

Judge Steven Leifman Wins 2018 Pardes
Humanitarian Prize in Mental Health

Ketamine Helps a Patient Recover from
Treatment-Resistant Depression

Brain & Behavior

M A G A Z I N E

MARCH 2019



DR. MARK S. GEORGE

Pioneering TMS Therapy for Depression



»»»»» *Brain & Behavior Magazine* presents the cutting edge research of our BBRF grantees. Three stories in this issue focus on innovative ways of treating people living with treatment-resistant depression who are not helped by the standard antidepressant medications.

We tell one of these stories in a new feature in the magazine which focuses on “high impact” and “transformative” grants. These are grants we have made that have resulted in major advancements in our knowledge of the brain and treatments for mental illness. Mark S. George, M.D., was twice a BBRF Young Investigator grantee. He credits BBRF with supporting him when the fate of Transcranial Magnetic Stimulation (TMS) technology—a way of non-invasively stimulating the brain to treat depression—was hanging in the balance. The government would not support its development at that time. George believed passionately that it needed to be tested in depression, but without our grants, he would not have been able to proceed. He ultimately designed and helped organize and run pioneering trials that began to demonstrate the effectiveness of TMS in people with treatment-resistant depression. The technology was approved by the FDA in 2008. Since that time, many people have received help with this new method of treatment.

This issue also features a story about a patient who had her life completely turned around by ketamine, an experimental rapid-acting antidepressant. BBRF grantees and Scientific Council members have conducted pioneering research on the use of this medication. This young woman had suffered from severe depression most of her life, had attempted to end her life several times, and was not helped by an extensive sequence of antidepressant treatments.

Participation in a clinical trial of the experimental drug led to a stunning reversal in her condition, albeit one that was short lived. She talks about how she is now able to receive periodic ketamine treatments and the impact that this is having on her life.

BBRF Scientific Council member Irwin Lucki, Ph.D., has devoted much of his distinguished career trying to determine in terms of brain biology how antidepressant therapies exert their benefits. According to Dr. Lucki researchers are excited about new ways of delivering antidepressant medications. Most recently, he and colleagues have used animal models of depression to explore a novel mechanism of action—the possibility of modulating our naturally occurring opioid system to reduce depression symptoms. Dr. Lucki and others have tested the use of low-dose buprenorphine as a possible antidepressant. Dr. Lucki is also working on research studies involving ketamine.

Our parenting piece focuses on the importance of prevention and features advice from M. Camille Hoffman, M.D., BBRF’s 2015 Baer Prizewinner, and an obstetrician who takes on “high-risk” cases, and is also a researcher who has been involved in innovative studies of how to fortify and supplement the diet during pregnancy to lower the risk that children will, after birth, go on to develop disorders including schizophrenia and autism. She offers steps for women to take before, during, and after pregnancy to lower risk.

BBRF serves as the catalyst to help a researcher pursue an out-of-the-box research idea. BBRF grantees are looking for answers. With your help, we will continue to fund creative and impactful research that will drive the field of mental health forward and bring about better treatments, as well as cures and methods of prevention for our loved ones.

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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MARK S. GEORGE, M.D.

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TRANSFORMATIVE GRANTS

Pioneering TMS Therapy for Depression

Luck, Hard Work...and Crucially Timed BBRF Grants



THERE IS A MOMENT IN the career of Mark S. George, M.D., that he thinks of as lucky.

It changed the course of his life and—though he could not have known it then—the lives of thousands of seriously depressed people.

It was 1989. A young physician-scientist then studying in London, Dr. George happened to be in a hospital elevator when a man, evidently a patient, turned to him and said: “Hey doc, a man just put a magnet over my head and made my thumb twitch!”

George remembers: “As he got off the elevator, I asked him: ‘What floor?’ He said ‘Eight,’ so I punched that button.” George found himself in the laboratory of a scientist who was in possession of one of the few machines in the world designed to deliver magnetic stimulation to the brain non-invasively, via the scalp. Called transcranial magnetic stimulation, or TMS, it was invented only 4 years before, and it was a subject of curiosity.

It was known at the time that TMS could make a finger move, by gently applying stimulation just above a motor area of the brain. That’s why it excited Dr. George. This made him wonder if there was a way TMS could be directed so that it affected areas of the brain involved in causing depression.

For decades, a technology called ECT (electroconvulsive therapy) had been used to deliver electromagnetic waves into the brain to alleviate difficult-to-treat

major depression. ECT was used when other forms of therapy failed. It could be administered only after a patient had been placed under anesthesia. It was powerful, and induced a seizure that was designed to be therapeutic. ECT was sometimes accompanied by cognitive side effects, most notably memory loss. Some people with major depression literally could not live without it, but others were either not helped or were not willing to risk the side effects.

TMS, as Dr. George quickly learned, was very different. The idea behind it was that a much less intense series of magnetic pulses, delivered into the outermost layer of the brain just beneath the skin, might induce electrical activity that would therapeutically alter neural connections in brain areas involved in depression. If such an approach worked, it would mean that brain-stimulating therapy could be delivered to patients who were wide awake and who would not have to endure a seizure to experience a reduction in symptoms.

These ideas were plausible to young Dr. George because, in his words, “I have had a life-long research interest of figuring out the road map of where depression lives in the brain.” It was indeed “lucky,” as he modestly says, that in the late 1980s he walked into one of the few rooms in the world housing a TMS machine. But rather than a story of pure luck, his story may more accurately demonstrate the truth of Louis Pasteur’s famous observation that “chance favors the prepared mind.”

When Dr. George fatefully met that patient in the elevator, “we were just starting to think about circuits in the brain—and it had been proposed that you might be able to stimulate the cortex [just beneath the scalp] and it would affect circuits that led to areas much deeper in the brain.” Knowing that non-invasive stimulation could alter circuits affecting motor and sensory systems, he now hoped that it would also work in circuits that regulated human emotions.

The path between that moment nearly 30 years ago and today has been anything but easy. Today, TMS in various forms is widely used and approved by the U.S. Food and Drug Administration for treatment of depression, epilepsy, and obsessive-compulsive disorder. And its use is being tested in a variety of other disorders including PTSD, Parkinson’s, and anxiety. It may prove to be a way to control pain and even to manage obesity.

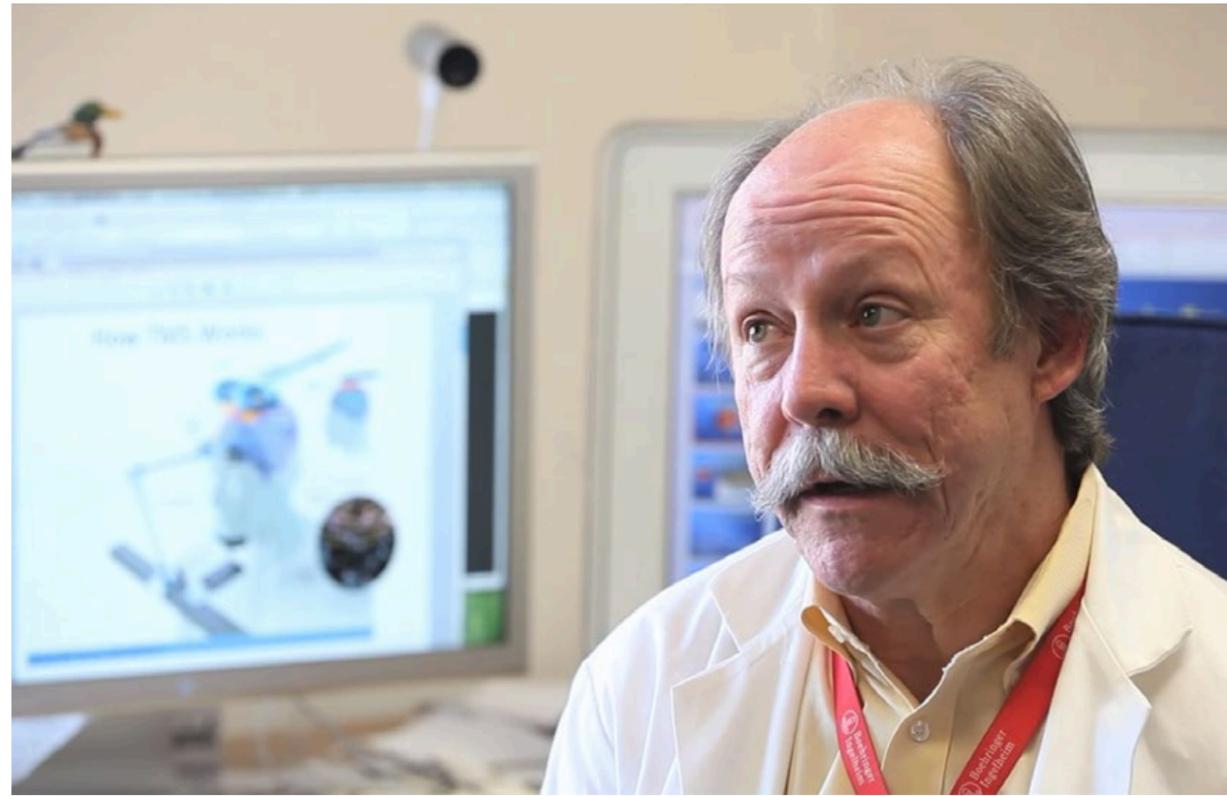
Dr. George had two very important bits of good fortune in the early stages of the journey. One was getting the go-ahead from Dr. Robert Post, with whom he worked at his next career stop, the National Institutes of Health, to test TMS as a non-invasive treatment for mood disorders. Dr. Post, who served for 20 years as the Chief of the Biological Psychiatry Branch at the NIH, is also a member of BBRF’s Scientific Council, and for many years has chaired the annual assessment of BBRF Independent Investigator grant applications. Dr. George recalls that because of Dr. Post’s openness to new ideas, “We were able to do the first safety studies, with healthy subjects, and were able to get an idea from that research of the effects of TMS on the brain.”

Though Dr. George was extremely excited that a new era of non-invasive therapy might be dawning, especially after publishing peer-reviewed safety data on TMS, it was not long before he ran into a brick wall. The early

“Without BBRF’s support during that really critical time, I don’t think we’d have the TMS technology that is currently available and that is now being applied beyond depression in other illnesses. That’s why I’m forever grateful.”

1990s was the moment of the “Prozac Revolution” in the United States, in which antidepressant medicines such as Prozac, Paxil, Celexa and others like them were first widely prescribed. All belonging to the class of SSRIs, or selective serotonin reuptake inhibitors, these oral medicines acted to sustain levels of the neurotransmitter serotonin in the synapses, or gaps, between brain cells, and in that way, it was thought, facilitated brain-cell communication, elevating mood.

At that time, transcranial magnetic stimulation therapy frankly seemed a bad idea to the scientific director of the intramural program at the National Institute of Mental Health. Dr. George was advised to not discuss his research for fear of “sullyng the name of the NIH,” he remembers, and his lab was closed. He moved to the faculty of the Medical University of South Carolina, where he has been ever since—now a Distinguished Professor of Psychiatry, Radiology and Neuroscience. He was first charged with building a



Dr. Mark S. George

center for functional MRI (fMRI) brain imaging, another of his specialties. This was another technology that would prove to have a very bright future. It was less controversial than TMS.

Dr. George continued to appeal to NIH for grants to continue his TMS work, without success. It was around that time that he experienced another stroke of good fortune. “With the NIH not receptive,” he remembers, “I wrote a grant application to NARSAD”—the organization that is now the BBRF.

“With that first NARSAD Young Investigator award in 1996, I was able to acquire a TMS machine that my supervisor in South Carolina had authorized. I immediately began to plan a whole series of clinical studies to further test and improve the technology. Eventually, a private company was formed by others that patented a particular form of TMS technology. But in the 10 years when there was no NIH funding and before there was a TMS industry, there was BBRF—two grants in succession that kept the thread going.

“The point I hope you can get across to donors and readers,” Dr. George stresses, “is that without BBRF’s support during that really critical time, I don’t think we’d have the TMS technology that is currently available and that is now being applied beyond depression in other illnesses. That’s why I’m forever grateful.

“I believe in the mission of BBRF because it was their support that enabled us—as intended—to figure out all of the things you have to have in hand before you can do a large clinical trial with a new technology.”

An industry-sponsored multicenter, randomized controlled clinical trial (RCT) involving 300 patients was indeed carried out, which Dr. George helped design and carry out. Demonstrating the safety and effectiveness of TMS in the acute treatment of depressed patients who had not responded to prior antidepressant treatments, the trial, whose results were published in 2007, helped persuade the FDA to approve TMS the following year, establishing as standards the treatment protocols used in the trial. In 2010, Dr. George and colleagues published the results of an NIH-sponsored RCT which confirmed those results and established TMS as a proven therapy.

