health care a primary objective in a variety of contexts, especially in increasing the efficacy of medical programs focused on treating HIV/AIDS, tuberculosis, malnutrition, and non-communicable diseases. MSF mental health care programs treat Syrian children at a hospital in northern Jordan, typhoon survivors in the Philippines, survivors of sexual violence in Haiti, cholera victims in Yemen, and displaced people across the globe, including Iraq, Lebanon, Italy, Mexico, Tanzania, and Sudan.



Dr. Norman Sartorius and Dr. William Carpenter, Members of the Pardes Prize Selection Committee

Accepting the award on behalf of MSF was Jason Cone, Executive Director of MSF-USA. He said, “We are grateful for this recognition from the Brain & Behavior Research Foundation. It is our hope that this award will shine a light on the immense mental health needs faced by people dealing with the scars of war and conflict, forced migration, sexual violence, the isolation of psychiatric disorders, and the stigma of devastating diagnoses, such as HIV and tuberculosis.”

Each year the esteemed International Selection Committee also chooses an Honorary Pardes Humanitarian Prize recipient, whose extraordinary contribution to mental health has been transformative and of great magnitude to those living with mental illness and their families.

This year’s recipient, Constance E. Lieber, transformed her family’s experience with mental illness into a lifetime of extraordinary advocacy and support for psychiatric research of schizophrenia, depression, and other mental illnesses. She was unwavering in her dedication to alleviating the suffering caused by mental illness and banishing the stigma that for too long has been associated with psychiatric disorders.

More than 30 years ago at a symposium at Columbia University, Dr. Pardes first met Connie and Steve Lieber. They spoke with him about supporting mental health programs and research on mental illness. That initial conversation led to more than \$380 million in grants from the Brain & Behavior Research Foundation to more than 4,500 of the most innovative scientists around the world. Under Connie’s leadership, the Foundation became a major global institution in mental health and psychiatric research.



Dr. Helen Mayberg, Member of the Pardes Prize Selection Committee

“Connie Lieber was a global champion for mental health and an extraordinary humanitarian. Not only did she work tirelessly to support scientists in the field, but guided by her own personal experience and compassion, she informally advised thousands of parents who were desperately seeking help for their children,” said Dr. Pardes. “Connie’s hope was to alleviate suffering by finding cures for mental illnesses and banishing the stigma that for too long has been associated with psychiatric disorders. Her work continues. We are dedicated to making her dreams a reality.”

At Columbia University, Connie and Steve founded two centers of excellence—the Lieber Recovery and Rehabilitation Clinic and the Lieber Center for Schizophrenia Research and Treatment. At Williams College, they were the founders of the undergraduate neuroscience program. In 2011, they created the Lieber Institute for Brain Development, affiliated with Johns Hopkins University.

Dr. Jeffrey Borenstein said, “Connie Lieber has left us an outstanding legacy of generosity, brilliance and compassion. She was our leader and guiding light, providing inspiration and motivation to all who ever had the honor and privilege of knowing and working with her.”

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New York State Psychiatric Institute

# Is Reversing Age-Related Memory Loss Possible?

Boosting Levels of a Protein Found in Bones and Brain Suggest a Possible Method By: Peter Tarr, Ph.D.



**Dr. Eric Kandel, M.D.**

University Professor and Kavli Professor of Neuroscience  
Columbia University

Senior Investigator  
Howard Hughes Medical Institute

Director  
Kavli Institute for Brain Science

Co-Director  
Zuckerman Mind Brain Behavior Institute

BBRF Scientific Council Member

Two things that we often associate with the normal human aging process are bone loss and memory loss. In a remarkable development, research in the Columbia University laboratories of Nobel laureate Eric Kandel, M.D. and colleagues has recently pointed to a possible connection between the two. Although still in its early phases, this research now “paves the way” for the development and testing of a new therapeutic strategy to combat age-related memory loss, according to Dr. Kandel, a Foundation Scientific Council member, and his collaborator Gerard Karsenty, M.D., who chairs the Department of Genetics & Development at Columbia.

It’s important to clarify the distinction between age-related memory loss, which is a normal part of aging, and pathologies of the brain such as Alzheimer’s disease, which affect only a fraction of people. In any group of 100 randomly selected 70-year-olds, Dr. Kandel explains, about 40 will exemplify “successful aging.” They will have memory skills comparable to what they had in their forties. The remaining 60 people will divide in two additional groups. About 30 of these 60 people will already be showing signs of mild age-related memory loss. This condition is normal, and may become more acute as the years pass. It typically involves forgetting people’s names or where one has placed the house keys. The

other 30 people will already be on a biological path that will lead to Alzheimer’s disease, assuming their lives are not shortened by other illnesses.

The recent discoveries of Drs. Kandel and Karsenty have relevance to people affected by normal age-related loss of memory. The biological factor their labs have identified that involves both bones and memory is called osteocalcin. It’s a well-known protein, a hormone manufactured in the bones that Dr. Karsenty has found to be involved in promoting the production of insulin in the pancreas, testosterone in the testes, and certain neurotransmitters in the brain. Osteocalcin is produced by cells called osteoblasts, which form groups of connected cells that join together to form new bone tissue. As people get older, bone mass decreases, so does the activity of osteoblasts and bodily levels of osteocalcin. Dr. Karsenty has begun to explore the idea of supplementing osteocalcin in bone tissue in the hope that it will restore bone mass during the aging process.

Over the last several years, Drs. Kandel and Karsenty and their colleagues have pursued an analogous line of investigation in mice to test osteocalcin’s role in memory. This was not a shot in the dark, but rather, research that followed upon the 2013

discovery by Dr. Karsenty that the formation of memory in the brain's hippocampus cannot occur unless osteocalcin is present. Mice that were unable to make osteocalcin were also observed to have anxiety symptoms, suggesting other functions for the hormone in the brain.

In the *Journal of Experimental Medicine* in August 2017, Drs. Kandel, Karsenty, and their colleagues reported their discovery of a neuronal receptor – a docking port – where osteocalcin binds. Called Gpr158, this receptor was found to be abundant in neurons located in a layer of the hippocampus called the CA3 region, an area critical in the formation of memory.

The Karsenty team did a wide range of experiments to determine osteocalcin's role in memory. In one experiment, aged mice were given continuous infusions of osteocalcin over two months, during which time their performance on two different kinds of memory tests not only improved but reached levels seen only in young mice. Similar improvements were noted when blood plasma sampled from young mice – rich in osteocalcin – was injected into another group of aged mice.

The team then performed the blood plasma experiment using plasma drawn from young mice that were unable to manufacture osteocalcin. This time, the aged mice receiving the plasma didn't improve on memory tests. But when the Karsenty and Kandel labs added osteocalcin to osteocalcin-deficient plasma prior to injection into aged mice, this time the recipients' memory performance was boosted. Finally, the researchers used an antibody to disable osteocalcin in young mice, and then observed the animals' performance on memory tests. They did poorly.

After discovering Gpr158, the cellular receptor for osteocalcin, the team did one additional experiment, blocking the receptor and then giving mice infusions of osteocalcin. These mice, not surprisingly, had no memory benefit from the injections.

Taken together, this evidence is impressive, Dr. Kandel says. He notes that unlike some proteins, osteocalcin can cross the blood-brain barrier, and we know that it targets a specific receptor in brain cells – importantly, he says, “in an area of the brain that is involved in age-related memory loss.” The experiments reported in August “show in some detail that giving osteocalcin to aged mice reverses age-related memory loss.”

Whether osteocalcin is alone responsible for normal loss of memory in the aging brain is still not possible to say, Dr. Kandel cautions. It's true that it is manufactured in our bones, and we know that its level drops off after early adulthood. “But there may be other reasons for memory loss that we don't know.”

“We now hope to make an arrangement with a pharmaceutical company that would develop a drug based on the concept,” Dr. Kandel says. “We would of course need to get FDA approval to do clinical trials, etc. But you know, it's a long road ahead. Drug development is never easy or straightforward.”

Dr. Kandel, Dr. Karsenty, and their team noted in their August paper that no toxic effects of osteocalcin injection or infusion were noted in mice – but added that “of course we need to do more research to translate our findings into clinical use for humans.”

Since osteocalcin is a protein, it has to be delivered via injection; one possible objective of a pharmaceutical developer would be to invent an analog compound that could be given as a pill. This would make its potential use as a drug for people much more practical, should it prove to benefit aging people as it appears to benefit aging mice.

### DR. KANDEL'S RESEARCH TAKES A THERAPEUTIC TURN

“When I talk at various seminars and meetings about our recent research on osteocalcin and age-related memory loss, the attention it gets is remarkable,” Dr. Eric Kandel reports. His career has included some of the most important discoveries of modern neuroscience; his Nobel Prize in 2000 recognized decades of his research that helped to establish the molecular basis of memory. This long record of achievement has taught Dr. Kandel the virtue of not assuming too much about research that is still in its early stages, no matter how encouraging. And this, he stresses, is where the osteocalcin research stands today.

“Memory loss is so urgent a public health issue,” he notes, that any suggestion of progress in combating it will naturally raise expectations. He hopes, of course, that the new research is opening a productive path. “Look – I'm 88,” he says. “I wouldn't mind having a drug of this type around! It's potentially very useful. But the difference between ‘potential’ and ‘definitive’ is a big step.”

While he is cautious about where the osteocalcin research will lead, Dr. Kandel is quick to say that he is “very excited that at this point in my career, I have a completely new and interesting direction in my work!”

In fact, the research on age-related memory loss is only part of a broader contribution his lab has made to neuroscience since 2010. Kandel thinks “one of the most important things to have emerged” from his group is research that pertains to Alzheimer's and other pathological conditions that devastate human memory – in contrast to the slow and comparatively mild deterioration that accompanies normal aging.

Pharmaceutical companies have spent— and lost — billions of dollars over the last decade in efforts, so far unsuccessful, to develop and test drugs designed to break up the plaque-like clumps of material whose toxic accumulation is seen in the brains of Alzheimer’s patients, as well as people with other neurodegenerative illnesses such as Parkinson’s and Huntington’s diseases. Several theories have evolved to explain these pathologies. Some focus on clumps of amyloid-beta protein as the culprit in Alzheimer’s. Molecules called apolipoproteins normally break down clumps such as those formed by amyloid-beta, and a faulty variant of one such molecule, made by a gene variant called APOE4, is thought to contribute to the pathology. Others have studied the possible contribution of faulty tau proteins, which can form tangles and disrupt brain structure.

Protein aggregation is commonly associated with pathology, in part because of the role played in certain degenerative illnesses by prions. Prions are proteins that assemble into clumps and spread like an infection, wreaking havoc. But in recent years, Dr. Kandel’s lab has made a major contribution to the discussion by proving something highly counterintuitive. They’ve shown that protein clumping or aggregation in the brain can also perform a vital role in normal brain function.

“The preponderance of amyloid-based illnesses in the central nervous system of man may reflect the presence of prions in the nervous system serving normal functions,” Dr. Kandel has written. In other words, prions help the body — including the brain — do various important things, so long as they are properly regulated.

