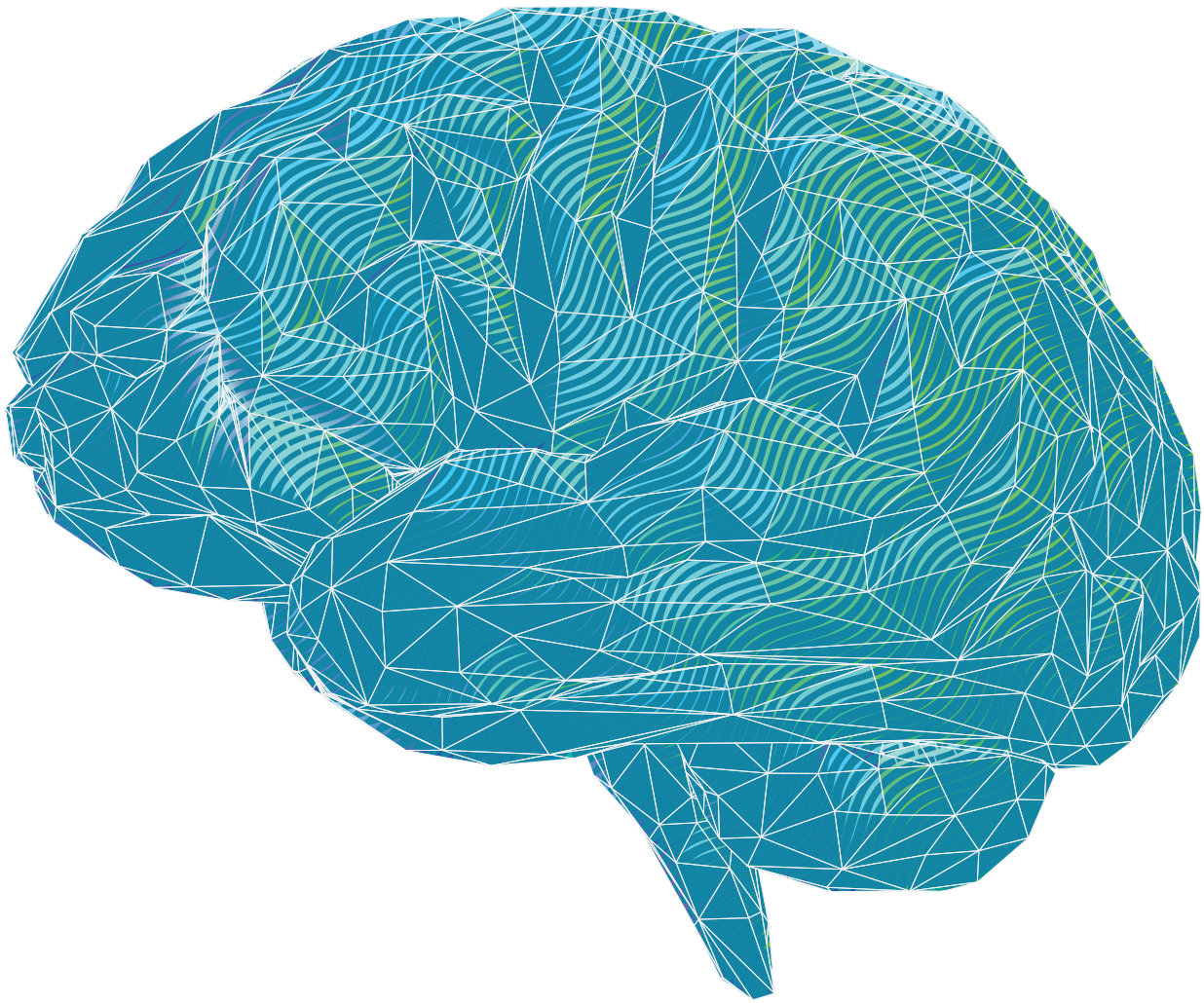
Using Brainwaves to Predict Mental Illness

Diagnosing & Treating Bipolar Disorder

MAGAZINE

# Brain&Behavior

MAY 2021



## Testing a New Approach to Accelerate Psychiatric Drug Development

# PRESIDENT'S LETTER

It was a little more than a year ago when the World Health Organization declared the COVID crisis a global pandemic, transforming the world around us. One thing that has remained constant during this difficult time is the importance of research. While all of us have been impacted by COVID-19, we are continuing forward in our important mission to alleviate the suffering caused by mental illness by awarding grants that will lead to advances and breakthroughs in scientific research.

This issue of *Brain & Behavior Magazine* features a number of articles that highlight the impact that research funded by BBRF is having, with broad implications for better treatments, cures, and methods of prevention for mental illness.

Recent years have seen the abandonment by many large pharmaceutical companies of clinical development of new medicines for psychiatric disorders. The reason is well known: the costs and risks are very high. Our **PATHWAYS TO THE FUTURE** story is about an unconventional approach to developing new psychiatric drugs. Based on an initiative by the National Institute of Mental Health, it's called "Fast-Fail" and is designed to weed out the weakest drug candidates early in the process, to save time and money. In its first comprehensive test, a team led by two BBRF grantees and including 11 other BBRF grantees, Scientific Council members and prize winners, demonstrated the approach using a potential drug to treat anhedonia—the inability to experience or seek pleasure—which is often seen in depression, but also in other disorders, including bipolar disorder, anxiety, PTSD, and panic disorder.

Our **SCIENCE IN PROGRESS** feature is about a well-established technology called EEG, or electroencephalography, which reveals brain-wave patterns generated by the activity of neurons in the cerebral cortex. This tool is now being used to predict the likelihood of onset of a number of psychiatric disorders, including autism and psychosis. It also has the potential to predict individual response to specific antidepressant treatments, and is helping researchers learn about pathologies underlying such disorders as schizophrenia and PTSD.

In our **ADVICE ON MENTAL HEALTH** article, we feature a thorough Q&A with one of the world's leading clinical authorities on treating bipolar disorder, David J. Miklowitz, Ph.D. He offers a wealth information about this complex disorder, including its range of manifestations, which are typically highlighted by periods of depression and at least a single episode of mania. Dr. Miklowitz also addresses the signs parents should pay attention to if they are concerned that their adolescent may have bipolar disorder; how to distinguish unipolar depression from depression that occurs in bipolar disorder; and how family-focused therapy, which he has championed, can help patients and families reach better outcomes.

This issue also highlights **A RESEARCHER'S PERSPECTIVE**, based on a presentation given by Lisa M. Monteggia, Ph.D., of Vanderbilt University, at a zoom event hosted by BBRF. The topic of her presentation was "Studying Ketamine's Rapid Effects to Unlock Secrets for Developing Better Antidepressants." In her remarks, Dr. Monteggia reflected on what she has learned about antidepressant mechanisms from the therapeutic results obtained with the experimental drug ketamine.

Together, we will continue to fund innovative and impactful research. Our shared goal of a world free from debilitating mental illnesses relies first and foremost upon you, our donors—in partnership with the exceptional scientists chosen by the BBRF Scientific Council—who are working to transform your donations into better treatments, cures, and methods of prevention for mental illness.

Thank you for your ongoing support.
Stay well and stay safe.

Sincerely,

**Jeffrey Borenstein, M.D.**

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

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# In Drug Development, An Unconventional Approach to Advance Only the Best Candidates

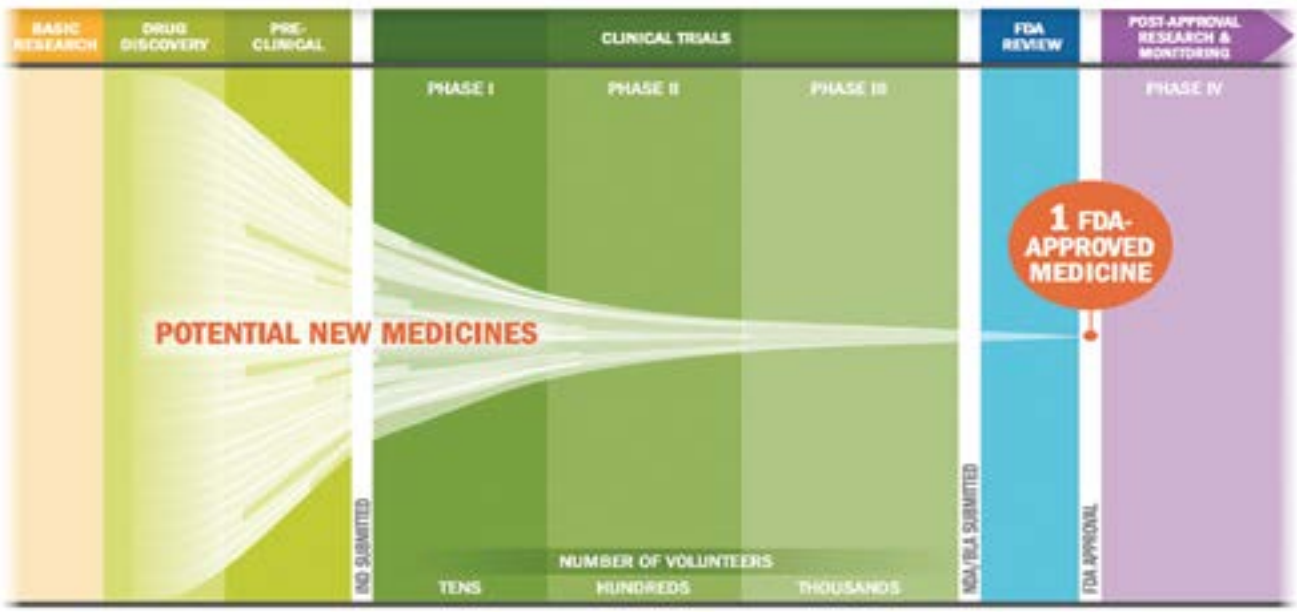
## The FAST-FAIL approach seeks to weed out weaker drug candidates early in the development process

"I have come to appreciate that there are some fundamental flaws in the way that we have tried to develop drugs." The speaker is Andrew D. Krystal, M.D., a 1997 and 1993 BBRF Young Investigator who is a professor of psychiatry at the University of California, San Francisco.

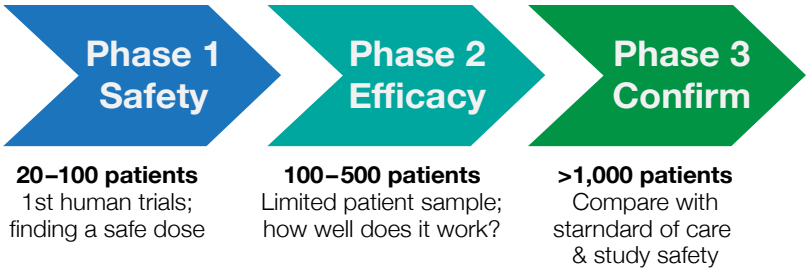
Dr. Krystal and a team that included 12 others who have received BBRF grants and prizes or serve on BBRF's Scientific Council, made news in the past year when they successfully demonstrated an alternative approach to drug development that stresses weeding out, at the earliest possible stage, candidate compounds that are less likely to succeed.

Ironically, in taking this unconventional approach focusing on the early elimination of weaker candidates, Dr. Krystal and colleagues generated impressive positive evidence for a first-ever drug to treat anhedonia, a major symptom of several common psychiatric illnesses including depression, anxiety, and PTSD. People with anhedonia are unable to experience pleasure. Across disorders, those with anhedonia tend to have poorer outcomes and a higher risk of suicide.

## The Drug Development Process




A multi-year period of basic research, which includes experimenting with compounds in test tubes and in animals, precedes the 3 main phases of human clinical trials. Still, the vast number of drugs that enter Phase 1 don't make it through Phase 3.




The unusual approach taken by Dr. Krystal and team was the first comprehensive test of a concept launched years ago by the National Institute of Mental Health (NIMH), dubbed "Fast-Fail." In the words of NIMH Director Joshua A. Gordon, M.D., Ph.D., a member of the BBRF Scientific Council and 2003 and 2001 BBRF Young Investigator, "The Fast-Fail approach aims to help researchers determine—quickly and efficiently—whether targeting a specific neurobiological mechanism has the hypothesized effect and is a potential candidate for future clinical trials."

## DAUNTING NUMBERS

The need for new approaches to drug development is dramatized by the statistics. According to the FDA, 70% of the drug candidates that manage to survive years of "preclinical" testing in test tubes and animals to enter Phase 1 human "safety" trials make it into Phase 2. In Phase 2, the drug is given to a comparatively small number of individuals affected by the condition the drug is supposed to address. But only 30% make it through Phase 2 and are advanced into Phase 3 trials which involve much larger patient populations—in other words, 21% of the drugs that entered Phase 1. Then, in Phase 3, only a quarter to a third of tested compounds meet the standard of effectiveness, which is typically pivotal for FDA approval. In the end, then, only 5% to 7% of drugs that entered Phase 1 meet their endpoints for effectiveness in Phase 3.

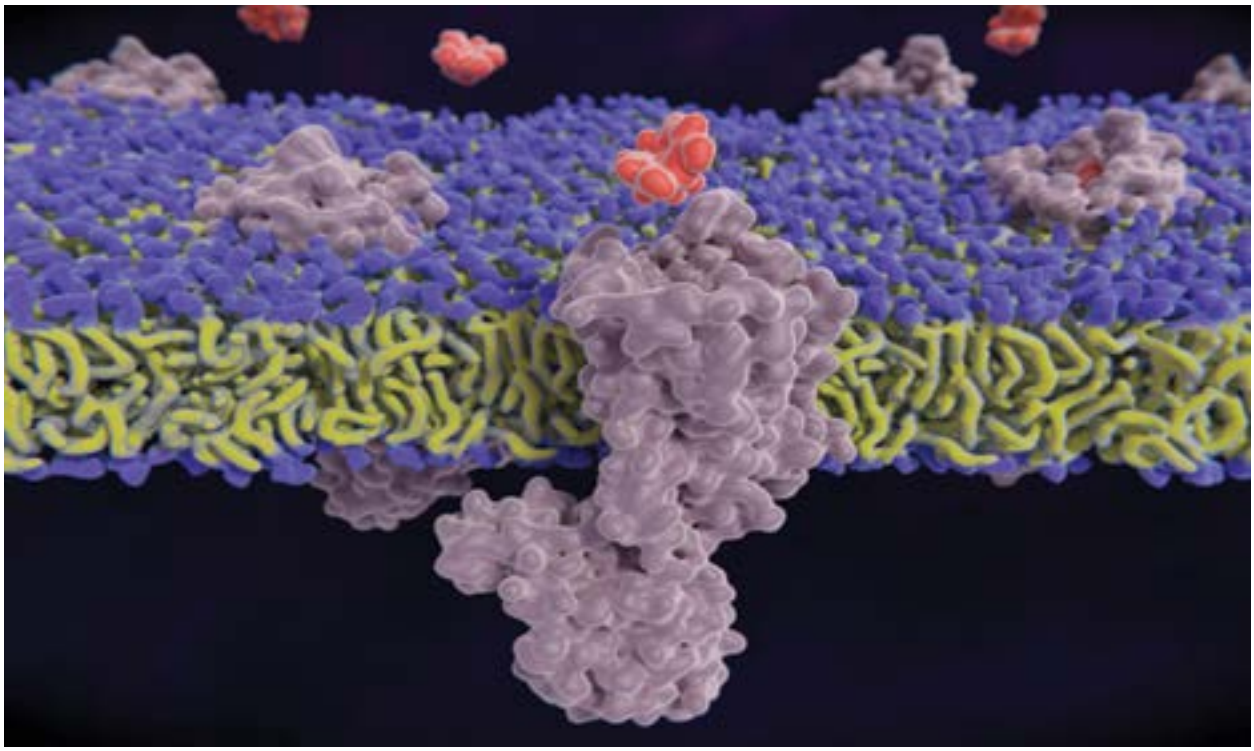
This great funneling process is even starker in its winnowing effect with drugs that are designed to affect the body's central nervous system (CNS), which includes the brain. Psychiatric drugs are among those in this subset. According to a 2019 report published in *Nature Reviews Drug Discovery*, based on data from 2010–2017, only 3% of compounds that enter Phase 1 testing in the CNS category eventually make it beyond Phase 3. In the eyes of major pharmaceutical companies, the risk of failure is simply too great.