The approval at that time was specifically for the treatment of treatment-refractory depression. Among the class of treatment-resistant patients are those with life-threatening depression who traditionally have had to turn to ECT for lack of another option. While ECT remains an important option today, TMS now provides an option that is available to all people with depression. In addition to being more convenient than ECT, it is much safer. Apart from transient headache, treatable with aspirin, TMS is generally free of side effects, according to Dr. George.

He says that he is proud that the technology and procedures used today [see next page] are actually superior to those he and colleagues devised years ago. Those procedures, developed with grant support, marked a truly novel approach to depression. They broke through the institutional resistance that had slowed its adoption and earned for TMS the government’s stamp of approval. ❖

PETER TARR

WHAT IS TMS TREATMENT AND HOW WELL DOES IT WORK?

"The basics of TMS treatment are simple," says Dr. Mark George, who performed research for more than a decade that led to its approval for treatment-resistant depression in 2008. "You have a patient who is awake and alert, sitting in a chair that's kind of like a dentist's chair. We place an electromagnet on the scalp, over a part of their brain that we think is dysfunctional in the disease." In the protocol approved by the FDA, Dr. George chose an area corresponding to a portion of the left prefrontal cortex, high on the forehead above the left eye. This area remains the focus of TMS treatments today.

Stimulation is applied repetitively: on and off in spurts for 4 seconds, then 25 seconds off before repeating, over a total of 37 minutes and delivering a total of 3,000 pulses. (Hence the treatment's technical name, rTMS, for repetitive TMS). "During those 37 minutes, patients are alert, there's no IV, they can do anything they want before or afterward—there are no restrictions on activity or diet," says Dr. George.

"After the first treatment, the patient usually doesn't feel any different. But if you treat over several weeks, gradually the symptoms of the depression begin to fade away."

And there are very few side effects. Most common is a mild headache, typically relieved with aspirin. As for impact, "After the first treatment, the patient usually doesn't feel any different. But if you treat over several weeks, gradually the symptoms of the depression begin to fade away" in patients who do respond. The FDA-approved treatment is once a day, five times a week for 6 weeks. "So that's 30 sessions, and then we do what's called a taper, where we give three treatments one week, and two the next, and then one. We keep our fingers crossed and hope to find that the depression has gone away."

Dr. George says that effectiveness usually follows "a rule of thirds." About one-third of treatment-resistant depressed people treated with TMS have a remission; there are no depression symptoms left after the taper period. In another third there is not a remission but instead a "response," meaning symptoms are cut at least by half. In the final third of patients, there is no response.

"Fortunately, no one seems to get worse with the treatment," Dr. George says. "Unlike with electroconvulsive therapy (ECT), where we worry about a problem with memory, there are no adverse cognitive effects with TMS at all—it's quite benign in that way. There are no drug interactions, so it's good for patients who are already on medications of various kinds."

For those who are helped by TMS, how long can they expect the benefits to last? "It varies from patient to patient," Dr. George says. "Some people never need TMS again—they're out of their depressed episode and they do fine. Others require tune-ups. Good studies have shown that if we swoop in quickly when people start to relapse, we can get them out of the depression very quickly. Instead of 6 weeks of treatment, we might be able to get them well again in 2 or 3 weeks. With only a few exceptions, if you responded in your initial course, you will re-respond if you go back in. It doesn't seem that patients build up a tolerance with this technology."

Over the long-term, "some patients require one or two treatments every couple of weeks to maintain their remission. We have some patients who have done that for up to a decade now and it seems to work quite well. Most of these people are also on [antidepressant] medications, but somehow with TMS they're able to get a quality of life that they were not before."

Dr. George says that he continues to get calls from patients across the country, asking to come to South Carolina in order to be treated by him. "I say, 'No, your doctor down there is just as good at TMS and it's much less stress and strain on you. You can sleep in your own bed and you can hug your dog, and that's better for your depression.' The treatment has been successfully standardized—there's nothing special about the technique, when properly applied." ❖ PT

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Marla and I are dedicated to helping people who live with mental illness and doing what we can to be a part of the solution by our continued giving to BBRF.

—Ken Harrison, Board Member

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After Every Available Option Was Exhausted, Ketamine Has Enabled Her Life to Resume



MAKING A PEANUT BUTTER-and-jelly sandwich is something people do almost mindlessly, or so you might say. But it is a task that involves a number of very real cognitive challenges: you have to remember where the peanut butter, jelly, and bread are. You then have to remember the steps involved, find the butter knife, and know what you're supposed to do with it. Not least, there's the energy-demanding task of eating it.

As 29-year-old Ashley Clayton stood in her kitchen, she found herself at a loss as to how to do any of those things.

"I never appreciated it until I couldn't do it," she recalls—what a complex series of brain functions are required to be able to hold all those things in your mind at once. And I couldn't do it."

Ashley had been undergoing intense electroconvulsive therapy (ECT) and it had impaired her cognition. This, compounded by her underlying condition, chronic major depression, made even the simplest cognitive tasks a challenge.

ECT, in which an electrical current is run through the brain of an anesthetized patient in order to induce a therapeutic seizure, is considered to be one of the best available treatments for treatment-resistant depression. And yet, after 17 sessions, three of which were of the more aggressive bi-frontal type in which both sides of the brain are stimulated, Ashley's depression remained relentless.

"I'm failing the best treatment they have," she thought, spiraling into despair. She felt like it was only a matter of time before her illness inevitably would kill her.

This wasn't the first time that Ashley had contemplated suicide.

A childhood marred with serious trauma had triggered her depression and PTSD when she was in middle school. On the outside she looked like a thriving teenager. She loved school, especially art class. She

walked around with a paintbrush tucked into her messy ponytail. She got straight 'A's. Yet, her feelings of guilt, shame, and loneliness grew stronger, until she tried to take her own life at age 14 and ended up in the psychiatric unit of a local hospital. Over the next 4 years, Ashley was hospitalized twice more, once after a near-death suicide attempt during senior year.

She made it through and became the first person in her family to go away to college. She came home that first semester after she began hurting herself again. However, Ashley had always loved school and wanted badly to go back. She worked hard at recovery, attending intensive outpatient clinical therapy and learning skills to manage her depression and PTSD.

She returned to college that spring, continuing to work through her trauma and developing coping skills in therapy. By the time junior year rolled around, she, for the first time in her life, felt well. In 2009, she graduated with honors and moved to New England from her home in Kentucky to earn a master's degree in community psychology.

At that time, in her early twenties, Ashley was successfully managing her symptoms with medication and psychotherapy. She fell in love with a man she would marry. She did her internship at a lab at Yale University. Feeling more rooted and settled than she had ever been, she graduated at the top of her class and was offered a full-time position as a researcher at Yale.

NEW DEPTHS

However, in 2012, stressful life events brought up past trauma, and set off a prolonged depressive episode, which only became worse with time. In 2014, the year she got married, Ashley's depressive symptoms came back full force. As she started a new position at the university, her mental health continued to decline.

She experimented with a dozen different medications—nearly every class of anti-depressants. She tried several different kinds of talk therapies, including dialectical behavioral therapy and cognitive behavioral therapy.

Nothing worked. And the loneliness and extreme fatigue consumed her.

"For the first time in my life I had a profound inability to experience any pleasure," she remembers.

As 2016 began, so did Ashley's severe functional impairments. She found it difficult to read, concentrate, and remember. Reading an academic article for work demanded more energy than she could muster. On the recommendation of her psychiatrist, she took a partial medical leave. Her inability to perform her cognitively demanding job



was particularly devastating, since she derived so much meaning and fulfillment from work.

Desperate for solutions, she reached out to a friend and colleague involved in research on ketamine, an anesthetic that has been used experimentally for two decades to generate rapid antidepressant effects. Ketamine has been handled carefully and its progress has been slow owing to its side effects which include addiction and dissociation, a disconcerting feeling of being detached or outside of one's own body.

Ashley was put in touch with Gerard Sanacora, M.D., Ph.D., a leading authority on ketamine and mood disorders. Dr. Sanacora is a professor at Yale and member of the Scientific Council, who, over the course of his career, has received four of the Foundation's grants—two as a Young Investigator and one each as an Independent and Distinguished Investigator.

After learning about Ashley's situation, Dr. Sanacora identified a double-blind Phase II clinical trial of ketamine in patients like her who were seriously ill and had not been helped by multiple prior antidepressant treatments. Phase II trials seek to determine the most effective dose, and in this trial, only a single "rescue" dose of ketamine was administered to each participant.

A STUNNING REVERSAL

About a week later, Ashley found herself in a hospital bed in Yale's hospital research unit, receiving an intravenous infusion. At the time she didn't know if she had received ketamine or a placebo. (Later it was confirmed to have been ketamine, administered at one of the four tested dosages). After getting the treatment, nursing nausea and a bad headache, she went home and slept it off.

When she woke the next morning, Ashley felt 50 pounds lighter. She could breathe. She wanted to go for a run. So, she did. Although she often ran to try to manage her depressive symptoms, she couldn't recall ever having wanted to go for a run.

"I can't even explain to you how dramatically different I felt when I woke up....It was a miracle," she says.

She could feel positive feelings, which had eluded her for the last two years.

"I looked at my husband and I felt love," she remembers. "Not being able to experience that is incredibly painful."

Approximately 2 weeks later, Ashley woke up to full-blown depression symptoms. It wasn't a gradual remission, but a precipitous fall off a cliff. For 2 weeks, then, she had experienced what her life could be. But now the grief of having that suddenly torn away accompanied the return of her depression.

The single dose of ketamine had worked, but only temporarily, as it does in most other patients. Could she arrange to have more treatments? Her university-sponsored insurance wouldn't cover a drug that the FDA has yet to approve for depression (FDA approval is closely tied to insurance coverage). At around \$1,000 a dose, ketamine, which remains "experimental," is a drug that only a few can access.

However, the Yale-affiliated hospital did have an Interventional Psychiatry Service which offered ketamine as a clinical treatment to individuals with severe, treatment-resistant depression. Her doctors said they would try to get Ashley into the program. In the meantime, her doctors made slight changes in her medication regimen, but very few treatment options remained.

At this point, Ashley felt certain of her suicide. It physically hurt to breathe.

"The amount of physical pain just from trying to function was just overwhelming," she recalls.

With suicide in mind and ketamine still out of reach, Ashley reached out to another colleague, who suggested ECT, an option she had not yet entertained, fearing its cognitive side effects, including memory loss. ECT is much safer and more effective than it was decades ago, but different patients respond differently to it. Some don't complain of cognitive effects such as memory loss. Others do.

"Ketamine not only saved my life, but has restored me to the joys, and pains, of full living. I feel, for the first time in my life, like there is air to breathe."

Feeling at the end of her options, Ashley admitted herself to a psychiatric hospital and began a series of acute ECT treatments. She was discharged after a month and continued her treatments as an outpatient. It was after the 17th session that Ashley found herself in her kitchen, unable to make that peanut butter-and-jelly sandwich. "It was like I didn't have a working memory," she says.

She still had no word on the status of her ketamine request. Her depression persevered, tangled with the side effects of the ECT.

"The most important thing to me was just my ability to think. And I was losing it," she says.

LIFE-SAVING NEWS

During what would be her final ECT session, Ashley reached out to the head of the ECT program about her earlier request to receive ketamine again. He promised to look into it. Two days later he gave her what turned out to be life-saving news: "It seems like ketamine is the best treatment for you. So, let's do that." And just like that, after months of waiting, she had been approved. That very day, a few days before Christmas of 2016, she received a ketamine infusion.

After four weekly treatments, Ashley began to feel almost like she had after that first infusion at the beginning of the year. She and her doctors faced what is a common barrier to continued ketamine therapy—finding a way to pay for the treatment. It appeared that her depression could not be managed without ketamine, and after a few months of receiving care on a treatment-by-treatment basis, her doctors

were able to convince the hospital administrators to provide her with free care over the long term.

Since then, she has received ketamine every 2 to 3 weeks, depending on her symptoms. She also continues to be on two other medications. She is in constant touch with her doctors.

"Ketamine not only saved my life, but has restored me to the joys, and pains, of full living. I feel, for the first time in my life, like there is air to breathe," she says.

Ashley's well-being depends on continued access to an experimental drug that her insurance will not cover, and whose safety and effectiveness with long-term use still has not been clinically demonstrated. Now 31, Ashley Clayton is likely among the people with treatment-resistant depression who have been treated with ketamine for the longest continuous period. This makes her case particularly valuable to researchers who can monitor her progress and any side-effects she might experience.

As a mental health researcher herself, Ashley recognizes this. "It's an amazing drug that needs more research, funding and insurance reimbursement," she says, "but also it needs to be done really thoughtfully. Patients need to be very followed very closely."

For now she is happy to know that she and her doctors have at last found something that can keep her depression, and thoughts of ending her life, at bay.

❖ **FATIMA BHOJANI**

Opioids, at Very Low Doses, May Provide a New Way to Treat Resistant Depression



ONE OF THE MOST PROMISING new therapy ideas for brain and behavior disorders may at first seem improbable: using opioid-based medicines to reduce the symptoms of depression. Isn't our society in the midst of an "opioid epidemic"? How might opioids help depressed people?