A flurry of papers suggesting a positive role for prions in the brain has been published by Kandel and colleagues since 2015. They have shown that a protein called CPEB3 has a necessary role in synaptic plasticity and memory — specifically, in the stabilization of long-term memory. The protein, in prion-like fashion, forms aggregates or clumps in the brain’s hippocampus after synapses (tiny gaps across which neighboring neurons communicate) have been activated, the initial step in the formation of a memory.

Some memories are short-term; they last a few hours, but pass out of memory when the synapses that contain their information are re-shaped. To retain a memory for a long time — days, months, years, or a lifetime — the brain needs a mechanism that stabilizes a given configuration of synapses and preserves it indefinitely. But how?

Some of the things we can do now were inconceivable even 10 years ago. The power of science — the kind of science that the Foundation funds every year — has matured.

Dr. Kandel and colleagues discovered the astonishing fact that CPEB3 (one of several variants of the CPEB protein) uses a prion-like mechanism to stabilize and preserve long-term memory in the hippocampus. When these neurons are stimulated, CPEB3 is transformed from an inactive form, in which individual CPEB3 proteins exist as single molecules, into an active form in which they clump together and begin to promote the activation of RNA messages copied from genes. These are blueprints that neurons use to manufacture other

proteins involved in memory preservation. The clumping or aggregation of the CPEB3 proteins thus sets off the process through which memory traces at synapses are stabilized and preserved.

In discovering this mechanism, Dr. Kandel and colleagues also gained insight into how helpful prions can be kept under control. When CPEB3 is in its inactive state, it doesn’t form clumps. This is because it interacts with a protein called SUMO. When a long-term

memory is formed, CPEB3 must be “de-SUMOylated,” to use the scientists’ terminology, so that it can form aggregates with other CPEB3 proteins. The clumping, in other words, is context-specific, associated specifically with memory stabilization.

Dr. Kandel, apart from being thrilled at the relevance of this new work, notes with interest that it is “moving, increasingly, in a therapeutic direction.”

“Now, on the one hand, that’s very pleasing,” he says. “I’m trained as a psychiatrist and I’ve been working on basic research involving marine snails and things like that! [His early work explained how the marine snail called *Aplysia californica* is able to learn and remember, based on its experiences.] It’s nice to think I’m working on things that pertain directly to clinical medicine.”

“But I also think this is about something much, much deeper. And that is that molecular biology has become so powerful and all-encompassing that its ability to address a range of problems, including therapeutic ones, has increased. Some of the things we can do now were inconceivable even 10 years ago. The power of science — the kind of science that the Foundation funds every year — has matured. All of this is supposed to lead to therapeutics, and in a number of cases, it’s beginning to do that!”

# 2017 Distinguished Investigator Grants

## The Vital Importance of Seed Capital for Research on Mental Illness



**Jack D. Barchas, M.D.**

Chair, Distinguished Investigator, Selection Committee  
Scientific Council Member

Chair, Department of Psychiatry  
NewYork-Presbyterian Hospital / Weill Cornell Medical Center

### **BASIC RESEARCH**

To understand what happens in the brain to cause mental illness.

### **EARLY INTERVENTION/ DIAGNOSTIC TOOLS**

To recognize early signs of mental illness and treat as early as possible.

### **NEXT GENERATION THERAPIES**

To reduce symptoms of mental illness and retrain the brain.

### **NEW TECHNOLOGIES**

To advance or create new ways of studying and understanding the brain.

**T**he Distinguished Investigator Grants provide support for experienced investigators conducting neurobiological and behavioral research. One-year grants of \$100,000 each are provided for established scientists pursuing particularly innovative project ideas.

The Distinguished Investigator Grants are among the most competitive of any honor in fields related to severe mental illness. Even before review, the criteria for submission are highly demanding: applicants must be at the rank of full professor or its equivalent; already have funding; have a history of demonstrated contributions regardless of their discipline; and are encouraged worldwide from persons in any field that may inform illness, knowledge of treatment, or prevention.

For some, this is their first venture into the field, and they have an idea that seems to fit the Foundation's goals and exhibit excellence. Grant applicants must have a demonstrated ability to do first-rate research with outstanding productivity and achievement. Those awarded grants are often given them based on a new direction for which results from the Distinguished Investigator program could lead to additional funding, if needed, from other sources.

Awards given for the Distinguished Investigator Grants can be considered as seed capital which permits vital steps forward. The results will be important whether positive or negative—if positive, they may represent a direction that will need to be replicated and extended; if negative, they provide an important answer about a step which may not now require follow-up or which may need further work in the future when there is still more related knowledge.

Applications are evaluated on the basis of innovation, quality of science, importance of results, feasibility, and their relation to the Foundation's mission. Grantees are selected by members of the Foundation's Scientific Council, a prestigious group of 176 leaders in brain and behavior research. This year's 17 Distinguished Investigators were selected from 140 applicants.

*"As funds for research from the National Institutes of Health have declined by 20 percent over the past decade, the Foundation's Distinguished Investigator program has become extraordinarily important for the field and its potential to help severe mental illness. This year's Distinguished Investigators use a remarkable range of methodologies to sharpen current treatments and define potential new targets, including previously*

unstudied or understudied neuroregulators, interactions, and circuits, using newer and more precise methods and improved psychosocial approaches. We were impressed by the variety of new approaches, which could prove helpful or even transformative. These include studies focusing on the immune system; looking at pre-birth events and stressors of all types; and examining large important databases for new clues.”

## 2017 DISTINGUISHED INVESTIGATORS GRANT SUMMARIES

### DEPRESSION



**Patricia A. Brennan, Ph.D.**, of the Emory Clinic, Emory University, will investigate how a mother’s depression during pregnancy affects her child’s risk of mental and behavioral deficits later in life. A child’s baby teeth contain a chemical record of the stress and immune system effects experienced while in the womb. Dr. Brennan will work with mothers who have previously participated in studies of prenatal maternal depression, whose children have already undergone extensive laboratory assessments and are approaching the age at which their baby teeth will begin to fall out. The project will test the hypothesis that depressive symptoms experienced by the mother are associated with higher levels of biomarkers for stress and immune function changes in the fetus, observed through analysis of the teeth. Dr. Brennan hopes that this research will inform clinical treatment guidelines for depression during pregnancy.

#### Early Intervention/ Diagnostic Tools

“My project is focused on intergenerational impacts of prenatal maternal depression. Methods used to measure maternal depression typically focuses on self-report of symptoms. However, maternal self-reports do not always correlate with hypothesized biological mechanisms such as levels of maternal cortisol or pro-inflammatory cytokines. In addition, measures of maternal biological functioning may not directly correspond to impacts on the fetus, due to potential placental or genetic protective factors. In this project, we will use a cutting-edge multimodal imaging technique applied to naturally shed baby teeth that will provide a direct ‘window’ into fetal exposures, thereby allowing for a more accurate assessment of the impact of maternal prenatal depression on fetal neurodevelopment and subsequent child outcomes. This project opens up a new

realm of discovery for our ongoing longitudinal studies of prenatal risk, and I am grateful to the Brain and Behavior Research Foundation for their funding and support.”



**Robert Dantzer, DVM., Ph.D.**, of the University of Texas MD Anderson Cancer Center, will investigate how inflammation may influence the changes in motivation seen in depressed patients. It is now widely accepted in psychiatry that the immune system reaction involved in inflammation contributes to the cause of at least some subtypes of depression. Previous research in rodents and humans show that a subtype known as inflammation-induced depression is associated with enhanced contrast in motivation, such that small rewards become less motivating more quickly than big rewards do. Working in rodent models of inflammation-induced depression, Dr. Dantzer will test the idea that inflammation causes chemical changes in the brain that impair its ability to use the neurotransmitter dopamine. He hopes that this work will help to identifying new biomarkers and reveal new drug targets for treating depression.

#### Basic Research

“Although inflammation is well known to be associated with certain forms of depression, we do not yet know how inflammation acts on the brain to induce depression. The BBRF grant will help us to understand how inflammation, by decreasing brain dopaminergic neurotransmission, reduces our propensity to engage in effortful behavior and at the same time enhances our sensitivity to the negative aspects of our environment.”



**Andrew H. Miller, M.D.**, of Emory University, will look to the immune system for biomarkers of depression that involve inflammation, a subset of the disorder that is now widely recognized in the scientific community. Focusing on peripheral blood monocytes, which are immune cells that get released from the bone marrow in response to stress, Dr. Miller will analyze blood samples from depressed patients and healthy people. To study the peripheral blood monocytes, Dr. Miller will employ high-resolution single cell analysis, a new

technology that allows scientists to look for biomarkers within a particular cell type. He will test the idea that compared to healthy people, peripheral blood monocytes from depressed patients will display higher levels of proteins involved in inflammatory responses. Dr. Miller strives to support the development and application of innovative technologies that will guide immune-based therapies for depression and other psychiatric disorders.

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#### Early Intervention/ Diagnostic Tools

*“Targeting the immune system and inflammation to treat psychiatric disorders represents one of the most exciting and innovative new developments in our field. Nevertheless, we have a limited understanding of the immunologic mechanisms by which inflammation affects the brain and behavior. Using novel high resolution, single cell analyses of specific immune cells, this study supported by the Distinguished Investigator Award will provide us the unique opportunity to reveal key molecules that drive the immune system to besiege the brain. This research will ultimately help identify new immunologic biomarkers and treatment targets to refine immunotherapeutic strategies for depression and other psychiatric diseases.”*



**Carmine Maria Pariante, M.D., Ph.D., FRCPsych**, of King’s College, London, UK, is leveraging the UK Biobank, a unique collection of genetic and other data on more than 150,000 patients, to learn more about why people with major depression have, on average, increased inflammation. In particular, Dr. Pariante hopes to learn more about how early life stress and immune genes interact in determining depression, with impact from other potential factors such as age, gender, weight, depression severity, and adult life stress. The study will be one of the first to look at the inflammation/depression problem using genome-wide association studies, rather than analysis of individual genes.

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#### Basic Research

*“I have felt part of the BBRF family since my first Young Investigator Award in 2003, which was truly a springboard for my academic career. This Distinguished Investigator Award will allow me to understand the interaction between genes and environment in determining the increased inflammation found in depression, which is one of the most important recent discoveries in mental health and a translational research area*

*that will change the lives of depressed individuals by delivering novel mechanisms for therapeutic interventions.”*



**Diego A. Pizzagalli, Ph.D.**, of McLean Hospital and Harvard University, will expand his research on the role of the Nociceptin/Orphanin FQ (N/OFQ) receptor system in the development of and treatment of major depressive disorder. Dr. Pizzagalli’s earlier studies in rodents suggest that decreasing the activity of these small molecules, which aid in neuronal communication, have antidepressant effects. But little is known about how the molecules operate in people with depression. The study will track and compare the receptor system in healthy individuals and those with depression, as well as look for traces of the molecules in postmortem brain tissues. These investigations may clarify whether the N/OFQ receptor system is a promising new target for depression treatment, providing an alternative for the 50 percent of patients who fail to respond to current treatments.