"It costs more than $1 billion to get a drug to market," Dr. Krystal says, "and often more than half that money is spent in Phase 3." Given the daunting statistics, "how many of those failures in Phase 3 can a company tolerate?" he asks. "I think the general sense has been that companies feel that the risk/benefit in neuroscience drug development is not acceptable. That's why some of the biggest pharmaceutical companies have decided over the last decade to pull out; they're no longer committing resources to developing psychiatric drugs."

Reversing this trend has been an urgent objective of researchers studying the brain and psychiatric illness. As far back as 2010, BBRF Scientific Council member Steven M. Paul, M.D., and colleagues asked in a paper appearing in the journal *Nature Reviews Drug Discovery*: "Given that the vast majority of drug candidates are destined to fail…can they fail faster and [therefore] less expensively?" In a nutshell, that is the question the NIMH's Fast-Fail approach was designed to answer.

Andrew D. Krystal, M.D.

Diego A. Pizzagalli, M.D.



Opioid receptors (grey) are large proteins that are embedded in the membrane (blue and green) of certain neurons. They protrude slightly above the cell surface to capture opioid molecules (red) floating in the space between cells.

## FAST-FAIL'S FIRST COMPREHENSIVE TEST

Dr. Krystal and Diego A. Pizzagalli, M.D., a 2017 BBRF Distinguished Investigator and 2008 Independent Investigator at Harvard University/ McLean Hospital, led "Fast-Fail" research in mood disorders that resulted in two published papers in 2020, one appearing in *Nature Medicine*, the other in *Neuropsychopharmacology*. They and colleagues subjected a candidate drug made by Johnson & Johnson to early Phase 2 testing, in a protocol that was carefully designed, per NIMH Fast-Fail guidelines, to respond to potential weaknesses in the conventional Phase 2 testing process.

Dr. Krystal explains that conventional Phase 2 studies often recruit too small a patient sample to indicate reliably whether success in meeting the trial's endpoints will actually result in a therapeutic effect. This raises the odds of subsequent failure when the patient sample is enlarged in Phase 3. Failure risk also rises in Phase 3, he notes, because of another commonplace Phase 2 feature: these studies typically don't test a specific hypothesis related to why the drug is believed to be promising. For example, a proposed antidepressant drug will be tested in a limited number of depressed patients in Phase 2, with the "endpoint" being defined as a certain amount of reduction in depression symptoms. "Trials of this kind don't really care about how the drug works so much as whether it has a positive effect."

This approach has many defenders. After all, the "mechanism of action" of many valuable drugs that have long been on the market remains uncertain. Among them are the SSRI and SNRI antidepressants (such as Prozac, Lexapro, Paxil, Effexor, etc.) that have been taken by tens of millions of Americans. First approved in 1987, these drugs have helped many; yet between one-third and one-half of those who take them do not have a sustained therapeutic response. Because the mechanism through which these drugs affect depression remains unclear, no one can be sure why they don't help some patients.

Making the matter more difficult, depression is a complex illness, in the dual sense that it is thought to affect many different aspects of brain biology, and that these impacts are believed to be the consequence of a wide array of causative mechanisms, which most likely vary from patient to patient.

The Fast-Fail approach tackles this problem in part by focusing not on broad illnesses like depression, as defined in psychiatry's *Diagnostic & Statistical Manual (DSM)* but rather on important symptoms like anhedonia which may affect patients across a number of different illnesses. This "symptom"

focus reflects another NIMH initiative, which establishes "Research Domain Criteria" (RDoC). These criteria are intended to provide meaningful biological frameworks for the study of pathologies involved in psychiatric illness. RDoC stresses aspects of behavior—for example, the ability of the brain to learn from past experience, or the ability to register and seek rewards—that pertain to multiple disorders. Learning and reward processing, for instance, are fundamental brain operations and can be disrupted in depression and addiction. Studying these operations may enable researchers to link pathologies across diagnoses in brain systems that are involved in generating symptoms like anhedonia.

## TESTING A DRUG FOR ANHEDONIA

Drs. Krystal, Pizzagalli and colleagues designed a Phase 2 trial for an anhedonia drug candidate using the following approach. First, following the NIMH's Fast-Fail concept, they sought to test an existing compound that already had been through preclinical testing and subsequently had been proven safe in Phase 1 human trials. Further, they sought a drug that had been shown in prior research to "hit" its biological target.

The question to be answered in their Phase 2 trial was: in people with anhedonia, does hitting the target at a known "safe" dosage actually change brain biology? Even more precisely, does it change brain biology in a way that supports the thesis for the drug's development? If this could not be demonstrated, then by Fast-Fail standards, the drug would "fail"—before another dollar, much less hundreds of millions, were spent on it. Those precious resources could be spent testing another drug with early-stage promise.

The drug selected by Drs. Krystal, Pizzagalli and team, called JNJ-67953964, was already understood from past animal and human experiments to block one of the several naturally occurring receptors for opioids in brain cells, called kappa-opioid receptors (KORs). This was considered interesting because of other pre-clinical research suggesting that activation of the KOR receptor blocks the release of dopamine in a region of the brain called the ventral striatum. Such release is thought to be correlated with the ability to seek and experience pleasure. The thesis behind the new drug was that blocking the receptor whose activation prevents dopamine from being released might help restore the brain's "pursuit-of-pleasure" circuitry.

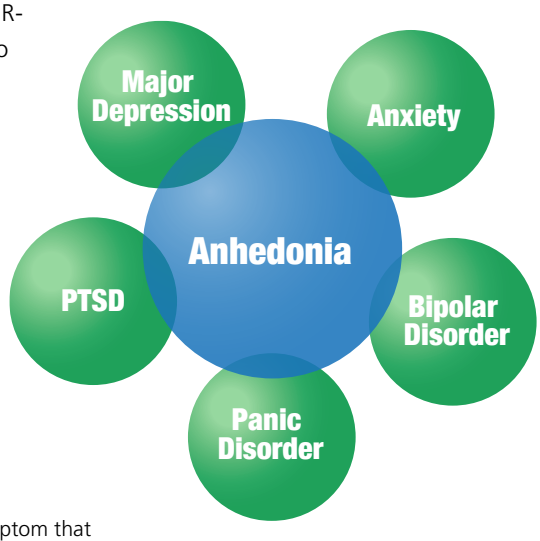
Thus, Drs. Krystal, Pizzagalli and colleagues set out in their Fast-Fail trial to determine whether or not such brain-circuit impacts could be seen in actual patients with anhedonia symptoms.

The patients—86 in all, half of whom received the KOR-blocking drug, and half a placebo—were recruited across six different U.S. testing sites. Although all of the participants had symptoms of anhedonia, and the majority had major depressive disorder, other participants had diagnoses of bipolar disorder, generalized anxiety disorder, social anxiety disorder, panic disorder, and PTSD. The trial was randomized and double-blinded, so that neither patients nor their doctors knew who was receiving drug or placebo.

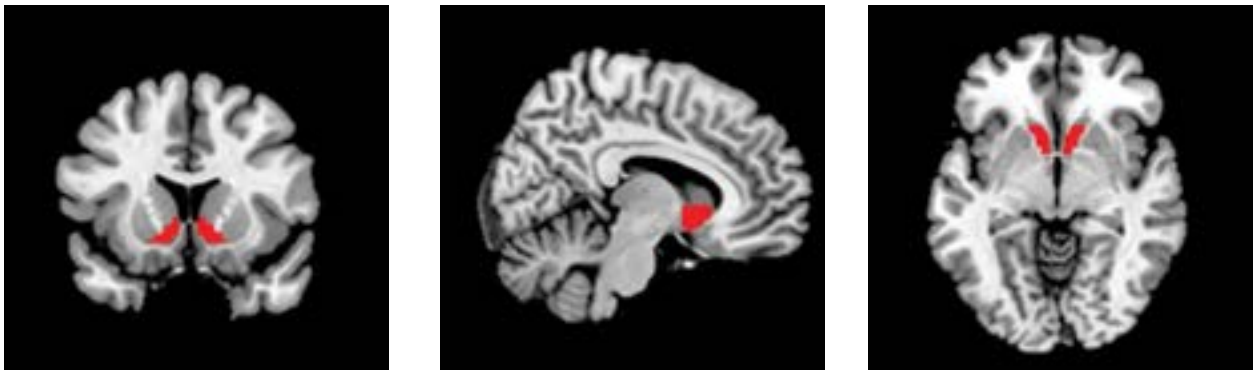
## UNCONVENTIONAL ENDPOINT

Importantly, unlike conventional Phase 2 trials, the primary endpoint for the Fast-Fail trial did not concern the impact of the drug on patients' anhedonia symptoms (or on depression, with which it is often associated). Rather, it was to gauge the drug's impact (if any) on reward-related neural activation in a part of the ventral striatum called the nucleus accumbens. One of the core hubs of the brain's reward system, it is located in the middle of the brain and involved in motivation, anticipating and pursuing rewards, and the ability to learn from rewards.

Participants took the KOR-blocking drug or placebo over an 8-week period. Before the trial began and after it ended, each participant was given a computer-generated task to perform while activity in the ventral striatum was being measured with an fMRI scanning machine. The task measured anticipation




Anhedonia is a symptom that is experienced across several diagnostic boundaries.



In each clinical trial participant, the team used fMRI to measure reward-related activation levels in the ventral striatum (red). A core hub of the brain's reward system, this structure is involved in motivation, anticipating and pursuing rewards, and the ability to learn from rewards.

of a reward, in this case, monetary gain, based on a computer game.

Compared with those who took placebo, participants who received the KOR-blocking drug showed increased activation in the ventral striatum when expecting a monetary gain.

Another key finding was that participants' levels of ventral striatum activation at baseline—before they took the drug or played the computer game—predicted the degree to which activation in their ventral striatum would change (if at all) during the trial.

The correlation was strongest for those who received the KOR-blocking drug—those with higher activation levels before the trial turned out have the greatest increases in activation after 8 weeks of taking the Johnson & Johnson drug. This suggests that the level of activity in the ventral striatum at baseline might serve as a biomarker—pointing to those, in advance of treatment, most likely to benefit from the drug.

As Drs. Krystal and Pizzagalli point out, these results, while gratifying to them and to leaders at the NIMH, may not have satisfied those who prefer to measure clinical trial effectiveness with the classic indicator: how much the drug helped relieve patients' symptoms. Here, they noted, was a great irony. It turned out that the KOR-blocking drug, in secondary analyses, did have an observable effect; it did lower anhedonia symptoms, as gauged by a standard clinical measure. It also improved an objective measure of anhedonia, as assessed with a computerized task performed outside the MRI scanner, which assessed participants' ability to change behavior after having received rewards. In the conventional sense, the Johnson & Johnson drug might be said to have "passed" this Phase 2 test.

## NEW PERSPECTIVES ON 'FAILURE' AND 'SUCCESS'

But as Dr. Krystal explains, this isn't what he, Dr. Pizzagalli, and colleagues set out to discover. "Does it work?" in the Fast-Fail context means: "Did the drug hit its biological target, and did hitting that target change brain biology in ways consistent with the hypothesis driving the drug's development? In this case, that hypothesis was confirmed: hitting the target (the KOR receptor in neurons) did change activation in the brain's reward system (measured by increased ventral striatum activation).

But isn't it better still that the drug also seemed to reduce anhedonia? Of course, the researchers acknowledge. But what if such benefit had not been observed? The entire approach, in a sense, centers on what action to take if a Phase 2 drug candidate does *not* yield a clinical benefit in patients. Would that mean that the risk of continuing with development was too high?

Perhaps. But recall the potential problems with Phase 2 trials. Was the 86-patient sample in the Fast-Fail test of the KOR-blocker sufficiently large to reliably determine the effects of the drug on clinical measures of anhedonia? Or what if the dose given, while known to be safe in people, had been too low to generate a change in symptom intensity? Not knowing the answer, would the drug's developer invest millions more in another multi-year effort to test the drug at higher dosages? Faced with such decisions, many companies have decided not to proceed.

The converse case is also relevant: to see a reduction in symptoms in Phase 2 with a small number of patients is encouraging, but does not guarantee that in a much larger Phase 3 trial, costing hundreds of millions, similar benefits would be observed. Drugs "promoted" from Phase 2 based on small sample sizes have often failed in Phase 3, and that problem runs to the heart of why major pharmaceutical companies stopped developing psychiatric drugs.

## 'SUCH AN IMPORTANT APPROACH'

"There are so many examples of really promising Phase 2 results, statistically significant findings, that then crash and burn when a Phase 3 trial is performed," says Dr. Pizzagalli. In contrast, he says, consider the advantage of the Fast-Fail approach: "You have a very small patient sample, and you try to see whether the intervention you're testing has an effect on a specific biological target. If it does, then you have to put down chips and say: These are my milestones. If you don't see that my drug generates the biological impact by a pre-specified amount (that we agree to be significant), then you don't progress to Phase 3. If you do see the impact, then you move forward. Some people question this, but I think it is such an important approach."

Also important to note, says Dr. Pizzagalli, the KOR-blocking drug he and colleagues tested did not show any appreciable therapeutic impact upon depression symptoms other than anhedonia. But there are currently no medicines approved for treating symptoms like anhedonia within larger disorders like depression, and depression is the largest "potential market" for such a drug. So despite the fact that many patients have anhedonia symptoms, the result Dr. Pizzagalli and colleagues obtained still might not be viewed as commercially viable. A developer might have to adopt the idea that it "pays"—whether in moral or monetary terms—to develop a drug that addresses important symptoms to justify investing in Phase 3, as in the case of the KOR-blocking compound.