There are strong reasons for considering opioids, at very low doses, as antidepressants. Although many people may not realize it, we are all born with a natural—or, as researchers say, "endogenous"—opioid system. Our bodies manufacture various opioid molecules and our cells are studded with keyhole-like structures called receptors that are specifically designed to fit these naturally occurring opioid "keys." There are four types of receptors that accept different opioid molecules. They are very common in brain cells, but also in the spinal cord, the digestive tract and in peripheral nerves.

"It has long been understood that the endogenous opioid system that we have is responsive to stress and mood—it helps regulate them," explains Irwin Lucki, Ph.D. An expert on the opioid system, Dr. Lucki is Professor and Chair of the Department of Pharmacology at the Uniformed Services University of the Health Sciences in Bethesda, Maryland. He is a member of the BBRF Scientific Council and a 2004 Distinguished Investigator.

Most of the opioid activity in our bodies is going on without any awareness on our



Irwin Lucki, Ph.D., a leading authority on pharmacology, has conducted extensive research on novel treatments for depression.

part. There are exceptions, however: "Many people become aware of the opioid system's impact on mood when they are exercising," Dr. Lucki says. "For example, there is a release of endorphins, which are naturally occurring opioids, that many runners feel as a 'runner's high' after they stop exercising."

Opioids are also involved in the experience of pain. "One of the four opioid receptors types, called the mu-opioid receptor, or MOR, is associated with the analgesic effects of morphine, and also morphine's mood-elevating effects," says Dr. Lucki.

But another opioid receptor can also become involved when pain is present. The kappa-opioid receptor, or KOR, receives signals from a naturally occurring opioid in the body called dynorphin. It's secreted during times of intense stress and distress. "Chronic pain patients who experience prolonged distress are likely experiencing the effects of increased secretion of dynorphin onto their kappa-opioid receptors," according to Dr. Lucki.

The example of pain makes clear how different parts of the body's opioid system can interact. One the one hand, pain,

especially chronic and acute pain, causes us to feel distress—the work of dynorphin and the KOR. On the other hand, mood-elevating opioids like morphine can be administered and will interact with the MOR to help alleviate pain.

The problem is that morphine or similar opioids are so pleasurable that they are highly addictive. The opioid crisis of the present is often traced to the over-prescription of powerful and highly addictive opioids to patients experiencing pain. When taking opioid medications for prolonged periods of time, often the effects of the medication "weaken," requiring the need for higher doses as the body becomes tolerant to the effects of lower doses. Chronic administration can also lead to dependence, and when such people are deprived of opioids, they experience withdrawal, which entails an often devastating and life-altering plunge in mood. Hence the urge to keep taking opioids.

GENESIS OF A NEW TREATMENT IDEA

This example provided an idea to Dr. Lucki and others involved in trying to develop new antidepressant medicines. In the laboratory, he and his colleagues have raised breeds of mice that lack functional mu and kappa opioid receptors. In animals that lack the kappa receptor, or in which the kappa receptor is blocked, stress is greatly reduced. In animals in which the mu receptor is stimulated, the animals are more sociable and less susceptible to environmental conditions that induce the mouse-equivalent of depressed mood.

What if these effects could be generated with medicines? It is not nearly as simple to do as it may sound. Dr. Lucki and his colleagues have been working on this problem for years.

"It occurred to us that since we have multiple opioid receptors that can mediate mood in different ways, it might be interesting to try to affect the function of the mu- and kappa-opioid receptors in a way that would be favorable for depressed patients."

BUPRENORPHINE HAS WORKED QUITE WELL IN VARIOUS ANIMAL MODELS OF DEPRESSION, SIGNIFICANTLY REDUCING SYMPTOMS ASSOCIATED WITH BOTH DEPRESSION AND ANXIETY. BUT RESEARCHERS HAVE HAD TO BE VERY CAREFUL IN TESTING THE DRUG IN PEOPLE.

DID YOU KNOW

WHAT EXACTLY IS BUPRENORPHINE? Buprenorphine (BYOO-pren-OR-feen) is a synthetic opioid first approved by the U.S. Food and Drug Administration in 1981 for use in treating people addicted to opioids such as morphine. It is typically given to patients in order to help them through the withdrawal period. It is now being tested on an experimental basis at very low doses in patients with depression who have not been helped by other forms of therapy. Recent clinical trials have paired low-dose buprenorphine with samidorphan, a compound added to minimize addiction risk.

One molecule he and others have extensively studied is called buprenorphine (pronounced BYOO-pren-OR-feen). It was invented to help people addicted to opioids successfully withdraw from their dependence. The molecule blocks kappa opioid receptors, helping to limit stress, and it also mildly stimulates mu opioid receptors, elevating mood. One characteristic of the drug is that it will not elevate mood beyond a certain point, a feature of its action in the body that generally prevents it from becoming addictive.

Buprenorphine has worked quite well in various animal models of depression, significantly reducing symptoms associated with both depression and anxiety. But researchers have had to be very careful in testing the drug in people. Owing to its mood-elevating characteristics, and despite evidence of its inability to do so beyond a certain point, some drug developers have worried about its potential to be abused. In various human trials, it has been administered at low dosages, a fraction of those used in the treatment of opioid addiction.

There are strong reasons for considering opioids, at very low doses, as antidepressants.

Dr. Lucki explains: “The fear was that in some individuals, buprenorphine may produce, still, too much activation of opioid receptors that could turn out to be addictive or reinforcing of addiction. Studies that have looked at the abuse potential of buprenorphine in people with former chemical dependencies, as well as in experimental animals, have shown that it has only very mild rewarding effects. But still, even at low doses, we don’t know if we need to

dampen that down even more, to guard against the development of addiction in some depressed patients.”

This was the thinking behind the development of a drug called BUP/SAM, which is a combination of buprenorphine and another drug called samidorphan. The “SAM” part of the combination partially blocks mu-opioid receptors, a way of damping down the degree to which the “BUP” portion of the drug stimulates the receptor. “The purpose of SAM in combination with BUP is to address the abuse and dependence potential of BUP,” say investigators who reported results of two Phase 3 trials of the drug in the journal *Molecular Psychiatry* on October 29, 2018.

The researchers, led by Maurizio Fava, Ph.D., a 1994 BBRF Young Investigator now at Harvard University and Massachusetts General Hospital, tested the BUP/SAM combination (consisting of each drug at a dosage of 2 mg) in two randomized, double-blind, placebo-controlled trials, one involving 385 patients, the other, 407 patients. All had major depressive disorder (MDD) that

had not responded to other treatments. Some received placebo for the first 5 weeks of the trial, then BUP/SAM for the remaining 6 weeks of the trial. Other participants received BUP/SAM for the entire 11 weeks. All participants continued to take the antidepressant drugs they had previously been taking.

Data from the two trials “support the view that the BUP/SAM combination represents a promising potential

adjunctive treatment for patients with MDD,” Dr. Fava and the team concluded. The drug was well tolerated, and there was “minimal evidence of abuse and no evidence of dependence or opioid withdrawal.”

Despite these results, the FDA in November 2018 decided it was not yet ready to issue an approval for the BUP/SAM combination, which is formulated by the pharmaceutical firm Alkermes under the designation ALKS-5461. The design of the two trials was unusual, involving a switch in some patients from placebo to the BUP/SAM drug after 5 or 6 weeks, and this generated data that the regulatory body found unpersuasive. More testing will be needed to validate the effectiveness of the combination drug, says Dr. Lucki, who was not involved in the trials.

THE APPEAL OF NEW APPROACHES

The larger point, Dr. Lucki stresses, is that BUP/SAM is one of several ideas representing a new approach to treating depression. “Since the accidental discovery of the first class of modern antidepressants in the 1950s,” he says, “all of the medicines approved by the FDA for major depression and dysthymia (depressed mood) have shared a common mechanism of action. All increase the transmission of neurotransmitters called monoamines.” This includes the extremely popular SSRI class of antidepressants, medicines like Prozac and Zoloft, which act to sustain serotonin levels in the brain, as well as so-called SNRIs, which sustain levels of serotonin as well as norepinephrine, another neurotransmitter. Earlier antidepressants, which were popular in years prior to the SSRI generation, also targeted levels of monoamine neurotransmitters.

Despite their widespread use, “as many as 50 percent of depressed patients are resistant to these therapies,” Dr. Lucki

notes, “and the significant length of time, often 4 to 6 weeks, to produce meaningful symptom relief, suggests that other mechanisms are likely involved” in causing depression.

Hence the appeal of drugs that modulate the working of the endogenous opioid system, like BUP/SAM. They “don’t directly target the monoamine neurotransmitter systems that all the other antidepressants work with,” Dr. Lucki stresses, which is why they are an attractive target for research. In animal testing, the evidence shows that BUP/SAM’s effect is specifically due to its modulation of the mu- and kappa-opioid receptors.

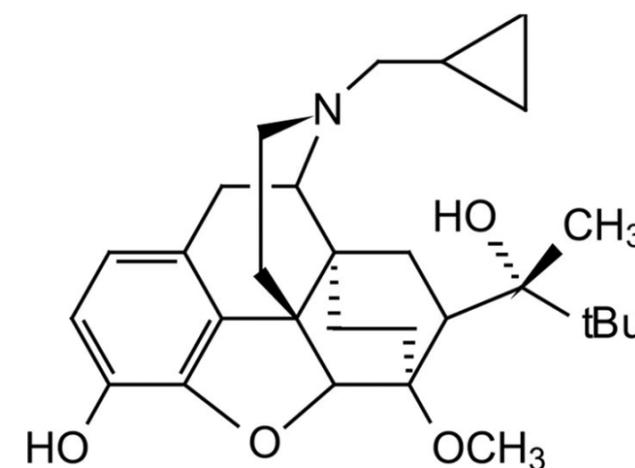
Currently, Dr. Lucki is focusing on another non-traditional drug for treatment-resistant major depression: ketamine. Developed originally as an anesthetic and tested intensively in recent years as an antidepressant, ketamine has repeatedly been shown to relieve the depression of many desperately ill depressed patients within minutes or hours. Its effect does not usually last longer than a week, however, and in its “street” form (“Special K”) has been a drug of abuse. For this reason, Dr. Lucki and many

other researchers have been trying to come up with a drug that acts rapidly like ketamine to reduce or eliminate symptoms, but is not addictive.

He is now collaborating closely with Carlos Zarate, Jr., M.D., a two-time BBRF grantee and winner of the Colvin Prize in 2011. Dr. Zarate is Chief of the Experimental Therapeutics & Pathophysiology Branch at the National Institute of Mental Health.

Drs. Lucki and Zarate are currently testing a compound called HNK, which is one of the byproducts of ketamine when it is processed in the body. In previous research, HNK was found to be capable of generating ketamine’s antidepressant effects in animal models, without being addictive. Yet that remains a controversial result, in part because of recent research led by Alan Schatzberg, M.D., a member of the BBRF Scientific Council, and Nolan Williams, M.D., a 2018 and 2016 BBRF Young Investigator, both of Stanford University, which suggests that ketamine cannot exert its antidepressant effects without engaging the body’s opioid system.

Should ketamine, then, be considered an opioid? That is not yet clear. What is clear, says Dr. Lucki, is that “our field is so excited now. After many years of not being able to produce novel compounds to help people with depression, we now have a lot of ideas and interest in different ways of being able to help the treatment-resistant patient, and to help people who contemplate suicide, and to help people with PTSD. The field is energized and the people in the lab are so excited about working on these problems. I think we’re going to make a big difference in the way that depression is treated in the future.” ♦ PETER TARR



BUPRENORPHINE

Steps to Take Before, During, and After Pregnancy to Help Assure the Child's Mental Health

A Q&A with M. Camille Hoffman, M.D., MSCS

Associate Professor, Maternal & Fetal Medicine
University of Colorado School of Medicine
2015 Baer Prize for Innovative &
Promising Schizophrenia Research



M. Camille Hoffman, M.D., MSCS, completed medical school at the Medical University of South Carolina, OB-GYN residency at University of Miami, and her maternal fetal medicine fellowship at University of Colorado Anschutz Medical Campus. Dr. Hoffman directs a clinical and translational perinatal mental health research program that she established to investigate maternal-child mental and physical health relationships and to promote maternal-child wellness.



M. Camille Hoffman

Dr. Hoffman, you are a “high-risk” obstetrician who takes care of women and their babies in the period surrounding birth, both before and after. But you’re also a researcher who looks at the 9-month period of fetal life. What happens during fetal development that can affect the baby’s mental health after birth?

A lot of research emphasis has been put on early childhood development and how that shapes a person’s health over the lifespan. However, in more recent years, researchers have backed that up into prenatal life. The second and third trimesters of pregnancy are critical periods for the wiring of brain pathways that lead to an overall well-functioning brain. Once the scaffolding for the brain is set in early fetal life, then different layers of brain development occur on top. If the scaffolding set-up is off, you can end up with a brain that doesn’t come together as it should or is dysfunctional in some way.

