A New Approach to Treating Cognitive Deficits in Schizophrenia

Dr. Kay Redfield Jamison: 'Talking Publicly About My Bipolar Illness'

MAGAZINE

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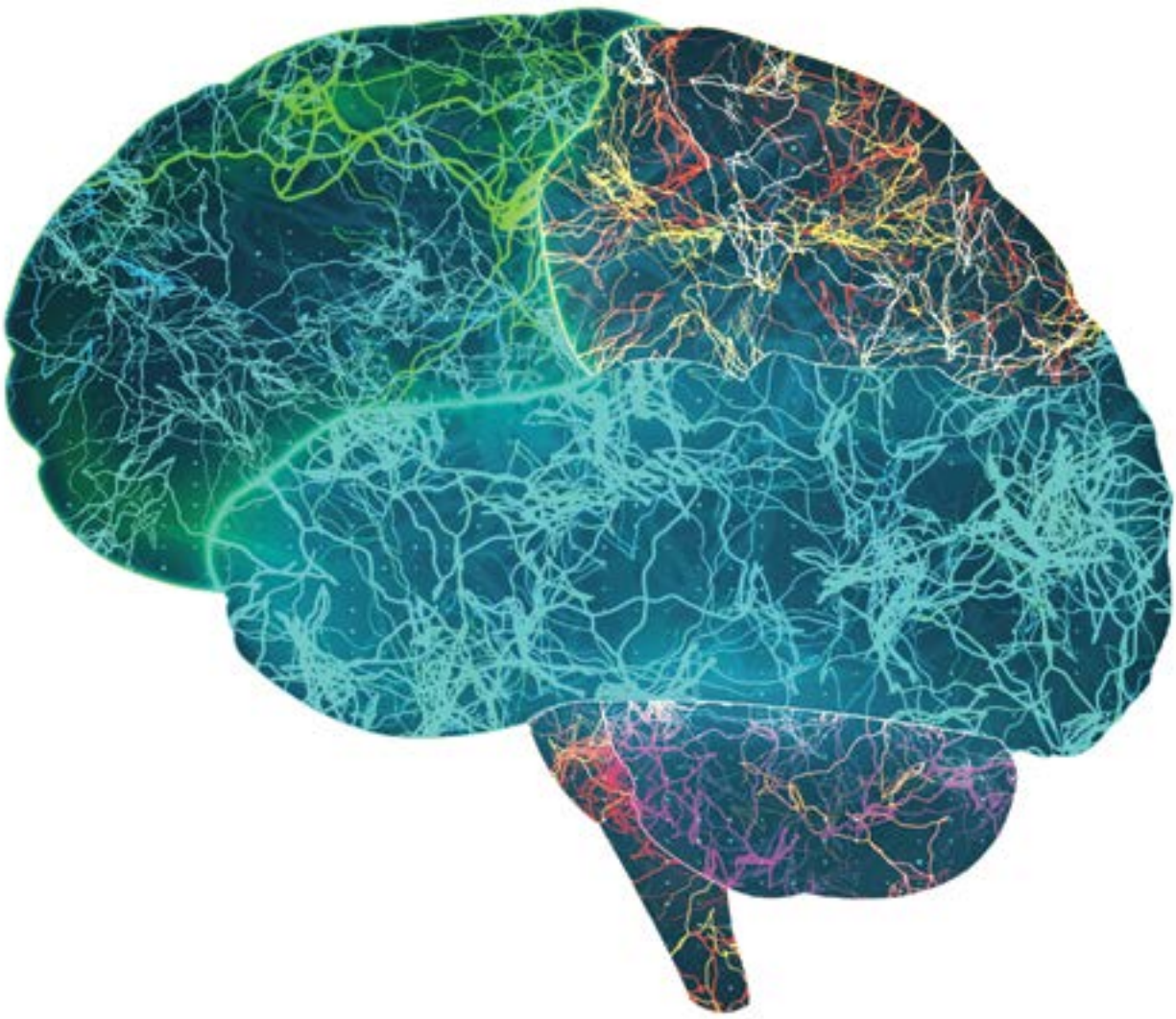

'We Are Witnessing a Revolution in Brain Stimulation'

RESEARCH 19 35 years 87 FOR CURES

PRESIDENT'S LETTER

This issue of *Brain & Behavior Magazine* captures some of the excitement surrounding brain stimulation treatments for psychiatric illness and showcases the impact that research funded by BBRF is having in the field of neuropsychiatry.

As Dr. Mark S. George, a pioneer in the field, tells us in an overview article, **A RESEARCHER'S PERSPECTIVE**, any brain illness whose causal circuitry we understand is a candidate for brain stimulation treatment. Dr. George notes that BBRF grants awarded to him early in his career helped him perform clinical research that became the basis of the most popular form of non-invasive brain stimulation, called TMS (transcranial magnetic stimulation). TMS is currently FDA-approved for depression, OCD, and smoking cessation. Future indications for TMS and related technologies include anxiety, suicidal behavior, alcohol withdrawal and abstinence, pain relief, and stroke recovery.

Our **IN THE NEWS** article conveys the recent announcement that a variation on non-invasive TMS technology called SAINT has now been approved for commercialization by the FDA. The SAINT protocol has been tested with great success in several clinical trials with treatment-resistant patients suffering from major depression. In SAINT, more stimulation is delivered in a much shorter period of time compared with standard TMS treatment. This technology was pioneered by one of Dr. George's protégés, Dr. Nolan Williams, at Stanford University. Dr. Williams has also benefited from early-career support from BBRF grants which helped him to develop SAINT.

Our **PATHWAYS TO THE FUTURE** article conveys the exciting story of research being performed by Dr. Vikaas Sohal and his colleagues at the University of California, San Francisco. They have used new technologies to discover biological processes that are likely involved in causing cognitive dysfunction in schizophrenia. This knowledge is helping to pave the way to new treatments for cognitive deficits, which are a major cause of disability in schizophrenia. One objective may be to restore normal gamma-frequency activity in the cortex to boost the efficiency of circuits involved in cognitive processing.

In our **MENTAL HEALTH & SOCIETY** feature, Dr. Kay Redfield Jamison explains that after making a public disclosure of her own history of bipolar disorder, she encountered a range of responses. More than a few of her colleagues in medicine and psychiatry seemed acutely uncomfortable. But, she says, for every negative reaction, there have been more acts of kindness. In addition to her other work, she is now dedicated to counseling young people, who are at comparatively greater risk of developing a mental illness and who may be particularly hurt by stigma.

This issue also features recent news on treatments for psychiatric conditions in our **THERAPY UPDATE** and important research advances that are moving the field forward in our **RECENT RESEARCH DISCOVERIES**.

Our shared goal of a world free from debilitating mental illnesses relies first and foremost upon you, our donors—in partnership with the numerous scientists chosen by the BBRF Scientific Council—who are working to transform your donations into improved treatments, cures, and methods of prevention for our loved ones. I am inspired by the magnitude and scope of the discoveries that are being made by the scientists we fund together and appreciate your ongoing generous support.

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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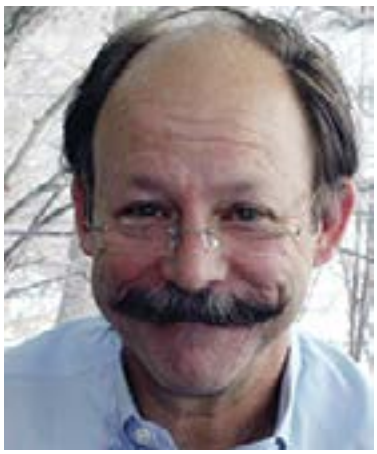
Writer
Peter Tarr, Ph.D.

Editors
Lauren Duran
Peter Tarr, Ph.D.

Designer
Gene Smith

We Are Witnessing a Revolution in Brain Stimulation

How TMS and Other Technologies Have Changed the Face of Psychiatry



By Mark S. George, M.D.

Distinguished Professor of Psychiatry, Radiology and Neuroscience
Founding Director, Center for Advanced Imaging Research
Director, Brain Stimulation Laboratory, Psychiatry
Medical University of South Carolina

Member, BBRF Scientific Council
2008 BBRF Falcone Prize for Outstanding Achievement in Affective Disorders Research
1998 BBRF Independent Investigator grant
1996 BBRF Young Investigator grant

IN BRIEF
According to Dr. George, a pioneer in the field, any brain disorder whose causal circuitry we understand and is reachable via TMS or related technologies is a candidate for TMS treatment. Right now, TMS is approved for depression, anxious depression, OCD, and smoking cessation. Future applications include suicidal behavior, alcohol withdrawal and abstinence, pain relief, and stroke recovery. It may also find application in reducing positive symptoms like hallucinations as well as negative symptoms like cognitive dysfunction in schizophrenia.

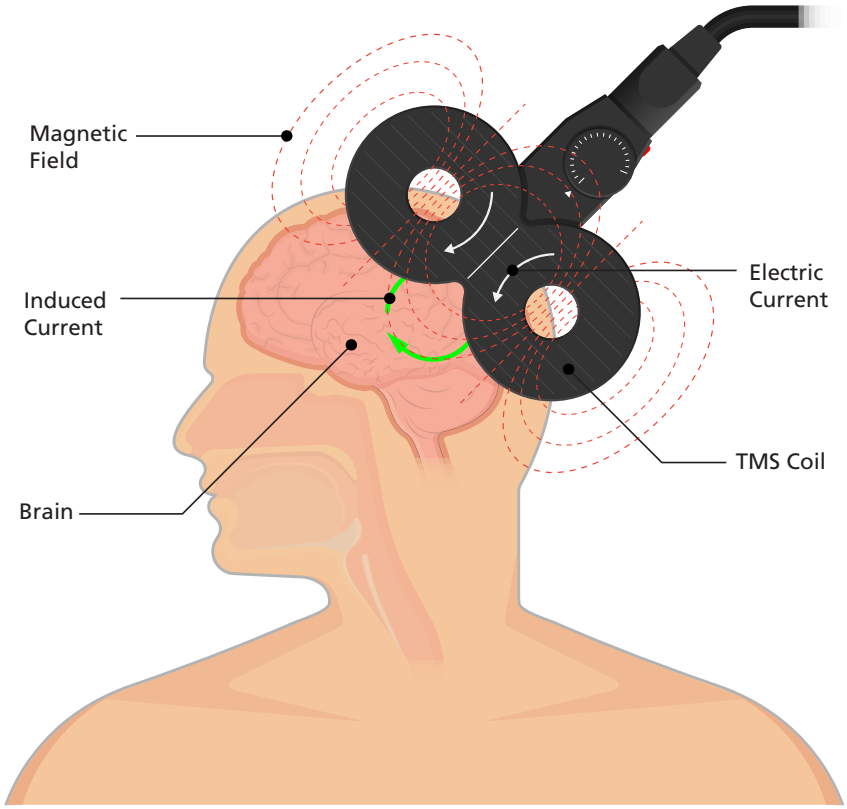
The field of brain stimulation is a fascinating one. It involves psychiatry and neurology, neuroscience, in some cases neurosurgery, as well as cognitive neuroscience and a whole world of bioengineering. My journey began with a BBRF grant which was given to me 26 years ago.

It has been wonderful to be able to see a revolution occur in this field. In this article, I want to try to give you a sense of this. I'll focus on **TMS—transcranial magnetic stimulation**—which is the technology that I've used for most of my career.

If you take electricity and run it through a coil, the electricity creates a magnetic field. The skull and skin stop electricity from passing through to the brain, but magnetic fields pass unimpeded. When these fields encounter a nerve cell, they will cause it to depolarize—its electrical charge changes, which is part of the process that causes a neuron to "fire." So we're electrically stimulating the brain, but using a magnet to be able to do so. It's really a wonderful technology.

I first stumbled onto this early in my career, when I was in London. I later moved to the National Institutes of Health and my boss there, **Dr. Robert Post**, who is now one of my colleagues on BBRF's Scientific Council, gave me license to do a clinical trial. I was able to do

If you take electricity and run it through a coil, the electricity creates a magnetic field. The skull and skin stop electricity from passing through to the brain, but magnetic fields pass unimpeded. When these fields encounter a nerve cell, they will modify its activity. "We're electrically stimulating the brain, but using a magnet to be able to do so," Dr. George explains.



the first 2-week double-blind, randomized trial of the method we now call TMS.

Later, I moved to Charleston, South Carolina, to take a position on the faculty of the Medical University of South Carolina. My lab was supported in part by BBRF, so from the very beginning, BBRF was important in the research that led to our first clinical trial of TMS and then other interventions.

I'll never forget when I "unblinded" the first double-blind study—the moment we could really interpret the results—and saw a TMS antidepressant effect. I was excited but also scared. My worry was that I would make wrong decisions or something would happen that would stop this technology from becoming a widespread treatment.

This is where BBRF was important. They gave money when no one else would. There was no "brain stimulation industry" at that time. I did not pursue getting a patent and thus there was not a patent that industry could organize around to then do the initial clinical trials. The NIH was not keen on the idea in those early days and was even actively against funding TMS, or even talking about it. There were no FDA-approved indications for TMS. But we've come a long way since then. It is fair to say we have really changed the face of neuropsychiatry now with the success of TMS.