**"Because of the 'proof of mechanism' that our trial provided, it need not be this specific compound. It could be any compound that robustly engages the same target; it should have the same effect."**

In the words of Dr. Krystal, the counter-intuitive thing about Fast-Fail is that "the goal is to fail drugs more reliably and definitively; it is not necessarily to succeed. Yes, we love to succeed. But with this method, the idea is to identify as early as we can those drugs that shouldn't move forward, thereby making it possible to devote precious resources to others which have a better chance of making it all the way through the process, all the way to patients."

It is not yet known if Johnson & Johnson or any other pharmaceutical company has plans to continue developing a KOR-blocking drug. "We do not know, but I will say that the natural next step would be to go ahead and perform Phase 3 trials in anhedonia," Dr. Krystal says. He adds, "because of the 'proof of mechanism' that our trial provided, it need not be this specific compound. It could be any compound that robustly engages the same target; it should have the same effect."

A final point: Dr. Krystal suggests that understanding how a drug works before testing it in a much larger group of patients enables researchers to better assess any failure or shortfall in Phase 3. Phase 3 failures, which are always possible regardless of prior results, are most troubling when the drug's biological mechanism is poorly understood. "Having established proof-of-mechanism," he says, should decrease the likelihood that any positive impacts (on anhedonia, in this case) in Phase 3 "will be due to 'non-specific effects'—cases where those who take the drug are helped, but for reasons which may have nothing to do with our theory of why it does."

The Fast-Fail program is now over at the NIMH, its officials say, but the ideas that set it in motion continue to influence the NIMH's Experimental Therapeutics Program, a cornerstone of its drug development research effort. ❖ **PETER TARR**

In addition to Drs. Krystal and Pizzagalli, the following were among the researchers involved in the first comprehensive test of the FAST-FAIL approach: **Joseph Calabrese, M.D.**, 2004 BBRF Falcone Prize winner; **Keming Gao, M.D., Ph.D.**, 2016 BBRF Independent Investigator, 2010, 2006 Young Investigator; **Gretchen Hermes, M.D., Ph.D.**, 2015 BBRF Young Investigator; **Dan Iosifescu, M.D.**, 2006, 2001 BBRF Young Investigator; **Richard S.E. Keefe, Ph.D.**, 2003 BBRF Young Investigator; **Sarah Lisanby, M.D.**, 2010 BBRF Distinguished Investigator, 2003 Independent Investigator, 1996 Young Investigator; **Sanjay Mathew, M.D.**, 2009 BBRF Independent Investigator, 2006, 2001 Young Investigator; **James Murrough, M.D.**, 2009 BBRF Young Investigator; **Gerard Sanacora, M.D., Ph.D.**, BBRF Scientific Council member, 2014 BBRF Distinguished Investigator, 2007 Independent Investigator, 2001, 1999 Young Investigator; **Moria Smoski, Ph.D.**, 2007 BBRF Young Investigator; **Steven Szabo, M.D., Ph.D.**, 2012, 2003 BBRF Young Investigator; **Alexis Whitton, Ph.D.**, 2015 BBRF Young Investigator.

# Using Brainwave Patterns to Predict and Understand Psychiatric Disorders

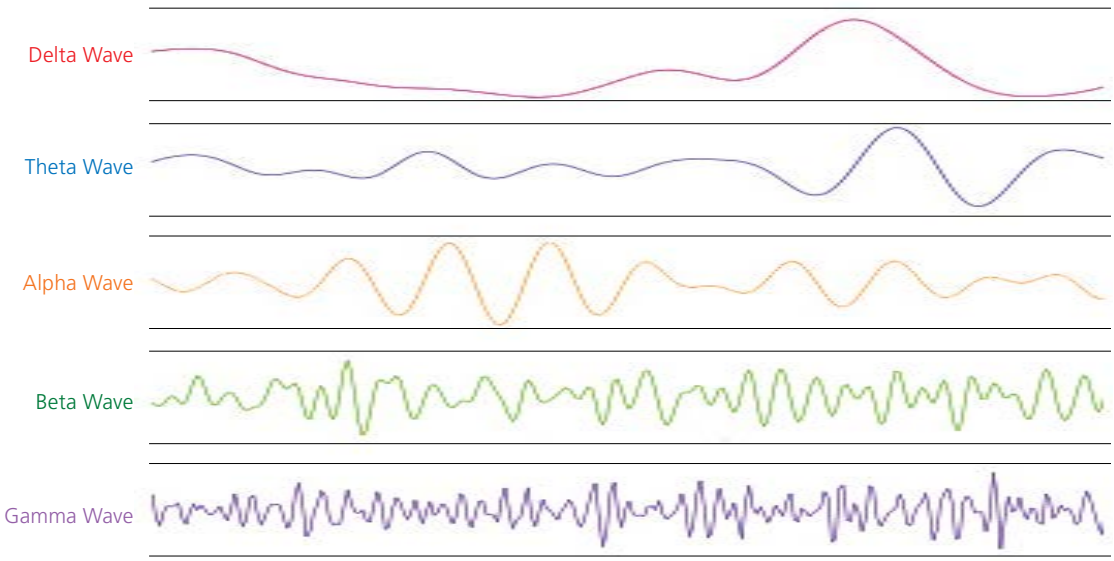
*5 recent studies involving 14 BBRF grantees help move the field toward the major goals of early treatment and prevention*

Using a well-understood, inexpensive and easy-to-deploy technology called electroencephalography, or EEG, as well as related technologies that also measure the activity of cells in the brain, researchers funded by BBRF grants are making impressive progress in predicting the likelihood of onset of a number of psychiatric disorders, including psychosis and autism spectrum disorder (ASD).

EEG has also shown promise in indicating the likelihood that individuals with major depression will respond to specific antidepressant treatments. Further, the technology is being used as a discovery tool to reveal underlying pathology, for example in schizophrenia and post-traumatic stress disorder (PTSD).

First demonstrated in a human subject in the 1920s (with a crude version of the technology), EEG measures electrical activity generated by the brain's neurons. It's non-invasive, detecting those signals from the surface of the scalp. A modern, highly sensitive EEG typically requires a test subject to wear a cap studded with electrodes which are wired together to form a dense array. Recordings can be made in a matter of minutes.

EEG "readouts" reflect neuronal activation relatively close to the scalp, meaning that billions of neurons of the cerebral cortex are within the reach of its detection. To the layman's eye, a readout from an EEG session looks like a collection of neatly stacked rows of squiggly lines. Each of these rows is registering neuronal activity in a specific "band," with different bands corresponding with different speeds of neural oscillation. These oscillations range from very




EEG "bands" show neural oscillations at different frequencies. Delta waves are slowest; gamma waves are fastest.

EEG differences in children who went on to receive an ASD diagnosis at age 3 were not only detectable but were clearest during the first year of life.

slow (1–3 oscillations per second) to very fast (up to 100 oscillations per second). The different bands are referred to with letters of the Greek alphabet. Delta waves, typically generated during sleep, are the slowest; gamma waves, reflecting brain operations involved in consciousness and perception, are the fastest.

## PREDICTING AUTISM

Brain mechanisms involved in causing autism's symptoms are still poorly understood. Yet certain biological correlates of these mechanisms have come to researchers' attention. One of these is a relationship between differences in brainwaves and autism pathology emerging in the first 3 years of life.

These brainwave differences—revealed by EEG and seen in comparisons of infants who go on to develop autism compared with those who do not—are now thought to be among "the core features of autism spectrum disorder pathophysiology," according to a team led by 2017 Ruane Prize winner **Charles A. Nelson, Ph.D.**, and 2016 BBRF Young Investigator **April R. Levin, M.D.**, both of Harvard Medical School and Boston Children's Hospital.

In a paper appearing in *Nature Communications* in December 2019, the team reported that it had recruited a cohort of 102 infants at high risk—children with one or more older siblings diagnosed with ASD. Such high-risk children are estimated to have a 1 in 5 chance of developing ASD—a rate about 10 times higher than that in the general population. EEG patterns of these children (of whom 31 ended up developing ASD) were compared with one another and with those of 69 children in the study with low familial ASD risk.

EEGs were performed in the study group every few months beginning 3 months after birth and ending in an assessment at 36 months, by which time ASD symptoms are typically apparent and diagnosis in the clinic is possible.

The team discovered that EEG differences in the children who did go on to receive an ASD diagnosis at age 3 were not only detectable but were clearest during the first year of life.

This early-appearing "signal" was seen particularly in slow-oscillation delta waves and in high-oscillation gamma waves. It is good news, Dr. Levin says, that readings during the first year were most predictive of future ASD outcome. It is widely thought that the earlier such children are identified, the better their chances of receiving care that might minimize the impact of the disorder.

Charles A. Nelson, Ph.D.

April R. Levin, M.D.

"What this research told us was that there is a signal in the EEG, in the brainwaves, that is likely to be helpful to predict who is likely to go on to develop autism," Dr. Levin says. "Our goal is to eventually move toward developing some sort of clinically relevant biomarker. The dream is that kids will come in to their 2- or 4-month pediatrician well-child checkup and in addition to getting their vaccines they will also get an EEG or something similar, to look at their risk for autism."

However, Dr. Levin stresses that there is an important ethical question in play. Even if a biomarker predicting a later autism diagnosis is fully validated for clinical use, "you don't want to be diagnosing a disorder early if you're not sure that treatments you have at hand are really going to be effective."

For this reason, she says, "it's really important to recognize that we're not yet at a point where we can make clinical recommendations based on the findings in our paper." Apart from the question of treatments, Dr. Levin adds, the EEG signal needs to be replicated experimentally and optimized, so that it is highly specific to future ASD diagnosis and sensitive enough to minimize the chances of generating false positives and false negatives. She and the team are also working on questions of logistics, she says—how to equip pediatrician offices to provide EEG tests for very young children, and how to implement software that will perform the analysis on-site.

On the research side, Dr. Levin says that she and colleagues are focusing on ways "to learn more from the millions of data points" generated even in a 5-minute EEG. "We're trying to pull out more information from these data points," with the hope of being able to know more about the mechanisms underlying the patterns so far detected, particularly in infants who go on to develop ASD.

## PREDICTING ANTIDEPRESSANT RESPONSE

Researchers using EEG have taken an important step toward objective biology-based markers on which to base depression treatment decisions.

**Amit Etkin, M.D., Ph.D.**, a 2012 BBRF Young Investigator at Stanford University, and **Madhukar Trivedi, M.D.**, a 2002 BBRF Independent Investigator and 1992 Young Investigator at the University of Texas Southwestern, led an international team that identified a brain-wave signature which enabled them to "robustly predict" whether depression patients would respond or fail to respond to the antidepressant sertraline (Zoloft).

The signature also enabled them to compare and distinguish "responders" to sertraline with other patients who responded to a different form of antidepressant therapy, the non-invasive brain stimulation method called repetitive transcranial magnetic stimulation (rTMS).

The team used a resting-state EEG, which measures brain waves while an individual is not engaged in a particular task. The signature they identified was discovered with help from a computer-driven machine-learning program called SELSER. The team's dataset was derived from four separate studies.

Multiple data sets enabled the team to develop a theory of what their EEG signature in "responders" to sertraline signified about activity in the brain. In a 2020 paper published in *Nature Biotechnology*, they proposed that better response to the drug correlates with greater excitability in the prefrontal cortex, compared with that in poor responders.

Amit Etkin, M.D., Ph.D.

Madhukar Trivedi, M.D.

Drs. Etkin, Trivedi and colleagues also made an intriguing observation about responders to sertraline vs. responders to rTMS brain stimulation treatments. Here they saw an inverse correlation: individuals who responded to one of the two rTMS protocols that were tested were less likely to be sertraline responders, and vice-versa.

An important question still to be answered about the potentially predictive EEG signature is whether it is specific to sertraline, or to the larger class of SSRI antidepressant medicines that includes sertraline, or if it has even broader applicability in predicting responses to other antidepressant therapies including electroconvulsive therapy (ECT) and psychotherapy. Dr. Etkin says he and colleagues are currently engaged in studies designed to answer such questions.

The research team also included: **Maurizio Fava, M.D.**, 1994 BBRF Young Investigator; **Myrna Weissman, Ph.D.**, BBRF Scientific Council member, three-time BBRF grantee, 2020 Pardes Prize winner and 1994 Selo Prize winner; **Patrick McGrath, M.D.**, 2002 BBRF Independent Investigator; **Thilo Deckersbach, Ph.D.**, 2004 and 2001 BBRF Young Investigator; and **Gregory Fonzo, Ph.D.**, 2019 BBRF Young Investigator.

## PREDICTING PSYCHOSIS

Predicting which individuals considered to be at high risk of developing psychosis will in fact go on to develop psychosis—thus potentially making early or preventive treatment possible—has long been among the objectives of neuropsychiatric research. The challenge is this: only a minority of individuals at clinical high risk will develop psychosis within 4 years. (A recently published analysis put the figure at 22%.) Can they be identified in advance?

High-risk individuals include those with a family history of psychotic disorder, since a significant portion of the risk is thought to be genetic. Other factors include the appearance of what doctors call "sub-threshold symptoms," which may include brief episodes of distorted thinking, paranoia, delusions, or hallucinations. High-risk individuals may also experience a decline in their ability to function socially.

**Peter J. Uhlhaas, Ph.D.**, of Charité Universitätsmedizin, Berlin, Germany, used his 2009 BBRF Young Investigator grant to explore the hypothesis that imprecise timing of neural activity—potentially detectable in brainwave signatures—is among the core aspects of schizophrenia pathophysiology. In a 2020 paper published in *JAMA Psychiatry*, Dr. Uhlhaas, with co-authors including 2009 BBRF Distinguished Investigator **Stephen Lawrie, M.D.**, reported that the timing of high-frequency oscillations in visual cortices of the brain "is the first impairment to emerge" in individuals at clinical high risk of first-episode psychosis, and that other features of brainwave oscillations may predict future clinical course.

The team recruited 232 participants, most of them in their late teens or twenties: 119 met criteria for being at clinical high risk (CHR) of psychosis; 38 did not meet these criteria but had been diagnosed with non-psychotic psychiatric disorders; 26 had experienced first-episode psychosis (FEP); and 49 were healthy controls. All were regularly evaluated over a 3-year period. And all were given, at baseline, a task to perform on a computer which required them to press a button in response to visual stimuli on the screen that varied in duration from ¾ of a second to 3 seconds.


Peter J. Uhlhaas, Ph.D.

While participants performed 3 blocks of 80 such tests, their brainwaves were monitored using magnetoencephalography (MEG), which records magnetic activity of the brain (as distinguished from EEG, which measures electrical activity). MEG, which like EEG is non-invasive, is performed by placing a magnetic coil just above the test subject's head. MEG is better than EEG in identifying locations in the brain where the waves it detects are generated.