How fast is the brain growing during the second and third trimesters?

Extremely rapidly. Between the second and third trimester it physically increases in size by 10-fold, with the formation and wiring together of billions of neurons. The brain triples in size during the last trimester alone.

What are possible events that may happen during a pregnancy that could affect a child’s brain development, and subsequently, his or her mental health?

One of the more common things to be aware of is infection of the mother with something such as the flu or a urinary tract infection early in pregnancy, and especially during the second trimester. Another thing to be aware of is extreme maternal stress, which can have a harmful impact. So can high levels of alcohol or marijuana use throughout pregnancy.

The more we look at the exposures that are detrimental to fetal brain development, the more we see the second trimester as a critical period for establishing the brain’s



For decades we've known that by simply adding folic acid to the diet, the risk of open neural tube defect is diminished tenfold—if the supplements are started before conception or at least early in pregnancy, which is the time just before the neural tube normally closes.

scaffolding. I'm not saying, by the way, that fetal brain damage only happens during the first or second trimester. It can be affected at any stage by something like heavy alcohol consumption by the mother. However, in the case of other risks like marijuana use or infection, earlier pregnancy exposures also matter more than we thought they did.

In general, we consider the fetal period, and indeed, the entire perinatal period, before and after birth, to be the main window for preventing illness later on, including mental illnesses.

This brings to mind a classic preventive measure, now universally recommended: taking folate supplements.

Yes, it's one of medicine's great prevention success stories. Folic acid is a vital dietary nutrient for both the mother and the fetus. Inadequate folate levels in the mother are linked with a very serious birth defect called an open neural tube defect (ONTD). The neural tube is a structure that forms in the first few weeks after conception. It is the basis for the entire brain and nervous system. Severe neural tube defects can result in miscarriage earlier in pregnancy, and later, when the tube fails to close somewhere along the developing spinal cord, it can cause an ONTD. This type of birth defect can be life-altering for infants who survive and sadly can also be life-limiting.

All women are advised to take folate supplements, beginning 3 months prior to conception, if possible. It's not hard to get adequate folate through the diet, but decades of research shows that women who get additional supplementation have far less chance of having a fetus with neural tube defects.

In your own research, you have identified another way of potentially preventing serious brain-related disorders by supplementing the mother's diet. I refer to your recent work on choline supplementation. Tell us about this very important discovery.

Just as a deficiency of folic acid in the mother can perturb the fetus' development, and specifically nervous system development (which includes the brain), so too can a deficiency of another essential nutrient called choline. I and others have come to this problem through research on factors involved in the causation of schizophrenia and psychosis. Genetic factors can predispose an individual to developing schizophrenia, but in those who eventually develop the illness it's usually a combination of genetics and other exposures—in fetal life and environmental exposures after birth—that can come



together and make a perfect storm that results in illness.

What does the level of choline in the mother's diet during pregnancy have to do with the risk that a fetus will develop, perhaps 20 years after birth, a serious illness like schizophrenia?

This is what our team at the University of Colorado, under the leadership of Dr. Robert Freedman (a BBRF Scientific Council Member, 2015 Lieber Prizewinner for Outstanding Achievement in Schizophrenia Research, and 2006 and 1999 Distinguished Investigator) and the late Dr. Randall Ross, has been studying. In broad terms, it has to do with what neuroscientists call neural inhibition. Early in development, there is a tremendous amount of excitation in and among brain cells as they develop, grow, and communicate. One of the final steps in fetal brain development has to do with the emergence of inhibitory mechanisms that enable brain circuits to modulate their output. If brain cells are constantly "on"—in excitatory mode, rather than be capable of exciting and inhibiting, as needed—then mental illness can result.



How does the brain do this?

There is a type of receptor on the surface of brain cells that becomes vital at the very end of gestation, when neural inhibition is emerging. This receptor is called the alpha-7 nicotinic receptor, and during fetal life it is stimulated by choline. In the fetus, it is choline coming from the mother, via the placenta, that activates these receptors and stimulates their development. Choline is needed throughout pregnancy

for various purposes and at the end of pregnancy it's needed by the fetal brain to promote the emergence of inhibition which leads to proper brain function for the remainder of that individual's life.

What's the connection between emergence of normal neural inhibition and the risk of schizophrenia?

It's thought that people with schizophrenia have an insufficiency in inhibition which leads to over-activity in brain areas involved in cognition and emotional processing. There's also evidence that in infants who go on to develop schizophrenia in later years, the brain's inhibitory system doesn't establish itself as robustly as it should.

Surveys have revealed that one pregnant woman in five does not receive adequate choline from her diet. This provides a rationale for choline supplementation during pregnancy, and is the purpose of our current and past research.

We conduct clinical research studies aimed at assessing the impact of choline supplementation—when started early in the second trimester and continued through pregnancy—compared to a placebo, in pregnant women and their fetuses. We also study the comparative impact on these fetuses as they grow into infants and toddlers. We measured impact through multiple maternal, fetal, and child measures. Among these are measures that we devised specifically to assess inhibition in newborns.

What did your research reveal about choline supplementation?

In our pilot trial, we found that moms who received choline during pregnancy had infants with better "auditory gating" very early in life, at about one month of age, compared to children of moms who received the placebo.

Auditory gating is a type of EEG measure that parallels an assessment of adults with schizophrenia. Infants are exposed to two virtually identical sounds, 50 milliseconds apart. In normal gating, we would suppress our brain's response to the second sound because it's similar to the first. Our brain perceives it as background noise. But in some babies, and in individuals with schizophrenia, there is a failure to inhibit the brain's response to the second sound.

Most people's brains help filter out distractions. Otherwise, you would hear everything all the time, which is commonplace in people with schizophrenia.



So, you're measuring this response in the babies after they're born, comparing those whose moms took choline supplements with those whose moms got a placebo.

Right. We measured it at one month of age, and saw a difference in choline-exposed versus non-choline-exposed babies. That effect was no longer evident at one year of life. But when we assessed the choline-exposed babies at age 4, we found that they performed better on the child behavioral checklist: they were more attentive, more interactive, and less withdrawn than the non-choline-exposed babies.

PARENTING

If I understand correctly, then, choline supplementation has proven itself well enough to be a recommendation at this point. It's not strictly experimental.

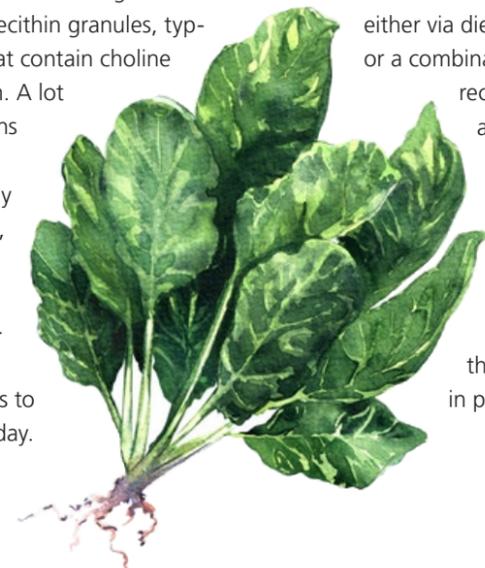
To us, it's not experimental any more. Additional studies are in progress and their results will be important in the issuance of general recommendations. That being said, the American Medical Association has already endorsed choline at 450 mg a day to be included in a prenatal vitamin regimen, because of evidence on how choline can buffer the impact of fetal alcohol exposure.

When should an expecting mother start this choline regimen?

Ideally she would start it before conception, just like supplementation of that other essential nutrient, folate, and in combination with a healthy diet. At the latest, it needs to be started in the early- to mid-second trimester to have the most potent impact.

Where can women find choline? How much should they take?

The highest dietary sources of choline are eggs, salmon, and animal livers. And then there are different choline supplements commercially available. For vegetarian moms, there are lecithin granules, typically from soy, that contain choline in vegetarian form. A lot of prenatal vitamins will also contain choline, but usually it's around 40 mg, which is a drop in the bucket as far as our recommendation goes. We advise our patients to take 900 mg per day.



Should women without any of the obvious family risk factors for schizophrenia or psychosis still take choline?

Think about what happened with folate. The risk of an open neural tube defect in the general population is one in 1,000. Folate supplementation reduces that risk to about one in 10,000. The rate of mental illnesses alone that we were talking about is one in 100 for schizophrenia, two in 100 for bipolar disorder, about three or four in 100 for autism spectrum disorder—which also has some potential preventive benefits from choline.

So, if we could reduce the risk of these conditions with choline supplementation, why wouldn't we do it? The population impact could be huge.

Which brings us back to something you mentioned earlier. You noted the importance of maternal infection and severe stress during pregnancy.

Yes, a mother should do whatever possible to minimize her risk of infection. However, many infections are not avoidable. So now, based on the research we've performed, I have started to recommend that women who develop an infection during pregnancy consider increasing their choline intake during pregnancy, either via diet or supplements or a combination of the two. I recommend choline also when a pregnant woman has other risk factors such as heavy alcohol or marijuana consumption, particularly if she has used these substances early in pregnancy.

What kind of interventions are possible for reducing maternal stress?

There are positive data on mindfulness-based cognitive therapy interventions, interpersonal therapy interventions and other psychotherapy modalities, and women should consult with their physician or midwife about these options. Also, there are several meditation apps that can be downloaded onto phones and a whole body of literature on how mindfulness practices are stress-reducing. We are doing a study on an app designed for the period prior to conception, as well as pregnant and post-partum women. It's a daily mindfulness meditation that's 15 to 20 minutes.

More generally, Dr. Hoffman, what are some things within the mother's power that could minimize the risks of a negative mental health outcome for the child?

First, planning pregnancy: planning your family size and spacing, and then achieving the best health possible before you get pregnant. Second, having a healthy diet that includes folate and choline, both in dietary and supplement form. Feed yourself the best nutrients and you'll grow your fetus from the healthiest building blocks. Third, avoiding infections as best as possible with hand-washing, and early prenatal care to identify any risk factors for infection. Also, avoiding alcohol consumption, marijuana, and other illicit substances throughout pregnancy. Lastly, incorporating movement and physical activity into your daily routine. Regular physical activity improves mood, helps moderate stress, and decreases anxiety—all of which can be detrimental to pregnant women and their developing fetuses (and all of us, really).

❖ PETER TARR

BECOME A RESEARCH PARTNER



Barbara Toll, Research Partner

UNITING DONORS WITH SCIENTISTS

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

—Barbara Toll, Foundation Board Member

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A Novel Way to Help People in Prisons and Jails with Severe Mental Illness

Q&A with Judge Steven Leifman

Associate Administrative Judge, Miami-Dade County Court-Criminal Division, Florida
 2018 Pardes Humanitarian Prize
 2012 Productive Lives Award



Judge, how do we find ourselves in the position we are in today, with an estimated half a million people with mental illnesses in our jails and prisons on an average day? How can this possibly have happened?

I think you have to put this into context. It's important to recognize that it's not due to intentional meanness or cruelty. A number of factors were in play, historically.

In 1963, for example, President Kennedy signed a \$3 billion bill creating a wonderful national community mental health system. It was his final public bill signing. Tragically, due to the president's assassination, and then the subsequent escalation of the Vietnam war, not one penny of those funds that were allocated were appropriated for a system designed to be responsive to the needs of people with the most debilitating psychiatric disorders.

Another factor was the introduction of the first antipsychotic medication, chlorpromazine. It had some important benefits but it was by no means a long-term cure for people with psychotic illnesses. In the 1960s, some people thought

that this medication alone would enable patients with psychosis to live successfully outside the state hospitals.

In the early 1970s, a brilliant federal judge in Alabama named Frank Johnson wrote a remarkable opinion on a case in which the state was being sued to keep its psychiatric hospitals in operation. Around this same time, exposés were coming out in the press about the horrible conditions that prevailed at state hospitals all over the country. Judge Johnson wrote an amazing opinion. It basically said that Alabama had the most despicable, grotesque psychiatric hospital in the United States at that time.

Judge Johnson ordered Alabama to make 80 specific improvements to its state psychiatric hospital. If it failed to comply, he put the state on notice that he was going to shut down the hospital and release all the residents into the community. My guess is that he expected that this would provide a strong incentive for the state to pony up the money and fix the hospital.

But they failed to fix it?

Actually, that's not what happened. Alabama started to put up the money and, at one point, probably had the

best psychiatric hospital in America, because they were under this tough federal requirement. But—they didn't complete all of the conditions set out by the Judge, who, as a result, stated his intention to follow through with his original order: the hospital was to be closed. Alabama then appealed to the U.S. Supreme Court.

The Supreme Court for the most part affirmed the Judge's decision, which noted that if you were in jail, you had a constitutional right to adequate healthcare. They extended that logic to those who were confined in state psychiatric hospitals—they had a right to adequate care, too. The precedent that emerged was that the states had a choice: either provide adequate care to patients in state psychiatric hospitals, or release the patients into the community.