I'll devote most of this piece to TMS. But before I do, it's important to mention that in addition to TMS, there are a variety of brain stimulation techniques in use today. You may have heard of **electroconvulsive therapy, or ECT**, which is the grandmother of the whole field. In ECT, a mild electric current is used to cause a brief seizure in the brain. This seizure often has therapeutic effects, perhaps most notably in severely depressed "refractory" patients who have not been helped by other forms of therapy. The patient is placed under anesthesia during the treatment. ECT is most often used in depression, but also in catatonia, schizophrenia and bipolar disorder.

Another form of brain stimulation you may have heard of is called **deep brain stimulation (DBS),** where we surgically implant a wire in the brain to deliver stimulation. This has proven to be really important for the treatment of Parkinson's disease, dystonia (involuntary muscle contractions), and essential tremor. It has also been used experimentally to treat severe, refractory depression, an application pioneered by **Dr. Helen Mayberg**, another of my colleagues on BBRF's Scientific Council.

tDCS—transcranial direct-current stimulation—is another stimulation technology in which you pass electrical current through the brain, but unlike DBS, it is delivered non-invasively.

Then, too, there has been an explosion of activity in investigating different ways to stimulate the vagus nerve, which is the body's most important nerve pathway connecting the brain with the heart, lungs, and digestive tract. There are FDA-approved indications for **VNS—vagus nerve stimulation**—for epilepsy, depression, and obesity. This can work either invasively with a wire implanted in the neck or noninvasively with a device that you hold up to the neck or connect through the ear.

Non-invasive stimulation of the vagus nerve.

A new technology called **pulsed ultrasound** is also being used experimentally to stimulate the brain. I'll discuss it in more detail later in the article.

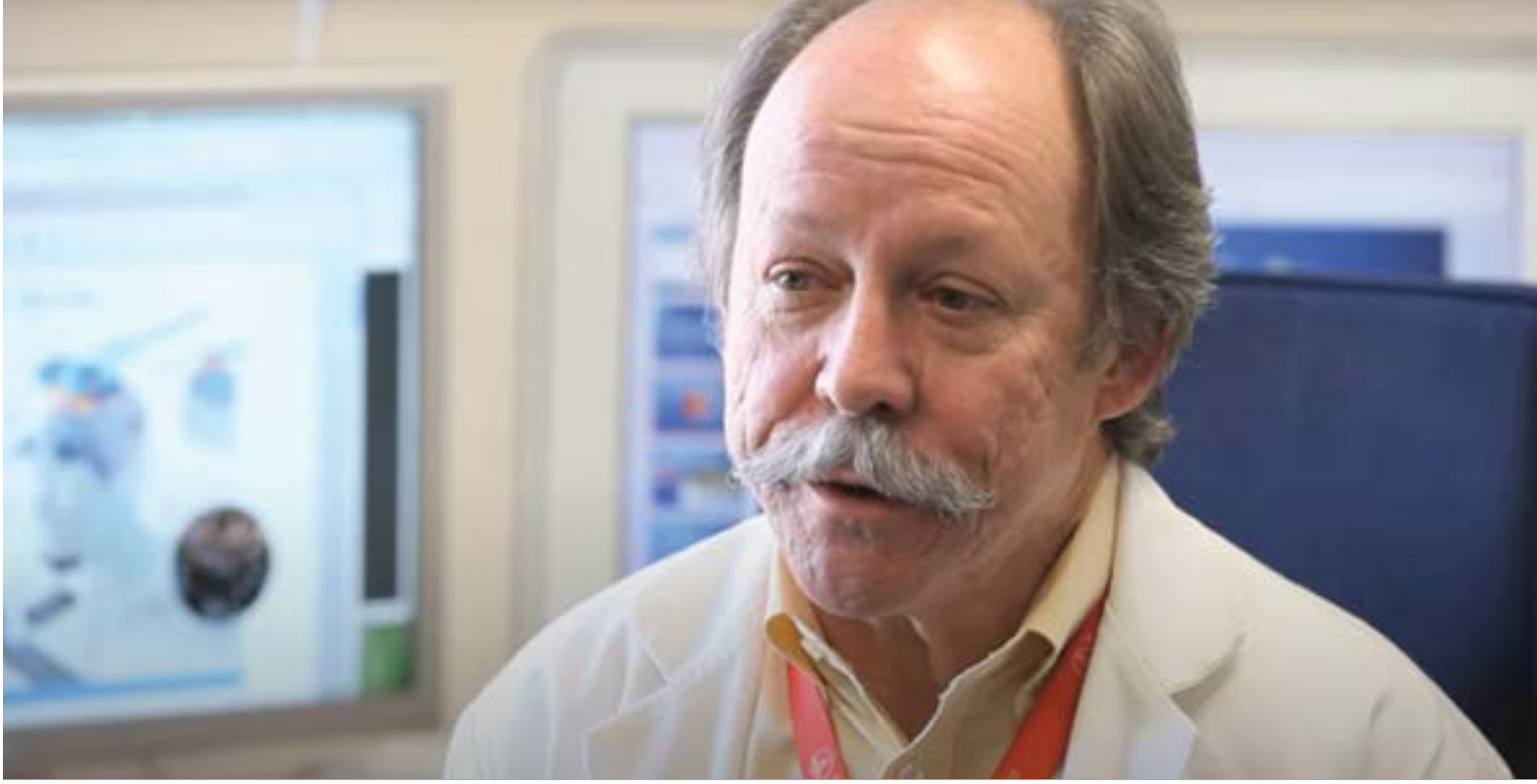
All these technologies will be improved in the future. And it will not be a matter simply of deciding to treat patients either with talk therapy or medications or brain stimulation. Rather, combinations seem likely. The key appears to be our ability to have a beneficial impact on synaptic plasticity—the ability of neurons to change the strength of their connections.

TMS AS 'EXERCISE' FOR THE BRAIN

What do we know about how TMS works? What does it do to the brain? We've put people in the [MRI] scanner. We've learned that when we're stimulating a part of the brain with TMS, we're actually just exercising it, like going to the gym. And that may be why results are not immediate—they're dose-dependent. Like going to the gym, you don't really get results after the first session, but over time. If it's true that we're making the brain do what it does naturally in an organized way, like exercise, you can see why TMS would have the excellent safety profile that it does. It's remarkably safe.

In the classic protocol we devised years ago that led in 2009 to FDA approval for TMS in depression, the treatment is given daily, five times a week for 4 to 6 weeks. Each stimulation session lasts about 40 minutes and the patient, who receives the treatment while reclining in a chair, can return to normal activities after the session ends. The treatment for depression now commonly used involves delivering repetitive magnetic pulses, and for this reason it's called **repetitive TMS or rTMS.** Variations include **intermittent theta-burst stimulation (iTBS)**, in which pulses are delivered at a different frequency, enabling a substantial reduction in the time of each treatment session—each is just a few minutes in duration.

There have been some exciting advances with TMS and one in particular seems to supply strong evidence of the relationship between "dose" and effectiveness. My former student, now a colleague and friend, Dr. Nolan Williams, at Stanford University, has tested the idea of accelerating TMS treatments and significantly increasing the total dosage given during a course of therapy. Dr. Williams and colleagues have developed **Stanford**



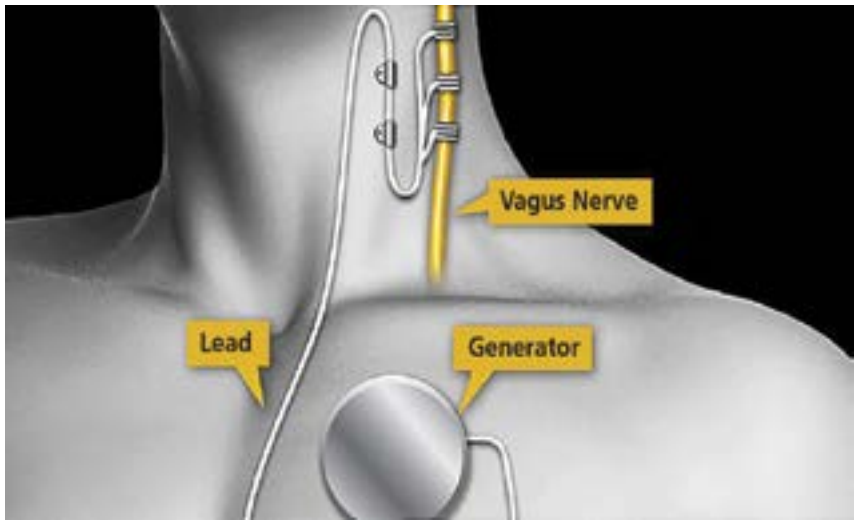
Neuromodulation Therapy, (referred to as SNT or SAINT), a protocol which instead of giving one TMS treatment per day over 4–6 weeks in sessions typically lasting about 38 minutes, delivers 10 treatments in one day—each session lasting just a few minutes—for 5 days running. The patient receives a great deal of stimulation concentrated in just those 5 days.

With SNT, Dr. Williams finds that he gets from 79% to almost 90% remission—an elimination of depression symptoms—in people who've tried and failed multiple other forms of anti-depression therapy. And the patients are getting well very quickly—within the week that they are treated. Because of the rapid action, there is the thought that this accelerated and intensified type of TMS can be useful in inpatient psychiatric units and emergency rooms, to treat people at high risk of suicide. This is a really important advance with TMS. BBRF funded this work with two Young Investigator grants to Dr. Williams. *[This technology has just been approved by the FDA—see p.12]*

We've learned that in trying to assess how well TMS is likely to work in a patient and how it might be combined with other treatments, we need to take into consideration what's going on in the brain while we stimulate. Specifically, we find that active circuits are more easily changed and modified by TMS than those that are not. An example of why this is important is the use of TMS in obsessive compulsive disorder (OCD). The FDA has approved TMS for OCD. But we find that TMS alone often doesn't work. For it to work, you have to deliver the stimulation while someone is actively obsessing or wanting to do their compulsion. Last year, we received FDA approval for smoking cessation. Again, we find that you have to have people craving a cigarette while you stimulate in order for TMS to work.

I think any brain disorder where we understand the circuitry involved in its causation and we can reach that circuitry with TMS is a candidate for eventually being treated by TMS. Ten years from now, how many TMS indications will we have? It could be as many as 10 or 15. Right now TMS is approved for depression, anxious depression, OCD, and smoking cessation. Future indications include suicidal behavior as well as alcohol withdrawal and abstinence, pain relief, and stroke recovery. It may also find application in reducing positive symptoms like hallucinations as well as negative symptoms like cognitive dysfunction in schizophrenia. The list will, I think, keep growing and growing year by year.

I mentioned the possibility of intervening with TMS in circuits causally linked with psychiatric and other illnesses. Some really interesting research by BBRF-funded researcher **Dr. Shan Siddiqi** and Dr. Michael Fox at Harvard sheds light on such circuits. They have figured out that under the big umbrella of "depression," there are two different types of patients—those who are "dysphoric" and those who are "anhedonic." Dysphoria refers to a feeling of unease, discomfort, anxiety. These patients often have physical symptoms. Anhedonia involves loss of interest in pleasurable activities—patients sleep a lot, lack energy. If you look at what parts of the brain are dysfunctional in these different kinds of patients, you find different circuits that are causally associated with dysfunction. This data can inform the targeting of TMS treatments—different targets for different individuals based on their type of depression.



Vagus nerve stimulation via an implanted device.

This idea is now being tested. It's a psychiatrist's dream—knowing exactly where you'd want to place the magnetic coil to have the greatest likelihood of reducing a patient's symptoms.

Another innovation in brain stimulation therapy came to fruition in the last year, when the FDA approved a cervical vagus nerve stimulation (VNS) device for use in stroke patients. Say you can't move your right arm because of a stroke. Well, you go to your physical therapist and you have this VNS device implanted in your neck. The therapist, while you're trying to move your hand, will stimulate your vagus nerve. And so you're being stimulated while moving. This pairing of VNS with the behavior you're trying to address seems to work. People with the device are able to recover from the stroke much better than those without it. We are also testing VNS delivered noninvasively, with a device that can be placed against the neck or over the ear.

This brings together brain stimulation with Eastern medicine, specifically acupuncture. Years ago we learned that there are acupuncture areas that have effects similar to vagus nerve stimulation. We can now target those areas electrically to stimulate the vagus nerve. As I just mentioned it is now FDA-approved for stroke rehab in adults. Could this work as well in newborns? This is the pioneering work of Dr. Dorothea Jenkins. Many babies are born with brain damage. The first thing a newborn needs to learn is to how to suck, swallow and breathe—the complicated skill of feeding. Those infants that cannot learn how to feed have to be given a feeding tube in the stomach before they can go home from the hospital.

Dr. Jenkins has delivered stimulation to the vagus nerve while the baby is learning to feed. This has enabled Dr. Jenkins to take half of the kids who are supposed to have a feeding tube and with this approach actually teach them how to feed so that it is unnecessary. We're now trying to apply this technology to children with cerebral palsy while they're trying to learn to move, as well as in children with autism spectrum disorder. Both involve stimulating the brain via the vagus nerve to promote learning-related brain plasticity.

THE FUTURE OF STIMULATION

Is there a holy grail? What is the best possible brain stimulation tool?

I prefer noninvasive stimulation. It means we don't have to do surgery. The ideal tool will enable us to stimulate deep in the brain *or* superficially—both. I want it to be inexpensive. I'd love for it to be portable. And I want it to just modulate the brain and not destroy brain tissue.