Results of the trial, published in *JAMA Psychiatry* in April 2020, corroborated past research highlighting the importance of the visual cortex in cognitive processing in the healthy brain—and offering new evidence suggesting how specific aberrations in brain waves generated by neural activity in the visual cortex relate to cognitive deficits seen in FEP, schizophrenia, as well as, in certain respects, in those at high risk of developing FEP.

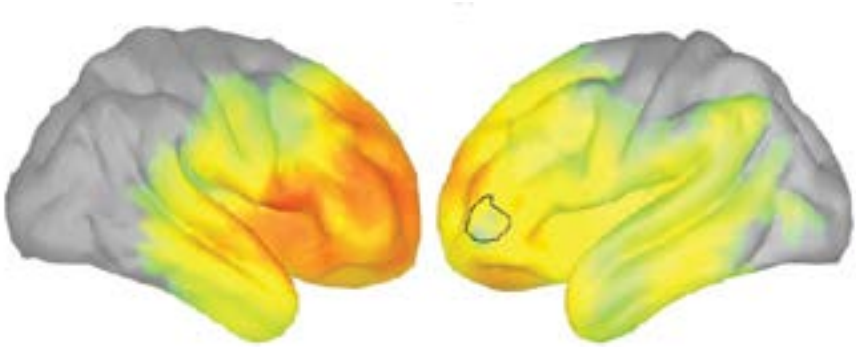
The team demonstrated that in both FEP and those at high risk for it, the "synchrony" of waveforms generated in the

visual cortex in two high-frequency bands—gamma waves (up to 100 oscillations per second) and beta waves (up to 40 oscillations per second)—was notably inconsistent. Importantly, this new research shows that such inconsistencies are present in people with pre-psychosis symptoms.

The research also revealed that in both FEP participants and those at high risk of psychosis, connectivity between the frontal portion of the brain and occipital areas containing the visual cortex was impaired; and that in contrast to participants at high-risk, those who already had a first psychotic episode displayed reduced power in high-frequency gamma waves emanating from the occipital lobe.

Yet another important finding from the research was the observation that those at high risk for psychosis who had displayed increased variability of certain waveform patterns between different "runs" in the visual processing test went on to have more persistent "sub-threshold" symptoms of psychosis—an indication that they would have poorer clinical courses and increased likelihood of progressing to a first psychotic episode and perhaps also schizophrenia.

"Impaired high-frequency oscillations in the visual cortex are an important aspect of circuit dysfunction, which could constitute a biomarker for clinical staging of emerging psychosis," Dr. Uhlhaas and colleagues concluded. Their future research will focus on circuit mechanisms regulating neural responses, "which may offer targets for preventive approaches."



Dr. Etkin's team used EEG to confirm below-normal connectivity (hypoconnectivity) in combat vets with PTSD, concentrated in the frontal cortex (here, the left orbital gyrus).

## PROBING PTSD

Pioneering research in recent years has suggested linkages between the presence of PTSD symptoms and specific changes in brain connectivity. Stanford University's **Amit Etkin, M.D., Ph.D.**, in addition to his research described above in using EEG to predict antidepressant response, has sought to translate fMRI imaging-based insights on changes in brain connectivity in PTSD patients to a technology that would be easier to use in the clinic, where it might help combat vets and others with the disorder. The results of their latest research appeared last year in the *American Journal of Psychiatry*.

Dr. Etkin and colleagues first tested their EEG-based technological package on 36 healthy subjects, demonstrating its ability to make fine distinctions in brain connectivity across different brain regions. The team's solution was based upon resting-state EEG brain-wave readings made when the brain is not engaged with a specific cognitive task.

This preliminary test enabled them to piece together a fine-grained "connectomic profile" of brain regions implicated in PTSD—a portrait of how different regions connect with one another. The key question was whether this method would enable the team to see changes in connections that fMRI studies have suggested may be occurring in PTSD. Assuming they were able to do so, the team also wanted to try to relate such connectivity changes with actual symptoms experienced by combat vets with PTSD.

Dr. Etkin's team next tested their EEG-based method in a group of 201 veterans who had been deployed to Iraq and Afghanistan: 95 were healthy controls without PTSD, while 106 met full or "sub-threshold" criteria for PTSD. Most were men.

The trial revealed 74 brain region connections that were "significantly reduced" in PTSD. The most prominent area of under-connectivity was in a large section of the frontal lobe called the middle frontal gyrus. This underconnectivity was seen in slow-moving theta waves. Such slow waves are associated with memory, emotion, and sensation. These findings were consistent with findings made in prior fMRI studies.

The team was also able to correlate the observed under-connectivity changes with symptoms in patients, involving working memory and inhibition.

The team, which is currently engaged in studies extending the work, hopes that validation of the EEG-based method of analyzing brain connectivity in PTSD patients might support clinical efforts to develop more targeted and effective treatments. These could include non-invasive brain stimulation technology (such as repetitive transcranial magnetic stimulation, or rTMS) to target specific brain areas to boost connectivity where it is reduced—it is hoped, with therapeutic impact.

## INSIGHTS ON SCHIZOPHRENIA

A research team led by **Gregory A. Light, Ph.D.**, a 2013 BBRF Independent Investigator and 2006 and 2003 Young Investigator at the University of California, San Diego, early this year reported using resting-state EEG to measure brain waves across a broad spectrum of frequencies in 139 schizophrenia patients and in 126 unaffected people who served as controls.

Their results, published in *Frontiers in Psychiatry*, identified widespread patterns of hyperconnectivity in schizophrenia patients compared with controls, in networks that involved the frontal, temporal, and occipital regions of the brain.

Gregory A. Light, Ph.D.

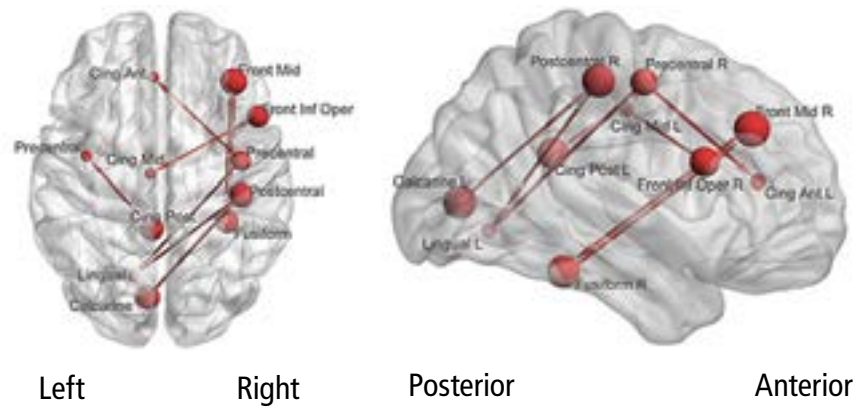
Specifically, the team identified two primary abnormalities in resting-state networks. Among the potential implications of these results, Dr. Light and colleagues noted, were that "patients may show abnormal excessive simultaneous activation of various perception-related brain regions." This abnormal activation, they said, "may ultimately contribute to clinical symptoms such as hallucinations and delusions" as well as problems assessing the salience, or relative importance, of incoming sensory information.

The researchers hope to confirm the observed brain-wave patterns and relate them to specific pathological processes in schizophrenia. Among other things, they said, it would be important to study whether the observed EEG patterns can also be seen in high-risk individuals prior to disease onset, as well as in those who have recently experienced a first episode of psychosis.

If validated in future studies, the team said, the resting-state EEG patterns they detected might be useful as biomarkers for schizophrenia.

The team also included **David L. Braff, Ph.D.**, 2014 BBRF Lieber Prize winner and 2007 BBRF Distinguished Investigator; and **Yash Joshi, Ph.D.**, a 2018 BBRF Young Investigator.

❖ **PETER TARR**




Dr. Light's team found widespread evidence of above-normal connectivity (hyperconnectivity) in schizophrenia patients compared with controls, in networks that involved the brain's frontal, temporal, and occipital regions. In resting-state EEGs, some of these are displayed in the gamma band, measuring the most rapid neural oscillations.

# Studying Ketamine's Rapid Effects to Unlock Secrets for Developing Better Antidepressants

Lisa M. Monteggia, Ph.D.


## Lisa M. Monteggia, Ph.D.

*Professor of Pharmacology, Vanderbilt University*
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Member, BBRF Scientific Council
2014 BBRF Distinguished Investigator
2010 BBRF Independent Investigator
2005 BBRF Freedman Prize for Exceptional Basic Research
2003, 2001 BBRF Young Investigator

# A RESEARCHER'S PERSPECTIVE

*This text is adapted from a recent presentation Dr. Monteggia made to BBRF donors.*

When you hear the word depression, everybody has an idea of what it means. A sad painting can make you feel unhappy or depressed. You can hear a sad song, or maybe you have had unhappy emotions—people talk about "feeling depressed." Depression is a serious mental illness and it's characterized by symptoms including anxiety, loss of pleasure, loss of appetite, sleep disturbances, and feelings of worthlessness, among others. There are a range of symptoms, which reflects the complexity of the disorder.

If you have 100 depressed people in a room, each could have somewhat different symptoms, even though they are all depressed. For a scientist to examine depression and try to really understand what causes it, that's one of the major challenges with researching the illness.

Depression is now the leading cause of disability in the world, according to the World Health Organization. People are surprised by that—they think first of cancer or heart disease. Depression is a disease that can impact not only you, but your family, for decades. Thankfully there are medications to help treat the illness. Conventional antidepressants such as the SSRI and SNRI medicines (Prozac, Lexapro, Effexor, Paxil, etc.) have changed the course of this disease in many ways. These antidepressants work for many patients, typically taking a couple of weeks to several months to have an effect. Unfortunately, a large number of patients, 30% or more, are not helped by antidepressant medicines.

But the fact is: those individuals who don't respond to antidepressants are often the ones most at risk for suicide. And if you look at the statistics on suicide, they're staggering. The latest estimates put the number of suicides in the U.S. at over 44,000 per year, which is beyond tragic. Compare that number with the number of homicides over the past year, around 16,000. You have more than two and a half times the number of suicides to homicides, yet you rarely hear people talk about suicide.

Ten years ago the number of suicides in the U.S. was around 30,000. So we've seen a huge jump. The number of annual homicides over the last decade, in contrast, has remained quite stable. There's been a lot of discussion of as to why there is this disparity. The reasons are being debated. But whatever the reasons are, the growing number of suicides highlights the need for better and faster-acting treatments for depression, including treatment-resistant depression.

## HOW DO ANTIDEPRESSANTS WORK?

Beginning with the first grant that I received from BBRF, my team and I have focused on asking "How do antidepressants work?" We've all seen the commercials for these medicines on TV. They draw a neuron and they show it releasing serotonin—the neurotransmitter—and then they say, "There's less serotonin in depression and if you take an antidepressant, now you have more serotonin and you feel better." But the reality of it is, there's very little data showing that less serotonin is what causes depression. Moreover, while typical antidepressants may increase serotonin, they do that very quickly, yet antidepressants take weeks before you feel better. So while the serotonin surge is important, you don't have this immediate antidepressant effect. This leads us to conclude that other things have to happen.

My lab was able to identify an important component of neuronal signaling, and a particular growth factor called BDNF (brain-derived neurotrophic factor) that appears to be required for an antidepressant response. A variant of the gene that directs cells to make BDNF contains a DNA "spelling" error that can change the activity of both the gene and the BDNF protein it encodes. Some studies have suggested that individuals who have this genetic variant may have an attenuated response to antidepressants.

As we were studying this question, research was published indicating that the anesthetic drug ketamine, when given at a sub-anesthetic dose, can have rapid antidepressant effects. Ketamine has been around for a long time. At moderate doses it can be a drug of abuse; it has many street names including "Special K."

What has been recently discovered is that at a very low dose, one that isn't going to induce anesthesia or trigger psychosis, ketamine can be effective in refractory depression patients, some of whom are among those most at risk for suicide. Refractory depression refers to situations in which patients are not helped by one or more standard courses of approved antidepressant therapies.

Ketamine, when tested experimentally in individuals with depression, is administered at sub-anesthetic doses, intravenously, under controlled conditions.

**"It's all about trying to develop better and faster treatments, treatments that can be maintained—things that are so important in view of the immense toll that depression takes on our society."**

With ketamine, the drug is infused intravenously in a clinical setting over 40 minutes. Patients can stabilize very quickly and they actually experience an antidepressant effect, sometimes as rapidly as within 30 minutes. If a patient doesn't start to experience a beneficial effect within 2 hours, then ketamine is probably not going to be effective for them.

What's remarkable is that a single infusion can have effects on some patients for several days to a week, and sometimes longer. It's not because the drug is staying around in your body—it isn't. So it's doing something in your brain to produce these lasting effects.

We became very interested in studying this drug. We want to use it as sort of a Rosetta Stone, if you will, for two important reasons. First, it may help us understand the mechanism behind how antidepressants work—a mechanism we've never seen previously. Second, ketamine is well characterized to have effects on a particular protein in the brain called the NMDA receptor. It's a receptor on certain neurons and ketamine appears to block its activity.

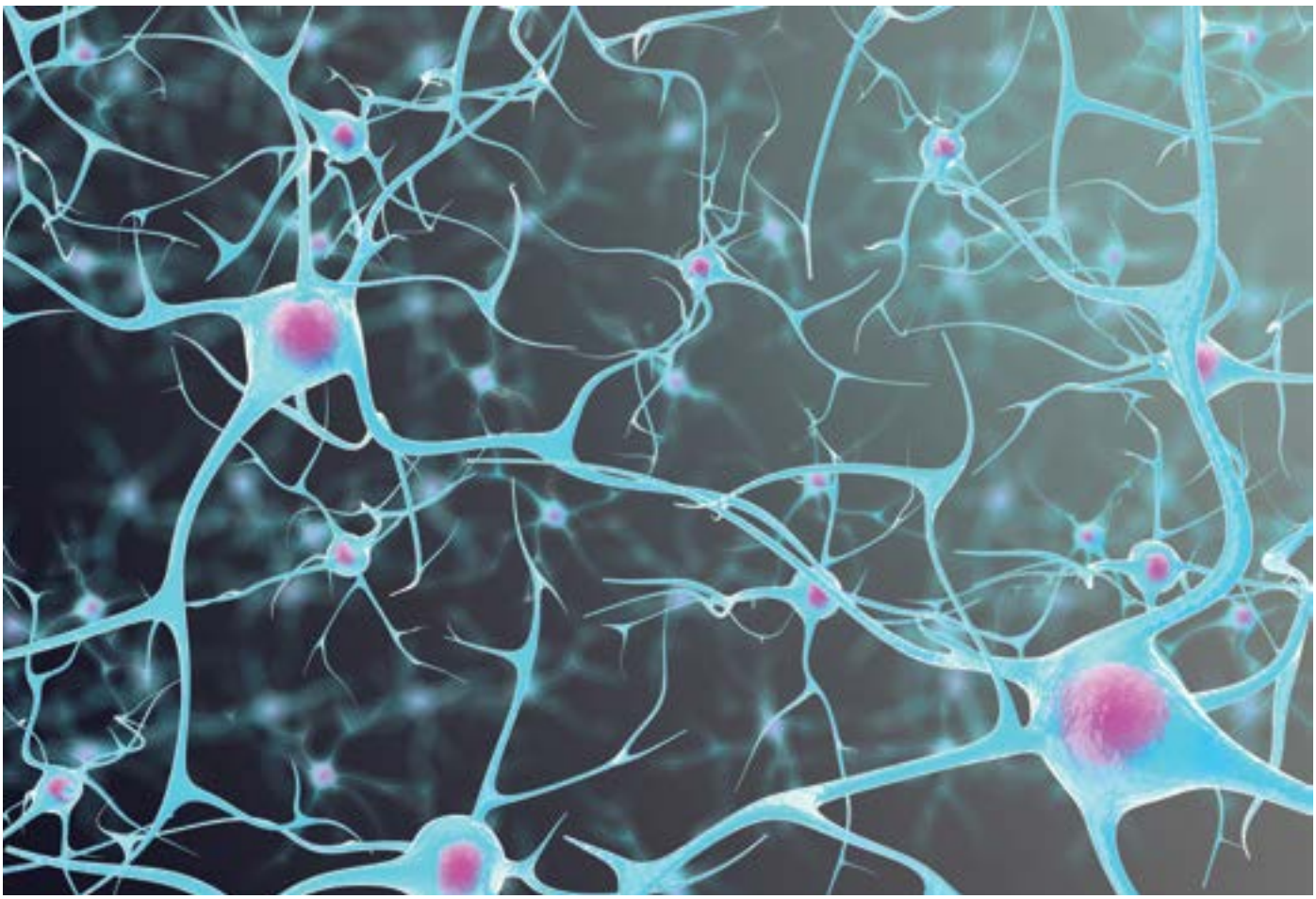
Could we show that by blocking this receptor, ketamine is triggering an antidepressant effect? And if we could do that, could we think of ways of manipulating this pathway to reduce potential side-effects that can occur with ketamine? (Ketamine can have side-effects, such as dissociation—a very uncomfortable "out-of-body" feeling. It is also potentially addictive.)