The states could not be forced to take care of the patients.

The rest of the states took one look at this decision—this

was a federal opinion so it applied to everyone—and realized that they had a choice. They could spend literally billions of dollars to upgrade their facilities; or they could close down their psychiatric hospitals and try to give the patients community-based treatment.

But as you said, the community mental health law passed under President Kennedy did not end up helping patients with serious psychiatric disorders such as psychosis—people at the time who were mostly confined to state psychiatric hospitals.

Exactly. So patients in the state hospitals ended up going from the state hospital to the street, and, too often, from the street to the jail.

There's a remarkable irony. In 1955 there were 560,000 people in state psychiatric hospitals in the United States. The equivalent number today—if we had kept those hospitals going and taking population growth into account—is about 1.5 million patients.

That figure is almost the exact number of people that were arrested last year with serious mental illnesses. About 1.5 million people with serious mental illness were arrested last year (in about 2 million



separate incidents). But the era of the large state psychiatric hospitals is long past. There are only around 35,000 state psychiatric beds left in this country today.

So “de-institutionalization” has a lot to do with the current crisis.

Yes, but to be accurate, we never de-institutionalized. There was trans-institutionalization. We effectively transferred responsibility from the really horrible state psychiatric hospitals to really horrible jails. And in many ways, in so doing we made things worse for people. When people with serious mental illnesses are incarcerated, they end up with a criminal record. They end up hanging out with real criminals, they can't get housing, they can't get employment. So they end up recycling through the criminal justice system throughout their entire adult life—because they're not getting treated, either.

We're now using the criminal justice system as we did in the early 1800s, as a place to hold people with serious mental illness, and it's much worse today than it was in the 1840s. The numbers are just staggering. Right now about 17 percent of the U.S. jail and prison population consists of people with serious mental illnesses—psychosis, schizophrenia, major depression, bipolar disorder. And it's significantly different between men and women. About 33 percent of all women in jail and prison have serious mental illnesses, compared with about 14 percent of men.



What accounts for the male-female difference?

I think it's because trauma plays a significant role in mental illnesses, and women are much more often the victims of trauma in our society. One study found that 92 percent of women in jail and prisons with serious mental illnesses were sexually abused as children. Those who were never treated end up with severe PTSD and often turn to prostitution, which is one way they end up in our criminal system. It's pretty horrible. When they were victims at a young age we didn't do anything to help or protect them.

You have won much praise for your plan to build what is called a "psychiatric diversion facility" in your jurisdiction of Miami-Dade County, Florida. Can you explain the purpose of this facility and why it is needed?

Rather than send people with serious mental illness who have committed misdemeanors or low-level felony offenses to prison, or even to a psychiatric hospital, the idea is to send them instead to a facility that emphasizes treatment, restoration, and reintegration into the mainstream of society. In recent years, the County has raised \$42.1 million through bond issues to support this project, and construction is scheduled to start in January 2019.

As for why we need it: remember, when the existing community mental health system was set up in the 1960s and 1970s, people with the most severe mental illnesses were still in state hospitals. The community mental health system was underfunded, and it wasn't even set up to handle the most seriously ill. So today the acutely ill are left with no state hospitalization and too often find themselves trapped in the criminal justice system.

What we're creating in our county is what they actually need, which is a structured environment focused on treatment and recovery rather than kicking them to the curb once we've handled their charges in court. We want to gently and slowly reintegrate people with serious mental illnesses back to the community with the services that they need.

The new facility will be a one-stop shop. It will have primary health care. It will have an eye and dental clinic. It will have a court room. It will have a crisis stabilization unit and a short-term residential facility. It will have a day activity program run by people with mental illnesses to teach self-sufficiency. And it will have a supportive culinary employment program so we can teach employment—there are lots of jobs in Miami in the culinary and hotel industries. The facility will have living space for up to a year for those who choose to live there. We are also working with the city of Miami and the Corporation for Supportive Housing on seeing if we can develop some really great supportive, affordable, and low-income housing on land surrounding the facility, so that we have a pathway for people as they leave.

Despite the evidence, some people continue to believe that the people you are trying to help, with serious mental illness, are risky because they tend to be violent.

People with mental illness are no more dangerous than the general population and, sadly, they're much more likely to be victims of violent crimes than perpetrators. When they are on their medications, they're much less likely to commit a violent crime than the general population. So it's really about getting their diagnoses right,



Judge Leifman receives William Rehnquist Award for Judicial Excellence from Chief Justice Roberts, November 2015

getting them on the right medications, working with the individual to develop a treatment plan that they're comfortable with. It's about developing really good case management, it's about having supportive housing so they're helped along the road, it's about having supportive employment so that they can do things that they like to do—which helps them stay in recovery.

Some communities in the United States have some of the aspects of our program in Miami, but no single community including Miami has all of the essential

"We're creating a structured environment focused on treatment and recovery rather than kicking people to the curb."

elements necessary for a complete system of care. For communities that have developed diversion programs for people with serious mental illnesses, it's still difficult for people with serious mental illness to navigate the system because it is so fragmented. This is why our new facility is so critical to our success.

Can your vision work in other communities, in other counties and states?

I certainly hope so. I logged about 120,000 miles in 2018 to visit communities that are desperate to do this. The level of enthusiasm and support has been impressive, and I like to think it's because we've turned a corner. I think people

are finally starting to understand that these are just illnesses and that you wouldn't allow your loved one to be treated like this. We've got to identify them earlier. We've got to treat them better.

So I'm actually cautiously optimistic. We've been able to help tens of thousands of people over the last 18 years just by diverting into the existing system, which isn't all that great. By diverting the most ill, whom we have not been able to help, into a better kind of care, I'm optimistic that this is a program that can be replicated.

My county deserves enormous credit. Our county gets it, because of the results of our program. In 18 years we've been able to reduce arrests in Dade County from 118,000, when we started, to 56,000 today. Much of that reflects the impact of our treatment of people with mental illnesses.

You were actually able to close a jail.

That's true. And that's saving the taxpayers in Miami-Dade \$12 million a year. We had a study conducted by the Florida Mental Health Institute of the University of South Florida. They used court records to identify the defendants with mental illness who made the largest demand on our resources. In a group numbering about 3,300 over a 5-year period, they identified a core group of 97 people who commanded a greatly disproportionate share of our resources. These 97 individuals, mostly men with schizophrenia, were arrested 2,200 times in the 5 years. They spent 27,000 days in our jail, the Dade County Jail; 13,000 days in a psychiatric ER; and they cost taxpayers almost \$14 million, and that's just the psychiatric side;

that doesn't even go into their primary health issues. The people of the county got nothing for it. The outcomes were horrible. That's why we need a facility like the one I've described. It's for the really acute population that cannot recover in the existing system.

To prevent the seriously ill from recycling through the system, year after year.

That is our intention—to have much better outcomes than we have today and to give people with serious mental illnesses hope for a life in recovery. ❖ PETER TARR

Recent Research Discoveries

Important Advances by Foundation Grantees That Are Moving the Field Forward

EARLY-LIFE COMPLICATIONS AFFECT THE PLACENTA AND RAISE SCHIZOPHRENIA RISK



Daniel R. Weinberger, M.D.

A team led by BBRF Scientific Council member Daniel R. Weinberger, M.D., Director & CEO of the Lieber Institute for Brain Development at Johns Hopkins University, has offered powerful evidence that problems in the placenta—the result of various early-life complications—directly affect the fetus’s risk of developing schizophrenia.

Variants of genes that are known to be linked with higher risk for schizophrenia are vigorously expressed, in the placenta, the researchers found, in complicated pregnancies. In *Nature Medicine* in June 2018, they explained that the presence of such risk genes is especially consequential when there is a complication during, at, or just after birth. The evidence also showed that the male fetus is more vulnerable to such complications than the female.

The research helps corroborate a “developmental hypothesis” of schizophrenia that Dr. Weinberger first advanced decades ago: that events which take place prior or around the time of birth can cause behavioral symptoms that typically don’t become evident until much later in life, in adolescence or early adulthood.

During pregnancy, what begins as a tiny grouping of cells undergoes a stunning metamorphosis, growing into a living, hard-wired brain. Like any living thing, the emerging brain is affected by its environment—the fetus’s home in the womb, fed by the placenta. Dr. Weinberger and colleagues looked at published data that marked single-DNA-letter gene variations in 501 Americans, 267 of whom were healthy and 234 were diagnosed

with schizophrenia. These were analyzed alongside “polygene risk scores” that are higher in individuals with schizophrenia, and in the context of complications during pregnancy, at delivery, and early in neonatal life.

This overlay of datasets revealed that those whose gestation was marked by an early-life complication also had, as a group, a greater burden of risk genes associated with schizophrenia. The specific risk genes these patients had were grouped into an identifiable “cohort” of genes that were abundantly expressed in the placenta. These genes play a role in the placental stress response, as well as and in metabolism and inflammation.

The researchers concluded that a subset of the most significant genetic variants associated with schizophrenia, as found in the genome-wide DNA scans, affect various processes before birth that impact the placenta’s response to stress and thus the risk for schizophrenia in the newborn.

The research team also included Karen Faith Berman, M.D., BBRF Scientific Council member, 2014 Distinguished Investigator and 2000 Independent Investigator; Giuseppe Blasi, M.D., 2007 BBRF Young Investigator; Dan Rujescu, M.D., Ph.D., BBRF 2006 Independent Investigator; and Alessandro Bertolino, M.D., Ph.D., BBRF 2013 Independent Investigator and 1999 Young Investigator.

A RAPID FORM OF BRAIN STIMULATION FOR TREATMENT-RESISTANT DEPRESSION

Since 2008, when transcranial magnetic stimulation, or TMS, was approved by the U.S. Food and Drug Administration (FDA), it has been available to people whose depression has resisted conventional forms of treatment. In the past decade, the effectiveness of TMS has been confirmed in a number of clinical trials, showing that as many as half of treatment-resistant patients respond to it (i.e., have at least a 50 percent reduction in symptoms) and up to one-third achieve full remission of symptoms.

But TMS is not as convenient for patients as drug therapy, a factor that has limited its use. TMS treatments must be delivered in the office of a doctor or facility with the



Daniel M. Blumberger, M.D.

required equipment. The state-of-the-art treatment for depression using repetitive TMS (rTMS) calls for patients to receive stimulation for 37 minutes, through a coil placed on the scalp. The treatment is non-invasive, requires no anesthesia, and does not interfere with the patient’s normal activities before or after treatment. TMS has an excellent safety record, with the main side-effect being headache, which typically fades following treatment.

But the duration of each rTMS session does impose an upper limit on how many patients can be treated in a single day with a single device. The entire session takes about 45 minutes per patient, including the time it takes for each patient to be put in position for treatment. It may now be possible to cut this to only 10 or 15 minutes, according to new research reported in *The Lancet*.

A team led by Daniel M. Blumberger, M.D., a 2010 BBRF Young Researcher at the Centre for Addiction and Mental Health at the University of Toronto, has successfully tested a new form of rTMS called iTBS (intermittent theta burst stimulation). It can deliver stimulation to brain areas affected by depression in only 3 minutes—delivering therapeutic benefits to patients that Dr. Blumberger and colleagues report are just as effective as standard TMS treatments.

The team’s clinical study involved about 400 patients aged 18-65, half receiving conventional rTMS treatments and

half the experimental iTBS treatments. Patients in both groups were treated 5 days a week for 4 to 6 weeks. The same brain area—a part of the prefrontal cortex—was targeted by both forms of magnetic stimulation, the only difference being that standard rTMS delivered 3,000 pulses per 37-minute session while iTBS delivered 600 pulses in only 3 minutes.

The iTBS method generated an impressive response rate of 49 percent and a remission rate of 32 percent for patients who had failed one or more antidepressant treatments. These results were just as good as those achieved by patients who received conventional rTMS.

“Broad access to rTMS treatment has been partly limited by the number of patients who can be treated with existing protocols,” the researchers said. With iTBS, “the number of patients treated per machine, per day can be tripled or quadrupled by use of iTBS. This could facilitate efforts to accelerate rTMS courses from weeks to days via several daily sessions,” they noted.

The team also included BBRF Scientific Council member Zafiris Daskalakis, M.D., Ph.D., 2004 and 2006 BBRF Young Investigator and 2008 Independent Investigator; and Peter Giacobbe, M.D., 2010 BBRF Young Investigator.

A TEST OF KETAMINE IN DEPRESSED ADOLESCENTS

A small study of intravenous ketamine treatment for adolescents with treatment-resistant depression indicates that the drug may be an effective treatment for some teens.

Results of the study, published in *The Journal of Child and Adolescent Psychopharmacology*, also suggest that it will be important to work out the exact dosage of intravenous ketamine in this population of patients, if further studies confirm that the treatment regimen is useful and safe.