I'm working right now with a new stimulation delivery method called pulsed ultrasound. It uses the same technology as ultrasound that enables us to "see" a baby in the womb, but instead of continuously generating the sound waves, we pulse them. For reasons we still don't understand, when you pulse ultrasound at a human neuron, it causes it to depolarize. In other words, the sound waves stimulate the neuron by changing its electrical activity.

You can use ultrasound to ablate the brain—destroy cells as a means of treating, for example, essential tremor (also FDA-approved). However, in our experiments, we use a much milder form of ultrasound that doesn't destroy tissue. We're just modulating the activity of neurons and circuits. Initially, being scientifically skeptical

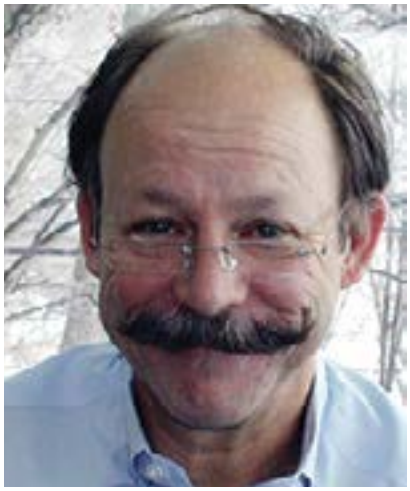
of any new way of stimulating the brain, I suggested that we should first use ultrasound to target the thalamus, which is deep in the brain. The aim was to see if we could reduce sensations of pain, which are modulated by the thalamus. I reasoned that if pulsed ultrasound can noninvasively modulate the thalamus and cause changes in pain perception, then it might have many other uses.

We designed a study where we stimulated the thalamus of healthy adults while they were inside the MRI scanner. And what we found in our first study was that we were able to modulate pain by stimulating the thalamus with ultrasound. We still need to do a lot more work in terms of targeting and optimal dosing, as well as looking at what happens over time and to see how long beneficial effects last. But at least in my mind, it does seem that ultrasound can go deep into the brain, non-invasively. We're a little further along now with ultrasound than where I was back in 1996 when we were developing TMS, so we've made a start and are doing small clinical trials right now. There's still a lot of work needed before this could become a therapy.

In reviewing the explosion of new ways to stimulate the brain. I've talked about electrical stimulation, magnetic stimulation, and stimulating with sound. I haven't talked about light. There's really interesting research being done in **"focal pharmacology," guided by brain stimulation,** in which a medication is delivered inside a carrier molecule, and then is guided to its target by brain stimulation technology. You release the medicine just in that part of the brain where you want it to go. This way, there are no "off-target" effects.

So we have so many new ways to stimulate the brain. However, the rate-limiting step in developing new treatments involving brain stimulation is not ideas or technology. It's actually people—people who know how to do clinical trials, who know patients, and who can do the initial small studies testing whether these technologies can be used as therapies. And that's where BBRF and other grant-giving agencies are so very, very important. Given sufficient research funding, I feel that for brain stimulation, the sky is the limit. But we need to grow and invest in the young researchers of the future. ❖

A Q&A with Dr. George follows on p. 10



Q&A with Dr. George

For someone reading this today who suffers from depression and wants to try TMS, what's the best way to go about it? How do you find a reliable place for treatment?

Today, almost every reasonably sized city in the U.S. has a couple of different providers. There are different ways that it's being provided. There are national chains that provide the TMS; your psychiatrist can refer you to one, kind of like a dialysis center or an imaging center. But maybe the easiest and most reliable approach would be to look up the Clinical TMS Society (https://www.clinicaltmssociety.org/) It's a national organization of psychiatrists who do TMS and their standards are high. They have a lot of information on their website about local providers. That's how I would do it.

Are there any "best places" you can recommend for TMS treatments?

The thing that's important about TMS is that years ago, we did the studies, we found the effect, and then we had to figure out a way that we could train psychiatrists how to do it. And we did. And so, most psychiatrists who have gone to a week-long training course, like one we offer here in Charleston, get results that are just as good as you would get at a major medical center. As long as the doctor has been well trained, the results tend to be good. And that's important to me because people are always calling up and saying, "We want to come to Charleston to have you do it." I say, "Look, it is so much better for you to see a local doctor—they will do just as good, and maybe better, because you won't be living in a hotel, be displaced and stressed while you're getting your treatments." So again, the Clinical TMS Society is probably the best first step.

You spoke about some of the future potential uses for TMS. Are those available for people now? Do these have to wait for FDA approval?

I'm pretty conservative clinically while I push the limit as a researcher. And I tend to be evidence-based. When you ask for things that aren't yet FDA-approved, it becomes an individual discussion with your doctor about the risk and benefits. And I think that's appropriate if the discussion is good and the evidence is there. But for those applications that aren't yet approved, it's really important to go to somebody who's well trained and who will give you an honest answer about what the evidence and risks are. It's likely that TMS is pretty risk-free. The side effects are minimal. But it's best to go to somebody who's well trained and has some experience.

Could you tell us a little bit more about the side effects of TMS that people may sometimes experience?

TMS is loud, so you have to wear ear plugs. People often feel a tapping sensation when the treatment is delivered, as the coil is placed against the scalp. Common side effects include minor headaches which usually go away after the treatment is over; also, transient scalp discomfort at the site where treatment is given, and sometimes, twitching of facial muscles, again. while the treatment is being given. In very rare cases, TMS can cause a seizure. Another rare impact in some people with depression is that they may feel a little elevated by the treatment—what we call hypomania.

Is it one course of treatment—or may some patients need ongoing "boosters"?

For the treatment of depression it's a rule of thirds. If you have treatment-resistant depression—for example, you have tried and failed two medications—then your chance of having a remission with TMS (full relief of symptoms, at least for a time) is one-third. For your symptoms to be reduced by half there is also a one-in-three chance. Finally, there's a one-in-three chance you won't have any benefit. After an initial course, for patients who responded or had a remission, there's another rule of thirds. One third of people who've remitted will never need TMS again after a single course. They may stay on medications. They may do talk therapy. But they've changed. They've gotten out of that hole. Another third will

need another TMS course within two years. Another third will go a couple of months before they relapse and they'll need another full treatment course. Those patients will also probably need what's called "maintenance," where we work out doing treatments once a week, or once every couple of weeks for them.

Is there a way to predict which group you are going to be in?

No, but we would love that. And it's part of the research that we're doing here. I'd love to have a sorting hat like in Harry Potter where we can predict who will respond or not. Research with brain imaging or genetics or a combination of both shows some promise in this area.

Could you tell us a little bit about the portable version of TMS that you're working on?

The question is, can you actually have at-home devices to deliver TMS. TMS requires a large capacitor and it might cause a seizure, so it is not easy to be made into a home-based treatment. But another less invasive approach shows promise. We've just finished a study of a taVNS device—transcutaneous auricular VNS—which is used at home for people with "long COVID" and depression. It looks like it might work and if it does, it will mean the patient never has to come in. [taVNS non-invasively delivers electrical stimulation to the auricular branch of the vagus nerve, an easily accessible target that innervates the human ear.] We send the device to you. We do everything online. So that's a possibility.

Then we have another device (Neurolief) that's in a pivotal clinical study. If this study is positive, it could be on the market in a year. It actually stimulates the trigeminal nerve and the occipital nerve. You would wear this device twice a day for 20 or 30 minutes. The study is in progress right now.

Can you speak about the extent to which research is being conducted with adolescents, 15- to 18-year-olds, and whether there are any cautions you have regarding this age-group?

I'm sympathetic. I think the earlier in life that we can make an intervention, the greater the potential is for lifelong improvement. And the brain is more plastic early in life and should be easier to change with brain stimulation. Yet TMS for adolescent depression is not yet FDA-approved. The problem is that it's hard to study adolescent depression.

Clinically, I have good reason to think that TMS works to treat adolescent depression. I have had many clinical patients who were students who got depressed, dropped out of school, isolated at home. And then we treated them with TMS and they get a lot better. They get back on their game. Years later they send me graduation pictures from college or wedding pictures. And it's so heartwarming because I think the brain is more plastic in adolescence. And so, the chances of moving the circuits involved in depression and actually changing the lifelong trajectory of depression are really good. It's not FDA-approved yet for this group, but we do it in my practice and find that it works. But this is still a gray zone and as I said, studies are hard to do.

Could you speak a little bit about the suicide prevention aspect of TMS, because that's obviously an important issue.

We need good, quick treatments for suicidality. The last two years have shown potential promise with ketamine, which is rapid-acting. We know that ECT works, but ECT has to be done on an inpatient basis. I refer back, then, to the research on accelerated and intensified TMS that my former student, Dr. Nolan Williams, has just done, which is so important. His 5-day course of accelerated TMS gets people un-suicidal often within a day or two. The accelerated TMS approach that Dr. Williams is using hopefully will be available in the period just ahead. Ketamine certainly is already making a difference.

Researchers now are putting TMS machines in psychiatric emergency rooms. There are so many people who now come to an emergency center who are terribly depressed and suicidal and they can't get a bed in a timely fashion. And so they spend two to three days waiting in the emergency room to get into the hospital. If we have TMS machines there and we can start treating, they may actually not even need to be admitted. So I'm excited that we could have treatments either like ketamine or TMS, or both, that can get quick resolution and then get people on the road to recovery. ❖

FDA Clears SAINT Rapid-Acting Brain Stimulation Approach for Those Suffering From Resistant Major Depression

On September 6, 2022, the U.S. Food and Drug Administration cleared the way for marketing of a rapid-acting brain-stimulation approach for major depressive disorder pioneered by **Nolan Williams, M.D.**, of Stanford University, and colleagues. Dr. Williams is a 2018 and 2016 BBRF Young Investigator and winner of the 2019 BBRF Klerman Prize for Exceptional Clinical Research.

The FDA issued a 510(k) clearance for a California company called Magnus Medical to commercialize the protocol developed in the Williams lab and tested in three clinical trials, results of which were published in *Brain* in 2018 and the *American Journal of Psychiatry* in 2020 and 2021. Magnus calls the protocol, which consists of several aspects, the "SAINT Neuromodulation System," following the acronym first adopted by Dr. Williams and colleagues for "Stanford Accelerated Intelligent Neuromodulation Therapy."

In the SAINT protocol, advanced imaging technology is used to individualize targeting of non-invasive stimulation to part of the brain's cortex, and significantly more non-invasive stimulation is delivered in much less time than is standard in TMS (transcranial magnetic stimulation), the most often used non-invasive treatment protocol now being offered to patients with depression.

The FDA marketing clearance specifically authorizes SAINT for use in individuals with treatment-resistant major depressive disorder, which can be a life-threatening condition. Resistance to treatment is defined as a failure to be significantly helped in one's current depressive episode by existing depression treatments—ranging from electroconvulsive therapy (ECT) to widely prescribed antidepressant medicines.

Dr. Williams is shown placing the magnetic coil just above the scalp on the left side above the eye, an area corresponding with the dorsolateral prefrontal cortex, which lies beneath.

SAINT turned heads in the psychiatric and medical communities when results of a clinical trial were reported in 2020. In that trial, 19 of 21 participants with refractory major depression achieved remission after only 5 days of treatment. Results of the next trial, in 2021, were no less impressive: 79 percent of 29 participants achieved remission after 5 days of receiving brain stimulation under the SAINT protocol. This result was considered even more significant, since participants were randomly assigned to "active treatment" and placebo groups, and doctors and patients alike were "blinded" as to which patients were receiving the active treatment.

Alan Schatzberg, M.D., of Stanford, and a member of BBRF's Scientific Council, says that the protocol cleared by the FDA "is groundbreaking and could help many patients with major depressive disorder who have not responded to treatment with antidepressants." Not only did SAINT help most of those who received it; the improvements, Dr. Schatzberg noted, "were dramatic, rapid, and frequently sustained through the study follow-up period."

Mark S. George, M.D., of the Medical University of South Carolina, also a member of the BBRF Scientific Council and a two-time BBRF grantee, pioneered the non-invasive brain stimulation technology called TMS (transcranial magnetic stimulation) upon which SAINT builds. Dr. George said clearance of the new protocol "is really exciting news." Dr. George, who was Dr. Williams' mentor when he was studying to become a researcher, said: "This is more than just clearance of just another device. It expands the way we can use TMS to treat depression. Older approaches often took 6 weeks for depression to respond, while this approach observed remission from depression in just 5 days. That opens up many new possibilities to use SAINT in hospitalized patients, and for patients who present to the emergency room."

"SAINT is groundbreaking and could help many patients with major depressive disorder who have not responded to treatment with antidepressants."
–Alan Schatzberg, M.D.

SAINT employs a kind of brain stimulation that is a refinement of a variant form of TMS called intermittent theta-burst stimulation, or iTBS. In iTBS, the patient receives the same "dose" of brain stimulation as in FDA-approved TMS over the same period of weeks, but receives it in much shorter treatment sessions, lasting 3 minutes per session as compared with 37 minutes in conventional TMS. One of the chief innovations of SAINT is to deliver 10 sessions of iTBS per day over 5 days. Each of the 10 daily sessions is separated by an interval of 50 minutes—as Dr. Williams has said, they are designed "to build upon one another to amplify the antidepressant effect."