On the question of "How does ketamine work?" our data shows that it really does block the NMDA receptor, and that it has very specific effects on a particular signaling pathway. If we experimentally interfere in that signaling pathway, ketamine doesn't produce an antidepressant effect, at least in experiments we've conducted in animals.

## A NOVEL FORM OF PLASTICITY

Perhaps more surprising, we were able to show that ketamine, by blocking the NMDA receptor and affecting signaling, triggers a novel form of plasticity in the brain. Plasticity is the ability of neurons to alter the strength of their connections. Ketamine appears to affect plasticity in a new and unexpected way. We've tested drugs similar to ketamine that have been tried clinically, like memantine, which also blocks the NMDA receptor, and found that memantine does it slightly differently. And we can show that memantine does not have the same effect on signaling and that it doesn't trigger this novel plasticity. We only see this plasticity with the rapid antidepressant action. What we think may be happening is that this type of plasticity may be a common mechanism in how antidepressants work— but whether this plasticity is actually "fixing" depression, we're not yet able to say.

While ketamine is probably having many different effects on the brain, not all of them are responsible for its antidepressant effects. We think that ketamine is having effects on a region of the brain called the hippocampus. Our idea is that antidepressants in general, not only ketamine but typical antidepressants also, are initiating plasticity processes in the hippocampus that then impact the prefrontal cortex and other brain regions. So in studying how ketamine triggers a rapid antidepressant effect, we hope



Changes in plasticity—the strength of connections between neurons—are likely crucial in depression and in treatments that relieve it.

to backtrack and use that knowledge to understand how conventional antidepressants work.

We've been able to show, then, that blocking NMDA receptors induces a novel form of plasticity. We think it's a form of what we call "homeostatic" plasticity. A different form of plasticity than the type involved in learning, for example. What we think may be happening is that this type of plasticity may be a common mechanism in how antidepressants work. But whether this plasticity is actually fixing depression, we're not sure. We'll see—but these are the focus of ongoing experiments right now.

If we can understand, "What is this plasticity doing in your brain? Why is it important?" then we can think about administering other drugs that trigger this kind of plasticity and perhaps find other ways to generate antidepressant effects.

One reason this is important is that even among individuals who are given ketamine, about 20% to 30% don't respond. Why not? Well, if you can identify other ways to trigger antidepressant effects, we might be able to develop a treatment option for these non-responders. Similarly, it may be, that the 30% to 50% of individuals who don't respond to conventional antidepressants may have a variation or a deficit in a gene somewhere along the pathway in which conventional antidepressants need to exert their therapeutic action. Maybe this is why such people don't respond to

conventional SSRI antidepressants. It's not necessarily one mutation; it could affect proteins anywhere along the pathway.

In other words: our goal is to see if we can find other ways to trigger an antidepressant effect, and then, try to parse out who can respond to different types of antidepressants. That would be the ultimate goal. But right now what we're trying to do is understand how ketamine triggers a rapid antidepressant effect, as well as trying to understand how it's sustained. If, as we have shown, ketamine triggers a novel form of plasticity, what is this plasticity doing to the brain? Why are we only seeing it with a drug that produces a rapid antidepressant effect?

Also, we have seen clinically that if you give a second dose of ketamine, individuals seem to have a cumulative effect—that if you give the second dose, the novel plasticity that we see is even further enhanced. We're trying to understand why. How is this really working and can we target this to maintain an antidepressant effect?

## THE IMPORTANCE OF BASIC RESEARCH

We're starting to understand why people respond and why they don't to conventional antidepressants and to rapid-acting ones like ketamine. It's all about trying to develop better treatments, faster treatments, treatments that can be maintained—things we all regard as extremely important, in view of the immense toll that depression takes on our society.

This is the power of basic research. We're seeing it play out right now in this time of COVID. Development of the vaccines was phenomenal, but it wasn't a matter of people just going into a lab and emerging a few weeks later with vaccines that work. That research, like ours, has been built on decades of basic research. Great advances don't come from out of nowhere. And in our work on the brain, there's a level of complexity that is unique; we have much yet to discover. People worry about having a heart attack. The reality is, if you have a heart attack, you get to a hospital and there's a lot they can do for you in terms of treatments and saving your life. A great deal is known about the heart. But with the brain, so little is known, still.

We're getting to piece things together and with the help of new technologies things are moving quickly. Our advances over the past decade have been remarkable. I think the future looks really bright. We're continuing to build on what we have learned. This is going to be important for depression. And lately, as we've seen in our work on bipolar disorder, it's interesting: with some of the drugs that help patients, such as lithium, we're seeing them elicit a novel form of plasticity, as well. It's slightly different than what we see with an antidepressant effect, but again, there are plasticity mechanisms that are engaged, which we're trying to understand. Perhaps this approach could also have implications for understanding schizophrenia; we don't yet know.

My take-home point is about the importance of basic research for discovery—discovery that may not come today, but which is the basis for advances in treatments. Even though we may not be where we want to be right now with disorders of brain and behavior, our progress provides a real source of hope. ❖

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

—Ken Harrison, Board Member

To learn more, please contact us at **646-681-4889** or **plannedgiving@bbrfoundation.org**

# Diagnosing and Treating Bipolar Disorder

## Q&A with David J. Miklowitz, Ph.D.

*University of California, Los Angeles*

2011 BBRF Colvin Prize for Outstanding Achievement in Mood Disorder Research
2001 BBRF Distinguished Investigator Grant
1987 BBRF Young Investigator Grant

*Dr. Miklowitz is Distinguished Professor of Psychiatry in the Division of Child and Adolescent Psychiatry at the UCLA Semel Institute, and Visiting Professor in the Department of Psychiatry at Oxford University. He is widely respected for his research focusing on family environmental factors and family psychoeducational treatments for adult-onset and childhood-onset bipolar disorder. In addition to his BBRF grants, Dr. Miklowitz has received research grants from the National Institute of Mental Health, the MacArthur Foundation, and the American Foundation for Suicide Prevention, among others. He has published over 300 research articles and 8 books, including* The Bipolar Disorder Survival Guide: What You and You Family Need to Know*, now in its 3rd edition.*

**Dr. Miklowitz, you have decades of experience in treating patients of all ages with bipolar disorder. Since the illness manifests in a variety of ways, can you go step by step and explain how bipolar disorder is properly defined, and how you recognize it when it occurs?**

In most cases, it is a disorder in which a person cycles between depression and mania. Most people understand what depression is. Depression is characterized by sadness, fatigue, suicidal ideation, sleep disruptions and a loss of interest in things. But some people may not understand precisely what we mean by mania. Mania is a period of a week or longer where someone is feeling "on top of the world"—euphoric, or, extremely irritable. There's a change in behavior, which can be marked by increased spending and impulsiveness, hypersexuality, risk-taking, things that could get someone in trouble with the police. And there's a change in thinking patterns, where one's thoughts go extremely fast and one speaks extremely fast, jumping from topic to topic. There are grandiose ideas (such as "I'm smarter than everyone else") or even full delusions of grandeur, such as believing one has special powers.

Mania tends to last at least a week and may be preceded by a buildup period that we call the "prodrome." Some people, however, don't get all the way out to mania. Instead, they get to a condition we call hypomania, which generally doesn't last as long (we require a four-day minimum). Hypomania involves the same symptoms as mania, but there's no apparent deterioration in functioning, whereas in mania, the person really does deteriorate. They lose their job, or they get arrested or break off relationships left and right. With hypomania, people around the person may notice the symptoms, and says things like, "Gee, you're wired today." The person with hypomania may or may not recognize it, but it doesn't necessarily change their day-to-day functioning.

**To be clear, you are saying that bipolar disorder involves both depression and mania—a cycling between them, or, in other cases, people who periodically have depression and at one or more times in life have also experienced a manic episode.**

Technically, "bipolar 1 disorder" means you've had one manic episode. You need not have experienced depression at this point, but most people have. More generally, in bipolar 1, you have major depressions and full manias. In "bipolar 2 disorder" you have major depressions and hypomanias. That's the key distinction.

On average, people with bipolar 1 spend three times as much time in depression as they do in mania. You can also have a "mixed episode," with both depression and mania at the same time. I've heard it described as the "tired-but-wired" feeling: thoughts going fast, mind full of "great ideas," and unable to sleep. During mania, people don't feel like they need sleep, whereas during depression, they can be sleeping all the time. In mixed episodes, they might have insomnia, rapid thinking, rapid speech, and increases in activity while also being suicidal and depressed.

**Are there some people who just have mania and never get depressed?**

There are, and they tend to have recurrent manic episodes. It's rare to have one manic episode and never have either a depression or mania after that. Most people who have unipolar mania tend to be men. When they crash, they don't crash down into full depression; they come down to some level close to normality or maybe just a milder depression. But more often what you see are people who periodically get hypomanias in between episodes of mania.

**There are so many ways in which bipolar disorder manifests itself. Between periods of mania and depression, or intervals of depression, isn't there a sort of a maintenance period where patients go to a "baseline" of feeling as though they're on an even-keel? Is that the way it goes?**

Yes. Now, there's a fair amount of debate about what being "even-keel" means because some people really do return to normality, and they're indistinguishable from you or me when they're feeling fine. But a lot of people with bipolar disorder return to a sort of low-grade depression that may not be noticeable to anybody but themselves. The low-level depression may make it hard to hold a job or maintain relationships.

**Let's talk about what to look for. First, what is the typical age of onset?**

The average age of onset is 18. But the range is anywhere from very young—i.e., children—to those who don't have their first episode until their 50s. One thing that is interesting is the average age of onset is getting younger with

Bipolar depression is characterized by sadness, fatigue, suicidal ideation, sleep disruptions, and a loss of interest in things.

successive generations. We used to think the average age of onset was about 25-28. Now, it's thought to be the late teens.

**On average I understand there is a lengthy delay between the first "prodromal" symptoms and the actual bipolar diagnosis. Why does that happen?**

In many cases, it can be 8 to 10 years. What often happens is that the first episode is a depression. Either the depression doesn't get treated or it's attributed to a normal reaction to "life events." In such people who are eventually discovered to have bipolar disorder, it isn't until they have their mania that the full diagnosis is recognized. A typical scenario might be: a teenage girl at age 14, right around the time of puberty, has a first major depression. Her pediatrician says, "Well it's probably a hormonal thing, or it's because she broke up with her boyfriend." It passes, and nobody thinks about it until she gets into college and has her first manic episode. In that case there's a 4-year gap.

In other cases, depression is longstanding, and may go on throughout the teen years and early adulthood. Then, when the person first tries taking an antidepressant, they get hypomanic, manic, or develop rapid cycling (frequent alterations between depressive and manic states). Bipolar disorder often goes unnoticed. There are people who have "cyclothymic patterns," in which their mood swings a lot, and people just think they're moody.

Another thing to think about is comorbidities. One of the reasons it takes so long to come up with the right diagnosis is often that the young person presents with ADHD, which can mask bipolar disorder or be comorbid with it.

**In view of bipolar's many manifestations, this raises an obvious question, especially for parents. When do they know if their child is "just being a teenager"? How do you know when to be worried?**

In bipolar disorder, it comes down to a question of degree and amount of impairment. First: is there only one symptom of mania? Or, are we talking about a cluster of symptoms of mania? A typical teenager will have rage once in a while or do something very impulsive. Or they will sexually experiment or do drugs. All those things are within the realm of typical teenage behavior. But when you combine impulsiveness with irritability, not sleeping, grandiose thoughts, and functional impairment, then you're into the bipolar realm.

I think impairment is really the big thing to consider. Lots of teenagers will wake up in the morning, and they'll say, "I'm too depressed to go to school," but they drag themselves out of bed. They go. By afternoon, they're okay, compared to the bipolar kid who honestly can't get out of bed. They feel like there's this 100-pound weight on them. It feels like they can't move.

Diagnosing depression in a teenager is tricky. We can't really tell what is a major depression of the unipolar type versus a bipolar depression—they can both be severe and the symptoms can be similar. So, we have to consider the severity of depressive symptoms, whether they ultimately prove to be the result of unipolar or bipolar depression. Is it so severe that they can't go to school, and they can't do their sports, or they don't want to play their music? And does it go on for weeks at a time?

The manic phase of bipolar disorder is a period of a week or longer when someone is feeling "on top of the world"—euphoric, or, extremely irritable. Changes in behavior include increased spending and impulsiveness, hypersexuality, and risk-taking.

That's very different from the kind of blues that teenagers have when they have a setback or obstacle in the usual course of things. Severe depression with impairment should be a trigger for concerned parents to seek professional advice.

And also, we must consider context. If a kid is giddy and silly when they're around their friends, that makes sense. But a bipolar kid will be laughing hysterically in church, or at a more serious gathering, or in the middle of class.