Ketamine has been studied as a fast-acting antidepressant drug in adults

with treatment-resistant depression and suicidal behaviors, but there has been little information on how the drug might act in adolescents. To address this, a research team studied intravenous ketamine treatments in 13 adolescents with depression who had failed to respond to two previous antidepressant treatments.

The study participants received six doses of the drug given over 2 weeks, with a 6-week follow-up period for those who responded to the infusions. Five of the patients had their depression symptoms decrease to a level that indicates a clinical response to the drug, and three of these patients were considered in remission after the treatment. In general, the drug was well-tolerated, with only passing symptoms of dissociation (a sense of detachment from reality) and changes in blood pressure among the patients.

The researchers noted that higher doses of ketamine appeared to be more beneficial, but they cautioned that more work is needed to learn what the optimal dose would be for teens.

The team was led by Kathryn R. Cullen, M.D., 2009 BBRF Young Investigator at the University of Minnesota, included BBRF Scientific Council Member Kelvin O. Lim, M.D., 1999 BBRF Independent Investigator and 1989 Young Investigator at the University of Minnesota, and Susannah J. Tye, Ph.D., 2009 BBRF Young Investigator at Mayo Clinic.



Kathryn R. Cullen, M.D.

BBRF Honors Remarkable Humanitarians in 2018



THE BRAIN & BEHAVIOR RESEARCH Foundation, the world's largest private funder of mental health research grants, presented its 2018 Outstanding Achievement Prizes to 10 scientists (featured in the Symposium story on page 34), and awarded the Pardes Humanitarian Prize in Mental Health at its International Awards Dinner on Friday, October 26, at the Pierre Hotel in New York City. The evening celebrated the power of neuroscience, psychiatric research, and humanitarian efforts to change the lives of people who are living with mental illness.

This year's Pardes Prize recipient was Judge Steven Leifman (featured in the article on



page 24) who was honored for his leadership in reducing the number of people with mental illness in the Miami-Dade criminal justice system and for getting them the care that they need.

Judge Leifman, an associate administrative judge in Miami-Dade County, is a national leader in solving the complex and costly problem of people with untreated mental illnesses being incarcerated rather than treated for their condition. In 2000, he launched a pioneering initiative called the Eleventh Judicial Circuit Criminal Mental Health Project, which steers people with mental illness who pose no threat to public safety away from the criminal justice system and into community-based treatment. The initiative also includes training police officers to recognize the signs of mental illness and de-escalate potentially dangerous situations, as well as assuring that individuals with mental illness who are taken into custody have their cases quickly transferred to the appropriate venue so they can be placed in treatment.

As a result of his initiatives, arrests in the county decreased from 118,000 to 56,000 annually and recidivism dropped by almost 50 percent. The jail population diminished from 7,300 to 4,000 inmates, closing a jail and generating \$12 million in annual savings. Crime and burdens on taxpayers have been reduced,

and public health, safety, and recovery outcomes have improved.

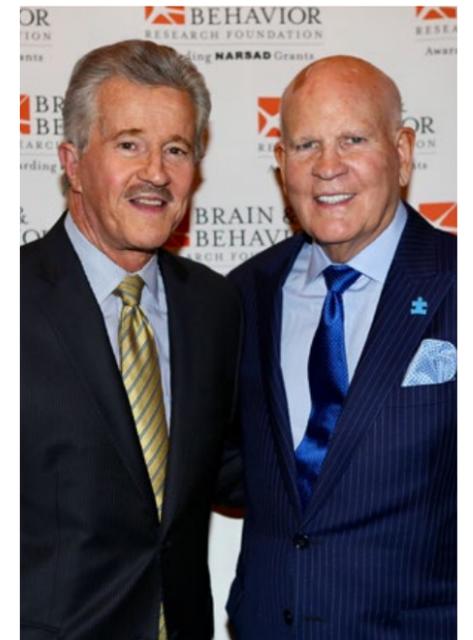
"Judge Leifman has been a passionate leader and unwavering agent of change in the shift away from the devastating and unproductive incarceration of people with mental illness. He has shown us how to use our resources to reverse the costly prison recidivism that strips people of their dignity and threatens public safety," said Dr. Herbert Pardes, President of the Brain & Behavior Research Foundation's Scientific Council.

Dr. Jeffrey Borenstein, President and CEO of BBRF added, "Judge Leifman is an extraordinary humanitarian, innovator, and transformative figure whose steadfast advocacy is changing the lives of people with mental illness and their families, and impacting our larger society."

"This is the one area of civil rights where we've lost ground in this country," said Judge Leifman. "I am extremely humbled and honored by this award which will serve as a vehicle to help educate people about this tragedy. The criminal justice system should not be a place where people come to get care for mental illness," he added. "People with mental illness need to live a life of recovery that enables them to contribute to society. We shouldn't allow people's lives to be ruined because they have an illness."

The Honorary Pardes Humanitarian Prize in Mental Health was given to Bob Wright and the late Suzanne Wright, the founders of Autism Speaks, for their unparalleled leadership in advancing autism research and increasing understanding and acceptance of people with autism spectrum disorder.

Bob and Suzanne Wright co-founded Autism Speaks in 2005, inspired by their grandson, Christian, who was diagnosed with autism. Guided by the Wrights' leadership and vision, Autism



ABOVE: Dr. Herbert Pardes, Bob Wright, Judge Steven Leifman and Dr. Jeffrey Borenstein; **CENTER:** Judge Steven Leifman and Dr. Herbert Pardes; **RIGHT:** Dr. Max Gomez and Bob Wright, Honorary Pardes Prizewinner

OPPOSITE PAGE: **LEFT:** Dr. Jeffrey Borenstein, BBRF President & CEO, and Dr. Altha Stewart; Stephen Lieber* and Dr. Herbert Pardes, President of the BBRF Scientific Council

*Brain & Behavior Research Foundation Board Members
** BBRF Scientific Council Members



FROM TOP LEFT: Dr. Maria Oquendo**, Carol Atkinson*, Carole Mallement*, Anne Abramson*; Dr. Saul Levin, Dr. Bruce Schwartz, Dr. Lloyd Sederer, and Dr. Dilip Jeste** Qian Lin and Dr. Xiao-Jing Wang, Goldman-Rakic Prizewinner; Back Row LtoR: Dr. Daniel Weinberger**, Alice Wexler, Dr. John Krystal**, Dr. Bonnie Becker, Dr. Helen Mayberg**, Dr. Robert Hirschfeld**, Dr. Bob Bazell. Front Row LtoR: Dr. William** and Carol Carpenter, Dr. Dilip Jeste**, Kari Stoever, Dr. Jack Barbas**, Room Shot; Dr. Kristen Brennand and Dr. Jeffrey Borenstein



Speaks has grown into the world's largest autism science and advocacy organization. The Wrights helped raise \$3 billion in funding for groundbreaking science, effective advocacy, and extensive family services, which improve lives of people and families affected by autism now and into the future.

The Centers for Disease Control and Prevention (CDC) estimates the prevalence of autism is 1 in 59 children in the United States. This includes 1 in 37 boys and 1 in 151 girls.

"Thanks to the extraordinary vision of Bob and Suzanne Wright, scientists have been able to develop a better understanding of autism, which is leading to helpful interventions. There are evolving trends in research that point to the interconnectivity between autism and other medical conditions," said Dr. Pardes. "These and other research findings, as well as the growing public awareness of what autism is, and isn't, are directly attributable to their pioneering leadership as philanthropists, catalysts for change, and humanitarians."

"Judge Leifman has shown us how to use our resources to reverse the costly prison recidivism that strips people of their dignity and threatens public safety."

—Herbert Pardes, M.D.

For many years BBRF has served as a leader in funding research on autism and has awarded over 175 grants totaling more than \$12 million to researchers.

The Pardes Humanitarian Prize in Mental Health was established in 2014, and is awarded annually to recognize individuals or organizations that are making a profound and lasting impact in advancing the understanding of mental health and improving the lives of people with mental illness. It focuses public attention on the burden mental illness places on individuals and society, and the urgent need to expand mental health services globally. Nominations are solicited worldwide. The recipient is chosen by a distinguished committee of 11 members internationally and is named in honor of Dr. Pardes, the first recipient of the award. ❖

PHOTOGRAPHER: CHAD DAVID KRAUS

The Prize is sponsored in part by Janssen Research & Development, LLC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Highlights from the 2018 International Mental Health Research Symposium



ON OCTOBER 26, 2018 THE BRAIN & BEHAVIOR RESEARCH FOUNDATION held its International Mental Health Research Symposium, with presentations by top researchers in the field of mental illness. The symposium at the Kaufmann Music Center in New York City featured research talks by 10 of the Foundation's 2018 Outstanding Achievement Prizewinners, along with two promising Young Investigator grantees.

The symposium featured a special presentation by Dr. Altha Stewart, the President of the American Psychiatric Association about using mental health research to achieve health equity. The afternoon's keynote presentation was made by Judge Steven Leifman, the BBRF 2018 Pardes Humanitarian Prizewinner (stories on pages 24 and 30), about ending the criminalization of mental illness. Both of these presentations are available for viewing on our website.

The BBRF Outstanding Achievement Prizewinners are selected by special committees of the Foundation's Scientific Council, which is comprised of 181 preeminent mental health professionals in brain and behavior research.

The 10 scientists, who are affiliated with universities in the United States, France and Canada, were recognized for their extraordinary achievements in research on schizophrenia, mood disorders, child and adolescent psychiatry, and cognitive neuroscience.

"These 10 exceptional scientists are dedicated to advancing the science that is changing what it means to live with a mental illness and open possibilities for more people to live full, productive, and joyful lives," noted Dr. Jeffrey Borenstein. "Their individual projects reflect the unprecedented depth and breadth of brain and behavior research."

Meet Our 2018 Outstanding Achievement Prizewinners and hear what they had to say about their work in their own words.

THE LIEBER PRIZE FOR OUTSTANDING ACHIEVEMENT IN SCHIZOPHRENIA RESEARCH

Anissa Abi-Dargham, M.D., *Stony Brook University, is an internationally recognized leader in the use of molecular imaging of the human brain to study schizophrenia and its co-morbidity with addiction.*

I've been really lucky to have my research funded by the Brain and Behavior Research Foundation, even when my work, when reviewed by government funders, was thought to be premature or too novel. Without the vision of a Scientific Council like BBRF's that's really expert and can see the big picture, it's almost impossible to move research in novel ways. It's something I've benefited from.

In my research, I've used PET, or positron emission tomography, a molecular imaging technique, to look at neurotransmitters and their receptors in the brain. We've done many studies over the years, and one story that has continued to evolve is our work on dopamine. Dopamine is a neurotransmitter that is involved in many functions, from reward to cognition to movement. In schizophrenia it has always been at the center of the story. One reason is that every drug we have for schizophrenia acts on one of the dopamine receptors, called the D2 receptor. We also have long known that if people take dopamine-like drugs, they tend to have psychotic symptoms. So it's been very important to understand dopamine in order to develop better treatments.

With PET we have the ability to look at the brain when people are alive—so we can try to correlate symptoms and response to treatments. We've found that in one part of the brain, the striatum—which is a structure deep in the center of the brain—there is an excess of dopamine in people with schizophrenia. This is what's producing hallucinations and the psychosis part of the illness. Yet everywhere outside the striatum, dopamine is in *deficit* in schizophrenia patients. This may contribute to the cognitive deficits and negative symptoms.

At this point we are trying hard to understand this disparity in dopamine in schizophrenia. The story is evolving, but I'm really honored to be recognized for this work.

Schahram Akbarian, M.D., Ph.D., *Icahn School of Medicine at Mount Sinai, studies genome organization and genome function, including gene expression, in brain cells. The goal of his research is to gain a deeper understanding of the molecular and cellular mechanisms associated with schizophrenia and related psychiatric disease.*

My research endeavor began almost a quarter-century ago in the early '90s, when we started to do some of the first molecular studies in postmortem brains of people with schizophrenia.

It was a time when a lot of credible investigators believed that studying brain tissue, let alone postmortem tissue—tissue collected after death—is a waste of time for a complex disorder such as schizophrenia. But we didn't shy away from the challenge and pushed the frontiers, in terms of developing methods and technologies. Back then we focused on a single messenger-RNA molecule from a single gene that is important for regulating the balance of neuronal inhibition and excitation in the cerebral cortex. That provided the foundation for what is now known as the GABA hypothesis of schizophrenia.

Fast-forward to today, where we are in a position of sequencing not only a single gene and a single messenger-RNA molecule. We can now sequence the entire 6 billion base-pairs of DNA in each of our cells, including those

of the human brain—and if needed, from single cells. This enables us to study hundreds of people with schizophrenia, comparing them [genomically] to hundreds of controls.

It's one of my favorite things to talk about. In each of our cells there are two meter-long threads of DNA that have to be packed into a tiny, tiny cell nucleus, only a few micrometers wide. So how does this happen? And how does this process impact the genetic architecture of schizophrenia?



Anissa Abi-Dargham, M.D.



Schahram Akbarian, M.D., Ph.D.