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#### Basic Research

*“A BBRF Distinguished Investigator Award will allow us to integrate state-of-the-art molecular imaging and neuropathological techniques in the search for novel treatment targets for depression, and thus fundamentally advance our research mission.”*

## EATING DISORDERS



**Cynthia Marie Bulik, Ph.D.**, of the University of North Carolina at Chapel Hill, will address the lack of genome-wide studies in search of factors that may contribute to eating disorders, particularly bulimia nervosa and binge-eating disorder. In addition to studying the genetic information of individuals with these disorders, Dr. Bulik will analyze microbiome samples, which represent the community of microbes that live in various places on the body such as the mouth. To gain an even deeper understanding of these disorders, subjects in the study will also be given Apple Watches that will enable the collection of both passive physiological data, such as heart rate, and active behavioral data, including episodes of bingeing. This work will

be the first and largest study to use an approach that combines genomic and microbiome data with extensive digital measurements of behavior and physiology in individuals with bulimia nervosa and binge-eating disorder.

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#### Basic Research

*"We are thrilled that BBRF has chosen to support the Binge Eating Genetics Initiative (BEGIN) thereby acknowledging the seriousness of eating disorders. This award will allow us to combine genomic, microbiota, and deep digital phenotyping data to rapidly advance our understanding of the biology and behavior of bulimia nervosa and binge-eating disorder and to build algorithms that predict impending binges or purges so that we can intervene in real time via wearable technology."*

## MULTIPLE MENTAL ILLNESS

### Early-Life Stress



**Elisabeth B. Binder, M.D., Ph.D.**, of the Max-Planck Institute of Psychiatry, Germany, aims to improve understanding of how stresses that occur before birth can increase the risk of various mental illnesses later in life. If a mother has a stressful or traumatic experience while pregnant, the fetus is more likely to be exposed to higher levels of a stress hormone called glucocorticoids. Dr. Binder will study how this hormone surge may be involved in registering early traumatic experiences in a child's DNA, through a process called DNA methylation. To do this, her team will use three-dimensional human brain organoids, grown from human stem cells, and compare the patterns they find in the organoids to those seen in postmortem tissue from individuals exposed to early adversity. Dr. Binder hopes this work will contribute to a map of the lasting effects of glucocorticoid exposure on DNA methylation, and therefore how early trauma can have lasting effects in the brain.

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#### Basic Research

*"This grant allows me to embark on a higher risk project using human brain organoids. We will use this model system to understand the epigenetic consequences of stress during pregnancy modeled by exposure to glucocorticoids on the developing brain and how this could translate into risk for psychiatric disorders by influencing cell type development trajectories."*

## Early-Life Stress



**Lourdes Fañanás Saura, M.D., Ph.D.**, of the University of Barcelona, Spain, will study the effect of stress factors in the uterus on a fetus's risk of psychiatric disorders later in life. Specifically, Dr. Fañanás Saura will search for differences in fetuses' epigenomes, where lasting changes to gene expression are made without changing the DNA sequence itself. Dr. Fañanás Saura will study these effects in cord blood samples from identical twins who share a placenta and have been exposed to different stress factors prior to birth. This can occur as a result of conditions such as selective intrauterine growth restriction or twin-to-twin transfusion syndrome. These fetuses will have identical genomes, but may have different epigenomes as a result of their exposure to different stressors in the womb. Through this analysis, Dr. Fañanás Saura hopes to identify new biomarkers of prenatal stress in neurodevelopmental psychiatric disorders.

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#### Early Intervention/ Diagnostic Tools

*"I am very grateful and honored to receive this BBRF award. This is a nice opportunity for our group to disentangle the epigenetic mechanisms underlying the association between prenatal suffering and mental disorders. It allows me the possibility to bridge together different disciplines with the aim of better understand the consequences of early stress."*

## Aggression



**Steven A. Siegelbaum, Ph.D.**, of Columbia University, is continuing his studies of the role of the CA2 region of the brain's hippocampus, building on previous research suggesting the region plays a significant role in aggression and other social behavioral changes in a variety of neuropsychiatric disorders such as schizophrenia. Aggression in mental illness increases the burden of these diseases on patients, their caretakers, and society. Dr. Siegelbaum and colleagues will be studying a mouse model of a genetic developmental disorder that causes a loss of key neurons in the CA2 region, similar to that seen in

humans with schizophrenia. Their goal is to discover whether this neuronal loss leads to aggressive behavior in the mice, and whether alterations to CA2 circuitry can restore non-aggressive behavior.

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#### Basic Research

*"This grant comes at a key time in our laboratory's research program, as we expand our focus from the basic neuroscience of hippocampal circuit mechanisms of learning and memory to how dysfunction in hippocampal circuits may contribute to neuropsychiatric disease. The support from BBRF will enable us to follow up on our initial results to investigate how the little-studied CA2 region of the hippocampus contributes to altered social behaviors, including social aggression, in mouse models of neuropsychiatric disorders. Our ultimate goal is to determine whether CA2 may provide a novel target for developing new approaches for disease treatment."*

### Gender Differences



**Paul Matthew Thompson, Ph.D.**, of University of Southern California, is launching the ENIGMA Sex Difference Initiative, a global effort to understand sex differences in schizophrenia, major depression, bipolar disorder, substance use disorders, and post-traumatic stress disorder (PTSD). Major depression, PTSD, and anxiety are more prevalent in women, but substance use disorders are more prevalent in men. The initiative will extend the ENIGMA network, founded in 2009, and its massive pool of genetic and neuroimaging data, to analyze how these five disorders affect the brain differently in men and women. The study will examine sex-specific differences in the trajectories of brain diseases worldwide; how these diseases may manifest differently in the brain over a lifetime in women and men; and whether the effect of genetic risk for these disorders on brain differences also differs by sex.

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#### Basic Research

*"BBRF's support makes a huge difference to our research. In our global studies of the most devastating mental illnesses, we are starting to see factors that predict recovery. We will be studying schizophrenia, bipolar disorder, and major depression, and substance use across 30 different countries. We are just beginning to understand how patients' treatment response depends on their sex, environment, culture, their genetic make-up, and*

*their support network. BBRF's support gives us the power to understand what helps patients recover and what treatments may work best for which patients across the world. We really deeply appreciate this support."*

### POST-TRAUMATIC STRESS DISORDER



**James Douglas Bremner, M.D.**, of Emory University, will test new and improved devices for a treatment known as vagus nerve stimulation (VNS) in patients with post-traumatic stress disorder (PTSD). The vagus nerve is one of the nerves that connect the brain with the rest of the body. Noting that VNS may act directly on the physical factors that give rise to PTSD, Dr. Bremner hypothesizes that this treatment will reduce symptoms. Unlike previous versions, the new VNS device is non-invasive and costs less. This project will be the first to test the efficacy of VNS in treating PTSD, and the first use of non-invasive VNS in patients with mental disorders. Dr. Bremner hopes that this new treatment will reduce PTSD patients' responses to reminders of traumatic experiences, including inflammatory, cardiovascular, and brain responses.

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#### Next Generation Therapies

*"This award will allow us to apply non-invasive vagal nerve stimulation (nVNS) for the first time to patients with mental disorders. I am very excited about this work because not only will it help us elucidate the neurobiology of posttraumatic stress disorder (PTSD), but if successful, this technology could have enormous implications for psychiatry, as a low cost, side effect free treatment that could potentially be applied to large segments of the population with disabling mental disorders and that would likely be reimbursed by insurance plans."*



**Stephen Maren, Ph.D.**, of Texas A&M University, will test a method to selectively erase traumatic memories like those involved in post-traumatic stress disorder (PTSD). Much the way that a combat veteran may experience inappropriate fear in response the sound of a car backfiring, Dr. Maren will condition rats to associate the sound of a tone with fearful memo-

ries. Once the rats are conditioned to recall the fearful memories on demand via the tone, he will use a system of designer drugs and designer drug receptors to gain control over the neurons in the hippocampus that are activated in response to the tone—in effect, “capturing” the memory. Then, Dr. Maren plans to erase the traumatic fear memories by disrupting the activity of the captured hippocampal neurons with drugs. Dr. Maren hopes this work will yield novel, targeted interventions for erasing traumatic memories such as those underlying PTSD.

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#### Basic Research

*“I am honored to be a recipient of a Distinguished Investigator Grant. My laboratory is fundamentally invested in discovering brain mechanisms underlying mental disorders, particularly PTSD, and this funding will allow us to pursue an exciting and novel research project that we believe has important implications for developing targeted neural interventions for these disorders.”*



**Kerry J. Ressler, M.D., Ph.D.**, of McLean Hospital and Harvard University, will be working to define a shared set of “fear-off” neurons in mice and humans—that is, specific populations of neurons that directly inhibit or extinguish the expression of fear. These populations could point the way toward a new toolbox of treatments for post-traumatic stress disorder (PTSD) and related illnesses. The study will examine and compare fear-related microcircuits in the mouse and postmortem human amygdala, to learn more about the genes and gene products related to fear-off neurons. These gene products will then be tested as potential targets for therapies that trigger or increase the fear-off response in preclinical studies, with priority given to pharmacological compounds that have been shown to be safe in humans.

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#### Basic Research

*“Receiving the Distinguished Investigator Award is both a tremendous honor as well as a terrific boost to our work. Grants from the Brain & Behavior Research Foundation provide the rare opportunity to pursue high-risk, high-benefit research that is not possible with federal funding. This award will be directed toward uncovering novel targets for the treatment and prevention of fear-based disorders such as PTSD.”*

### SCHIZOPHRENIA



**Joseph A. Gogos, M.D., Ph.D.**, of Columbia University, aims to define the specific brain abnormalities that arise due to increased levels of a molecule called L-proline in the central nervous system, which may contribute to disorders such as schizophrenia. Prior research suggests that L-proline is involved in behavioral changes across species ranging from humans to flies. These changes also arise when there is a lack of the enzyme PRODH, which degrades L-proline. People who cannot make PRODH due to genetic mutations have higher levels of L-proline, and show increased risk of schizophrenia and schizoaffective disorder. Working in mutant mice that cannot produce PRODH, Dr. Gogos will study the brain abnormalities that result from elevated L-proline levels and evaluate the efficacy of clinically available treatments in correcting these abnormalities.

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#### Basic Research

*“It is an honor and a privilege to be awarded a Distinguished Investigator Award. Support from BBRF in the early stages of my career greatly facilitated our efforts to decipher the genetic and neurobiological origins of schizophrenia. The new award will allow us to apply innovative techniques to understand a newly discovered neurophysiological deficit in schizophrenia and aid timely translation to clinical intervention.”*



**Robert T. Malison, M.D.**, of the Yale University School of Medicine/Yale University, will use a new technique to image the brain in schizophrenia patients in order to gain a better understanding of how a gene known as C4 may be involved in the disease. Previous work in postmortem brain tissue and in mice suggests that variation in the C4 gene may contribute to increased schizophrenia risk by disrupting the normal pruning of connections between brain cells, known as synapses. Dr. Malison aims to show whether this disease mechanism is relevant in the living human brain by using a new, best-in-class radiotracer called C-UCB-J that his group developed. This radiotracer will enable Dr. Malison to use positron-emission tomography (PET) scans to image the density of synapses in the brain of schizophrenia patients whose genetic dose of C4

risk variants is known. By mapping the association between C4 risk variants and synaptic density, Dr. Malison hopes to further the translation of this line of research to the clinic.