**When you have a teenager who is clearly depressed in a non-trivial way, it makes perfect sense to treat them as if they have some form of depression, I would imagine. But if I hear you correctly, it could turn out that that's the depressive phase of bipolar disorder. Would treating them with antidepressants pose any sort of risk?**

They can pose a risk, but it's not inevitable. Parents should get a full evaluation of the child, which includes a family history of mood disorders. If a kid has a family history of bipolar disorder, and she's depressed, that increases the probability she will go on to have a manic or hypomanic reaction to antidepressants. It doesn't mean she will, because we also know that depression and bipolar disorder can run in the same families. So, you might have a bipolar parent and only develop unipolar depression yourself, i.e., depression with no mania or hypomania. But it's one of those things where you have to rule out bipolar as the likely cause of a depression.

What some doctors will do if there's severe depression and a family history of mania is that they will start the patient on a mood stabilizer and an antidepressant together. If the parents and kid don't like this idea, and just want to try antidepressants, they should be informed of what the signs of mania look like. That way, they'll be able to catch it earlier if it does occur.

**What are the signs to suggest that it's not "just" depression?**

There are a couple of ways to tell. One is that bipolar depression might have a few mixed features with it. A typical scenario would be someone is depressed but their mind is going a mile a minute, and they're ruminating over things. There's a sort of frantic quality to it. Or the adolescent might come up with elaborate ways to commit suicide. They're getting online and making lists and calling numerous people for help.

In kids, one predictor of developing bipolar disorder—especially if they also have a family history of mania—is "mood instability," the tendency to change moods all of a sudden. Parents describe that the kid has a "hair trigger" for getting angry, or will be laughing one moment and crying the next.

Depression of the bipolar type tends to occur at a younger age (e.g., 11) than depression of the unipolar type (e.g., 14-15). If a parent has bipolar disorder and also developed it at a young age, that indicates a greater likelihood in the child. Another thing to notice is if there is any psychosis. If the kid has delusions that their body is rotting, or they're responsible for something that happened in a faraway place, that's more likely to be a sign of bipolarity.

**Would you recommend that a concerned parent have their child take the Mood Disorder Questionnaire, which is posted online?**

You can, but the problem is that it has a lot of false positives, meaning it can look from the results like you're bipolar when you're not. I wouldn't rely on it as a diagnostic instrument. I think it might be a way of deciding whether you should get a full psychiatric evaluation. If a kid's depressed, and they fill out that questionnaire, and it comes up positive, that's a sign that you need to get an evaluation.

**Where should parents take their child for a serious evaluation? If they're urban or live close to an urban area, where should they go? A university hospital? What about people not near cities?**

There is a huge difference between urban and rural settings. If you're in Los Angeles or New York, you can always find a bipolar specialist. We have a childhood mood disorder program at UCLA. New York has a bipolar family center at Beth Israel Hospital. If not, you have to go with whoever the local psychiatrist is, and that person may or may not know bipolar disorder. The one good thing that's come out of the pandemic is that we're all doing telehealth now. Presumably, you could get on the phone with a bipolar specialist at a university depression center anywhere. But these evaluations with specialists can be quite expensive.

**The aspect of suicide risk in this diagnosis is considerable, is it not?**

It is. I hear estimates of anywhere from 15 to 30 times the population base-rate of suicide. When people are so depressed that they can't move, that actually poses a lower risk than when they're depressed and agitated and anxious. A mixed episode is a very high-risk factor.

**It's been well demonstrated that the mood-stabilizing medicine lithium reduces suicide risk. But people looking at 20-year trends in outpatient treatment see lithium is less likely to be given as the first-line treatment. Today, someone in outpatient treatment would be more likely to be prescribed an atypical antipsychotic medicine and/or an SSRI antidepressant, correct?**

Dr. Miklowitz is a pioneer in using Family-Focused Therapy (the kind of session pictured here) to improve outcomes in bipolar disorder. One aspect, communication training, involves teaching kids and family members how to talk to each other, how to listen, and how to ask people to change behavior.

That is true. I think it's because of two reasons. I still think it's the best medication we have for bipolar disorder, but it has a tougher side-effect profile than other mood stabilizers or antidepressants. For some it also has a stigma associated with it. Everyone has heard of lithium but not everyone has heard of risperidone or lamotrigine or valproate. Lithium has side effects like acne, weight gain, and jitteriness of the hands. But it's got an anti-suicidal effect, more pronounced than other medicines.

If somebody is suicidal and has bipolar disorder, I would say lithium is the first choice.

**We know that people with a bipolar diagnosis usually get a medication, whether it's an anticonvulsant, a mood stabilizer, an antidepressant, or a combination of these. But you've discovered and demonstrated in your research that you can get much better outcomes and more adherence to medications if you combine medication with family-focused therapy. Can you tell us about how you came upon this discovery?**

I have a background in schizophrenia research. When I was getting my degree, there was a lot of interest in family treatment. There was this finding that if you combined antipsychotic medications with family education and skill training, patients did better over time. I was interested in trying to extend that model to bipolar disorder. I was running support groups at the time for bipolar patients. And a lot of them said that their episodes were set off by family conflicts and poor boundaries with family members. The first study I did was on "expressed emotion," which in the family setting takes the form of criticism and hostility and over-protectiveness in parents. When parents are highly reactive to the kid (or young adult) and get set off easily by their kid's behavior, that creates an environment where the kid has a tougher time recovering and staying well. What we did basically was to say, "Okay, let's take family education and skill-building and see if we can modify communication patterns after an illness episode when all these sparks are flying." And that's how Family-Focused Therapy came about.

**"If you go from the night shift to the day shift on a job, or stay up all night studying for an exam, those changes can be triggers for a manic episode. When you anticipate having to make these changes, you've got to adjust your sleep cycles accordingly."**

**Walk us through how the therapy happens.**

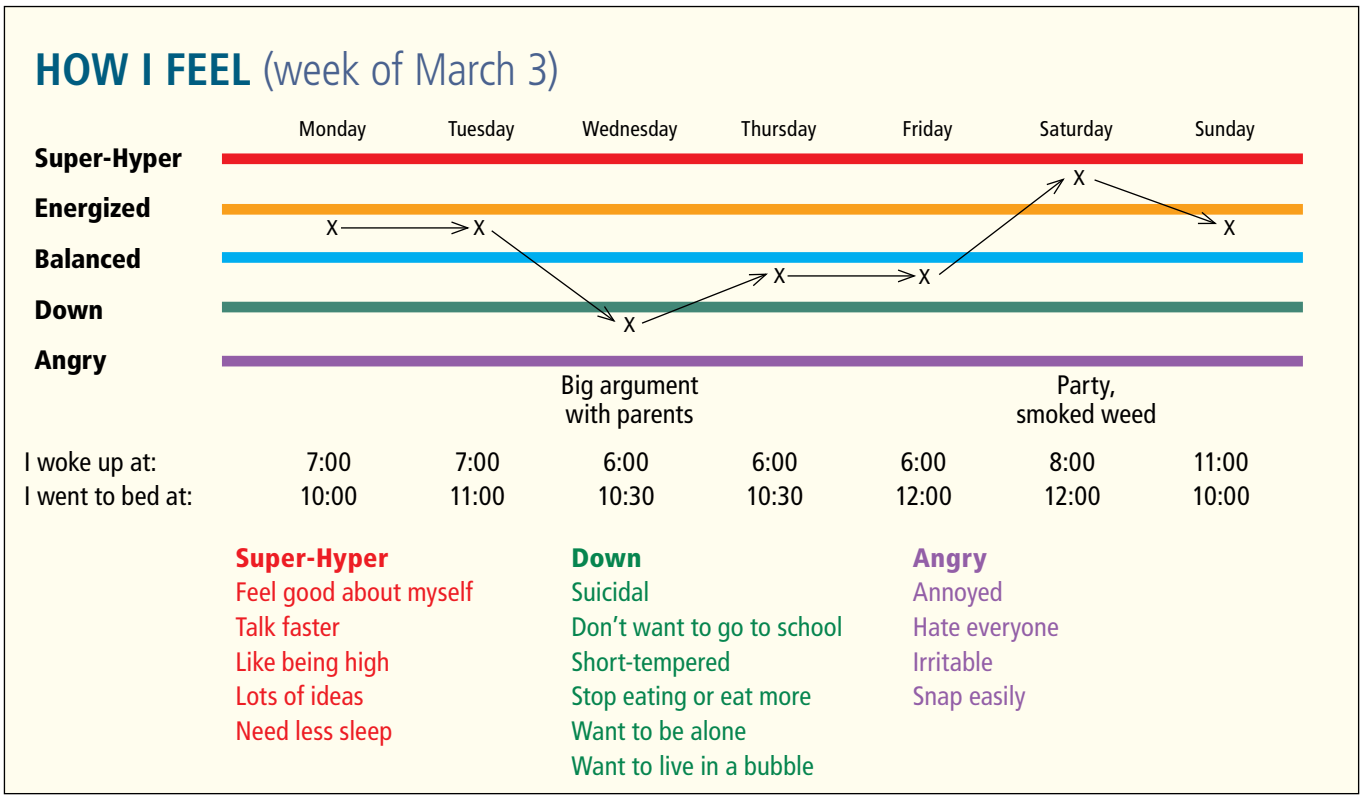
Today, this kind of therapy happens in 12 sessions over 4 months and involves three things: psychoeducation for the family on how to cope with bipolar disorder; communication training; and problem-solving training.

In the first couple of sessions, we teach the family about what a mood disorder is, what does it mean for moods to cycle, and what are the early warning signs of a new episode. The kid's experience of mood cycling takes center stage. Then we talk about what you can do as a family when you spot the early signs—things like calling the doctor and getting a change in medications, encouraging regularity of sleep-wake cycles, keeping family intensity to a minimum, and lowering expectations during those times. The idea is for families to have a plan for when the kid shows a deterioration in mood or an increase in manic symptoms. That's psychoeducation.

The second aspect, communication training, involves teaching kids and family members how to talk to each other, how to listen, and how to ask people to change their behavior. It's a little bit like what's done in marital therapy when you're training people how to be empathic, how to validate, how to listen, and how to keep the environment cohesive.

The third part of the therapy is providing problem-solving techniques for conflicts the family has not been able to resolve on their own (such as those around medications, schoolwork, or household tasks). And we teach them a structured way of breaking a problem down and solving it.

Families feel like they have a better understanding of the illness at the end of treatment. And patients feel like their family is more of an advocate than they had thought before.




**So, part of this is consciousness-raising.**

Absolutely. In fact, I had this very conversation with a patient yesterday. The young person won't take his medication, and he said, "It's my body, and it only affects me if I take my meds or not. So, I should be able to decide." And we pointed out, "Well, you live with your mother. So, if you go off your meds, and you're angry and irritable and anxious, that's going to affect her. It's not just you." Parents sometimes bring out the heavy hammer and say, "You have to take your meds, otherwise, get out of my house." Or imagine a dad who says, "There's nothing wrong with you. You're just being a brat. You're disrespectful, and you don't listen to anybody." These are wrong ways to handle it—you need to be able to understand the kid's point of view, and they need to understand yours.

**The idea of making a list of things that have "triggered" an individual's bipolar episodes sounds very useful to me.**

It is. There's a distinction, please note, between triggers and prodromal signs. Prodromal signs are the symptoms before an episode, like not needing sleep or feeling suicidal. But a trigger could be a life event. It could be breaking up with your girlfriend or a change in work hours. There's a whole theory about sleep/wake regularity and daily rhythms. If you go from the night shift to the day shift on a job, or stay up all night studying for an exam, those changes can be triggers for a manic episode. When you anticipate having to make these changes, you've got to adjust your sleep cycles accordingly: go to bed at the same time each night and get up at the same time the next day.

**Ultimately, if all the stars align—you have a good therapist, the family is conducive to being involved constructively, and the patient is willing to submit to this process—it would seem there's a way of actually moving toward prevention here.**

Yes. And that's what we try to do in the most straightforward way possible. We give people a chart with four columns: What are triggers, what are prodromal signs, what can you do about it, and what could get in the way. So: the trigger might be, I'm going from summer to fall, and school is going to start. I have to get up earlier. What are the warning signs? Getting depressed and feeling anxious. What can the family do? Talk to me. Help me get my medication changed. What are the obstacles? That I may not want to talk about it. [See chart, above right]

**Is it helpful to chart moods?**

It helps to a certain extent. [See chart, above left] I think it helps in consciousness-raising for the kid, especially for one who doesn't recognize they have mood swings. So, you tell the

## PREVENTION ACTION PLAN

| Stressors or Triggers | Early Warning Signs | Coping Skills | Obstacles to Overcome |
|---|---|---|---|
| Arguments with dad, brother | Sleeps less, gets up during night | Contact Dr. Stevens for medication check | Find doctor's best phone number |
| Fired from after-school job | Irritable, picks fights | Use meditation, deep breathing | Feeling angry and resentful, want to blunt feelings |
| | Talks loudly about ways to make money | Stay away from friends who make me want to smoke weed | |
| Signed up for Summer Game Fest (video game competition) | Became obsessed with collaborative video games | Agree with parents on hours for computer usage | Computer games involve other people |
| | Speaking rapidly | Stick with sleep/wake routine | Want to stay up late playing |

kid, "Every day, make a rating of how high or how low you feel, or whether you're feeling normal." Sometimes, we ask the parent to do the same thing to see if the mood charts have any discrepancies. We may say to a kid, "Wait a minute, you say you were stable all last week, but mom says you were up and down. Let's talk about what really happened." That's where it can be useful.

Or, if you start a new medication, and you want to know how it leads to highs or lows, or you're worried about some sort of manic rebound. So, we ask you to keep a mood chart, and see if there's a trend. But it's not natural for people to want to rate their moods every day. Patients who take it up the most, I think, are young adults who have had a couple of really damaging manic episodes. They will be motivated to keep a mood chart. With a teenager, it's a tougher sell.

**Let's conclude by discussing the findings of a very important paper about treating bipolar disorder that you and colleagues published in the journal *JAMA Psychiatry* within the past year. You surveyed the available literature and tried to discover, in a sample of 39 prior studies involving almost 4,000 bipolar patients, whether there are certain ways of delivering therapy that tend to deliver superior results.**

Yes. It indicated the effectiveness of combining psychoeducation therapy with medications. The most surprising finding for me was that on average, doing psychoeducation in a family or a group setting was more effective in terms of preventing recurrences than doing it in an individual setting. I think the reason is that bipolar disorder is one of those illnesses in which the patient really needs a support system to recognize their episodes. It doesn't have to be a family. It could also be a group of other people who have the illness. Many patients cope that way. They go to bipolar support groups and learn about the illness, and develop relapse prevention plans.