Dr. Williams has also explained another important difference between SAINT and conventional iTBS and TMS. Each patient receives an 8-minute resting-state fMRI scan to pinpoint the target of the magnetic stimulation, which is approximately located beneath the upper-left forehead. The exact location of the underlying dorsolateral prefrontal cortex varies from person to person by as much as several millimeters, and is sometimes not "hit" when targeting is not guided by imaging results. This does add cost to SAINT, but is thought to greatly increase its accuracy and effectiveness—which can amount to saving lives in patients with highly refractory major depression. SAINT has also been shown in the trials to eliminate suicidal thinking in those who are affected, although the duration of this benefit as well as the antidepressant effects are still not yet clear and will be studied further.

For now, however, the remarkable clinical results achieved in deeply depressed and treatment-resistant people, some suicidal, over the course of only a few days, suggests that the SAINT protocol has immediate value for those who, as Dr. George points out, are hospitalized or who go to the emergency room while experiencing a suicidal crisis.

Magnus Medical says it is now performing research aimed at investigating the use of SAINT more broadly and in other psychiatric disorders. Drs. Williams, Schatzberg, and George serve on the Scientific Advisory Board of Magnus Medical. Dr. Williams holds patents and resultant equity on SAINT technology. ❖ **PETER TARR**

A New Approach to Treating Cognitive Deficits in Schizophrenia

Dr. Vikaas Sohal used a new technology to understand why cognition is impaired in schizophrenia and now is exploring how it might be targeted

Vikaas S. Sohal, M.D., Ph.D.

Associate Professor, Psychiatry
UCSF Weill Institute for Neurosciences
University of California, San Francisco

BBRF Scientific Council Member
2009 Young Investigator grant

IN BRIEF
Dr. Sohal and colleagues have used new technologies including optogenetics to discover biological processes that are likely involved in causing cognitive dysfunction in schizophrenia. The road to bold new treatments is being paved with this new knowledge. One objective may be to restore normal gamma-frequency activity in the cortex to boost the efficiency of circuits involved in cognitive processing.

Decades of observation and experiment have established that cognitive deficits are among the core features of schizophrenia. As one recent paper on the subject notes: "Studies have shown that compared to healthy controls, schizophrenia patients have impaired cognitive performance across all cognitive domains including processing speed, attention and vigilance, working memory, verbal learning, visual learning, reasoning/problem solving, and social cognition."

Patients find it difficult to focus or concentrate; to organize their thoughts; to keep newly acquired information "in mind"; to modify or adapt their behavior in response to new sounds and sights; to make sense of perplexing experiences or unfamiliar information.

These cognitive difficulties directly affect the ability to get along in society. Resulting problems in social functioning can lead to social isolation, and to interpersonal problems which can exacerbate symptoms and thus significantly impair quality of life, interfering with rehabilitation or efforts to get and keep a job.



Cognitive deficits in schizophrenia make it hard for patients to focus or concentrate; organize their thoughts and keep newly acquired information "in mind"; and deal with new or unexpected information.

All of this is well known. But one thing is not often said: no one really understands why cognitive dysfunction occurs in people with schizophrenia.

Cognitive impairment is the "major cause of disability" in schizophrenia, and helps explain why the illness remains stubbornly disabling for many patients, according to BBRF Scientific Council member **Vikaas S. Sohal, M.D., Ph.D.**

A practicing psychiatrist and a leading neuroscience researcher, with a lab at the University of California, San Francisco (UCSF), Dr. Sohal notes that antipsychotic medicines, which are essential tools in managing psychotic symptoms such as hallucinations and delusions, don't address cognitive impairment. And while many cognitive remediation treatment strategies have been tested and have helped some patients, their effectiveness varies, he says. Like antipsychotic medicines, "they have not really been developed on the basis of understanding the biological mechanisms that actually cause cognitive deficits."

Thanks to a new technology that was emerging just as Dr. Sohal completed his training—developed in part with help from BBRF grants—and to experiments performed with that and other advanced technologies, he and his colleagues in recent years have made discoveries that have revealed, at last, biological processes that are likely involved in causing cognitive dysfunction.

In an "Overview" paper he published in April 2022 in the *American Journal of Psychiatry*, Dr. Sohal suggested how this new knowledge might be translated in the coming years into new treatments for cognitive deficits in schizophrenia.

'RIGHT PLACE, RIGHT TIME'

Dr. Sohal's highly productive research career, still in its early stages, exemplifies how investments in basic research and in the development of new technologies can pay great dividends in ways that cannot possibly be predicted in advance. Apart from his academic brilliance—he studied Applied Mathematics at Harvard as an undergrad, Mathematics at the University of Cambridge, UK, and then went on to complete an M.D.-Ph.D. program at Stanford University in 2005—Dr. Sohal's early orientation as a neuroscientist did not indicate a particular focus on cognitive deficits in schizophrenia.

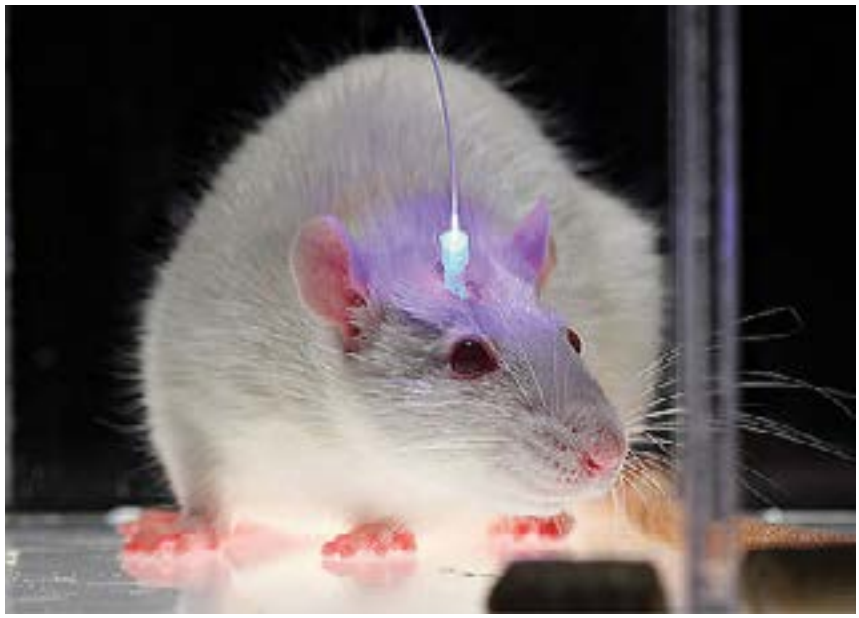
His early career parallels that of one of his mentors, **Dr. Karl Deisseroth**, who preceded him in the Stanford M.D.-Ph.D. program by a few years. Last year, Dr. Deisseroth received

Cognitive impairment is the major cause of disability in schizophrenia, and helps explain why the illness remains stubbornly disabling for many patients.

the highly prestigious Lasker Basic Medical Research Award, sharing it with two others who helped develop optogenetics. In essence, optogenetics enables experimenters to switch specific neurons, or groups of them, "on" and "off," doing so with beams of colored light directly conducted into the brain via optical fibers no wider than a thread.

Dr. Deisseroth received BBRF Young Investigator awards in 2005 and 2007, which helped support him as he was setting up his Stanford lab where some of the earliest optogenetics research was conducted. This is when he and Dr. Sohal met. "When I graduated [the Stanford M.D.-Ph.D. program], Karl had just finished his [medical] residency and was starting his lab," Dr. Sohal remembers. "It was an example of being at the right place, at the right time. We got along, and he was interested in the same general things that I was. I was able to join his lab, before returning to my own residency and then starting my own lab after that."

Dr. Karl Deisseroth



Experiment with a mouse fitted with an optogenetic probe.

Just as Dr. Deisseroth had received early-career support from BBRF, so did Dr. Sohal, when he finished his medical residency and began his own research program. His Young Investigator award was made in 2009, and by 2017 his accomplishments merited his election to BBRF's Scientific Council—just as Dr. Deisseroth's had in 2008, at a similarly early point in his career.

When Dr. Sohal says he and Dr. Deisseroth shared research interests, he means a passion for understanding mechanisms in the brain, at the level of cells and the complex circuits they form. In ways that until very recently have been a black box, brain cells and circuits give rise to astonishing properties such as memory, the ability to learn, and that ultimate miracle and mystery, consciousness itself.

Like many other contemporary researchers, Drs. Deisseroth and Sohal have made it their life's work to devise ways to study the brain at the cellular and circuit level *while it is operating*, in living beings, and to use these technologies to begin to unpack how, for example, circuits appear to function differently when someone has major depressive disorder or obsessive-compulsive disorder, or, indeed, schizophrenia. The road to bold new treatments is being paved with this knowledge.

OPTOGENETICS UNRAVELS A MYSTERY

A major milestone in the careers of these colleagues occurred while Dr. Sohal was working in Dr. Deisseroth's Stanford lab. These were the years in which optogenetics, with its stunning capability of controlling specific neurons and circuits, was put to a test. These early experiments were opportunities to show how the new technology could not only reveal something previously unknowable about how the brain works, but also how brain biology might be perturbed in mental illness.

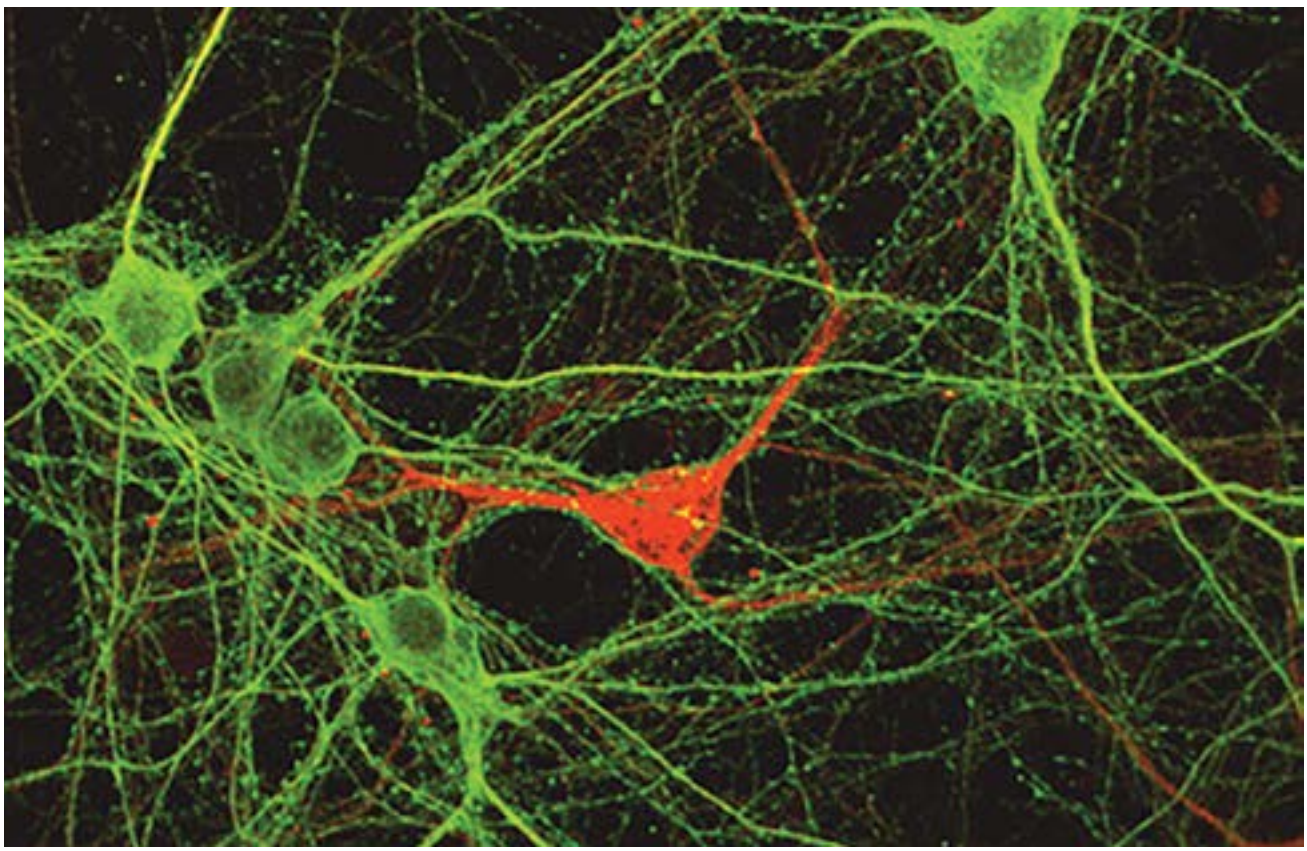
In 2008 and 2009, Drs. Sohal and Deisseroth used optogenetics to test the validity of a theory that until then was impossible to prove or disprove. They were interested in a subclass of neurons: neurons that release the inhibitory neurotransmitter GABA. These specialized cells reduce

or suppress neural signaling. They sit in the middle of local brain circuits composed mostly of excitatory neurons. The brain's proper functioning vitally depends upon them. Without properly functioning inhibitory cells, circuits can overload with excitation, resulting in seizures.