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Basic Research

*"I am deeply honored to have been awarded a 2017 Distinguished Investigator Grant. The funding will enable our group to immediately capitalize upon recent breakthroughs in the genetics of schizophrenia and the imaging of neuronal connections, in an effort to understand whether and how these so-called synapses may be altered in the brains of individuals with the disorder. By definition, such "first of its kind" research is at a very early and vulnerable stage—which while highly promising and of potentially high impact is nonetheless often viewed as too risky by other funding agencies. Thus, we are enormously grateful to BBRF for their support and consider ourselves truly fortunate to have the opportunity to pursue this crucially important work."*



**Robert Alan Sweet, M.D.**, of University of Pittsburgh, will examine alterations in the MAP2 protein in the pyramidal cells of the brain in postmortem schizophrenia patients, to determine whether "MAP2opathy" is behind some of the characteristic sensory, cognitive, and social deterioration in patients that continues despite the use of antipsychotic medications. Early studies by Dr. Sweet and colleagues discovered that MAP2 is altered in auditory cortex neurons. The current study will examine where MAP2 alterations take place, as well as the functional impact of some of these alterations. The researchers note that MAP2 shares many similarities with the Tau protein (implicated in disorders such as Alzheimer's disease), which may mean that Tau knowledge could be useful in developing treatments to prevent or reverse pyramidal cell impairment in people with schizophrenia.

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Basic Research

*"The early course of schizophrenia is characterized for many individuals by progressive cognitive and functional disability. Developing treatments to prevent or reverse this loss is an important target for recovery in schizophrenia, represents a radical departure from current therapeutics, and is central to the BBRF mission. I am excited to receive the Distinguished Investigator Award as it will allow us to pursue a highly innovative line of research examining whether schizophrenia is a*

*"MAP2-opathy", analogous to Tauopathies that are central to many neurodegenerative illnesses. We anticipate that we will be able to use the deep knowledge of Tau biology, including emerging Tau therapeutics, to enhance treatment development in schizophrenia."*



**Henrik Walter, M.D., Ph.D.**, of Charité Universitätsmedizin in Berlin, will link genome-wide association studies (GWAS) of schizophrenia with brain imaging to determine how genetic risk scores for the disease might correspond to specific structural differences in the brain and to aberrant behaviors. Whole-genome genetic risk scores can explain about 20 percent of the risk for schizophrenia, but much less is known about how this genetic risk impacts brain structure and function. In his study, Dr. Walter will compare genetic risk scores with neuroimaging data taken from the UK Biobank and IMAGEN database, to discover any associations between brain structure, behavior, and genetic risk. The next step will be to assess whether these patterns can be detected and confirmed in schizophrenia patients with high and low genetic risk scores.

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Basic Research

*"The Award is of great importance for our lab. Imaging genetics has become a Big Data enterprise and it is of crucial importance to have data scientists working in this field with experience in both fields, imaging and genetics. This award will allow us to continue our work in schizophrenia and integrate results from large cohorts that hopefully will advance the field and yield robust insights into the factors that determine if a high genetic risk will result in overt schizophrenia or not."*



## BECOME A RESEARCH PARTNER

### *UNITING DONORS WITH SCIENTISTS*

“My brother first exhibited symptoms of schizophrenia in 1960 at age 17. When we were able to support psychiatric research as a family, we found the Brain & Behavior Research Foundation. I became a Research Partner because the satisfaction of enabling a Young Investigator’s work to unlock the pathways to understanding the sources of psychiatric illness is incredibly satisfying. Now I support three Young Investigators each year. My brother knew that whatever science discovered, it would be too late for him, but he wanted to know that others could avoid the illness that had ruined his life. I donate to honor his wish.”

—*Barbara Toll, Foundation Board Member*

### *BENEFITS OF BECOMING A RESEARCH PARTNER*

- Personally select & sponsor a scientist conducting research that is important to you and your family
- Receive annual scientific updates and progress reports
- Interact one-on-one with your scientist partner through email, phone or a laboratory visit



Barbara Toll, Research Partner

Please contact us at  
**800-829-8289**

[bbrfoundation.org/plannedgiving](http://bbrfoundation.org/plannedgiving) or visit [bbrfoundation.org/researchpartner](http://bbrfoundation.org/researchpartner)

# Parenting: Diagnosing and Treating Anxiety Disorders in Children and Adolescents

By: Fatima Bhojani



**Francis S. Lee, M.D., Ph.D.**

Weill Cornell Medical College

BBRF Scientific Council Member

2010 Independent Investigator

2005, 2002 Young Investigator

**D**r. Francis Lee, is the Mortimer D. Sackler Professor and Vice Chair for Research in the Department of Psychiatry at Weill Cornell Medical College, and an attending psychiatrist at NewYork-Presbyterian Hospital. He is also the Co-Research Director of the Youth Anxiety Center at NewYork-Presbyterian Hospital. His research focuses on leveraging molecular neuroscience tools to improve our understanding of anxiety disorders. His current research has centered on factors that influence the plasticity of the brain – its ability to change in response to experiences, both good and bad. Dr. Lee additionally sees patients with a focus on anxiety disorders.

## **Over 20 percent of adolescents have anxiety disorders. How does this compare with other mental health issues?**

Anxiety disorders are the most common psychiatric disorder in children and adolescents. Studies differ, but most suggest between 15 percent and 30 percent of youth will have an anxiety disorder before age 18. This is more than other common childhood and adolescent conditions, such as ADHD (eight to 10 percent), or depression (10 to 20 percent). The prevalence of anxiety disorders in adults is around 30 percent, and the prevalence of depression in adults is about seven percent, schizophrenia is one percent, bipolar disorder is about three percent.

## **And yet you say that anxiety disorders are under-recognized and misdiagnosed in young people. Why?**

Anxiety disorders are under-recognized because everyone, children and adults alike, experience anxiety. In children, for

example, it is normal to be anxious before an exam or on the first day of school. Your child comes to you and says they are anxious. You yourself are anxious at times, so you don't recognize the difference in degree. Your hope is that this is due to an adjustment to routine, for example going to a new school. You figure this will all go away on its own.

Anxiety is also frequently misdiagnosed because of the way it manifests sometimes as a bodily symptom, like a stomach ache. If a child has chronic stomach aches, they might refuse to go to school. This could be a tip off that there may be something more there.

## **Compared to the anxiety that any young person normally feels, how does anxiety in a young person with an anxiety disorder differ?**

Feeling anxious about a few things some of the time, like giving a speech or taking a test, is in itself not a disorder. An anxiety disorder is a condition in which there is a significant distress and functional impairment. When a child's severe distress or avoidance of anxiety-provoking situations gets in the way of the child's day-to-day life, and/or the family's daily life, then the anxiety has likely crossed a threshold that would warrant a professional assessment and intervention. An obvious warning sign would be if your son or daughter refuses to go to school. This is probably one of the most severe manifestations. Other warning signs would be if your child does not seem to spend much time outside his or her room, or does

not seem to want to interact or be part of various activities. Anxiety is a normal emotion to have. It's when it gets to an extreme level that you should start keeping track, like when you see your child avoiding things that other children are not avoiding, like going to parties, hanging out with friends, or joining school activities, clubs, or team sports.

#### Is avoidance the main symptom parents would see?

There are a panoply of symptoms. Anxiety is also associated with frequent worry or reassurance-seeking, chronic irritability, difficulty sleeping, and anxiety-related physical symptoms, which for some youth can progress to a panic attack (a brief period of intense fear and inability to act).

#### What should parents do if they think their child might have an anxiety disorder? Who should they consult first?

There are very good national organizations such as the Anxiety and Depression Association of America (ADAA), the Association for Behavioral and Cognitive Therapies, and the National Institute of Mental Health (NIMH), as well as our organization, the NewYork-Presbyterian Youth Anxiety Center, all of whose websites provide a very detailed description of each type of anxiety disorder, as well as information on the recommended evidence-based treatment options, and often links to well-trained providers in your geographic area. Looking at those websites should be step one. Step two would be to meet with your child's primary care doctor, and get a referral to a psychologist or psychiatrist for an assessment.

If you start to have a sense that there seem to be greater levels of fear-related symptoms as well as avoidance behavior, then you want to see a professional to get a sense of whether the anxiety warrants a diagnosis and treatment.

What we have learned, from both clinical experience and from research, is that these disorders don't go away on their own. They need to be treated.

#### Tell us about the different types of anxiety disorders and the different treatments for them.

The first anxiety disorders we tend to see in youth are separation anxiety disorder, a fear of being separated from one's parents or safety figure, or a specific phobia, for example fear of the dark, heights, animals, insects, getting sick, etc. Many youth have these fears to a certain extent, but for some it becomes extreme, interfering with the child and family's functioning.

In later childhood, generalized anxiety is characterized by frequent worry about many things, including school, friends, family members, world events, health, and safety. Obsessive compulsive disorder has specifically to do with intrusive, unwanted obsessive thoughts or urges that cause distress and anxiety, and associated compulsions, habits, or behaviors that temporarily relieve the anxiety but cause other impairments in daily life.

Social anxiety disorder is more common in adolescence and is focused more on anxiety symptoms related to social events, meeting new people, or public speaking. Panic disorder is typically not seen until later adolescence, but includes out-of-the-blue panic attacks and invokes fear and avoidance of situations that might cause a panic attack.

**Anxiety disorders are the most common psychiatric disorder in children and adolescents. Studies differ, but most suggest between 15 percent and 30 percent of youth will have an anxiety disorder before age 18.**

#### Is there a reason why anxiety peaks early in life?

Anxiety disorders seem to peak at two main times: during childhood (between five and seven years of age), and during adolescence.

There is definitely a cohort of patients who have anxiety disorders in childhood, which corresponds to when they have to leave the house and go to school. This environmental change seems to trigger

these symptoms. The second wave of anxiety in early- to mid-adolescence is harder to understand. There is still great debate amongst psychiatrists and epidemiologists whether there is a second wave, or whether these adolescents have had low levels of anxiety all along throughout childhood, and it is only now finally getting to the attention of a care provider. As I said, there is a significant under-diagnosis of this disorder.

If the child has had symptoms during childhood, his or her chances of also being diagnosed with depression and substance use disorders during adolescence also increase. This is one of the main reasons why diagnosing and treating anxiety early is so important. If not treated, these disorders build upon themselves. If parents notice a significant level of anxiety, irritability, or even a persistent stomach ache, or some other type of symptom, they should not ignore it.

If an anxiety disorder is allowed to linger for, say, five years from onset, not only do the symptoms get worse, but you then have a child who has a very limited world, in which they have been avoiding things. At that point, you're starting treatment at a different point than you might have five years earlier and it's more difficult to treat.

### **Does anxiety disorder run in families?**

Just as with many other psychiatric disorders, there is high heritability. But heritability is difficult to explain, because it's not like getting a diagnosis of Huntington's disease, where there is a genetic test and if you have the gene, you have the illness. Heritability for anxiety disorders, like any psychiatric disorder, just means that there is a higher chance of having an anxiety disorder if it runs in your family. Parents who have anxiety themselves may also model or reinforce anxious or avoidant coping with their children, which can send an unhelpful message to a child who is genetically predisposed to anxiety.