**Your study also had important things to say about psychoeducation and structured support. What does structured support mean?**

Structured in the sense that the therapy follows a script. There's a session on understanding and monitoring symptoms. There's a session on developing a relapse prevention plan. There might be a module on how to keep regular sleep-wake cycles. This typically works better for people with bipolar disorder than free-form talking, whether in a group or a family setting. Other specifically helpful things that we found included patients working with their therapists to regularly challenge negative "self-talk," keep their sleep-wake cycles consistent, and learn communication skills in the family setting. These components prove to be important interventions for managing bipolar depression. ❖ **FATIMA BHOJANI & PETER TARR**

*Editor's Note: Dr. Miklowitz's book,* The Bipolar Disorder Survival Guide: What You and Your Family Need to Know *(Guilford Press), is now in its 3rd edition and was most recently updated in 2019. It contains a wealth of practical advice that may help patients and family members who are learning to cope with bipolar disorder.*

# Recent Research Discoveries

Important advances by Foundation grantees, Scientific Council members and Prize winners that are moving the field forward

## People With Schizophrenia Have Increased Risk of Dying From COVID-19, Study Reveals

A newly published study based on data from a 2020 peak period of the pandemic in New York City indicates that people previously diagnosed with schizophrenia or a schizophrenia spectrum disorder who contracted a COVID-19 infection had a significantly increased risk of mortality. Specifically, their risk of death from COVID within 45 days of infection was 2.7 times the risk in people without a psychiatric diagnosis who contracted COVID.

The observed increase in COVID mortality risk for people on the schizophrenia spectrum was second highest in the study, following the elevated risk associated with age. By comparison, people who had previously suffered heart failure had 1.6 times the risk of those without a psychiatric diagnosis, while those with a history of diabetes had 1.27 times the risk.

The mortality risk within 45 days of COVID diagnosis was also elevated in people who had a recent diagnosis of mood disorders, after demographic factors were factored into the calculation. But this excess risk was not present statistically after various medical risk factors were taken into consideration.

There was no observed relation detected between COVID-related mortality and a stable, established mood disorder or recent or previously established anxiety disorders.

The study, appearing in *JAMA Psychiatry*, was based on medical records complied in the spring of 2020 at the NYU Langone Medical Center in New York. **Donald C. Goff, M.D.**, of NYU Langone was senior member of the team. He is a 2009 and 2003 BBRF Independent Investigator. The team also included 2005 BBRF Distinguished Investigator **Mark Olfson, M.D., MPH**, of Columbia University.

Electronic medical records of 26,540 patients tested within the multi-center NYU Langone health system were the basis for the study. Of these individuals, 7,348 tested positive for COVID-19; 53% were women and the average age was about 54.

75 (1%) of those receiving a positive COVID test had a history of schizophrenia; 564 (7.7%) had a history of a mood disorder; and 360 (4.9%) had a history of an anxiety disorder. The sample was demographically diverse and reflected a consecutive stream of adult patients tested in the NYU Langone system between March 3 and May 31, 2020. Outcomes including mortality (death or discharge to a hospice) were monitored for 45 days following each positive COVID diagnosis.

A systematic study led by BBRF Scientific Council member **Nora Volkow, M.D.**, and based on the electronic health records of over 61 million American adults recently found that people with a diagnosis of a mental disorder within the last 12 months have a significantly increased risk for COVID-19 infection and tend to have worse outcomes than people infected with COVID-19 who don't have a mental disorder.

Donald C. Goff, M.D.

Results of the new study revealing the elevated risk of death in people with schizophrenia should be important, the researchers said, in "guiding clinical

decision-making, including the need for enhanced monitoring and targeted interventions" in such patients.

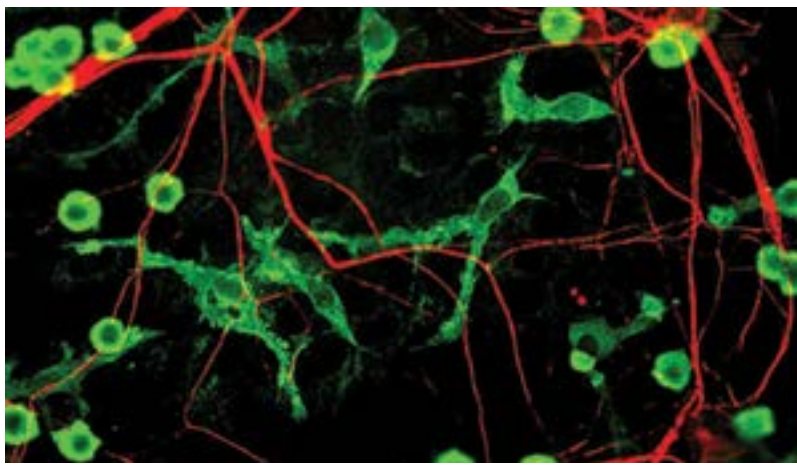
The result in schizophrenia may have reflected "unmeasured medical comorbidities," the researchers said. It has been noted previously that people with severe mental illness are more likely to live in crowded housing, institutional or otherwise, and may either lack or eschew the need for personal protective equipment to avoid COVID inflection. Yet the increased risk of death from COVID seen in people with schizophrenia may also indicate the presence of biological factors related to schizophrenia or to treatments for it that the current study was not designed to detect, the researchers said.

The team speculates that among the biological factors that may make people with schizophrenia more vulnerable to COVID infection are dysregulation of the body's immune system, deficits in cellular immunity, and irregularities in immune-system signaling. Evidence for all of these has been generated in many previous studies of schizophrenia, including studies of the genes that tend to be perturbed in people who have the illness.

The researchers stressed the practical clinical need of "targeted interventions for patients with severe mental illness to prevent worsening health disparities" in circumstances such as are being faced in the continuing COVID pandemic.

# Researchers Discover a Role for Immune Cells Called Microglia in Inhibiting Brain Activity and Regulating Behavior

Researchers have discovered an entirely new way in which the healthy brain keeps neural activation within normal bounds. The finding, which uncovers an unexpected role of immune cells called microglia, has implications for our understanding of behavior as well as a number of illnesses that affect the brain.



For many decades, scientists have understood that brain activity, in broad terms, is the net result of forces that excite and inhibit neurotransmission. Excitatory neurons account for the bulk of activity, but a comparatively small number of inhibitory neurons strategically situated throughout the brain perform the essential role of tamping down excitation when it reaches critical levels.

This prevents neural circuits from becoming overexcited—a condition that can lead to brain seizures like those seen in epilepsy. Overexcitation also may be a factor in some psychiatric illnesses. A failure of the fetal brain to develop proper inhibitory circuitry is hypothesized to have a role in causing or raising risk for schizophrenia, autism, and possibly other disorders.

A team led by **Anne Schaefer, M.D., Ph.D.**, of the Icahn School of Medicine at Mount Sinai, now reports in the journal *Nature* that cells called microglia—plentiful immune cells in the brain and spinal cord whose main functions include removal of dying neurons and pruning of unneeded synapses—also have a role in neural inhibition. They play this role, the researchers say, in the healthy brain, but this function is lost when their number is depleted and/or when inflammation is present in the brain or body, such as in neurodegenerative illnesses including Alzheimer's and Parkinson's diseases.

Dr. Schaefer was a 2010 BBRF Young Investigator. The team also included **Paul Kenny, Ph.D.**, a 2015 BBRF Distinguished Investigator and 2004 Young Investigator; **Erin Calipari, Ph.D.**,


Anne Schaefer, M.D., Ph.D.

a 2018 BBRF Young Investigator; **James Surmeier, Ph.D.**, a 1996 BBRF Distinguished Investigator; **Munir Gunes Kutlu, Ph.D.**, a 2019 BBRF Young Investigator; and **Pinar Ayata, Ph.D.**, a 2016 BBRF Young Investigator.

"When we think about brain function," Dr. Schaefer says, "we typically think about how neurons control our thoughts and behavior. But the brain also contains large amounts of non-neuronal cells, including microglia, and our study puts a fresh spotlight on these cells as partners of neurons in the regulation of neuronal activity and behavior."

The team's experiments in mice revealed that microglia can sense neural activation by detecting a molecule called ATP that is released into extracellular space by active neurons and neighboring support cells called astrocytes. When microglia sense ATP, they physically extend tiny protrusions out into the environment toward the activated neuron, and trigger a cascade of chemical reactions that result in the local suppression of neural activity.

Dr. Schaefer explains that when inflammation is present, or in neurodegenerative diseases like Alzheimer's, microglia lose their ability to sense ATP and thus their ability to regulate neural activity—perhaps a factor in the pathology associated with these conditions.

Since dysregulated neuronal activity is part of the pathology of an illness like Alzheimer's, it means the regulatory role played by microglia also has an impact, indirectly, on behavior. This could also apply in the case of depression, which is hypothesized to involve inflammation in at least a subset of patients. In general, says Dr. Schaefer, "behavioral changes associated with certain diseases may be mediated, in part, by changes in communication between microglia and neurons."

In future studies Dr. Schaefer and colleagues will explore the possibility that the ability of microglia to sense ATP may mean they are also involved in regulation of other biological functions, including sleep and metabolism.

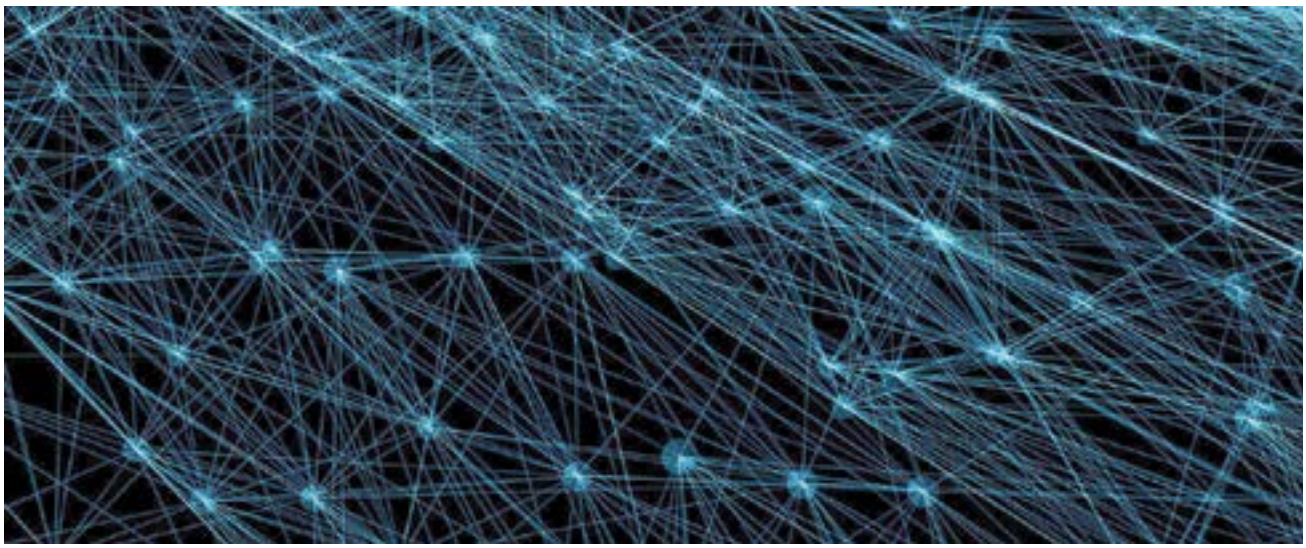
# Investigators Discover Brain Proteins That Protect Synapses From Being Eliminated

A research team led by a BBRF grantee has shown for the first time that the brain contains specialized proteins whose function is to protect synapses from being eliminated. Synapses are the connection points at which the brain's tens of billions of neurons communicate. The discovery may have valuable implications for development of future treatments for Alzheimer's disease, as well as schizophrenia and possibly other psychiatric illnesses that involve synapse loss.

At the dawn of life, when the brain of the fetus is beginning to form, an excess of synaptic connections are made. This vigorous process of synapse formation, which is normal, gives way to an equally normal process of synapse elimination, or "pruning," which begins in the first years of life and reaches its peak in mid-adolescence.


Gek-Ming Sia, Ph.D.

While synapse creation and synapse elimination are both essential, it is vital that they occur at the proper times and places, in the brain and the rest of the body. During adulthood, the two process balance out. But in certain illnesses, notably Alzheimer's disease, synapse elimination occurs at an abnormally high rate, a phenomenon associated with memory loss. At the beginning of life, abnormal regulation of synapse formation and pruning has been linked with schizophrenia risk in the child.



**Gek-Ming Sia, Ph.D.**, of the University of Texas Health Science Center in San Antonio, devoted his 2016 BBRF Young Investigator grant to comprehensive study of a protein called SRPX2, which had been linked with increasing the number of synapses formed by neurons in the brain's cerebral cortex. In a paper recently published in *Nature Neuroscience*, Dr. Sia and colleagues show that this protein, SRPX2, is present in the brain, and, rather than promoting the formation of new synapses, actually acts to inhibit the mechanism designed to eliminate synapses.

Dr. Sia explains that SRPX2 is part of an immune pathway in the brain called the complement system. "Complement-system proteins are deposited onto synapses," he says. "They act as signals that invite immune cells called macrophages to come and 'eat' excess synapses during development. We have now discovered proteins that inhibit this function and essentially act as 'don't eat me' signals to protect synapses from elimination."

It is normally the role of SRPX2 and likely other complement inhibitors to prevent runaway activation of the complement system, as may be occurring in Alzheimer's. Dr. Sia and his team reason that when and where in the brain and body these synapse protectors become active is therefore crucial.

In their paper, the team shows that in the brain, SRPX2 acts to restrict the complement system from eliminating synapses in specific synapse populations and time periods during development. These findings were made in genetically modified mice, in which the specialized functions of SRPX2 and other parts of the mechanism could be isolated and defined.

Knowing that complement-mediated synapse loss occurs in "many neurological diseases," says Dr. Sia, the challenge for research is to clarify the precise relationship between various inhibitors of the system like SRPX2 and the specific sets of neurons and synapses that they are designed to protect.

It's possible, his team writes, that "changes in levels of complement inhibitors" could account for different levels of resistance and vulnerability in individuals to various illnesses, from schizophrenia to Alzheimer's.

In the near term, Dr. Sia's team will address the specificity issue: whether different neurons produce different complement inhibitors—each, perhaps, protecting a certain subset of synapses. "This could explain why, in certain diseases, there is a preferential loss of certain synapses. It could also explain why some people are more susceptible to synapse loss—because they have lower levels of certain complement inhibitors," Dr. Sia says.

As this line of research advances, it might eventually test the possibility of using a drug to vary the level of a complement inhibitor such as SRPX2 to protect specific synapses and either lower the risk for an illness or reduce its severity once the disease process has begun.

# Therapy Update

Recent news on treatments for psychiatric conditions

## REPEATED KETAMINE INFUSIONS OVER 2 WEEKS SIGNIFICANTLY REDUCED CHRONIC PTSD SYMPTOMS

Adriana Feder, M.D.

A new window may be opening on the treatment of chronic post-traumatic stress disorder (PTSD). Results of a newly published clinical trial suggest that repeated infusions of the drug ketamine over a 2-week period can significantly reduce symptom severity in many patients, while also helping to reduce depression symptoms that often accompany PTSD.

