Q&A on Fentanyl, the Opioid Crisis, Psychedelics, and Cannabis Risk

2023 BBRF Research Symposium and International Awards Dinner

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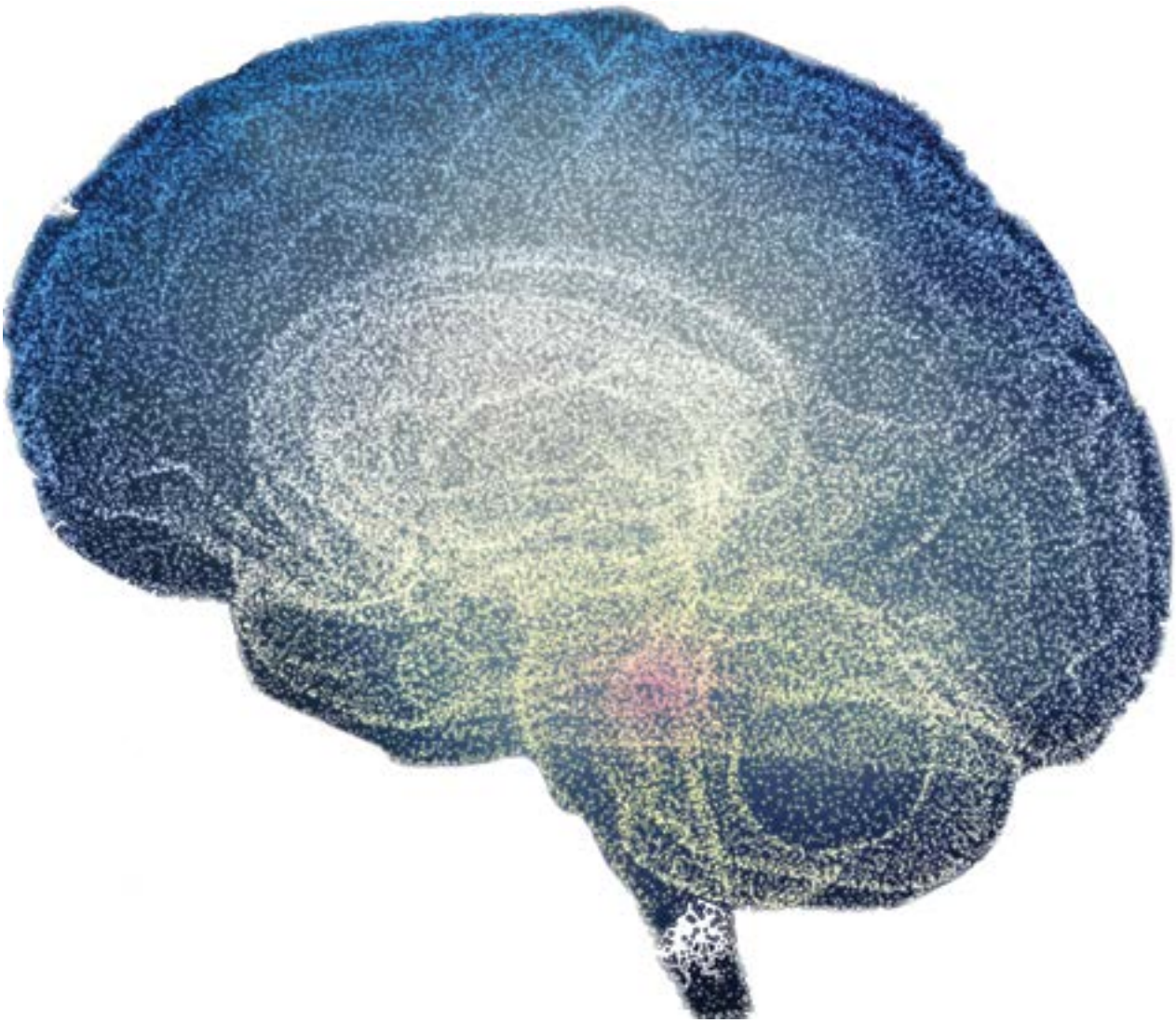

ECT, MST, and Other Neuromodulation Therapies to Relieve Severe Psychiatric Illness

PRESIDENT'S LETTER

This issue of *Brain & Behavior Magazine* focuses on research that will help us achieve our shared goal of a world free from debilitating mental illness.

In our **PATHWAYS TO THE FUTURE** article, we highlight the research career of Dr. Sarah Lisanby, who directs the Noninvasive Neuromodulation Unit at the National Institute of Mental Health. She is a past recipient of BBRF Distinguished, Independent and Young Investigator grant awards, has been honored with BBRF's Klerman Prize, and is a member of the BBRF Scientific Council. Dr. Lisanby has been deeply involved in developing new technologies to stimulate the brain such as MST (magnetic seizure therapy) and improving existing treatments like ECT (electroconvulsive therapy), which can save lives of people with severe psychiatric illness. Reducing or eliminating the impact of seizure-based therapies on memory is among her chief objectives, as our story details.

Two stories in this issue touch on the pressing subject of addiction and substance use disorders. Our **MENTAL HEALTH & SOCIETY** piece features a Q&A conducted with Nora Volkow, M.D., a BBRF Scientific Council member, who for 20 years has directed the NIH's National Institute on Drug Abuse. A world expert on the science of addiction and in explaining why it should be regarded an illness involving dysfunction in the brain, Dr. Volkow helps us understand the challenges of the opioid crisis, and the state of what we know and don't yet know about using psychedelics to treat mental illness.