### **Can factors in the environment, such as trauma, trigger anxiety disorders?**

When you try to do a natural history intake [asking patients and their family members] of what environmental factors or other circumstances caused or contributed to the disorder, it's very difficult to pin down [the cause]. There is a biological component, including genetics, which we don't understand, which obviously interacts with the environment. There is nothing that suggests there is something in the environment itself that causes an anxiety disorder. There is no direct correspondence with, for example, the way the child was reared — except for significant trauma. But in such a case, that anxiety disorder when diagnosed is referred to as post-traumatic stress disorder, since it is the result of an earlier trauma or chronic acute stress.

### **What are the therapeutic options?**

All of these anxiety disorders are amenable to the same type of therapy, called cognitive behavioral therapy (CBT). The patient meets with a therapist, usually on a weekly basis, and gets exposed in a controlled environment to things that make them anxious. The point of the treatment is to ensure that adolescents will be able to confront their anxieties and work through them using adaptive coping strategies. The goal is to experience the anxiety and learn that the feeling can be tolerated and managed, and will likely get better the more the adolescent confronts the experience instead of avoiding it. Thus, therapy may consist of going to a nearby Starbucks, or some other public place, and interacting with strangers, or touching something "germy," speaking in public, or purposely practicing another feared experience.

This is why it's so helpful to see a professional, because there are certain things that they do that may seem a little bit counterintuitive — like having a socially anxious person go into a crowded place where they have to interact. But this is ultimately the bedrock of this kind of behavioral treatment. These treatments usually last 12 to 16 weeks. This will not only help the child in the moment, but also help them equip themselves on how they can manage their own anxiety going forward, post-treatment.

Medication within the serotonin reuptake inhibitor class, such as fluoxetine [Prozac] is an additional option. Usually, one follows a stepped-care model, where you start with psychotherapy, and consider adding medication depending on the severity of symptoms.

### **What role do parents play in treatment?**

The family plays a significant role. Parents have to stay actively involved in the various behavioral measures taken during the treatment, not only during the therapy hour, but also outside the therapy.

So, for example, if the child refuses to go to school, the parent has to make sure their child goes to school. The normal impulse is to not subject your child to stressful scenarios. Therapists discuss with parents ways to push their child to confront their anxiety, and not enable avoidance behavior. Avoidance behavior leads to overdependence on parents. Therapy tries to place the responsibility of growing independence back on the adolescent.

Working with a skilled therapist will always involve not only the parent but also siblings, on how to deal with a situation where one person in the family seems to take up more attention.

### **When someone who has had anxiety symptoms early in life goes to high school or begins college, what can a parent expect?**

If you have an anxiety disorder or depression before the age of 18, we know exactly what to do: you go to a pediatrician, who then refers you to a psychologist or psychiatrist who specializes in children and adolescents. When you turn 18, it's unclear whom you should see. The young adult has outgrown pediatric care, but is not the typical patient seen in the adult mental health care system. This change occurs when youth are transitioning to college, or another post-high school experience. So, you might have been in a very protected environment at home, possibly seeing a therapist, and then when you go to college, you jump into a new context, possibly hundreds of miles away, with none of the same support systems in place. It's estimated that over 20 percent of the adolescents who are going to college have a diagnosable anxiety disorder, and the mental health services at colleges are usually not equipped to handle the large number of cases.

### **If my child is going off to college, what kind of support network can I create?**

Start by having a fairly long discussion with their current mental health care team. It might be possible to maintain continuity of care with their current provider through Skype or other tele-health methods. Also find out what services are available in the college and the city your child is going to.

HIGHLIGHTS FROM THE

# 2017 International Mental Health Research Symposium



Symposium Moderator  
Robert M.A. Hirschfeld, M.D.



Symposium Commentator  
Myrna Weissman, Ph.D.

On October 27, 2017, the Brain & Behavior Research Foundation held its International Mental Health Research Symposium, with presentations by top researchers in the field of mental illness. The symposium at the Kaufmann Music Center in New York City featured research talks by eight of the Foundation's 2017 Outstanding Achievement Prizewinners, along with two promising Young Investigator grantees. Herbert Pardes, M.D., Executive Vice Chairman of the Board of NewYork-Presbyterian Hospital and President of the Brain & Behavior Research Foundation Scientific Council was the event's keynote speaker.

The Prizewinners are selected by special committees of the Foundation's Scientific Council, a volunteer group of 176 preeminent mental health professionals in brain and behavior research.

## 2017 LIEBER PRIZE FOR OUTSTANDING ACHIEVEMENT IN SCHIZOPHRENIA RESEARCH



**John M. Davis, M.D.**  
**Gilman Professor of Psychiatry and Research**  
**Professor of Medicine**  
University of Illinois at Chicago

Dr. Davis devised a statistical method in the early 1970s, called meta-analysis, to combine results from multiple controlled trials of antipsychotic drugs to treat patients with schizophrenia. This was the first meta-analysis in psychiatry and psychology. In his talk, Dr. Davis discussed how these early analyses showed consistent evidence that long-term antipsychotic treatment could prevent many recurrences of acute psychotic episodes, and that long-term lithium use prevented relapses of both manic and depressive phases of bipolar disorder.

More recently, Dr. Davis and his colleagues have used a type of analysis called network meta-analysis to compare the efficacy and side effects of many antipsychotics, to give physicians and their patients a better idea of how well and how safely each drug works. This type of meta-analysis can help to clarify contradictory results from similar but not identical drug studies, he said, identifying the mechanism that is responsible for the difference in treatments. Dr. Davis also reviewed recent work on the regulation of the expression or repression of certain genes, as well as other biomechanical mechanisms, that may lead to the development of new drugs for schizophrenia.

Dr. Davis acknowledged the generosity of Constance and Stephen Lieber during the symposium, noting that "advances in schizophrenia research in the 30 years since the [Lieber Prize] was established are exponential and linked definitively to their support and that of the Brain & Behavior Research Foundation. "Clinical scientists form a bridge between basic research and the patient and can translate clinical findings or observations back to the basic scientists. My hope for this award is to serve as a stimulus to encourage more clinicians toward clinical research."

## 2017 MALTZ PRIZE FOR INNOVATIVE & PROMISING SCHIZOPHRENIA RESEARCH



**Deanna L. Kelly, Pharm.D., BCPP**

**Professor of Psychiatry**

University of Maryland School of Medicine

**Affiliate Professor**

University of Maryland School of Pharmacy

**Director, Treatment Research Program**

Maryland Psychiatric Research Center

**President**

College of Psychiatric and Neurologic Pharmacists (CPNP)

Dr. Kelly noted that the development of novel treatments for schizophrenia has been a slow process, in part due to the fact that most treatments available now have been studied without regard to differences in the disease's potential causes and in the patient populations with the disease. She discussed her work with schizophrenia patient populations that have a high degree of inflammation and a unique immune response to gliadin, a protein found in wheat and other foods. Dr. Kelly and her colleagues have shown that certain antibodies formed in response to gliadin are high in some, but not all people with schizophrenia and these same people may have improvements in inflammation and psychiatric symptoms with the removal of gluten from the diet. She and her colleagues are working on a large confirmatory study where they hope to prove the effectiveness in the specific schizophrenia population having this antibody biomarker, and they hope to better understand the reasons why it may be effective.

In her symposium presentation, Dr. Kelly also discussed her work on a large multinational clinical trial of the medication clozapine, focused on ways to better use the medication and in safely showing its efficacy in a population of African descent patients who may have a genetic predisposition to certain side effects.

## 2017 COLVIN PRIZE FOR OUTSTANDING ACHIEVEMENT IN MOOD DISORDERS RESEARCH



**Hilary P. Blumberg, M.D.**

**John and Hope Furth Endowed Professor of Psychiatric Neuroscience**

**Professor of Psychiatry, Radiology and Biomedical Imaging and in the Child Study Center**

**Director, Mood Disorders Research Program**

Yale University School of Medicine

**Scientific Council Member**

**Klerman Prize for Exceptional Clinical Research 2006**

**2006 Independent Investigator**

**2002 Young Investigator**

Dr. Blumberg presented her state-of-the-art brain scanning research that has had a tremendous impact on the field in advancing knowledge about brain circuitry of bipolar disorder. These data could help better establish the causes of bipolar disorder and contribute to new methods for detection, intervention, and prevention.

Using these brain scanning methods, she has shown structural differences in the gray matter nodes, and integrity of the white matter wiring, in emotion brain circuitry underlying its different functioning. Her neuroimaging work has also shown the negative influences of genetic variations and early life stress, such as child abuse and neglect, on these circuits, as well as beneficial influences of drug and non-drug interventions on the structure and function of the circuitry.

More recently, Dr. Blumberg has focused her research on evidence of differences in the trajectories of the development of the brain circuitry during adolescence, shaping the view of bipolar disorder as a disease of neurodevelopment and of adolescence as an important period. In her symposium presentation, she spoke about the role of brain circuitry of suicide risk in adolescents and young adults, changes in the brain in bipolar disorder with age later in life, and her Brain Emotion Circuitry-Targeted Self-Monitoring and Regulation Therapy (BE-SMART) psychobehavioral treatment.



**Mary L. Phillips M.D., M.D. (Cantab)**

**Pittsburgh Foundation-Emmerling Endowed Chair in Psychotic Disorders**

**Professor in Psychiatry and Clinical and Translational Science**  
University of Pittsburgh, Western Psychiatric Institute and Clinic

**Scientific Council Member**  
**2005 Independent Investigator**

At the symposium, Dr. Phillips spoke about her laboratory's work to examine the brain mechanisms underlying the development of bipolar disorders in people across childhood and adulthood. She and her colleagues use different types of brain imaging techniques with the goal of identifying patterns of abnormal brain activity in people with bipolar disorders, in order to identify brain-based markers of these disorder.

Her team has shown that the cross-talk between brain regions important for experiencing emotions (subcortical regions) and brain regions important for controlling emotions (prefrontal cortical regions) is disrupted in children and adults with bipolar disorders, and likely underlies the difficulty in controlling emotions experienced by people with these disorders, she said.

They have also shown that a particular prefrontal cortical region, the left ventrolateral prefrontal cortex, is overactive in people with bipolar disorders when they are asked to take part in a gambling task. This pattern of abnormal brain response is not present in people with depression. This brain region is important for learning about the chance of rewarding events happening in the future — for example, winning money. The fact that this region is overactive in people with bipolar disorders during gambling suggests that people with these disorders may be abnormally sensitive to the chance of future rewards, and is a promising brain-based marker of bipolar disorders. Dr. Phillips' team is now using this marker to help develop new treatments, including new brain stimulation treatments, for bipolar disorder.