I think we've learned a lot by pursuing this kind of research. The core mission of my lab is to import technologies that are well-established in the basic sciences, bring these very basic molecular techniques into study of the human brain.

This is often work for which you later get a lot of NIH money. But for the first few years you don't get a lot of money. There's a lot of skepticism and questions what your work is good for. And I have to say, ever since 1993 when I started this work, each and every time we had a milestone achievement, each and every time it was BBRF seed money that helped to grow a nucleus of work that then ended up in a big multimillion-dollar NIH grant.

THE MALTZ PRIZE FOR INNOVATION & PROMISING SCHIZOPHRENIA RESEARCH

Kristen Brennand, Ph.D., Icahn School of Medicine at Mount Sinai, has helped to pioneer a new approach in the study of psychiatric disease by combining her expertise in stem cell biology and neurobiology.



Kristen Brennand, Ph.D.



Guillermo Horga, M.D., Ph.D.

I don't think you can say it enough: that by giving Young Investigator awards, BBRF changes careers. The first award I ever received for my lab was the Young Investigator award. That's for sure the most important one, because at the start you have all this doubt. Can I do this? Is this even possible? And that allowed my lab to really begin to grow, and so it's so important to me to thank you for believing in me before anybody else did.

I am not a psychiatrist by training. I'm a stem cell biologist, so I did my Ph.D. in a stem cell lab, and when I finished there was an amazing discovery made by a scientist named Yamanaka in Japan, which we knew was going to change everything. And in fact, he won the Nobel Prize four years after making his discovery.

This discovery was that you could take skin cells from anybody on the planet and turn those into stem cells that have the capacity to become any cell type in the body. And so, what that instantly meant was that obtaining samples from patients was no longer limiting. It's really hard to get enough brains from patients, and impossible while they are alive. That's where all the good experiments are, on live brain tissue. And it's just as hard to get brain samples from the controls. So what we can now

do in the culture dish is miraculous: we make neurons and astrocytes (helper cells) that are genetically identical to those in the donor's body. They are generated with harmless skin cell samples, and we have them growing on in plastic dishes in the incubator, the starting point for experiments on brain cells and mental illness that were never before possible.

We can ask all sorts of questions of those. We can try to understand how the cells from patient are different from those of controls—and they are in many subtle ways. We can test the genetic variants that are coming out of the genome-wide studies to ask, "Well, which cell types do those genetic factors impact?" And ultimately what we think we have is the ideal drug-screening platform, because I can make limitless numbers of cells from any patient and screen them for limitless numbers of drugs to begin to understand in a patient-by-patient approach how we can predict which drugs might work best for which patients.

Guillermo Horga, M.D., Ph.D., New York State Psychiatric Institute, Columbia University, focuses on the neurobiological and computational mechanisms of psychotic symptoms in schizophrenia and of related cognitive functions in health, including sensory and reward-based learning and decision making.

My research started during my residency. I saw a lot of patients who were psychotic, and I knew some of the findings about the implications of dopamine in the expression of these psychotic symptoms, like hearing voices or having delusional thoughts. I

always had the idea that this might not be the full picture. It is obviously relevant for treatment and in understanding the neurobiology, but it seems like there is something missing, in terms of understanding how you go from dopamine dysregulation in the striatum that Dr. Abi-Dargham described, to patients' experiences, like hearing voices. How do you have excess dopamine in the striatum and then suddenly you hear voices?

My main interest was to try to apply cognitive and computational models of perception to understand the different pieces, the different sorts of information that go into our subjective experiences. What are the aspects that are disrupted with dopamine dysregulation? We use a variety of behavioral paradigms and also functional MRI to understand the neural underpinnings of these processes.

The second goal of my lab is to develop imaging biomarkers, in particular MRI-based biomarkers, to provide non-invasive measures of the types of dopamine dysregulations that Anissa and others have studied. This would be interesting to use in younger people who are at risk for schizophrenia who can't undergo PET scans; or in people in whom we might want to track progression of the illness, who can't undergo PET repeatedly because of radiation and other issues. We've been working on validating an MRI measure that we think is pretty promising in establishing risk for psychosis.

THE COLVIN PRIZE FOR OUTSTANDING ACHIEVEMENT IN MOOD DISORDERS RESEARCH

Benjamin I Goldstein, M.D., Ph.D., FRCPC, University of Toronto & Sunnybrook Health Sciences Centre, is an international leader in child-adolescent bipolar disorder and in the link between bipolar disorder and cardiovascular disease.

I wanted to say two specific things in terms of gratitude. One is that many of us are from other countries—I'm from Canada—and are supported by BBRF, which I think is an exception among a lot of organizations. The second is that with BBRF, once you've been chosen for an award, you become part of a family or a village that is not forgotten and that is not neglected. It's been my experience that in addition to receiving awards, people are supported in terms of having attention brought to their work in a way that's very well-digested for the general population. This really helps us convey the influence of our science to people affected by the diseases that we treat and study.

My work focuses on early-onset bipolar disorder and vascular co-morbidity. It's known that in people with bipolar disorder there are increased rates in premature onset of heart disease. There were a lot of assumptions that this relates to smoking and sedentary lifestyle and obesity, and all those things are true. But the link exceeds what you can explain by all of the usual suspects, and the question arises: What else explains this link between bipolar disorder and heart disease? The focus of my career is on that difference, factors that may explain bipolar disorder not as having a co-morbidity of cardiovascular disease but of *being* in part a vascular disease.

Our work focuses on magnetic resonance imaging that can probe blood flow, blood vessel reactivity in the brain. I think that in addition to understanding what underlies the disease, an approach that integrates vascular considerations could open up avenues for treatments that are currently available that don't need to be "discovered." These would be treatments that we're not currently using in the treatment of bipolar disorder. All of this, I hope, may help reduce the shame and the stigma of an illness that is seen as very different from other diseases, which I don't think that it really is.

Lakshmi N. Yatham, M.B.B.S., F.R.C.P.C., M.C.Psych (UK), MBA (Exec), University of British Columbia, focuses on the neurobiology and treatment of bipolar disorder. His research on first-episode mania has demonstrated the benefits of early intervention in improving clinical and cognitive outcomes and halting the progression of brain changes in bipolar disorder, especially in those who remain episode-free.



Benjamin I Goldstein, M.D., Ph.D., FRCPC



Lakshmi N. Yatham, M.B.B.S., F.R.C.P.C., M.C.Psych (UK), MBA (Exec)

The focus of our program is translational research. We do brain imaging studies to understand neurochemical and neurostructural alterations in people with bipolar disorder. These include studies of the serotonin receptor and of the dopamine system. We do studies, for example, on first-episode mania, to understand the course and evolution of the disease. We are involved in a number of clinical trials to look at developing new treatments. And we do a lot of knowledge-translation, including the development of treatment guidelines for clinicians.

I would like to give you an example of how we take something from the lab bench and try to bring it to the patient's bedside. It has to do with our research on dopamine. Manic symptoms in bipolar disorder can be treated with drugs that block the dopamine-2 (D2) receptor. This includes patients with non-psychotic mania. But: do these patients actually have an abnormality in the dopamine system? This is a question we set out to answer using PET scans.

After realizing that D2 receptors are not abnormal in these patients, we asked whether they were making excess dopamine in their neurons. But there was no difference in dopamine synthesis between patients and healthy controls. Yet following treatment with Valproate, the rate of dopamine synthesis in patients goes down—you can see this in the PET scans. So if you reduce dopamine transmission by blocking D2 receptors, or by reducing the rate of dopamine synthesis, you're actually improving manic symptoms. The question then becomes: where is the abnormality in the dopamine system in manic patients? We then looked at the dopamine transporter, a protein which returns dopamine in the synapse into the presynaptic neuron. We found that patients with acute mania actually have a lower dopamine transporter density compared with controls. And we've found a nice correlation between the severity of manic symptoms and the amount of dopamine transporter. The lower the amount of dopamine transporter, the greater the severity of manic symptoms. Based on this we thought that if you could develop a drug to enhance the uptake of dopamine into presynaptic neurons, you might have a new way of treating manic symptoms. We identified an herbal product that does that—so we have been working with industry to synthesize this drug. We've done some preliminary animal studies with it, looking at its effect on altering the hyperactivity that is induced by a novel environment, and it does seem to have some effect. So we are moving forward with testing the



Ami Klin, Ph.D.



Joseph Piven, M.D.

drug in animal models of mania. If we have good results it is our intention to bring this to clinical trial in humans.

THE RUANE PRIZE FOR OUTSTANDING ACHIEVEMENT IN CHILD AND ADOLESCENT PSYCHIATRIC RESEARCH

Ami Klin, Ph.D., *Marcus Autism Center, Emory University School of Medicine and Children's Healthcare of Atlanta, studies mechanisms of socialization and their disruptions in infants, toddlers, children, and adolescents with autism spectrum disorders.*

I'm a clinician and an investigator. My teachers challenged me to elevate my clinical instincts to the level of quantitative science. I started in this field working with adults, living in a residential unit for adults with autism, adults who had been all their lives in long-stay hospitals. So they were profoundly disabled. And then sometime around 10 or 12 years ago, we started seeing babies. We always asked the question, what is autism like in the beginning?

This is what we found out. We found out the miracles of neuroplasticity. We found out that some of the greatest burdens of autism, the intellectual disability, the language disability, and the severe behavioral challenges, these are not part of the definition of the condition. These are *results* of the condition. And in fact, if we were able to identify these children early and intervene early, we might, just might, afford them what they need to fulfill their promise, which is really, for us, reaching the age of 36 months without language and intellectual delays. With that, they would live very different lives.

Since 1999, a colleague and I have been trying to quantify this thing called "social interaction." We've used eye-tracking technologies in order to measure the way that all of us, and certainly babies, go through the process of socialization from the first days and weeks of life, as they are engaging with others.

We found out that autism really is the result of a deviation from normative socialization, because babies really need others. And those disruptions happen from the first days and weeks of life. Using the technologies we developed, we're able to quantify the way that children

learn to be social. And in so doing, it has given us an opportunity to intervene. What we're learning is that we were able to do that in our practice, which made us think of doing it at the level of the community, where we might be able to make a great dent in what is really one of the massive public health challenges of our time. You all know there are 66,000 children born every year who will have autism. This has a societal cost of over \$120 billion a year. And most of those funds go to support individuals who are older and in their adult life are very disabled. Imagine a world in which we could make sure that each one of those 66,000 is going to reach the age of 3 without those delays. Their lives will be different. And so, I've become a major advocate for the possibility of redefining autism, not as a genetic liability that has inevitable disabilities as a destiny, but changing that narrative from something that is potentially a devastating condition into something that is really a unique way of being in this world.

Joseph Piven, M.D., *University of North Carolina, Chapel Hill, has studied various aspects of the pathogenesis of autism and related neurodevelopmental disorders, conducting family behavioral, molecular-genetic, and neuroimaging studies, as well as more recently conducting research on the late-life manifestations of autism.*

I have been focused on early development of autism. Probably 99.9 percent of the research that's been done since we first discovered this disorder has been of people once they have the diagnosis of autism. We've known for a long time that there's a high risk of developing autism or a higher risk than in the population if you have an older sibling with autism. But what we didn't know until recently was that these children go through a period of time in the first year or two of life when they don't really look like they have autism. So they have this pre-symptomatic or "prodromal" period. They don't display any of the defining features of autism. This is really a unique opportunity to study autism as it emerges.

We've had the distinct privilege over the last 10 years of running a large network of researchers doing brain imaging as these children develop from 3 and 6 months of age onward. What we found is that there are remarkable changes in the brain that precede any of the defining features of autism.

There are disorder-specific, age-specific changes that change over time during this period. It's a very dynamic time in normal development, but it's a strikingly aberrant developmental trajectory in autism and this gives us clues about where to intervene in a rational way. It gives us clues about mechanisms, and most recently, it's given us insight into prediction, so that we think that from brain imaging we can predict during this pre-symptomatic time which kids in the high familial risk group are likely to get autism.

That gives us an opportunity. We have this disorder. We haven't had our lithium equivalent in autism [i.e., a drug that works to lessen symptoms], and there's a lot of work being done, but our treatments are still having only a modest impact. So this period of time before symptoms emerge is very exciting. If we can really identify who these kids are, maybe we can treat them when the brain is most malleable, before these symptoms emerge and really have a great impact on their lives.

GOLDMAN-RAKIC PRIZE FOR OUTSTANDING ACHIEVEMENT IN COGNITIVE NEUROSCIENCE RESEARCH

Jean Pierre Changeux, Ph.D., *Collège de France & Institut Pasteur, France, widely acknowledged as one of the fathers of modern neurobiology and neuroscience, has combined biochemical, physiological and behavioral experimentation together with theoretical modeling to discover the mode of action of nicotine in the brain.*

I started my research career in molecular biology. I worked, when I was in [Nobel laureate] Jacques Monod's laboratory, on basic regulatory mechanisms, specifically the allosteric interaction between sites which are topographically distant on a protein. This is the key for regulation.