The randomized trial, led by **Adriana Feder, M.D.,** of the Icahn School of Medicine at Mount Sinai, was small, involving 30 chronic PTSD patients with moderate to severe symptoms, half of whom received 6 infusions of ketamine over 2 weeks while half received 6 infusions of the psychoactive placebo control drug midazolam over the same period. Both drugs have been used for many years as anesthetics, although in the trial both were given at a sub-anesthetic doses. The trial was fully blinded, with neither patients nor the doctors or clinical raters assessing them knowing who was receiving the two medicines.

Dr. Feder is a 2015 BBRF Independent Investigator and 2002 Young Investigator. Co-senior authors on the paper reporting the trial, which appeared in the *American Journal of Psychiatry*, were **Dennis S. Charney, M.D.**, an Emeritus member of BBRF's Scientific Council and 2019 winner of BBRF's Colvin Prize for Outstanding Research in Mood Disorders; and **James W. Murrough, M.D.**, a 2009 BBRF Young Investigator. The team also included **Laura Bevilacqua, M.D.**, a 2017 BBRF Young Investigator.

Ketamine has attracted much interest because of its rapid antidepressant effects in patients with treatment-resistant depression. Shown to reduce symptoms in as little as a couple of hours, its effects typically do not last longer than one week.

A chemical derivative of ketamine called esketamine was approved by the FDA in 2019 for use in refractory depression. Tests are under way to gauge whether it can safely be given repeatedly over long periods of time—on a "maintenance" basis—to sustain remission or major symptom reduction in depressed patients.

The newly reported trial involving patients with chronic PTSD aimed in part to test whether repeated ketamine infusions are safe and effective in reducing symptoms. Chronic PTSD refers to symptoms extending well beyond an immediate or acute response to trauma—debilitating symptoms continuing 3 months or more after the traumatic exposure.

In the ketamine trial, the average duration of PTSD symptoms for the 30 enrolled patients was 15 years. Three-fourths of participants were women, with an average age of about 40. Thirteen of the 30 had been traumatized by a sexual assault; 8 had endured physical assault or abuse; 2 had been traumatized during combat; 7 had witnessed violent events.

The persistence of PTSD in the participants reflects the difficulty in treating PTSD with psychotherapy and existing medicines. Both have demonstrated efficacy, but some patients are unable to tolerate "exposure therapy," which requires re-exposure under controlled conditions to triggers for fear responses. Similarly, while many patients respond partially to the two SSRI antidepressants that are FDA-approved for the disorder, only 20%–30% achieve remission.

The Mount Sinai team had previously tested ketamine in a proof-of-concept trial that involved a single infusion. That trial, led by Dr. Charney, showed significant PTSD symptom reduction 24 hours following the infusion. The current study

is the first randomized study to test the efficacy of a course of repeated infusions in individuals with PTSD. The participants were assessed before treatments began, as well as 24 hours and 2 weeks after the first infusion. Those responding to ketamine were followed until their symptoms returned. A "response" was defined as a reduction in PTSD symptoms of 30% or more following the 2-week course of infusions.

While some patients in both the ketamine and midazolam groups responded to treatment, many more in the ketamine group were responders—10 of 15 (67%) vs. 3 of 15 (20%) in the midazolam group. (In this trial, midazolam was employed as a psychoactive placebo control; a tranquillizer, midazolam can temporarily mitigate anxiety symptoms in some patients).

The bottom line was that improvement in the ketamine group, beginning 24 hours after the first infusion, was "significantly greater" at 2 weeks than that observed in the midazolam group. Response to ketamine lasted, on average, 27.5 days after the 2-week course of infusions, although in one participant it lasted at least 102 days. This extended benefit, the researchers propose, may be due to the repetition of ketamine infusions, as compared with the potential benefit of just one infusion. While dissociation (a floating or out-of-body feeling) was reported by some in the ketamine group during infusions, this side effect did not persist beyond the 2-hour observation period that followed each infusion, and usually resolved shortly after the end of the infusion. There were no other serious side effects.

The other major finding of the trial was that ketamine responders showed "marked improvements" in three of four PTSD symptom areas: intrusive thoughts, avoidance, and negative alterations in cognition or mood. This was in addition to significant reductions in comorbid depressive symptoms.

The "large-magnitude improvements" in PTSD symptoms and comorbid depressive symptoms and illness severity, as well as indications of the safety of multiple ketamine doses given over 2 weeks, led Dr. Feder and colleagues to urge that additional trials follow this one. These might test whether esketamine has similar benefits in chronic PTSD; and whether psychotherapy, added to a course of ketamine or esketamine, might reduce the likelihood of relapse once the infusions end.

## NEW STUDY DEMONSTRATES NON-INVASIVE tDCS BRAIN STIMULATION CAN ENHANCE COGNITIVE CONTROL IN SCHIZOPHRENIA PATIENTS

Cameron S. Carter, M.D.

Impaired cognition—operations of the brain that enable people to understand and react to the world that surrounds them—is one of the aspects of schizophrenia that makes it hard for patients to function successfully in society.

Cognitive deficits are among the most disabling and treatment-resistant aspects of schizophrenia, and include difficulty learning and retaining information as well as paying attention and using "working memory," a form of short-term memory needed for tasks immediately at hand.

Reporting in the journal *Neuropsychopharmacology*, a team of clinical researchers now reports early success in using a method of non-invasive brain stimulation called tDCS (transcranial direct current stimulation) to improve the ability of patients with schizophrenia to perform an important type of cognitive task. The task calls for "proactive cognitive control"—the ability to mentally prepare to respond to an upcoming challenge by observing context and rules.

The team's senior member was **Cameron Carter, M.D.**, of the University of California, Davis. He is a member of the BBRF Scientific Council and a 2007 BBRF Distinguished Investigator, 2001 BBRF Klerman Prize winner and 1997 and 1994 Young Investigator. First author of the paper reporting the results was Megan Boudewyn, Ph.D.; **Katherine Scangos, M.D., Ph.D.**, a 2018 BBRF Young Investigator, was also part of the team.

The researchers recruited 27 patients diagnosed with schizophrenia or a schizophrenia spectrum disorder. They were divided in two groups, one of which received a 20-minute tDCS treatment before being asked to perform a task requiring proactive cognitive control. Members of the other group received a "placebo" version of tDCS stimulation before the task.

Days later, members of the two groups returned, with those who had received placebo now receiving active tDCS stimulation and those who had received active stimulation now getting the placebo version. The groups were blinded, meaning participants didn't know when they were getting real or placebo tDCS stimulation.

The placebo version of tDCS provided participants with the sensations of the "real thing," but with active current not being delivered beneath the scalp. It is thought that the "real" version of tDCS alters the excitability of neural networks in the brain where the current is targeted. How that generates potentially therapeutic effects remains a question under study.

In the trial, the active tDCS treatment was targeted to the brain's dorsolateral prefrontal cortex, a brain area linked in past research with a type of brainwave activity thought to underlie proactive cognitive control. The waves affected are called gamma-band waves, and are created by neural activity oscillating between 30 and 80 times per second. Called "high-frequency" waves, they are broadly linked with cognition and are thought to operate over short distances in the brain. Their strength is measured using a technology called EEG, or electroencepthalography (see story, p. 10).

The task that participants had to perform, minutes after their (real or placebo) tDCS session was designed to show how well they could use cues to prepare successfully for a visual task. It measured the ability to anticipate and make use of cues.

EEG measurements enabled the team to conclude that tDCS stimulation enhanced brainwave activity in the gamma band within the prefrontal region of the cortex. This was related to the period of delay in anticipating cues. The net effect was that active tDCS—as opposed to placebo—"significantly enhanced proactive cognitive control" in this comparatively small sample of schizophrenia patients.

The team said their results justify conducting a larger study to replicate their result. They have begun such a study, which aims to enroll a larger number of participants. The team said that further research also should try to gauge the impact of schizophrenia medications, if any, on cognitive effects induced by tDCS treatments.

## COMBINING THE ANTIPSYCHOTIC OLANZAPINE WITH AN OPIOID-RECEPTOR BLOCKER LIMITED WEIGHT-GAIN RISK IN SCHIZOPHRENIA PATIENTS

Christoph Ulrich Correll, M.D.

A clinical trial involving over 500 adults diagnosed with schizophrenia has found that by adding the drug samidorphan to the antipsychotic medicine olanzapine, it was possible to substantially reduce patients' likelihood of significant weight gain.

Weight gain and related impacts on the body's metabolism are a common side effect of olanzapine and other atypical or "second-generation" antipsychotic medicines, and have limited their clinical utility to varying degrees. Significant weight gain capable of making patients overweight and even obese can cause major problems beyond increasing cardiovascular and metabolic risks. By damaging self-esteem, significant weight gain can serve as a rationale for avoiding the medication altogether—even though it is the very cornerstone of schizophrenia treatment.

To further test the idea that weight gain and metabolic complications might be minimized or prevented by combining samidorphan and olanzapine, a multicenter clinical trial was led by BBRF Scientific Council member **René Kahn, M.D., Ph.D.**, of the Icahn School of Medicine at Mount Sinai, and **Christoph U. Correll, M.D.**, of the Feinstein Institutes for Medical Research.

Samidorphan, under development by its maker Alkermes for use in several psychiatric disorders, is an antagonist of the body's naturally occurring opioid receptors, particularly the mu-opioid receptor. A prior 12-week clinical trial had provided preliminary evidence of the promise of a samidorphan-plus-olanzapine combined treatment.

In the newly reported clinical trial, a single tablet combining samidorphan and olanzapine was compared with a single tablet containing only olanzapine. In all, 561 patients aged 18-55 were randomized to receive the two treatments. The

dose of olanzapine was increased from 10mg/day to 20mg/day at the beginning of the second week of the 24-week trial, in order to allow patients to become acclimated to that dosage. For those receiving the combination treatment, the dosage of samidorphan was kept constant at 10mg/day throughout the trial.

Dr. Correll's 2007 BBRF Young Investigator grant supported his early work focusing on discovering the molecular mechanisms behind the weight gains associated with atypical antipsychotics. In the paper reporting on the new trial, published in the *American Journal of Psychiatry*, he and colleagues hypothesize that samidorphan minimizes changes in fat mass associated with olanzapine by blocking the uptake of sugar in fatty tissue and/or by preventing insulin resistance induced by olanzapine.

René Kahn, M.D., Ph.D.

The trial did not shed new light on the mechanism, but it did clearly confirm the impact of the combined treatment. It both mitigated weight gain and reduced the number of patients who had substantial increases in weight and in waist circumference (one way of measuring body fat), as assessed at the end of the trial. Weight gain did occur during the first 4 to 6 weeks of the trial, even in the "combined treatment" group, but it then stabilized in that group, the researchers reported.

The team noted that the risk of "clinically significant" weight gain—at least 10%—was reduced by 50% in the group that received the combined treatment, compared with the group that received olanzapine only.

Importantly, the combined treatment was just as effective as olanzapine alone in continuing to control patients' psychotic symptoms. Also, patients receiving the combined treatment had about a 50% lower risk of having their waist circumference increase by 5cm (2 inches) or more.

Curiously, measurements of the body's lipid (fat) and glucose (sugar) metabolism were not significantly impacted in this trial by the combination treatment, relative to olanzapine-only treatment. There are several possible reasons for this, but the researchers noted that there was "extensive evidence [in the scientific literature] supporting the expectation that mitigation of olanzapine-associated weight gain should ultimately lead to metabolic benefit."

The metabolism of glucose and lipids is directly related to the body's ability to regulate weight, so this part of the trial results will have to be further examined in current and future trials testing the combination therapy. It is possible, the researchers said, that their trial was too brief to show the ultimate impact of combined treatment on cardio-metabolic indicators.

For now, the team suggested that "by mitigating weight gain after an initial [4- to 6-week] period and reducing the number of patients who have substantial increases in weight and waist circumference, combined treatment mitigates one of the key safety risks that has limited the use of olanzapine."

The team included **John Newcomer, M.D.**, a 2001 BBRF Independent Investigator and 1998 Young Investigator. Several team members, including Drs. Kahn and Correll, have had consulting relationships with Alkermes, which sponsored the trial.

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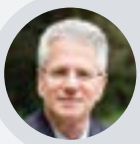

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# GLOSSARY

**ANHEDONIA (pp. 4–9)** A reduced interest in seeking pleasure, or an inability to experience it. Often a symptom in depression, but also in anxiety disorders, PTSD, schizophrenia, and the depressive phase of bipolar disorder.

**OPIOID RECEPTORS (p. 7)** Cell-surface receptors that engage with the body's naturally occurring opioids. These receptors, common in the brain, include the kappa opioid receptor (KOR). Blocking the KOR may help raise levels of the neurotransmitter dopamine, important in the brain's reward system.

**VENTRAL STRIATUM (p.7)** A portion of the brain structure including the **NUCLEUS ACCUMBENS** that plays an important role in reward, motivation, certain aspects of learning, and the experience of pleasure.

**EEG (pp. 10–15)** Electroencephalography is a technology used to record brainwaves, which are generated by the electrical activity of brain cells. EEG monitoring is non-invasive, accomplished via electrodes, often wired together in a cap that fits over the scalp. EEGs can be taken while a subject is performing a task or while at rest ("resting-state EEG"). A related technology called MEG (magnetoenephalography) records magnetic activity of the brain (p. 13).

**BRAINWAVES (p. 10)** EEGs generate rows of "squiggly lines" each registering neuronal activity in a specific frequency band. Different bands correspond with different speeds of neural oscillation. These oscillations range from very slow (1–3 oscillations per second) to very fast (up to 100 oscillations per second). The bands are referred to with letters of the Greek alphabet. Delta waves, typically generated during sleep, are the slowest; gamma waves, reflecting brain operations involved in consciousness and perception, are the fastest.

**NMDA RECEPTOR (p. 18)** One of the cellular receptors for the excitatory neurotransmitter glutamate. Many studies have indicated that the drug ketamine blocks the NMDA receptor, but it is not known how this action is related, if at all, to ketamine's rapid antidepressant effects.

**HOMEOSTATIC PLASTICITY (p. 19)** Plasticity refers to the capacity of neurons to change the strength of their connections. It has been speculated that antidepressant effects reflect or are caused at least in part by changes in plasticity. Homeostatic plasticity refers to the capacity of neurons to regulate their own excitability relative to actions taking place across larger networks.

**MANIA (p. 22)** Mania is a period of a week or longer where someone is feeling "on top of the world"—euphoric, or, extremely irritable. Speech is often very rapid; grandiose ideas are often expressed. There's a change in behavior, which can be marked by increased spending and impulsiveness, hypersexuality, and risk-taking. One must have at least one manic episode to be diagnosed with bipolar disorder. Symptoms of mania also occur, reduced in intensity, in **HYPOMANIA**. In contrast with mania, hypomania typically does not impair function.

**BIPOLAR 1 / BIPOLAR 2 (p. 23)** Those with bipolar 1 disorder have had at least one manic episode and in most cases they have also had a major depressive episode. In bipolar 2 disorder, individuals have major depressions and hypomanias.

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