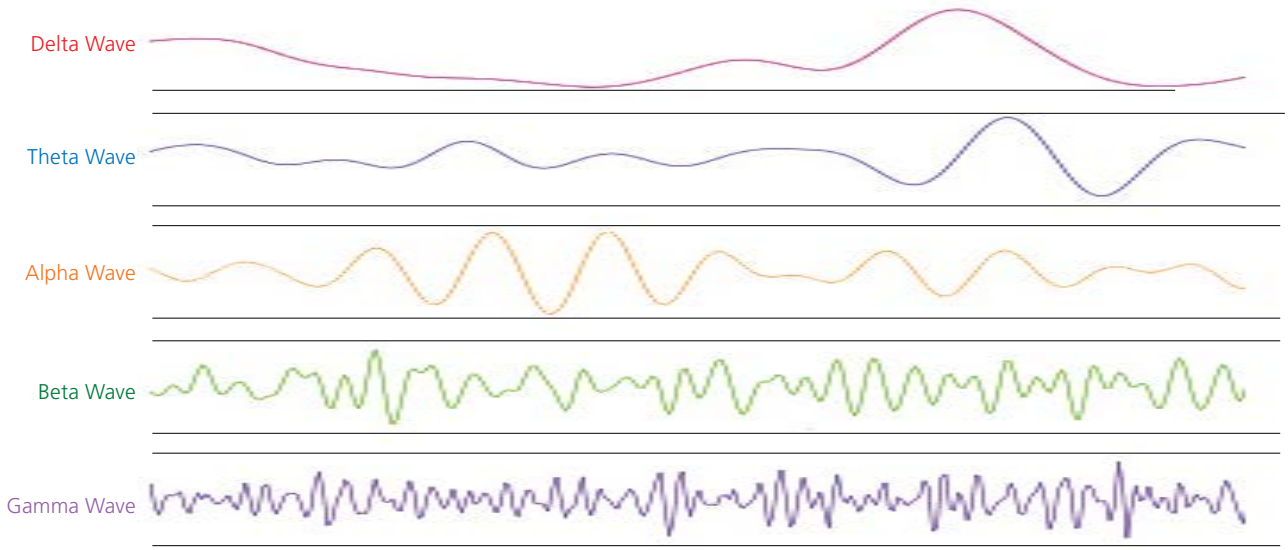
Drs. Deisseroth, Sohal and colleagues focused on a subtype of inhibitory cells called PV interneurons, named for a protein (parvalbumin) that they express which distinguishes them from other inhibitory cell types. PV interneurons make up about 40 percent of inhibitory neurons in the cerebral cortex, seat of the brain's higher functions. There had been speculation that they played an essential role in enhancing information processing; they were thought to be associated with a kind of rhythmic activity in the brain called gamma oscillations. There are irregularities in gamma oscillations in people with schizophrenia. But until optogenetics, there was no precise way of proving how PV interneurons affected gamma oscillations, and in turn, how gamma oscillation irregularities might impair information processing in schizophrenia—a potential clue to explain cognitive deficits.

The team used optogenetics to switch off PV interneurons in part of the rodent cortex. This provided direct evidence that inhibiting these inhibitory cells *reduced* gamma oscillations. In related experiments, the team

Gamma oscillation irregularities might impair information processing in schizophrenia—a potential clue to explain cognitive deficits.



An inhibitory PV interneuron (red) situated within a local network of excitatory neurons (green).



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

stimulated PV interneurons in the rodent brain, and found that this not only increased gamma oscillations, but tended to establish a gamma-frequency *rhythm*. This rhythm was the result of synchronized activity between excitatory and inhibitory cells within the circuit being studied. Perhaps most intriguing, the team was able to show that when a gamma rhythm was established, signal transmission was enhanced: "noise" in the circuit (useless information) was reduced, and the important "signal" carried by the circuit was enhanced.

These experimental results, reported in *Nature* in 2009, helped establish the utility of optogenetics, which is now a staple research tool in labs around the world. They also help to explain important aspects of the career that Dr. Sohal was just embarking upon, which has since blossomed in many directions. One unifying feature is his consistent fascination with systems composed of relatively simple parts, which, when functioning together, give rise to what are called *emergent properties*. The early experiments with PV interneurons provided a wonderful example: when these inhibitory cells were spurred, using optogenetics, they promoted a "gamma rhythm" across the circuit, which enabled the rodent brain to process information more efficiently.

Neural rhythms turn out to be very important in understanding how the brain works, and while Dr. Sohal has performed research involving other frequencies of neural oscillations, the gamma frequency, which captures fast neural oscillations (each cycle lasting 10 to 30 thousandths of a second) has turned out to have important implications for understanding cognitive dysfunction in schizophrenia.

Like most research, Dr. Sohal's has built upon prior clues. By studying postmortem brain tissue, other researchers had learned that various kinds of pathologies involving PV interneurons are commonplace in people with schizophrenia. BBRF Scientific Council Member, 2008 Distinguished Investigator, and 2005 Lieber Prize winner **David A. Lewis, M.D.**, of the University of Pittsburgh, has led studies in schizophrenia patients revealing deficits in the ability of cortical circuits to generate gamma-frequency activity. Some scientists have speculated that irregularities in gamma-frequency activity are a precursor of a first psychotic episode—typically, the event which immediately precedes the onset of schizophrenia.

Yet there is a pivotal question about these gamma-frequency clues. As Dr. Sohal put it in his recent "Overview" paper: "Do gamma oscillations simply indicate that brain circuits are active—akin to the roar of a car's V8 engine—or do they actually perform functions that enhance the performance of brain circuits?" There was a suggestion of the latter in the 2009 paper. But additional research was needed to know more.

In 2015 and 2020, Dr. Sohal's team published papers, respectively, in *Neuron* and *Nature Neuroscience*, describing experiments which shed

new light on this question—mouse studies that gave direct evidence that gamma oscillations aren't just the "sound" of the brain doing its job, but actually contribute to cognition. The experiments also suggested that restoring normal gamma-frequency activity in the cortex might reduce or even reverse the kind of cognitive deficits seen in schizophrenia.

In the 2015 paper, experiments were led by **Kathleen K.A. Cho, Ph.D.**, a 2013 BBRF Young Investigator who studies and works with Dr. Sohal and **John Rubenstein, M.D., Ph.D.**, a three-time BBRF grantee, 2016 BBRF Ruane Prize winner and emeritus Scientific Council member who is also at UCSF.

The team worked with mice that were bred with deficiencies in PV interneurons. These mice develop deficits in cognitive flexibility, a trait that is impaired in schizophrenia. Like normal mice, the mutant mice were able to learn a rule governing a particular task; but unlike the normal mice, those with PV interneuron abnormalities were unable to adapt when the rules were shifted. They "perseverated" in their behavior—kept going back to the rule they learned initially even though it was no longer effective.

REVERSING COGNITIVE DEFICITS

Two fascinating things emerged from this. First, it was shown that when normal mice learned the "new" rule, gamma oscillations in the prefrontal cortex were increased, while in the mutant mice, they were deficient.

Second: when the team used optogenetics to increase gamma oscillations in the cortex of the mutant mice, they were then able to learn the new rule and obtain a reward. And this ability persisted over a period of weeks: the corrective was long-lasting in its effect. "Performance was completely normalized," Dr. Sohal comments. This suggested—but did not prove—that certain cognitive deficits in schizophrenia might likewise be reversed, at least in principle.

The second paper, of 2020, put the same team to work on discovering why the enhancement of gamma oscillations was effective in boosting cognitive capacity. This time, key experiments were performed in normal mice. The researchers looked at what happened in PV interneurons when the mice were in the process of learning a new rule. This revealed the importance of what Drs. Sohal, Cho and colleagues call *gamma synchrony*. Not only did cortical gamma oscillation levels increase when a new rule was learned; in fact, oscillations became synchronized across the brain's two hemispheres. Optogenetics was used to disrupt this cognition-boosting synchrony. Doing so prevented the mice from learning the new rule. Restoring synchrony restored the animals' ability to learn the new rule.

Speaking about this experiment today, Dr. Sohal, after prompting, conceded that it was indeed a "wow" result. "But remember," he added, with the caution that characterizes most scientists, "We are talking about mice, not people."

Just as the sound of rhythmic cheers in a crowded stadium might mystify someone standing outside the stadium, the meaning of rhythmic patterns generated by firing neurons—for instance, gamma rhythms—has long perplexed scientists, who are now beginning to understand their import.

It may be advantageous to administer a drug that enhances gamma synchrony in concert with with a behavioral intervention like cognitive training, meditation, or biofeedback.

Although research in the Sohal lab is wide-ranging and has potential relevance for many psychiatric illnesses, the line of work on gamma oscillations has implications that Dr. Sohal has now explained in some detail to the psychiatric community. In his recent "Overview" paper he explains that there are, in principle, a number of ways to enhance gamma synchrony in the human brain.

While optogenetics can establish gamma synchrony in mice, it can only be used, ethically, in laboratory animals, since it involves brain surgery. In humans, gamma oscillations might be altered with a number of pharmaceutical compounds, Dr. Sohal says, for instance "low doses or well-titrated doses of benzodiazepines [anti-anxiety agents] or drugs like clonazepam or lorazepam, which are commonly used at higher dosages to sedate people." But these drugs have actions that are not specific to PV interneurons and may have unwanted side effects.

It is possible, Dr. Sohal says, that current pharmaceutical technology can support the development of agents that specifically target a subset of cellular receptors for GABA, the neurotransmitter that is released by PV interneurons. The idea would be to selectively modulate the action of PV interneurons, as a way of addressing gamma oscillation and promoting gamma synchrony.

Another possibility is being explored by **Cameron Carter, M.D.**, of UC Davis, who is also a BBRF Scientific Council member as well as 2-time BBRF grantee and winner of the BBRF Klerman Prize. As Dr. Sohal notes, Dr. Carter is exploring the use of non-invasive brain stimulation—tDCS (transcranial direct current stimulation)—to alter gamma oscillations as a possible way of addressing cognitive dysfunction.

A number of questions remain before these treatment approaches can be tested in healthy people and then in patients with cognitive dysfunction. If drugs are to be used, it will be important to understand what they target in the brain and what their off-target effects might be; what doses to use and how to predict which patients might benefit and which might not.

Dr. Sohal also says it will be of great value to know more about where and when to boost gamma activity. Circuits in the cortex are famously complex, consisting of many different types and subtypes of both excitatory and inhibitory neurons. Are there specific places, even specific synapses, in the brain to target to boost gamma activity and cognition? Or should large areas be targeted? Should treatments be continuous or need they be given only occasionally or rarely or even just once? All of these questions and many others remain to be explored in the next several years before it is reasonable to test these concepts in people.

Yet Dr. Sohal is hopeful. In his recent "Overview" paper, he wrote: "It is now clear that gamma synchronization contributes to the function of brain circuits in ways that could be highly relevant for treating cognitive deficits in condition such as schizophrenia. In fact, the complexity of cortical microcircuits may turn out to be a major asset, not a barrier, by enabling us to target particular aspects of gamma synchrony in a relatively specific manner."

Elsewhere he adds: "There is no reason to assume that interventions should be limited to pharmacology. It might be possible to administer a drug that enhances the capacity for a circuit to generate gamma synchrony in concert with a behavioral intervention such as cognitive training, meditation, or biofeedback, or noninvasive brain stimulation (e.g. tDCS) to enhance gamma oscillations." ❖ **PETER TARR**

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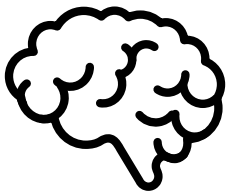

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Carlos A. Zarate, Jr., M.D.
Jon-Kar Zubieta, M.D., Ph.D.

The Consequences of Talking Publicly About My Bipolar Illness

Psychologist and prize-winning author Dr. Kay Redfield Jamison reflects on her decision and efforts to reduce stigma

By Kay Redfield Jamison, Ph.D.

Co-Director, Johns Hopkins Mood Disorders Center
Dalio Professor in Mood Disorders
Professor, Department of Psychiatry and Behavioral Sciences
Johns Hopkins University

2021 Pardes Humanitarian Prize in Mental Health
2010 BBRF Productive Lives Award
2007 BBRF Falcone Prize for Outstanding Achievement in Affective Disorders Research

The following text is based on a recent lecture given by Dr. Jamison.

IN BRIEF
After making a courageous public disclosure of her own history of bipolar disorder, Dr. Jamison encountered a range of responses. More than a few of her colleagues in medicine and psychiatry seemed acutely uncomfortable. But, she says, for every coldness or drawing back, there have been more acts of kindness and of drawing her in. She is especially dedicated to counseling young people, who are at comparatively greater risk and who may be particularly hurt by stigma.

When I am asked to talk about the stigma of mental illness, I balk a bit, because I think the term itself is stigmatizing. But it may be useful if I provide a personal example, one that suggests what happens when you write about having a psychotic illness and describe having tried to kill yourself, and how you nearly did so. I would like to share with you the public reaction to that memoir and the reaction of some of my colleagues.

Before I published my book about my own experiences with bipolar illness, *An Unquiet Mind,* I decided to talk about my illness with a journalist who was writing a story for *The Washington Post* about my work. I knew that before the newspaper article came out, I was going to have to tell my patients about my illness.

I didn't look forward to insinuating my own life and problems into longstanding psychotherapeutic relationships, but I had no choice. I sought out the advice of two experienced clinicians and colleagues and discussed with them a variety of ethical and clinical issues that might arise. None of us could predict what was likely to happen. There were, for me and for Johns Hopkins University, where I work, very real legal issues, issues of licensing for me, and issues of whether or not I could continue my clinical practice—which I did not. Stopping my clinical work was something I knew I would have to do and was very reluctant to do, but I felt strongly that it was advisable.