Jean Pierre Changeux, Ph.D.

I tried to extend this view very early on to receptors. The receptors are present, as you know, in our brain to recognize neurotransmitter molecules. I had the privilege to identify the first receptor for a neurotransmitter, which is the acetylcholine receptor. This receptor was purified, and indeed I'm still working on it now at the atomic level, to try to understand how at the atomic level and at the microsecond level, one can follow this allosteric transition, this conformational change in the protein that has regulatory impact.

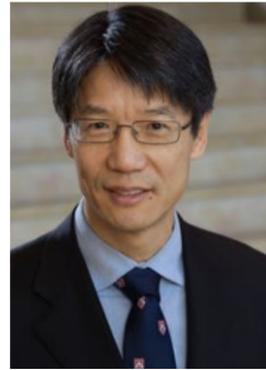
But in parallel with this work, we've always been concerned by the whole of the acetylcholine receptor in networks. And surprisingly, it's present in our brain. It is the receptor of nicotine, a well-known drug. Then we identified some of the regulatory elements working through nicotinic receptor and leading to nicotine dependence and adaptation.

Last, but not least, we have been concerned by consciousness—access to consciousness and its regulation. The interesting thing is that, here again, nicotinic receptors are involved, in what is called cognitive enhancement. Therefore we have a dual use of nicotine: one as an enhancer, the other as a drug of addiction. And this is often the case with morphine, with cocaine, and other compounds like that.

Finally, I am pleased to say that these last results lead to the idea that there is a perturbation of the nicotinic receptor in schizophrenia. As you may know, many schizophrenia patients self-administer nicotine through smoking and there is a possibility here to have some kind of drug development.

My last word is that I think we have to think more on the biochemistry of the brain in general, of receptors and how to design new drugs, for the future, in order to help patients.

Xiao-Jing Wang, Ph.D., *Center for Neural Science, NYU, uses mathematical models along with experiments to investigate neural circuits dedicated to cognitive functions. He is a leader in theory and modeling of the prefrontal cortex, which is responsible for planning complex cognitive behavior, personality expression, decision making, and moderating social behavior.*



Xiao-Jing Wang, Ph.D.

Let me tell you a bit about what I do. This really also speaks to the vision of the Foundation. I'm probably one of the few in the room who doesn't see patients and who doesn't work in a "wet lab." What I do is to use mathematics to build models that are very strongly informed by biology. I collaborate with people who do experiments, who work with patients, but my lab only uses mathematics and computational models.

This recognition by the BBRF is a sign that theory and mathematical models are becoming more and more important.

With big data, with the recognition that the brain system is so complicated, with all these reverberations, these feedback loops, it's perhaps time to bring in people who can use theory and mathematics. Working with experimentalists I try to help understand what's going on in the brain.

Using mathematical models for more than two decades, we have been trying to understand the prefrontal cortex, which is a core structure that's implicated in many psychiatric disorders. And we use our models, designed for normal functions, to also try to

figure out diseases, like cognitive deficits in schizophrenia or autism. The hard part is trying to go across levels, from genes to cells and synapses to circuits and systems in behavior. So we use our computational platform to go across levels. Hopefully it's bringing into the world a new technology, a new platform. It's a new field. So I want to thank the Foundation for its vision, enabling us to bring computational tools into the field of psychiatry. ❖

SAVE THE DATE
May 1, 2019

**BREAKING
THE SILENCE
ABOUT MENTAL
ILLNESS
LUNCHEON**

Hosted by
Dr. Jeffrey Borenstein
President & CEO,
Brain & Behavior Research Foundation



Therapy Update

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

INTERACTIVE PARENT-CHILD THERAPY REDUCED DEPRESSION SYMPTOMS IN VERY YOUNG CHILDREN

Young children who have been diagnosed with depression can benefit from an interactive form of therapy involving a parent, according to a clinical trial reported June 20th in the *American Journal of Psychiatry*.

The trial evaluated the effects of a new form of parent-child therapy on children between the ages of 3 and 7 who had been diagnosed with depression. The new treatment approach was modeled after a widely used program of parent-child therapy in which a therapist coaches a parent as they interact with their child, but included an added emphasis on emotional development.

The randomized trial included 229 parent-child pairs. Those in the treatment group participated in 20 therapy sessions over 18 weeks, during which time therapists guided the parents to better help their children recognize and regulate their emotions. At the end of the study, children who participated in the therapy had significantly lower rates of depression and less severe symptoms than those in the study group that did not receive the therapy. Parents who participated in the study with their children also experienced a reduction in their own depression symptoms and reported a decrease in parenting stress.

"The findings suggest that earlier identification and intervention in this chronic and relapsing disorder represents a key new pathway for more effective treatment," the team concluded. Clinical depression in children as young as age 3 has been validated, and prevalence rates are similar to those in school-age children, the researchers noted, adding that there is continuity between early and later childhood depression. The team is continuing to follow the children who participated in the study to determine if the benefits of the interactive therapy are long-lasting.

The research was led by Joan L. Luby, M.D., winner of the 2004 Klerman Prize for Exceptional Clinical

Research, a 2008 and 2004 BBRF Independent Investigator and a BBRF 1999 Young Investigator, at Washington University School of Medicine. Also on the research team was Deanna Barch, Ph.D., a Scientific Council Member, 2013 Distinguished Investigator, 2006 Independent Investigator, and 2000 and 1995 Young Investigator, also at Washington University.

INTENSIVE OUTPATIENT TREATMENT REDUCED VETS' SYMPTOMS OF PTSD WITHIN WEEKS

Three weeks of intensive outpatient treatment can significantly reduce the symptoms of post-traumatic stress disorder (PTSD) in veterans who suffer from the illness, according to a study reported July 27th in the journal *BMC Psychiatry*. The short course of treatment also enabled most of the participants to stay with the program to its conclusion, an important factor in its success, researchers noted.

Psychotherapy can help people with PTSD, but studies have found that many veterans discontinue treatment before their symptoms improve. Residential treatment programs can improve retention, but these typically last 6 to 12 weeks—a period that can be disruptive to work and family life. Recently, studies have found that intensive, 3-week treatment programs can also be effective for relieving PTSD in military veterans.

The new study was designed to evaluate how participants' symptoms improved over the course of such a program, and whether certain changes in thinking were particularly important in order for the treatment to be a success. The team tested the effects of a 3-week outpatient program involving daily trauma-focused psychotherapy called Cognitive Processing Therapy, as well as mindfulness-based resiliency training, which teaches patients to focus on the present moment to reduce stress and improve tolerance to trauma-related stimuli. Psychoeducation, art therapy, acupuncture, sessions on healthy living, and other services were also available to program participants.

Of the 191 veterans who began the program, 176 completed it. Depression symptoms declined steadily throughout the program, whereas PTSD symptoms began to decline after the first week, and reduced more quickly as the therapy continued. By the program's end, participants had achieved large reductions in both PTSD and depression symptoms. Those who experienced the greatest changes in trauma-related thoughts and beliefs during the treatment benefited the most, suggesting that cognitive processing therapy was an important aspect of the program's success.

"I also think the fact that we can get 90 percent of participants to stick with treatment is a big part of the success of intensive programs," commented the team leader, 2016 BBRF Young Investigator Alyson Kay Zalta, Ph.D., now at the University of California, Irvine. The team included 2003 BBRF Independent Investigator Mark H. Pollack, M.D., of Rush University, Chicago.

COMPUTER-DELIVERED COGNITIVE TRAINING HELPED SCHIZOPHRENIA PATIENTS IN REHAB SETTING

Cognitive difficulties experienced by people with schizophrenia have great impact on daily functioning and overall quality of life. Individuals who have reduced interest in activities, problems remembering and learning, or interpreting verbal cues, find it very difficult to hold jobs or cultivate social relationships that are central in normal functioning.

Researchers have been trying for years to find therapies that will specifically improve cognitive functioning. Targeted cognitive training (TCT) has recently been shown to have moderate to high effectiveness when administered in carefully controlled academic settings. This training method targets the brain's auditory processing system, in which deficits have been shown to correlate with patients' deficits in auditory perception and verbal learning.

Now, researchers have put TCT to a difficult real-world test. They provided TCT to schizophrenia patients receiving court-mandated care in a locked residential rehabilitation center. In this setting, they set out to discover whether some of the most seriously afflicted patients could be helped. Participating patients suffered

from severe symptoms and required stabilization on high dosages of antipsychotic medications, and, on average, had been sick for over 15 years.

A commonly held assumption of the field was that cognitive remediation would work less well or not at all in these patients. But to the team's delight, this was not the case. The researchers followed 46 patients in this trial, all of whom received ongoing medication management, individual and group therapy, and structured social activities. Half of the patients also received 3-5 hours of TCT training per week. This training consisted of various tasks delivered via laptop computers, focusing on a variety of auditory processes.

"TCT produced significant improvements in auditory perception and verbal learning," the team reported July 25, 2018 in *Schizophrenia Research*. They also experienced a "significant reduction in auditory hallucinations." Age, symptom severity, medication dosage, and illness duration did not reduce TCT's effectiveness.

"The findings indicate that even highly symptomatic, functionally disabled patients with chronic illness benefit from this emerging treatment," the team said. Unfortunately, nearly one-third of the patients receiving TCT did not show a significant benefit, they noted, and continuing research will address how to boost the response rate.

The team was led by Gregory A. Light, Ph.D., of the University of California, San Diego, a 2014 Sidney R. Baer, Jr. Prizewinner, 2013 BBRF Independent Investigator, and 2006 and 2003 BBRF Young Investigator. The team also included Andrew Bismark, Ph.D., a 2016 BBRF Young Investigator; Yash Joshi, M.D., Ph.D., a 2018 BBRF Young Investigator; David L. Braff, M.D., 2014 Lieber Prizewinner and 2007 BBRF Distinguished Investigator; Sophia Vinogradov, M.D., a 2000 BBRF Independent Investigator, and Neal Swerdlow, M.D., Ph.D., a 2016 BBRF Distinguished Investigator, 1995 BBRF Independent Investigator and 1990 BBRF Young Investigator.

Acetylcholine: A type of message-carrying neurotransmitter. It has a critical role in activating muscles as well as in the function of the autonomic nervous system, which controls involuntary processes such as the beating of the heart, respiration, and digestion.

Allosteric site: An alternative location on a molecule where another can bind. It is physically separated from what biochemists call the molecule's main or "active site."

Base pairs: The molecular building blocks of DNA. They form a double-helix structure by pairing. The base called "A" (adenine) always pairs with the base called "T" (thymine); "G" (guanine) always pairs with "C" (cytosine).

D2 receptor: One of several subtypes of receptor—a kind of docking port—for the neurotransmitter dopamine. Every existing antipsychotic drug targets the D2 receptor.

Endogenous opioids: Opioids that are synthesized naturally in the human body. They are involved in our experience of pleasure, but also pain and anxiety.

GABA: A message-carrying chemical in the brain that has inhibits the strength of signals traveling between neurons.

Messenger RNA (mRNA): When a gene is activated—a process called gene expression—the cell makes a copy of the information contained in the gene's DNA. This copy is rendered in a closely related molecule, called RNA. RNA "messages" then instruct the cell to make a particular protein, based on the blueprint copied from the gene.

Monoamine neurotransmitters: A large class of message-carrying neurotransmitters that share certain structural and biochemical features. Examples include dopamine and serotonin, whose systems are the targets of some antidepressant drugs. Monoamine neurotransmitters are deactivated by enzymes called monoamine oxidases. MAOIs are a class of antidepressant drug that inhibit these enzymes.

Polygene risk score: A number that represents the impact of hundreds or thousands of genes that contribute to specific human traits. These scores are being developed to predict health risks, and in some cases, behavior.

Pre-synaptic neuron: Messages are transmitted between neighboring nerve cells across a tiny gap, called the synapse. The pre-synaptic neuron releases neurotransmitter molecules, which travel across the gap and occupy receptors on the post-synaptic neuron. Neurotransmitter molecules left over in the synapse then bind to transporter molecules which return them to the presynaptic neuron for reprocessing. Some popular antidepressants, including SSRIs and SNRIs, prevent this reabsorption, to promote additional neuronal signaling.

Psychiatric diversion facility: A facility being built in Miami-Dade County, Florida, designed to prevent low-level offenders with serious mental illness from repeatedly recycling through the criminal justice system (i.e., "diverting" them) by providing them with psychiatric treatment, medical care, social and occupational rehabilitation and training, and temporary housing support.

Trans-institutionalization: An historic and unintended yet devastating relocation of individuals with serious mental illness from state-run psychiatric hospitals—which were shut down or sharply downsized—to federal, state, and local jails and prisons. This relocation was not direct, but occurred gradually, as released state hospital patients were left to fend for themselves in local communities that were unprepared to help them, leading in many cases to their incarceration, typically for low-level offenses.

Valproate: An anti-seizure medication sometimes used to treat epilepsy and bipolar disorder.

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