**2017 RUANE PRIZE FOR OUTSTANDING ACHIEVEMENT IN CHILD & ADOLESCENT PSYCHIATRIC RESEARCH**



**Nathan A. Fox, Ph.D.**

**Distinguished University Professor**  
**Chair, Department of Human Development and Quantitative Methodology**

Neuroscience and Cognitive Sciences Program  
University of Maryland, College Park

**2007 Distinguished Investigator**



**Charles A. Nelson III, Ph.D.**

**Professor of Pediatrics and Neuroscience**  
**Professor of Psychology in Psychiatry**

Harvard Medical School

**Professor of Education**

Harvard Graduate School of Education

**Richard David Scott Chair in Pediatric Developmental Medicine Research**

**Director of Research, Division of Developmental Medicine**  
Boston Children's Hospital



**Charles H. Zeanah, Jr., M.D.**

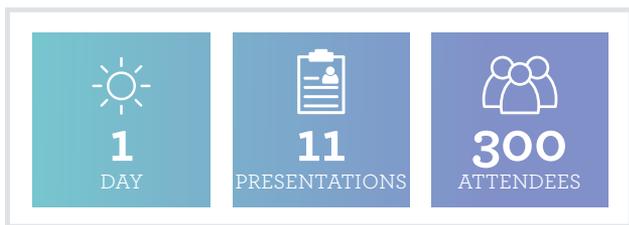
**Mary Peters Sellars Polchow Chair in Psychiatry**  
**Vice Chair for Child and Adolescent Psychiatry**  
**Professor of Psychiatry and Pediatrics**

**Director of the Institute for Infant and Early Childhood Mental Health**

Tulane University School of Medicine

In the joint presentation by the Ruane recipients, the researchers spoke about their work on the Bucharest Early Intervention Project (BEIP), launched 17 years ago and based in Bucharest, Romania. Dr. Nelson discussed the project's conceptual framework and experimental design, as well as the ethical considerations and interventions. In the BEIP, three groups of Romanian children are being studied: infants abandoned to institutions and who remain in institutional care; infants abandoned to institutions but then placed in high quality foster care; and infants who have never been institutionalized. These three groups have been studied through age 16, with a 20-year follow up being planned.

Dr. Fox discussed the effects of institutionalization on BEIP children's behavior and brains, noting whether there were effects in these domains as a function of the intervention that were sustainable over time, and if timing effects such as the age at which children were removed from an institution and placed into families mattered. He also identified factors in the lives of the children that affected developmental outcomes, including the number of transitions and disruptions in a child's caregiving context. The pattern of results suggests that early adversity has lasting effects upon behavior and brain, he said.



Emotional disorders, aggressive behavior disorders and inattention/over activity were evident in early childhood among children who had been deprived, said Dr. Zeanah. Randomization to foster care led to substantial reductions in emotional disorders, especially for girls. Later in childhood, children who had histories of institutional rearing showed signs of social communication problems that were as severe as children with autism, though most did not have other features of autism spectrum disorder. Foster care significantly reduced these social abnormalities. Dr. Zeanah noted that both boys and girls who had been randomized to foster care showed fewer signs of attachment disorders. Throughout the study, quality of foster care, stability of foster care, and early placement in foster care substantially enhanced recovery for children who had experienced deprivation.

## 2017 GOLDMAN-RAKIC PRIZE FOR OUTSTANDING ACHIEVEMENT IN COGNITIVE NEUROSCIENCE



**Trevor Robbins, Ph.D.**

**Professor, Cognitive Neuroscience**

University of Cambridge

**Director**

Behavioural and Clinical Neuroscience Institute

Dr. Robbins discussed the concept of “self-control” in the context of substance use addiction and treatment. Addiction is difficult to treat because of its relapsing nature.

Neuroscience research has established that initial effects of many drugs of abuse are mediated by a subcortical reward system in the brain served by the chemical messenger dopamine which provides initially strong motivation for drug-seeking, but may then become more automated and habitual, and hence even harder to control, he said.

In his symposium talk, Dr. Robbins spoke about how self-control is mediated by the brain and how it bears on addiction. A major question, he said, is whether impairments of specific brain networks headed by the frontal lobes of the brain are caused by drug abuse or whether they were pre-existing and hence contribute to the tendency to take drugs in vulnerable individuals. He provided evidence for both types of effect, through investigations of non-drug abusing relatives of drug addicts, large samples of healthy adolescents, and appropriate animal models. He also discussed whether this realization of the brain basis of “willpower” may possibly help in the treatment and management of drug-addicted individuals.

## 2017 YOUNG INVESTIGATOR PRESENTATIONS



**Mary C. Kimmel, M.D.**

**Assistant Professor**

**Medical Director, Perinatal Psychiatry Inpatient Unit**

University of North Carolina at Chapel Hill

**2016 Young Investigator**

Dr. Kimmel spoke about her research in an emerging area of study: the role of the gut microbiota (the bacteria and organisms that populate the intestinal tract) in antenatal depres-

sion, prenatal depression, and postpartum depression. The gut microbiota may serve as both a biomarker for and a new treatment target for these illnesses, she noted. Furthermore, the microbiome may serve in communicating information from mother to child and be important in the child’s development.

Dr. Kimmel discussed a preliminary feasibility study of thirty women, in which many women were found to be using different forms of probiotic pills and dietary choices in hopes of improving their health—a finding especially true for women with histories of depression and anxiety. Women with histories of anxiety had elevated symptoms on a depression screener in the third trimester. Some of the women in the study developed postpartum depression. She is now pursuing a project to analyze microbial composition over the course of pregnancy by following a sample of 50 women (35 women with and 15 women without histories of major depression or anxiety disorders) across the perinatal period, and to study the relationship of the microbiome to stress reactivity of mother and child six to eight weeks postpartum. She also discussed how information about the microbiome might be combined with other genomics research to improve the ability to create personalized treatments.



**Anna V. Molofsky, M.D., Ph.D.**  
**Assistant Professor of Psychiatry**  
 University of California, San Francisco

**2016 Young Investigator**

Dr. Molofsky’s research group is working to understand how brain synapses—the essential connections between nerve cells in the brain—form and how stress impacts this process. In many mental health conditions, stress and trauma can trigger the emergence of symptoms or worsen their severity. Dr. Molofsky’s lab is particularly interested in the long unappreciated brain cells known as “glia.” These cells play key roles in brain development and are also the first responders when the brain is under stress.

Dr. Molofsky’s project stems from the discovery that glial cells produce a potent immune signal that triggers brain synapses to get “eaten” away. She discussed how studying this immune signaling pathway will address the hypothesis that the immune system is both essential during brain development, and an important regulator of the brain’s stress response. These studies may lead to future strategies to protect the developing brain from stress and to restore synapse balance in psychiatric disorders.



Herbert Pardes, M.D.



Jeffrey Borenstein, M.D. and Robert Hirschfeld, M.D.



Charles H. Zeanah, Jr., M.D., Charles A. Nelson III, Ph.D., and Nathan A. Fox, Ph.D.

# Recent Research Discoveries

## Important Advances by Foundation Grantees that are Moving the Field Forward

### **Ketamine Rapidly Reduces Suicidal Thoughts in People with Depression**

*In an analysis of data from 10 past studies, researchers found that more than half of patients at high suicide risk treated with ketamine were free of suicidal thoughts within one day.*

Ketamine is an anesthetic drug that has been found to rapidly relieve the symptoms of depression. Due to its side effects and high potential for abuse, it is unlikely to be widely used as an antidepressant medication. But because it is so fast-acting—reducing symptoms within hours—many researchers believe that it may be appropriate for stabilizing patients at imminent risk of suicide.

In new research published in the October 3, 2017 issue of the *American Journal of Psychiatry*, researchers led by Samuel T. Wilkinson, M.D., a 2016 Young Investigator at *Yale School of Medicine*, used data from 10 previous studies to specifically assess ketamine's effects on suicidal thoughts. Not only did they find that suicidal thoughts declined significantly following a single dose of the drug, but their analysis suggests these effects are partly independent of ketamine's effects on depression.

Dr. Wilkinson and his team focused on data from 167 participants in past ketamine studies who had reported thoughts of suicide prior to their treatment. Participants in the 10 studies had been diagnosed with a range of psychiatric conditions, including major depression and bipolar disorder.

The researchers analyzed how a single dose of ketamine affected both suicidal thoughts and scores on standard clinical depression scales, comparing the scores of patients who received the drug to those of patients who received placebo treatments. They found that both suicidal thoughts and overall depression were relieved significantly by ketamine: More than half of patients who received the drug were free of suicidal thoughts within 24 hours of their treatment. These benefits

persisted for up to a week—the latest time point considered in the analysis.

Overall, patients whose depression diminished the most experienced the greatest reductions in suicidal thoughts, but the researchers found that ketamine's effects on suicidal ideation were significant even after controlling for changes in depression severity.

Dr. Wilkinson and his colleagues caution that while their findings suggest ketamine can be useful in reducing acute suicide risk, further studies are needed to determine which patients are most likely to benefit from ketamine treatment and whether the early reduction in suicidal thoughts is sustained longer-term.

The team that conducted the study included grantees Michael H. Bloch, M.D., M.S., a 2013 and 2009 Young Investigator at *Yale University*; Sanjay J. Mathew, M.D., a 2009 Independent Investigator and 2006 and 2001 Young Investigator at *Baylor College of Medicine*; James W. Murrough, M.D., Ph.D., a 2009 Young Investigator at *Icahn School of Medicine at Mount Sinai*; Adriana Feder, M.D., a 2015 Independent Investigator and 2002 Young Investigator at *Icahn School of Medicine at Mount Sinai*; Carlos A. Zarate, Jr., M.D., at the *National Institute of Mental Health*, winner of the 2011 Bipolar Mood Disorders Award and a 2005 Independent Investigator and 1996 Young Investigator; and Gerard Sanacora, M.D., Ph.D., at *Yale School of Medicine*, a 2014 Distinguished Investigator, 2007 Independent Investigator and 2001, and 1999 Young Investigator.



**Samuel T. Wilkinson, M.D.**  
**2016 Young Investigator**

## Brexanolone Rapidly Reduces Postpartum Depression in Clinical Trials

*In a small phase 2, placebo-controlled clinical trial, 70 percent of women with severe postpartum depression achieved remission after treatment with the experimental drug brexanolone. New phase 3 data also support these findings.*

Brexanolone, an experimental drug that acts on hormone-sensitive receptors in the brain, has effectively reduced symptoms of postpartum depression in clinical trials.

In the June 12 issue of the journal *The Lancet*, a team of researchers reported that a single dose of the drug rapidly reduced the symptoms of severe postpartum depression in a small Phase 2 clinical trial. Samantha Meltzer-Brody, M.D., MPH, at the *University of North Carolina School of Medicine*, led the study. The team included Handan Gunduz-Bruce, M.D., a 2007, 2005, and 2003 Young Investigator at *Yale School of Medicine*, and Cynthia Neill Epperson, M.D., a 2005 Independent Investigator and 1997 and 1995 Young Investigator at the *Perelman School of Medicine at the University of Pennsylvania*, as well as Steven M. Paul, M.D., a Scientific Council Member at the *California Institute of Technology*.

Based on the positive results of this trial, two larger, Phase 3 trials have since been conducted, measuring the drug's efficacy in women with both moderate and severe postpartum depression. The company that makes the drug, Sage Therapeutics, announced in November 2017 that in both trials, treatment with brexanolone, administered via intravenous infusion, resulted in a rapid reduction of depressive symptoms, with this effect maintained for at least 30 days following treatment.