I was curious and concerned about the reactions of people who were in charge of academic and clinical affairs at John Hopkins. The chairman of my department and the president of Johns Hopkins Hospital could not have been more supportive, more generous in their response. And for that, I am eternally grateful. Theirs was not a typical response, I think, but it was certainly exemplary.

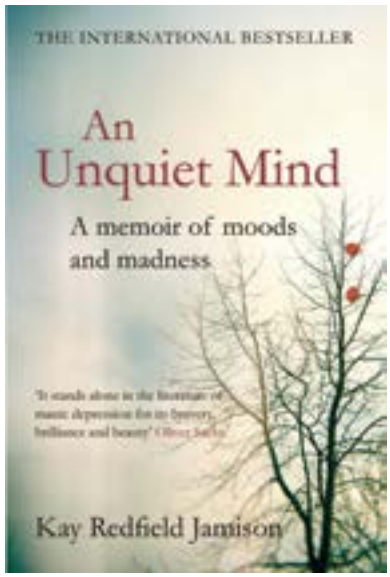
I was concerned about my patients. I'm not a therapist who believes in talking about my personal life to patients, and I certainly had not done so prior to disclosing my illness to them. Therapists have different perspectives on personal disclosure, but I had not ever talked about my illness to my patients.

I thought that I knew my patients well, but telling them that I had had a psychiatric disorder was not something that had been covered in textbooks, nor had it been discussed during sessions with clinical supervisors. I had no idea what to expect. As it turned out, I didn't find it as difficult to tell my patients as I had imagined. Most of them were just simply stunned. "You seem so normal," said one. "So Brooks Brothers-ish!" And indeed, over the next several weeks as I told my patients one by one, it was quite surprising to me the number of people who used Brooks Brothers to describe me. After my initial disclosure, and a session or two of discussing related issues and concerns, psychotherapy with my patients reverted to normal. I did find myself keeping more detailed clinical notes, however, as I was newly sensitive to potential legal issues.

Two fellow professors, whom I had been treating for years, expressed the hope that the academic and medical communities would become more aware of the extent of mental illness, and mental illness in their own ranks, and both remarked, with a surprising degree of bitterness, that they hoped that the academic and medical communities would become more tolerant. They made it clear they weren't going to wait for this with bated breath. They both had been profoundly affected by stigma and the negative attitudes of their colleagues.

The responses to the *Washington Post* article, in which I openly discussed my illness, were various and complicated. I felt a discomfort in many of my colleagues and acquaintances, an awkwardness that made me cringe and want to bolt, but there was no place to run. Reactions from others were variously funny, insensitive, generous, wonderful, or cruel. The responses were, in short, very human.

Several of my colleagues at Hopkins told me that the chairman of my department had made it clear that I should not be made to feel that I was "alone out there." I owe him and Johns Hopkins, the hospital, the administration, and faculty, an immeasurable debt. One day, the chief resident dropped by my office. She told me she had distributed the *Washington Post* article to all the residents, several of whom suffered from mood disorders themselves. Residents and medical students, as well as nurses and others on the staff at the medical school, called to talk about their own experiences



Dr. Jamison's courageous, pathbreaking first book.

Dr. Jamison makes it a special point to reach out to young people, noting that the student years represent the age of greatest risk for developing mental illness.

with mental illness. So, too, did many of the faculty: surgeons, internists, oncologists, psychiatrists, cardiologists, basic scientists. Few specialties were unrepresented.

Not long after my public disclosure, I went to the annual meeting of the American Psychiatric Association. Most of those I spoke with were warm and supportive. More than a few, however, seemed acutely uncomfortable. They averted their eyes, drew away, said nothing. I was struck by the silence; it was bone-chilling. There was a sense from some that I should be embarrassed by my revelations. And when I was not, that they were embarrassed for me.

KINDNESS I COULD NOT HAVE IMAGINED

For every coldness or drawing back, however, there have been far, far more acts of kindness and of drawing me in. As a child I had been quiet and invisible when troubled. As an adult, I had hidden my mental illness behind an elaborate construction of laughter and work and dissembling. Now my mind and heart were bright lit on a page, behind a lectern, or on a television screen. Yet, despite this, it felt good to be honest, to be a part of the community which until recently I had kept to the edges of. I was no longer just a researcher and a clinician answering questions about diagnosis and treatment. I could talk of my own madness, my own fears, feel not so distant, not so hypocritical.

I received many thousands of letters in response to the publication of my book, *An Unquiet Mind*. Most were generous, but many were deeply disturbing. Religious diatribes were common. I received hundreds of letters from fundamentalist Christians berating me for turning my back on God and abandoning my Christian faith, which I had not been aware that I had or had not done. I got more than a taste of the intolerance and hatred that religious extremes bring to those with mental illness. It was unpleasant and deeply frightening. I was taken aback by the medieval qualities of some of the beliefs held.

Many letters were anti-science, anti-genetics, anti-psychiatry. It was not new to me that a large number of people resent doctors or mistrust scientists, but I'd been relatively spared from this. I was surprised by the extent of the mistrust and the resentment. Many railed on about the depravity and cluelessness of myself and my scientific and medical colleagues.

Some people expressed resentment that I had had the advantage of financial security and supportive friends, colleagues, and family. What right did I have to complain? I could not possibly understand the real pain of mental illness, they suggested. One colleague, hard-edged and drunk, in front of many of our colleagues, snapped that she thought because I had had a privileged upbringing, which was a bit of a stretch, I had no right to discuss the suffering caused by mental illness.

It was presumptuous, she said, to write about it. I found this outrageous. It seemed beyond the pale to have to explain to a professor of psychiatry that the pain of bipolar illness, like the pain of cancer, does not discriminate on the basis of "privilege." Despite this, most people were incredibly kind. They were kind in ways I could not have imagined.

TALKING TO OTHERS ABOUT YOUR ILLNESS

Everywhere I have gone, I have seen the wreckage left by mental illness, and the resilience, inventiveness, and generosity of those who contend with it. More than anything, I have been impressed by what people survive—the pain, the injustices of a healthcare system that makes no pretense of fairness toward those with mental illness; financial ruin, violence, and most devastating, the suicide of a child, husband, or wife, or parent.

Nowhere has this mixture of devastation and bounty been more obvious than in talking with students who struggle with mental illness. I had been particularly eager to reach out to students, in part because the student years represent the greatest age of risk, and in part, because I, at that age, I had felt so terribly alone with the uncertainty and terror of my own mental illness. For students who are depressed or who have other mental illnesses, the contrast is razor sharp between how they feel and the energy and high spirits they observe in their fellow students. On every campus where I have spoken, students describe to me not only the pain and hopelessness they feel from their illnesses, but the lack of understanding they feel from their professors and college administrators, the lack of adequate health insurance, their fears about being asked to go on medical leave and not being allowed to return, and how aware they are that their behavior is frightening and disruptive to their roommates.

Students invariably ask me, "Do you worry about getting sick again? How have you stayed well?" And I tell them, "Yes, of course I worry, but it is good to worry." I tell them it's hard to get well, and it's hard to stay well, but that it certainly can be done.

When I talk to students, so many of whom have tried to kill themselves, I usually ask them, "Did you talk with your parents about this?" Few say that they have.

I have been deeply touched by the courage of these students, struggling as they do to study and to compete, to love and to stay alive. I admire how they have played the cards, the hard, unpredictable cards they have been dealt.

I have spoken with hundreds of children and adolescents with depression or bipolar illness. They experience the same pain and have the same fears as those who are older, but because the illness is usually more severe in the very young, and because they cannot understand as much about their illness as those who are older, they have a particularly difficult time of it.

I was in Colorado several years ago, talking to children from 7 to 17, all of whom suffered from bipolar illness. As I was leaving, a young boy, perhaps 8 years old, came up to me and put his hand in mine. He looked up at me and said, "Are you really okay?" I put my arms around him, and I felt him sobbing. "Yes, I am," I said to him, "I really am. You will be too." I reached into my handbag, held out my key chain, and removed the plastic Bugs Bunny charm I had carried for years. I told him it was my extra lucky charm because it had not just one rabbit's foot, but four. A small smile appeared. I gave him the key chain and assured him that Bugs Bunny would bring him the same good luck he had brought me.

I am an optimist. I tell the young people I talk to that bipolar illness is a bad illness to get, but that now is a great time to get it: the science is advancing rapidly, and public understanding is better than it has ever been. People talk about these things more. They write about them more. They are lucky to have benefited from early diagnosis and treatment—which was not the case years ago.

Science and more effective treatment are the ultimate de-stigmatizers of mental illness. ❖

Excerpted in part from Kay R. Jamison,
Nothing Was the Same
(New York: Alfred A. Knopf, 2009)

"I was no longer just a researcher and a clinician answering questions about diagnosis and treatment. I could talk of my own madness, my own fears, feel not so distant, not so hypocritical."

The 2022 BBRF Klerman and Freedman Prize Winners

Awarded at BBRF's Scientific Council Dinner, July 29, 2022

The BBRF Klerman and Freedman Prizes recognize exceptional clinical and basic research conducted by BBRF Young Investigator Grantees. The prizewinners are selected by committees of the Foundation's Scientific Council, led by its founding President, Dr. Herbert Pardes.

The Klerman and Freedman Prizes pay tribute to Drs. Gerald L. Klerman and Daniel X. Freedman, whose legacies as researchers, teachers, physicians and administrators have indelibly influenced neuropsychiatry. Their outstanding contributions to the field of brain and behavior research continue to inspire scientists who knew them, as well as those who are just entering the field.

This year, six young researchers were recognized for significant findings related to schizophrenia, psychosis, depression, neurodevelopmental disorders, and the biology of brain circuitry. Their important work is furthering the quest to identify the biological roots of mental illness to enable the development of new diagnostic tools, more effective and targeted treatments, and to pave the way toward prevention.

ANNUAL KLERMAN PRIZE FOR EXCEPTIONAL CLINICAL RESEARCH

Shan H. Siddiqi, M.D.

Harvard University; Brigham and Women's Hospital

Dr. Siddiqi's research is focused on causal mapping of human brain function and dysfunction. Using techniques such as functional connectivity MRI, he maps brain circuits to link brain lesions and brain stimulation sites that can modify different psychiatric symptoms. These circuits can then be targeted with treatments such as transcranial magnetic stimulation and deep-brain stimulation to alleviate symptoms in psychiatric disorders.

ANNUAL FREEDMAN PRIZE FOR EXCEPTIONAL BASIC RESEARCH

Antonio Fernandez-Ruiz, Ph.D.

Cornell University

Dr. Fernandez-Ruiz is investigating the computations and underlying cellular mechanisms that support the role of hippocampo-cortical interactions in learning, memory, and decision-making during normal and pathological states.

KLERMAN PRIZE HONORABLE MENTIONS

Rachel Emma Lean, Ph.D.
Washington University School of Medicine, St. Louis

Dr. Lean's research broadly focuses on the neurobiological and socio-environmental mechanisms of executive dysfunction, which is a major transdiagnostic risk factor for developmental psychopathology. She is currently examining the very early development of top-down cognitive processes such as executive function in early childhood in a cohort of socially diverse children followed from birth to age 3 years.

Sunny Xiaojing Tang, M.D.
Feinstein Institutes for Medical Research, Institute of Behavioral Science
Zucker School of Medicine, Hofstra/Northwell Health

Dr. Tang's area of expertise is in technology and psychosis, particularly using automated computerized methods to generate quantitative markers of psychosis and related disorders. She uses the latest technology to better understand and treat psychiatric disorders—particularly psychotic disorders, like schizophrenia.

FREEDMAN PRIZE HONORABLE MENTIONS

Chandramouli Chandrasekaran, Ph.D.
Boston University
Boston University School of Medicine

Dr. Chandrasekaran's scientific objective is to understand neural circuit dynamics in cortical and subcortical areas of the monkey brain that mediate decision-making, an integral part of everyday life profoundly impacted by mental illness.

Mohsen Jamali, M.D., Ph.D.
Massachusetts General Hospital
Harvard Medical School

Dr. Jamali shares a long-standing goal in cognitive neuroscience: to unravel the neuronal basis of social cognition and the processes underpinning its dysfunction in humans.

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There are many ways to support the Brain & Behavior Research Foundation during your lifetime and one particularly meaningful way is through planned giving.

When you include BBRF as part of your legacy plan, you help ensure that our groundbreaking research continues.

Gifts which benefit the Foundation also personally benefit its donors by helping to fulfill important family and financial goals and ensure that our scientists will have the resources to continue making advances in mental health research, today and tomorrow.

"My late husband Arthur and I have supported BBRF for 30+ years, and as part of our estate plan, we were looking to fund the extraordinary work of the foundation's Young Investigators in the future. My husband recently left a generous bequest gift and I have identified BBRF as a beneficiary from my IRA account."

– Miriam Katowitz, BBRF Board Vice President

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

Recent Research Discoveries

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

Difficulty Updating Prior Knowledge With New Perceptions Is Linked to Psychosis Symptoms

The delusions and distortions of reality reported by people who experience psychosis are one of the most difficult aspects of the illness from the standpoint of the patient. No one wants to be told that what they perceive in the world around them is either not real or is in some fundamental way inaccurate or distorted.

As researchers have long known from observation of patients, their "delusions are tenaciously maintained, even in the face of clear evidence" that refutes their reality. This is the starting point for new research by 2020 BBRF Young Investigator **Sonia Bansal, Ph.D.**, of the University of Maryland School of Medicine, and colleagues. She was first author of the team's paper in *JAMA Psychiatry*; **James M. Gold, Ph.D.**, a 1997 BBRF Young Investigator, was the team's senior member.