Postpartum depression occurs in up to 20 percent of mothers, and is thought to be triggered in part by the abrupt changes in hormone levels that a woman experiences after giving birth. If it is left untreated, women can experience feelings of extreme sadness, anxiety, and exhaustion for months or years. Severe post-partum depression, which affects about 5 to 10 percent of women with the disorder, puts women at risk for suicide and often requires hospitalization.

Currently, postpartum depression is treated with psychotherapy and the same medications that are used to treat major depression unrelated to pregnancy. These treatments can take a long time to work. Brexanolone appears to be a faster-acting treatment that shows great promise in treating postpartum depression. "The exciting thing about these results is that this is an entirely new treatment paradigm, and that the effect of brexanolone is unlike anything else available currently," says Dr. Meltzer-Brody.

Brexanolone is a synthetic form of ALLO (allopregnone), a naturally occurring metabolite, or byproduct, of the hormone progesterone. It acts on neural receptors in the brain called GABA-a receptors. It's not yet clear whether its impact on these receptors is due only to hormonal sensitivity.

For the Phase 2 trial, 21 women with severe postpartum depression were randomly assigned to receive a single dose of either brexanolone or a placebo. Both were administered by intravenous infusion in a clinical setting, over a 60-hour period, after which study participants' symptoms were reassessed.

The researchers found that depression symptoms declined dramatically in women who received brexanolone, and that these effects were sustained over a 30-day follow-up period. According to a standard clinical rating scale, seven of the 10 women who received the experimental drug were no longer experiencing depression after their treatment, whereas only one woman in the placebo group achieved remission.



**Handan Gunduz-Bruce, M.D.**  
2007, 2005, and 2003 Young Investigator



**Cynthia Neill Epperson, M.D.**  
2005 Independent Investigator  
1997, 1995 Young Investigator



**Steven M. Paul, M.D.**  
Scientific Council Member

## Better Understanding of Lithium's Effects Points to Improved Therapeutics

*By revealing how lithium alters neuronal communications in the brain to control manic episodes, researchers have opened a path toward better treatments for bipolar disorder.*

Bipolar disorder affects nearly four percent of Americans, and for many, lithium—an old and poorly understood drug—is a mainstay of treatment. It is usually the first treatment patients try when they are diagnosed with bipolar disorder, and it can effectively control episodes of both mania and depression. But it doesn't work for everyone.

Although lithium has been used as a mood stabilizer for more than 60 years, little has been known about how it works. That has impeded the development of new drugs, which might work more effectively or cause fewer side effects.

In research reported June 16, 2017 in the journal *eLife*, grantee Lisa Monteggia, Ph.D., and colleagues uncovered important clues about how lithium acts in the brain to prevent manic episodes. By pointing scientists toward specific biological pathways involved in mania, their findings could give researchers a handle on how to begin developing new treatments.

Dr. Monteggia is at the *University of Texas Southwestern Medical Center*. She received a Distinguished Investigator Award in 2014 and was the recipient of the Daniel X. Freedman Award in 2005. She also twice received Young Investigator grants and in 2010 was an Independent Investigator grantee. Her UT Southwestern colleague Ege Kavalali, Ph.D., recipient of a Distinguished Investigator grant in 2013, was also involved in the research.

Through a series of experiments in mice and in brain cells grown in a plastic dish, Dr. Monteggia and her colleagues discovered that a protein called brain-derived neurotrophic factor (BDNF) is critical for lithium's anti-manic effects. BDNF supports the growth of neurons in the brain and influences the degree to which the cells form connections with one another. People with bipolar disorder often have low levels of BDNF, and lithium treatment boosts these levels. It has not been known, however, whether this is how the drug stabilizes patients' moods.

Dr. Monteggia's team showed that lithium works through BDNF and its receptor inside cells, called TrkB, to reduce the presence of certain neurotransmitter receptors located on the outer surface of neurons. The reduction in these receptors, known as AMPA receptors, alters the way neurons communicate with other cells. In the team's animal experiments, lithium weakened communications between neurons and reduced mania-like behavior—but only if BDNF was present. Under-

standing how these specific molecules mediate lithium's effects will now help researchers identify new strategies for drug development.

Although lithium reduces the symptoms of both mania and depression in people with bipolar disorder, the study did not uncover a cause for lithium's antidepressant effects. In fact, the team found that lithium reduces depression-like behavior in mice even when they lack the gene for BDNF—a mystery about this important drug that future studies may solve.



**Lisa Monteggia, Ph.D.**

**2014 Distinguished Investigator**

**2010 Independent Investigator**

**2005 Freedman Award Winner**

**2003, 2001 Young Investigator**

## An Old Medication Points the Way to a New Class of Antidepressants

*Studies of tianeptine, an antidepressant medication used in several countries, show that depression symptoms may be relieved by targeting opioid receptors in the brain.*

New animal research reported in the September 2017 issue of *Neuropsychopharmacology* has shown that targeting docking ports in brain cells for naturally occurring opioids can relieve the symptoms of depression. These receptors, called mu-opioid receptors, are the same ones that are stimulated by morphine and related pain relievers. Importantly, the study also suggests that it is possible to achieve these antidepressant effects without a high risk of addiction and abuse. The discovery comes from studies of tianeptine, a drug that has long been used as an antidepressant in Europe, Asia, and South America.

Until now, no one has known how tianeptine works. Back in 2014, a team of researchers including Jonathan A. Javitch, M.D., Ph.D., of *Columbia University*, a Scientific Council member, 2010 Distinguished Investigator, 2003 Independent Investigator and a 1992 and 1990 Young Investigator, uncovered a major clue when they showed that tianeptine binds to mu-opioid receptors. In the new study, a team led by René Hen, Ph.D., a Scientific Council member at *Columbia University*, a 2003 and 2009 Distinguished Investigator and a 1998 Independent Investigator grantee, established that the drug's interaction with these receptors is responsible for its antidepressant effects. Their experiments showed that the drug reduces depression-like behaviors in mice, but if the animals' mu opioid receptors are missing or blocked, this effect is lost.

Recognizing's tianeptine effects on opioid receptors could open a path to a new class of antidepressants. The antidepressant medications available today, most of which are selective serotonin reuptake inhibitors (SSRIs) in the Prozac class, do not work for everyone, and there is a great need to develop alternative therapies.

Tianeptine relieves the symptoms of depression as effectively as SSRIs, without some of SSRIs' potential side effects. However, it breaks down quickly in the body and must be taken three times a day, which can make patients less likely to adhere to their medication.

Tianeptine has never been marketed as an antidepressant in the United States, and there are no plans now to test it in the large, expensive clinical trials that are needed for U.S. Food and Drug Administration approval. Now that researchers understand how tianeptine exerts its antidepressant effects, however, they can begin developing and testing new drugs

that target the mu-opioid receptor. The hope is that such drugs will have longer lasting effects or be more effective than tianeptine.

Although most drugs that work through opioid receptors carry a high risk of addiction and abuse, almost no such problems have been reported with tianeptine, despite decades of use. The new research suggests that tianeptine may interact in an unusual fashion with opioid receptors: Mice that received tianeptine for 30 days did not develop tolerance to the drug or exhibit withdrawal symptoms when tianeptine was discontinued.

The research team included Dr. Javitch, Benjamin A. Samuels, Ph.D., a 2014 and 2012 Young Investigator grantee at *Rutgers University*, and Katherine M. Nautiyal, Ph.D., a 2015 Young Investigator at *Columbia University*.



**René Hen, Ph.D.**

**Scientific Council Member**

**2009, 2003 Distinguished Investigator**

**1998 Independent Investigator**



**Jonathan A. Javitch, M.D., Ph.D.**

**Scientific Council Member**

**2010 Distinguished Investigator**

**2003 Independent Investigator**

**1992, 1990 Young Investigator**

# Frequently Asked Questions

## The Opioid Crisis in the United States



### WHAT IS AN OPIOID DRUG?

Opioids are a class of drugs most often used to reduce pain, by acting on opioid-sensitive receptors or chemical “docking ports” in the nervous system<sup>1</sup>. These drugs can also produce a feeling of euphoria. Prescription opioids include medicines such as morphine, oxycodone (OxyContin), and hydrocodone (Vicodin), and the synthetic drug Fentanyl, which is most often prescribed for severe pain such as that experienced by terminal cancer patients. Heroin is an example of an illegal opioid drug.



### HOW MANY PEOPLE IN THE U.S. SUFFER FROM OPIOID ADDICTION?

The U.S Department of Health and Human Services estimates that in 2016, 11.5 million Americans misused prescription opioids and 948,000 Americans used heroin.<sup>2</sup> There were 17,087 deaths resulting from prescription opioid misuse and 15,469 heroin overdose deaths in that same year.<sup>3</sup>



### ARE THERE ANY LINKS BETWEEN PRESCRIPTION OPIOID ADDICTION AND HEROIN ADDICTION?

The connection between prescription opioid and heroin addiction has changed over time, according to several studies. In the 1960s, more than 80 percent of patients who sought treatment for an opioid addiction began their drug use with heroin.<sup>4</sup> Today, nearly 80 percent of heroin users say that their first opioid use was a prescription drug.<sup>5</sup>



### WHY HAVE PRESCRIPTION OPIOIDS BECOME SO WIDELY MISUSED IN THE U.S.?

There are several possible reasons for the recent increase in prescription opioid abuse, according to National Institute of Drug Abuse Director and BBRF Scientific Council Member Nora D. Volkow, M.D. In her 2014 testimony before Congress, Dr. Volkow cited a drastic increase in opioid prescriptions filled; greater acceptability among the public for opioid medications being used for several purposes; and aggressive marketing of opioid drugs by pharmaceutical companies as reasons for crisis levels of opioid abuse. The number of prescriptions has increased from 76 million in 1991 to almost 207 million in 2013, she testified.<sup>6</sup>



## ARE THERE REGIONAL OR POPULATION DIFFERENCES IN OPIOID OVERDOSE ACROSS THE U.S.?

Yes. A 2017 study of opioid overdose hospitalizations from 2000 to 2014 found that hospitalization rates for prescription opioid overdose were highest in the South and lowest in the Northeast; while hospitalization rates for heroin overdose were highest in the Northeast and grew at the fastest rate in the Midwest.<sup>7</sup> Overdose rates are highest among people ages 25 to 54 years old, and higher among white and American Indian or Alaskan Native populations, compared to black and Hispanic populations.<sup>8</sup>



## HOW HAVE RATES OF OPIOID MISUSE AMONG TEENAGERS IN THE U.S. CHANGED OVER TIME?

According to an annual survey of 8<sup>th</sup>, 10<sup>th</sup> and 12<sup>th</sup> –graders nationwide, pain medication misuse has dropped from 9.5 percent in 2004 to 4.2 percent in 2017. 35.8 percent of 12<sup>th</sup>-graders in 2017 said that the drugs were “easily available” to them, compared to more than 54 percent in 2010.<sup>9</sup>



## WHAT ARE THE BEST TREATMENTS FOR OPIOID ADDICTION?

There is a growing consensus that opioid addiction should be treated with medications along with counseling, and that counseling alone may not be effective in preventing drug overdose and death.<sup>10</sup> Medication treatment uses drugs, such as methadone, buprenorphine (Suboxone, Subutex), and naltrexone (Vivitrol). In essence these drugs substitute for the opioid and are prescribed to reduce opioid dependency and to prevent death by overdose. The length of the treatment course varies depending on how well a patient tolerates the medication, the type of substitute medication, and whether the patient relapses during treatment, but can run from 90 days to several years.<sup>11</sup>

<sup>1</sup> Centers for Disease Control and Prevention, “Opioid Basics,” <https://www.cdc.gov/drugoverdose/opioids/index.html>.

<sup>2</sup> Substance Abuse and Mental Health Services Administration, “Key Substance Use and Mental Health Indicators in the United States: Results from U.S. National Survey on Drug Use and Health 2016,” <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf>.

<sup>3</sup> Centers for Disease Control and Prevention, “Mortality in the United States, 2016 NCHS Data Brief No. 293, December 2017,” <https://www.cdc.gov/nchs/data/databriefs/db293.pdf>.

<sup>4</sup> TJ Cicero et al. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA Psychiatry*, Volume 7, Pages 821-826, 2014.

<sup>5</sup> Substance Abuse and Mental Health Services Administration. “Associations of nonmedical pain reliever use and initiation of heroin use in the United States. CBHSQ Data Review,” <http://www.samhsa.gov/data/2k13/DataReview/DR006/nonmedical-pain-reliever-use-2013.pdf>.

<sup>6</sup> National Institute on Drug Abuse, “America’s Addiction to Opioids: Heroin and Prescription Drug Abuse,” Congressional testimony by Nora D. Volkow, M.D., <https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse>.

<sup>7</sup> GJ Unick and D Ciccarone. U.S. regional and demographic differences in prescription opioid and heroin-related overdose hospitalizations. *International Journal of Drug Policy*. Volume 46, Pages 112-119, August 2017.

<sup>8</sup> Substance Abuse and Mental Health Services Administration, “Results From the 2014 National Survey on Drug Use and Health,” <https://www.samhsa.gov/data/sites/default/files/NSDUH-DeT-Tabs2014/NSDUH-DeT-Tabs2014.pdf>.

<sup>9</sup> National Institute on Drug Abuse, “Monitoring the Future 2017 Survey,” <https://www.drugabuse.gov/related-topics/trends-statistics/monitoring-future>.

<sup>10</sup> M Pierce et al. Impact of treatment for opioid dependence on fatal drug-related poisoning: a national cohort study in England. *Addiction*, Volume 111, Pages 298-308, February 2016.

<sup>11</sup> L. Sordo et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *British Medical Journal*, Volume 357, Pages 1-14, April 2017.

# Discovery to Recovery: Therapy Update

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

By: Bahar Gholipour

### **Lithium Better than Valproate in Lowering Suicide Risk in Bipolar Disorder**

Risk for suicide is a concern in patients with bipolar disorder, but research on anti-suicidal effects of different medications for the condition has been inconclusive. Now a large study in Sweden has found that people treated with lithium have lower risk of attempted or completed suicide than people treated with an alternative drug called valproate, an anticonvulsant.

Using health records from multiple Swedish national health registers, the researchers followed 51,535 people with bipolar disorder from 2005 to 2013, and compared the rate of suicide among those taking either lithium or valproate. During the eight years of the study, 10,648 attempted or completed suicides occurred. The rate was decreased by 14 percent when patients took lithium but it did not change when patients took valproate, according to the study published online June 9, 2017 in *The American Journal of Psychiatry*.

Using these findings, the researchers estimated that 12 percent of suicide events could have been prevented if patients had taken lithium during the entire study period.

The findings suggest that, all things being equal, lithium may be a better option for patients with bipolar disorder who have suicidal intentions, the researchers said.

The team was led by Paul Lichtenstein, Ph.D. of the *Karolinska Institute in Sweden* and included Sarah E. Bergen, Ph.D., a 2012 Young Investigator, also at the *Karolinska*.

Full text: <https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2017.16050542>

### **Light Therapy to Reduce Depression in Bipolar Disorder**

Choosing a treatment for addressing in bipolar disorder is a delicate clinical decision. There's often a concern that the treatment might increase the risk of the patient crossing over to a manic state. A new placebo-controlled study finds that light therapy, an effective treatment for seasonal depression, can reduce depression in people with bipolar disorder without inducing mania.

The study included 46 depressed adults diagnosed with bipolar I or II disorder who were taking anti-manic medication. Half of the patients were randomly chosen to receive a daily 15 minutes of bright white light at midday, while the other half received a dim red placebo light.

In the beginning of the study the patients had moderate depression and no manic symptoms. After four to six weeks of treatment, those treated with bright white light had significantly lower depression scores and 68 percent experienced remission, compared with 22 percent of those in the control group.

Moreover, no mood switches were observed. The timing of light therapy may be important for keeping the risk of mood switch low. In a previous study the team found that some patients receiving light therapy in the morning experienced episodes of mania.

The findings, published June 29, 2017 in *The American Journal of Psychiatry*, suggest light therapy may be a safe and effective adjunctive therapy for people with bipolar disorder.

The study was led by 2013 and 2002 Young Investigator Dorothy K.Y. Sit, M.D., and 1998 Independent Investigator Katherine L. Wisner, M.D., M.S., both at *Northwestern University*.

Full text: <http://ajp.psychiatryonline.org/doi/full/10.1176/appi.ajp.2017.16101200>

### **Children with Severe Anxiety Fared Better With Combined Behavioral Therapy and Medication**

Either medications or behavioral therapy is often enough to relieve anxiety in children and teenagers. But for those struggling with severe anxiety, a combination of both may be necessary, according to a study published October 2, 2017 in the *Journal of Clinical Child & Adolescent Psychology*.

The findings come from a new analysis of a previous clinical trial, which included 488 participants, aged 7 to 17, diagnosed with anxiety disorders. The trial compared the effects of receiving cognitive behavioral therapy, the antidepressant sertraline (Zoloft), the combination of both, or a placebo. The results showed that therapy alone or medication alone were equally able to reduce anxiety overall.

In the new analysis, however, the team found that this is not true for the 220 patients in the study who had severe symptoms. Of these patients, only those who received the combination of sertraline and therapy achieved remission. Those who received only therapy or only medications did not fare any better than those who received placebo.

These findings suggest that for children with severe anxiety, having both forms of treatments at once makes it more likely that symptoms will be reduced.

The team was led by Michael H. Bloch, M.D., M.S., a 2013 and 2009 Young Investigator and Associate Professor in the *Yale Child Study Center*, and included 2017 Young Investigator Jerome H. Taylor, M.D., at the *University of Pennsylvania* and 2013 Young Investigator Eli R. Lebowitz, Ph.D., at *Yale University*.

Full text: <http://www.tandfonline.com/doi/full/10.1080/15374416.2017.1371028>

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# Glossary

**AMPA Receptor:** a docking port for glutamate that mediates fast synaptic transmission in the central nervous system and is important in brain plasticity.

**Blood-Brain Barrier:** membrane barrier separating blood circulating in the body from the brain and the extracellular fluid in the central nervous system. The membrane can be breached by water, some gases, and some molecules on a selective basis. The barrier acts primarily to protect the brain against infection.

**Brain-Derived Neurotrophic Factor (BDNF):** a protein that acts on certain neurons of the central and peripheral nervous systems, to support the survival of neurons and to encourage the growth and development of new neurons and their connections. The protein plays an important role in memory and learning.

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

**First-episode psychosis (FEP):** In trying to reduce the harm to people with psychosis, some researchers and clinicians are exploring the potentially beneficial impact of engaging and treating the patient within a few months before or after their first psychotic episode, sometimes called a "psychotic break."

**Functional Remission:** a term used by clinicians indicating patients whose symptoms of a given illness have been reduced or eliminated, to the point when the individual is able to function successfully in society, e.g., in a job or in relationships. Compare with Symptomatic Remission.

**Microphenotype:** a term used by Dr. Patrick McGorry to signify various behaviors, symptoms, and biological correlates which in themselves do not justify a traditional diagnosis, but which often form a constellation that can help clinicians plan a course of treatment. McGorry believes these sub-diagnostic signs of "mental ill-health" are often highly changeable and

cross traditional diagnostic boundaries in young people as their conditions begin to manifest.

**Osteocalcin:** a protein hormone manufactured in bone-building cells called osteoclasts. Osteocalcin is also found in neurotransmitters in the brain, and is thought to be important to forming new memories.

**Prion:** a protein substance located in the brain that can fold in multiple ways, and can in some cases transmit its form to other prion proteins in a manner that resembles viral infection. Prions are the cause of some degenerative brain diseases such as bovine spongiform encephalopathy ("mad cow disease") and the rare brain disorder called Creutzfeldt–Jakob disease.

**Psychosis:** refers to conditions that affect the mind, where there has been some loss of contact with reality. When someone becomes ill in this way it is called a psychotic episode. During a period of psychosis, a person's thoughts and perceptions are disturbed and the individual may have difficulty understanding what is real and what is not. Symptoms of psychosis include delusions (false beliefs) and hallucinations (seeing or hearing things that others do not see or hear). Other symptoms include incoherent or nonsense speech, and behavior that is inappropriate for the situation. A person in a psychotic episode may also experience depression, anxiety, sleep problems, social withdrawal, lack of motivation, and difficulty functioning overall.

**RAISE:** In 2008, the National Institute of Mental Health (NIMH) launched the *Recovery After an Initial Schizophrenia Episode (RAISE)* project. It showed the advantage of coordinated specialty care (CSC) treatments, for people who were experiencing first-episode psychosis.

**Symptomatic Remission:** a term used by clinicians indicating patients whose symptoms of a given illness have been reduced or eliminated, usually in response to treatment. Criteria can differ as to what magnitude of reduction constitutes a "remission." Compare with *Functional Remission*.

## 2018 » A Free Monthly Series



### What's New with TMS for Depression and Other Brain Diseases

Tuesday, April 10th, 2:00PM EST

**Mark S. George, M.D.**

*Medical University of South Carolina*

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### Genomics Across Diagnostic Boundaries to Improve Precision Medicine in Psychiatry

Tuesday, May 8th, 2:00PM EST

**Stephan Ripke, M.D., Ph.D.**

*Charite' University Medicine Berlin Freie Universitat, Berlin, Germany*

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### Ketamine: Why now? How? Where do we go from here?

Tuesday, June 12th, 2:00PM EST

**John Krystal, MD**

*Yale University School of Medicine*

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### Rare Misspellings in the Genome, Dopamine Mishandling, and ADHD

Tuesday, July 10th, 2:00PM EST

**Randy Blakely, Ph.D.**

*Florida Atlantic University*

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### MODERATOR

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The Brain & Behavior Research Foundation is committed to alleviating the suffering caused by mental illness. We award scientific research grants to improve treatment and ultimately develop cures and methods of prevention to enable people to live full, happy, and productive lives.

### OUR CREDENTIALS:

Since 1987, we have awarded more than \$380 million to fund more than 5,500 grants to more than 4,500 scientists around the world.

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