Drs. Bansal, Gold and colleagues wanted to know more about the relationship between psychosis symptoms like delusions and hallucinations and mechanisms in the brain that process perceptions on a real-time basis. They note recent research suggesting that delusions and hallucinations may result from alterations in the way prior knowledge is integrated with new information.

At issue, they explained, is whether this is the result of problems with perceptual mechanisms or higher-order reasoning processes.

By comparing individuals diagnosed with schizophrenia or schizoaffective disorder who experience delusions and/or hallucinations and comparing them with healthy controls, the researchers sought to discern any difference in the two groups' ability to update beliefs based on new evidence.

To make this determination, the team chose a relatively simple perceptual task, which they asked a total of 160 individuals in two independent samples to perform. Ninety of the participants were patients and the remainder were demographically matched controls; the average age was about 35, and a majority were male.

It was important to the team that the task they assigned participants posed minimal demands on conscious reasoning ability. In this way they could hope to capture potential problems in the processing of perceptions. The task called upon subjects to repeatedly respond to brief half-second or one-second trials, all of which involved dots in motion across a computer monitor. For each trial, participants were instructed simply to report the direction of the dots' motion at the end of the trial.

This was potentially revealing because in half of the trials, the direction of the dots did not change ("no-change trials"). But in the other half of the randomly assigned trials ("change trials"), the direction of 35% of dots shifted 90 degrees halfway through the trial. The question was: would those who suffered from delusions and hallucinations be able to update their initial impressions in trials in which dots suddenly changed direction?

The team found that those with psychosis tended to overweight initial information coming from sensory evidence in the "change trials," and thus tended to be unable to correctly report the change in the dots' direction.

The team interpreted this result as follows: "Even in a relatively simple perceptual paradigm patients with psychotic

disorder fail to update their perceptual beliefs when faced with new information." They went on to note that the degree of updating failure was correlated with the severity of patients' symptoms and their degree of conviction about delusions they had previously experienced.

"This suggests that the severity of psychosis may reflect a fundamental alteration of basic perceptual and cognitive processes," the researchers suggested.

For a variety of reasons, the team rejected other possible explanations for the observed result. One was that patients with psychosis might be more likely to report the dots' initial direction of motion because of another symptom of the illness, slower neural processing speed. In this scenario, the patients might not have had enough time to process the second direction of the dots. But if this were the case, the team said, it would be more likely they would report the second direction, not the first.

In the end, the team said its results "suggest that failure to integrate new sensory evidence with prior knowledge may be associated with psychotic symptoms in schizophrenia." ❖

The team also included **Phillip Corlett, Ph.D.**, 2008 BBRF Young Investigator; **Molly Erickson, Ph.D.**, 2017 BBRF Young Investigator; and **Britta Hahn, Ph.D.**, 2010 BBRF Young Investigator.

A Molecule Tested in Higher Primates Reduced Alcohol Consumption By Half

Mammals—including great apes and monkeys as well as early humans—began consuming alcohol from fermented fruit long before humans developed methods to distill alcohol. It is therefore not surprising that multiple bodily systems in mammals, including humans, evolved over time to sense and regulate alcohol consumption.

The prevalence of alcohol use disorder (AUD) in humans indirectly suggests that naturally evolved regulatory systems can become dysfunctional (due to genetic and/or environmental factors), removing the inherent "brake" on excessive or health-impairing alcohol intake.

Although various pathways in the body have been targeted to therapeutically address AUD, none of these approaches has proven consistently successful in addressing chronic or excessive alcohol use. A team of researchers led by 2019 BBRF Young Investigator **Kyle H. Flippo, Ph.D.**, and Matthew J. Potthoff, Ph.D., both of the Carver College of Medicine at the University of Iowa, now reports intriguing results of experiments to substantially reduce alcohol consumption in primates by administering a molecule called FGF21. Their paper appeared in the journal *Cell Metabolism*.

In prior research, administration of FGF21 (fibroblast growth factor 21), which is a hormone of the body's endocrine system, had been shown to suppress alcohol consumption in rodents conditioned to prefer alcohol over water. In parallel, recent genome research has revealed that genes associated with signaling by the FGF21 hormone are associated with alcohol consumption habits in humans.

FGF21, other research has shown, is produced in the liver and has various roles in regulating energy expenditure in the body as well as the intake of carbohydrates, fats and protein. The molecule is capable of crossing the protective blood-brain

barrier which keeps most toxins and viruses out of the brain, meaning that it can act upon brain cells and circuits involved in reward, including those implicated in alcohol consumption.

Drs. Flippo, Potthoff and colleagues set out to test whether administration of FGF21 as well as a synthetic analog molecule called PF-05231023 would reduce alcohol intake in alcohol-preferring non-human primates as it previously has been shown to do in rodents. They used vervet monkeys in their experiments.

The experiments yielded a wealth of results. Most important, perhaps, was that the FGF21 analog reduced alcohol consumption by about 50% in monkeys exhibiting a strong preference for alcohol.

The experiments also provided evidence of a liver-to-brain circuit that specifically regulates alcohol consumption. They also showed how administration of the FGF21 analog apparently targeted the circuit: by enhancing signaling in a subset of neurons in the basolateral amygdala (BLA)—a neuronal subpopulation that projects directly to the brain's nucleus accumbens (NAc), which is involved in regulating feeding and reward behavior that includes drug-taking.

Interestingly the team was also able to show that FGF21's suppression of alcohol consumption operated via circuitry that is distinct from circuitry through which it regulates sugar consumption (another of its important functions). The researchers believe that the two separate pathways of action do not overlap, which could be important in applying FGF21 or an analog molecule to treat AUD.

FGF21's role in regulating both alcohol and sugar intake may reflect "an endocrine feedback loop that presumably functions to protect the liver from damage," the team wrote.

By showing that FGF21 and its analog could specifically target the postulated liver-to-brain regulatory circuit in a way that sharply reduced alcohol consumption in alcohol-preferring higher mammals, the team said that FGF21 could prove a "future treatment option" for AUD in people as well as in illnesses such as cirrhosis. They called for further research to investigate these possibilities. ❖

The research team also included **Brad A. Grueter, Ph.D.**, a 2016 and 2014 BBRF Young Investigator.

Researchers Discover Potentially Targetable Brain Circuit Controlling Cocaine Withdrawal Anxiety and Relapse

In the past several decades, the field of addiction research has been revolutionized by new findings about the role of the neurotransmitter dopamine in affecting the brain's reward pathways. For example, the powerfully addictive effects of cocaine have been linked to the release of dopamine in a brain structure called the nucleus accumbens. But knowledge about dopamine release has not yet provided the key to treating cocaine addiction.

One reason for this is that dopamine is released throughout the brain, and has a role in many functions and processes that affect a wide range of brain activities. It cannot simply be targeted brain-wide with drugs designed to inhibit its activity. Even within the circuitry implicated in addiction, dopamine has proven to have complex roles.

Untangling these different roles in the hope of finding highly specific targets for effective addiction treatments is among the objectives of research being conducted by **Kevin Beier, Ph.D.**, of the University of California, Irvine. Dr. Beier is the 2020 BBRF Freedman Prize honorable mention for exceptional basic research and is a BBRF 2017 Young Investigator.

In a paper published in *Cell Reports,* Dr. Beier and colleagues say they have identified a specific circuit in the midbrain that controls a key aspect of cocaine addiction: the anxiety induced by withdrawal from the drug. They also found that a part of the same extended circuit is involved in a behavior called "reinstatement": the urge during the drug-withdrawal state to seek and use the drug again.

Both discoveries could inform future efforts to develop novel treatments for cocaine and other forms of addiction.

Dr. Beier and his team note that addiction occurs in three distinct phases: initial drug exposure, which produces a feeling of reward; repeated administration, which leads to a tolerance or "sensitization" to the addictive substance; and withdrawal from the substance, which leads to anxiety and a negative emotional state—which, in turn, fuel the urge to find and take the drug again. Each of these phases involves dopamine neurons in the midbrain.

To understand how drug use and withdrawal contribute to long-lasting changes in behavior, say Dr. Beier and colleagues, "a more nuanced picture of how select midbrain dopamine cells contribute to specific aspects of behavioral adaptation" is needed.

In a series of experiments involving rodent models of cocaine addiction, the team was able to trace with great precision an extended circuit that extends from a midbrain structure called the BNST (bed nucleus of the stria terminalis) to another structure called the VTA (ventral tegmental area), and from the VTA on to the amygdala.

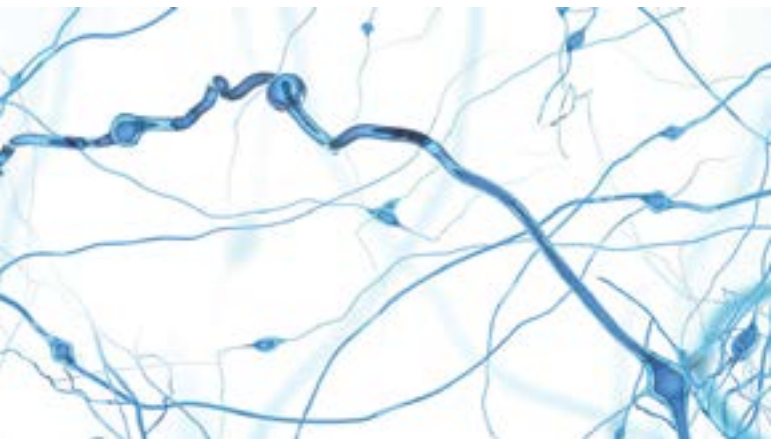
Even after a single exposure to cocaine, the team found elevated activation of a population of inhibitory neurons in the BNST. These neurons release the neurotransmitter GABA, and project to dopamine neurons in the VTA. This same pathway, in particular VTA dopamine neurons projecting to the amygdala, was also found to drive reinstatement—the urge during withdrawal to find and ingest more cocaine.

The team discovered that the portion of the circuit leading from the VTA to the amygdala was itself able to generate a general anxiety state in the addicted animals.

An equally important conclusion drawn by Dr. Beier and colleagues has direct implications for future therapeutic targeting of the circuit they discovered. "Our data show that the anxiety that develops after repeated drug exposure is facilitated by circuit elements that are independent of those that mediate drug reward or sensitization."

The fact that reward and sensitization to cocaine are driven by different circuitry than circuitry the team identified as controlling withdrawal anxiety and relapse is a potential boon to therapeutic targeting because of the latter's specificity.

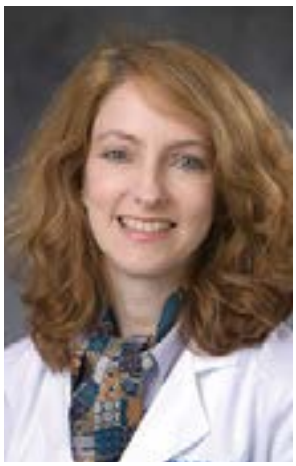
"Pharmacologic intervention for psychostimulant abuse has remained elusive in part because drugs that target the entire dopamine system have many 'off-target' effects, including on the brain's reward system," the team noted. The researchers' elucidation of the extended BNST-VTA-amygdala circuit that regulates withdrawal anxiety and reinstatement "suggests specific [circuitry] outside dopamine reward circuits that could be used as targets for development of addiction therapeutic agents to reduce the negative affect that develops during withdrawal as well as to prevent reinstatement/relapse." ❖



Therapy Update

Recent news on treatments for psychiatric conditions

USING NON-INVASIVE TMS BRAIN STIMULATION TO ACTIVATE A DEEP-BRAIN REGION IMPORTANT IN DEPRESSION



Sarah H. Lisanby, M.D.

A research team led by a three-time recipient of BBRF grants has successfully tested a method of using transcranial magnetic stimulation (TMS), a non-invasive method of brain stimulation, to activate an important depression-related target located deep within the brain.

TMS, first approved by the FDA for treatment of depression in 2008 and since approved to treat obsessive-compulsive disorder and for aiding in smoking cessation, involves using powerful magnetic fields to generate electrical current in brain areas just beneath the scalp. Standard TMS effectively penetrates about 1.2 inches into the brain, and for treatment of depression is typically focused on an area called the dorsolateral prefrontal cortex (DLPFC), which corresponds with a "surface" location on the left side of the forehead.

It's still unknown precisely how the stimulation delivered by TMS alters brain circuitry to generate an antidepressant effect, although it has been suggested that it has effects on brain areas beyond the DLPFC, perhaps including some that are deeper in the brain. Still, TMS currently cannot be used to directly target deep-brain locations thought to be involved in depression causation.

One such area is Brodmann's Area 25, a small region located in the subgenual cingulate region of the cortex. Area 25 may be part of a large network in the brain that includes the hippocampus and amygdala, two important parts of the limbic system implicated in depression that are central in mood and the processing of emotions. Area 25 has been the prime target of experimental deep-brain stimulation (DBS) in treatment-resistant depression. DBS is an invasive brain stimulation method that involves surgical implantation of electrodes and a pacemaker-like device that delivers the stimulation.

Sarah H. Lisanby, M.D. and colleagues at the National Institute of Mental Health and Duke University, now report their use of a novel method of precisely targeting TMS to generate stimulation deep below the scalp in Area 25. It may be the best indication to date of the potential ability of TMS to effectively target deep-brain targets, for both research and therapeutic purposes.

Dr. Lisanby is Director of the Noninvasive Neuromodulation Unit at the NIMH and is on the faculty of Duke University School of Medicine. A member of BBRF's Scientific Council, she is the 2001 BBRF Klerman Prize winner, as well as 2010 BBRF Distinguished Investigator, 2003 Independent Investigator and 1996 Young Investigator. **Zhi-De Deng, Ph.D.**, a 2017 BBRF Young Investigator, also of NIMH and Duke, was a co-author on the paper, which appeared in *NeuroImage*. The paper's first author was Bruce Luber, Ph.D.

The team recruited 6 healthy men and an equal number of healthy women, aged 19-33, two of whom were not included in the analysis for technical reasons. The 10 who were part of the final dataset underwent preliminary brain-scanning using two types of imaging: functional MRI (fMRI) and diffusion tensor imaging (DTI). The former, as its name implies, is used to show activation in the brain, while the latter is used to reveal brain structure. Together, they were used by the team to identify an area called the right frontal pole, located just behind the forehead. It is the nearest TMS-accessible brain area that is connected with Area 25. Location of the right frontal pole site directly connected to Area 25 was mapped precisely in each trial participant and used to target TMS stimulation.

The participants received TMS in a follow-up session, in several pulses delivered at several levels of intensity. While the stimulation was being delivered, the researchers used fMRI to measure neural activity in each participant's brain.

This enabled the team to show that in 9 of 10 subjects, TMS

pulses to the right frontal pole caused increased activation in Area 25, with increasingly strong pulses producing proportionately increased activation.

One key to their success in this demonstration, the team said, was likely their coupling of DTI structural mapping of each participant's brain with standard TMS procedures. The results, they wrote, "suggest a new tool to extend the utility of non-invasive stimulation, enabling researchers to target deeper brain areas which previously were thought beyond reach."

Their ability to use TMS to activate Area 25, "a key node in the neurocircuitry of depression," suggests, they said, "an initial step toward using DTI-guided TMS to noninvasively target areas for therapy no matter where they are situated in the brain." This could have implications for treating not only depression, but potentially a range of other psychiatric conditions such as OCD, PTSD, anxiety and possibly others.

Follow-up research, they suggested, should use larger and more diverse groups of subjects and test other TMS sites and other deep-brain targets in order to better grasp how the new approach might be most useful and effective. ❖

COMBINING ANTIDEPRESSANTS CAN IMPROVE OUTCOMES IN PATIENTS WITH SEVERE DEPRESSION

Christopher Baethge, M.D.

A study analyzing the results of 39 previous clinical trials involving 6,751 depressed patients concludes that it can be more effective to treat with two antidepressant drugs rather than a single drug, especially in severe cases.

In this study of studies (called a meta-analysis), combination antidepressant treatment across the 39 trials was associated with "superior outcomes" relative to treatment with a single drug ("monotherapy"), the difference being "statistically significant."

A measure called "standardized mean difference" (SMD) is used in meta-analysis to help gauge the importance of observed differences across many clinical trials that assess the same outcome (in this case, relief from depression symptoms) but measure it in a variety of ways.

In the sample of 39 trials studied by a team co-led by 2004 BBRF Young Investigator **Christopher Baethge, M.D.**, of the University of Köln, Germany, the SMD associated with the superiority of combination treatments was 0.31, which is considered "small" to "moderate" in magnitude. The result is arguably more significant than that figure would suggest, the team noted, since the improvement with combination treatment was relative to treatment with a single antidepressant drug, not an inactive placebo.

The team also assessed secondary measures of combination vs. single-drug antidepressant therapies across the 39 trials, considering such factors as the percentage of patients who experienced a remission (reduction in symptoms of 50% or more); the number of patients who dropped out of trials; and the number of dropouts attributed to adverse effects of the medications.

Dr. Baethge, co-team leader Jonathan Henssler, M.D., and colleagues explained the significance of their findings for doctors and patients in a paper appearing in *JAMA Psychiatry*.

Treatment guidelines for depression advocated by health agencies and adopted by practitioners in the U.S. and Europe currently recommend the same first-line treatment for severe depression: a single antidepressant medicine that is not in the class of so-called MAO inhibitors. (Monoamine oxidase inhibitor drugs were among the earliest antidepressant drugs and have side effects that more recent antidepressants such as SSRI drugs [serotonin reuptake inhibitors such as Prozac] don't have).

For the significant portion of patients (one-third to one-half) whose symptoms do not respond to monotherapy or in whom a response is followed by a recurrence of symptoms, standard guidelines offer several courses of action to doctors: they can raise the dosage of the drug; switch the patient to another drug; or "augment" the first drug with a second one. In some cases, this second agent is not an antidepressant: lithium and second-generation antipsychotics are sometimes prescribed. A final second-course option is to combine two

antidepressants. This is a commonly taken step in primary-care settings, Drs. Baethge, Henssler and colleagues note.

After analyzing the data, the team reported two main results. Perhaps the most important was that combination treatment "as a general principle" appeared to be more effective than monotherapy without being associated with a higher number of patients dropping out of trials. The drugs used in combination varied, as did results associated with different combinations.

The second important finding was that the best patient outcomes were associated with trials in which patients took a monoamine reuptake inhibitor medicine (the most common are SSRI drugs) plus an atypical antidepressant of a particular class: so-called presynaptic alpha2-autoreceptor antagonists. These drugs include mianserin and mirtazapine. These agents inhibit receptors which help mediate the action of the neurotransmitters serotonin and norepinephrine. Another atypical antidepressant, bupropion (Wellbutrin) did not appear to generate superior outcomes when taken in combination with a monoamine reuptake inhibitor (although sample sizes for this drug were too small to consider this outcome definitive).

The researchers concluded that combination therapy "may be applied as a second-step treatment after insufficient response to initial antidepressant monotherapy." Although the reason for the enhanced effectiveness seen in the meta-analysis is not clear, the team suggested it may be due to synergies in the action of the combined drugs upon the brain.

Since combination therapy was not associated with more dropouts from the clinical trials, the team also suggested it may be a relatively safe treatment alternative compared with other second-step strategies in treatment-resistant depression, including augmenting a first antidepressant with lithium or a second-generation antipsychotic.

Perhaps more controversially, the team also proposed that in view of the "relative tolerability" of combination therapy, it might make sense in some cases of severe depression to use as a first-line treatment: a monoamine reuptake inhibitor plus one of the "aytpical" antidepressants that block presynaptic alpha2 autoreceptors.

They add that combination treatment was effective across the 39 trials regardless of initial illness severity. ❖

A SPUR TO IMPROVING PSYCHIATRIC DRUGS: PRECISE IMAGING REVEALS HOW A KEY RECEPTOR'S SIGNALING IS MODULATED

Wesley B. Asher, Ph.D.

Jonathan Javitch, M.D., Ph.D.

Researchers have obtained powerful new insights into mechanisms involved in a class of ubiquitous cellular receptors whose signaling functions are implicated in many psychiatric disorders.

The receptors, called G Protein-Coupled Receptors (GPCRs), are the target of one-third of all approved drugs, including therapeutics prescribed for psychiatric disorders including schizophrenia, bipolar disorder, and depression. The dopamine D2 receptor, which is the target of all current antipsychotic medicines, is a GPCR, for example.

The human genome encodes about 800 different GPCRs, which are found in cells throughout the body and are involved in regulating many of the body's functions. They are found throughout the brain and engage with a variety of neurotransmitters, hormones, and other molecules.

A neurotransmitter (or drug) from outside the cell that binds and activates a GPCR is called an agonist: its docking within the receptor sets off a cascade of events that lead the receptor to engage with and activate G-proteins located inside the cell. G-proteins carry signals that can switch on or off a variety of cellular processes. In this sense, the GPCR can be thought of as a structure that transmits signals from outside the cell to the cell's interior.

A complex biochemical process is initiated when the moment arrives for a G-protein signal to cease or be diminished in

intensity. At the center of this process is a protein called beta-arrestin. The new research explains in unprecedented detail how beta-arrestin is able to halt or modulate GPCR signaling. This provides insight into ways to potentially improve the action of drugs that interact with GPCRs, including psychiatric drugs, to make them more effective and/or to reduce side effects.

Wesley B. Asher, Ph.D., whose 2014 BBRF Young Investigator grant addressed the way beta-arrestin interacts with cellular receptors to modify their signaling, was one of three co-first authors of a paper published in the journal *Cell*, describing beta-arrestin—GPCR interactions. The other co-first authors were Daniel S. Terry, Ph.D., and G. Glenn Gregorio, Ph.D. The team's senior members were Scott C. Blanchard, Ph.D., and **Jonathan A. Javitch, M.D., Ph.D.**, a member of BBRF's Scientific Council, and a 2010 BBRF Distinguished Investigator, 2003 Independent Investigator, and 1992 and 1990 Young Investigator.

The team used a new technology called smFRET (single-molecule fluorescence resonance energy transfer) to resolve events at the level of individual molecules that help explain the beta-arrestin—GPCR interaction and activation mechanism.

The researchers knew that the interaction begins when part of the GPCR structure, referred to as its "tail", lying below the cell surface, is phosphorylated. This means that molecules bearing phosphorous—called phosphate groups—are added to the receptor tail. It was also known that the phosphorylated receptor tail in turn binds to a groove on the surface of the beta-arrestin protein. When beta-arrestin is not engaged with a GPCR, however, this groove on its surface is occupied by beta-arrestin's own tail structure.

The team's research with smFRET imaging reveals how beta-arrestin's tail gets released to make way for binding the phosphorylated tail of the GPCR. All of these changes can be thought of as changes in shape—"conformational changes" in the beta-arrestin—GPCR complex.

The team's research showed that when not engaged with a GPCR, beta-arrestin exists in a very stable state that they call "autoinhibited"—and it remains so as long as its own tail structure is tightly bound to the groove in its surface. Beta-arrestin will remain in this stable state unless an agonist like a drug or neurotransmitter interacts with the GPCR from outside the cell.

The research demonstrates how the balance between the autoinhibited and activated states of beta-arrestin controls the intensity and duration of GPCR signaling. Systematic studies tweaking this balance could lead to improved drug therapies or even new drug designs for a variety of illnesses.

"Now that we know GPCR receptors can both activate G-proteins and mediate signaling through beta-arrestin, the hope is that we can develop more specific drug therapies by finding small molecules that preferentially activate one pathway or the other," Dr. Javitch commented. ❖

GLOSSARY

NON-INVASIVE BRAIN STIMULATION (pp. 4–11) The term encompasses a variety of technologies and protocols for using powerful magnets placed just above the scalp to therapeutically alter the activity of cortical and subcortical brain cells.

VAGUS NERVE STIMULATION (p. 6) Stimulation, which can be delivered by a surgically implanted device or non-invasively, to the body's vital nerve pathway connecting the brain with the heart, lungs, and digestive tract. Currently, there are therapeutic applications for VNS in depression, obesity and epilepsy.

FOCAL PHARMACOLOGY (p. 9) An experimental application in which medication is delivered inside a carrier molecule and guided to its target by brain stimulation technology. The medicine is released only in the part of the brain that is being targeted, potentially precluding or reducing off-target effects which generate side effects.

SAINT (p. 12) A technology package now cleared by the FDA for commercialization that delivers more non-invasive stimulation to the brain in a shorter time than conventional TMS. Remissions from refractory depression have been reported after just one 5-day course of treatment, making SAINT a potentially powerful tool in helping psychiatric patients in crisis.

OPTOGENETICS (p. 16) A technology that enables experimenters to switch specific neurons, or groups of them, "on" and "off" in laboratory animals, doing so with beams of colored light directly conducted into the brain via thin optical fibers.

PV INTERNEURON (p. 17) A neuronal subtype that plays a crucial role in regulating excitation in cortical circuits. Most cortical neurons are excitatory; PV interneurons and other types of inhibitory neurons situated within excitatory circuits can transiently block or reduce their signal. PV interneurons have been shown to be involved in generating gamma rhythms (see below) which in turn promote efficient information processing. Pathologies involving PV interneurons are commonplace in people with schizophrenia and may help explain, at least in part, the biological roots of cognitive deficits.

GAMMA OSCILLATIONS (pp. 18–19) A kind of rhythmic pattern in the brain generated by neuronal activity. Gamma oscillations are the fastest of several brain-wave types. They are related to the functioning of PV interneurons, and are known to be irregular in people with schizophrenia.

EMERGENT PROPERTIES (p. 19) The ability of systems composed of relatively simple parts such as brain cells and circuits to give rise to astonishingly complex phenomena such as memory, the ability to learn, and consciousness itself. Using optogenetics to spur comparatively simple PV interneurons, researchers have promoted a "gamma rhythm"—an emergent property—across brain circuitry, which enables the rodent brain to process information more efficiently. This is a model for potentially alleviating cognitive dysfunction in schizophrenia.

GPCR (p. 37) Acronym for "G protein-coupled receptor," ubiquitous cellular receptors whose signaling functions are implicated in many psychiatric illnesses. GPCRs are the target of one-third of all approved drugs, including therapeutics for schizophrenia, bipolar disorder, and depression. New research explaining in unprecedented detail how a protein called beta-arrestin is able to halt or modulate GPCR signaling is a spur to development of more precise and effective drugs.

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