In **A RESEARCHER'S PERSPECTIVE**, 2018 BBRF Young Investigator Sandra Sanchez-Roige, Ph.D., explains what large-scale genetics research has begun to reveal about the biology underlying substance use disorders.

This issue also features accounts of **BBRF's 2023 MENTAL HEALTH RESEARCH SYMPOSIUM** and **INTERNATIONAL AWARDS DINNER,** including the winners of the annual Pardes Humanitarian Prize in Mental Health. As always, we also report recent news on treatments for psychiatric conditions in our **THERAPY UPDATE** and important research advances that are moving the field forward in **RECENT RESEARCH DISCOVERIES.**

I am inspired by the magnitude and scope of the discoveries that are being made by the scientists we fund together and appreciate your ongoing generous support to help find improved treatments, cures, and methods of prevention for people living with psychiatric illness.

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.

CONTENTS

PUBLICATION CREDITS

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THIS ARTICLE DESCRIBES THE RESEARCH OF

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ECT, MST, and Other Neuromodulation Therapies to Relieve Severe Psychiatric Illness

IN BRIEF
Dr. Lisanby has been deeply involved in developing new technologies to stimulate the brain such as MST (magnetic seizure therapy) and improving existing treatments like ECT (electroconvulsive therapy), which can save lives of people with severe psychiatric illness. Reducing or eliminating the impact of seizure-based therapies on memory is a particular objective, with success that has been demonstrated in clinical trials.

While she was a medical student at Duke University Medical Center—after earning undergraduate degrees in mathematics and psychology at Duke—Dr. Sarah Lisanby had an experience that would deeply influence the course of her career.

"I had a patient with catatonia, a very serious, even life-threatening condition in which the person can't speak, can't eat, can't move." Catatonia is sometimes seen in patients with mood disorders, including major depression, as well as in schizophrenia and other disorders featuring psychosis. In this case, catatonia occurred in the context of a major depressive episode, and the treatment prescribed was electroconvulsive therapy (ECT).

ECT, which is well known to be highly effective (up to 80%) and rapid-acting (2–4 weeks), is designed to induce a brief therapeutic seizure in the brain of the patient, who receives the treatment while under general anesthesia. It is underutilized relative to other treatments, even ones likely to be less effective. This is because of ECT's impact on memory; some degree of impairment frequently follows treatments for some period of time, before, typically, resolving or lessening.

In this seriously ill patient, the potential benefits of treatment were deemed to outweigh side-effect risks relating not only to memory loss but also to any treatment that involves placing someone under general anesthesia.

A typical course of ECT therapy is 6 to 12 sessions (3 per week) over 2 to 4 weeks. Dr. Lisanby attended the catatonic patient's first ECT session. "On the afternoon of her first treatment,"

she recalls, "she started speaking. This was a really amazing experience—to see someone go from death's door to having a dramatic improvement after a single treatment. It really piqued my interest in ECT. How does it work? My mentor at the time, very well known in the field of ECT therapy, replied, honestly: 'Well, we don't exactly know.'"

"I thought: wow; this is a powerfully effective treatment with a lot of mystery and misunderstanding surrounding it. That attracted me. Primarily because I saw how beneficial it was and thought maybe I could learn more about how it works." Learning how it works was a potential starting point for thinking about how to reduce the side effects of ECT, and also, as Dr. Lisanby would discover, a basis for exploring a range of other technologies also involving the modification of electrical activity in the brain—neuromodulation—to generate therapeutic results for patients with incapacitating psychiatric illnesses.

'THE BODY ELECTRIC'

Many of us have an almost automatic fear of electricity when it is mentioned in connection with the body. We all learn as children to avoid dangers associated with live wires and the shocks they can deliver. The use of electricity in ECT for treatment of psychiatric conditions—first attempted in 1938 with technology that today would be regarded as primitive—has been explicitly presented to the mass audience over the years as a frightening procedure, perhaps most damningly in the 1975 film *One Flew Over the Cuckoo's Nest*. One inaccuracy in that film is the depiction of a patient having convulsions while the therapy is being administered. This never happens in the modern application of ECT, in which the patient is premedicated with strong muscle relaxants that prevent convulsions. The procedure, conducted while the patient sleeps, is brief and painless.

Lingering fears about electricity-based treatments of brain disorders can be confronted with several basic facts. The most important is that *the brain is an electrochemical organ*. Neurotransmitters like dopamine and serotonin act at the trillions of synapses, or points of connection, between neurons. But it is electrical energy within nerve cells that makes them fire: after chemicals bind at neuronal receptors, an electrical signal is triggered whose intensity, if above a certain threshold, will induce an "action potential" that sends an electrical pulse down axons and dendrites to other neurons. In other words, as Dr. Lisanby puts it, "neurons speak to each other using both chemical and electrical signals."

Another basic fact: not only are electrical fields *generated* by components of the brain; the brain also *responds* if you apply electrical fields to it, whether from the outside or within the brain itself. Precisely what happens within the brain when ECT is applied is part of what research on ECT

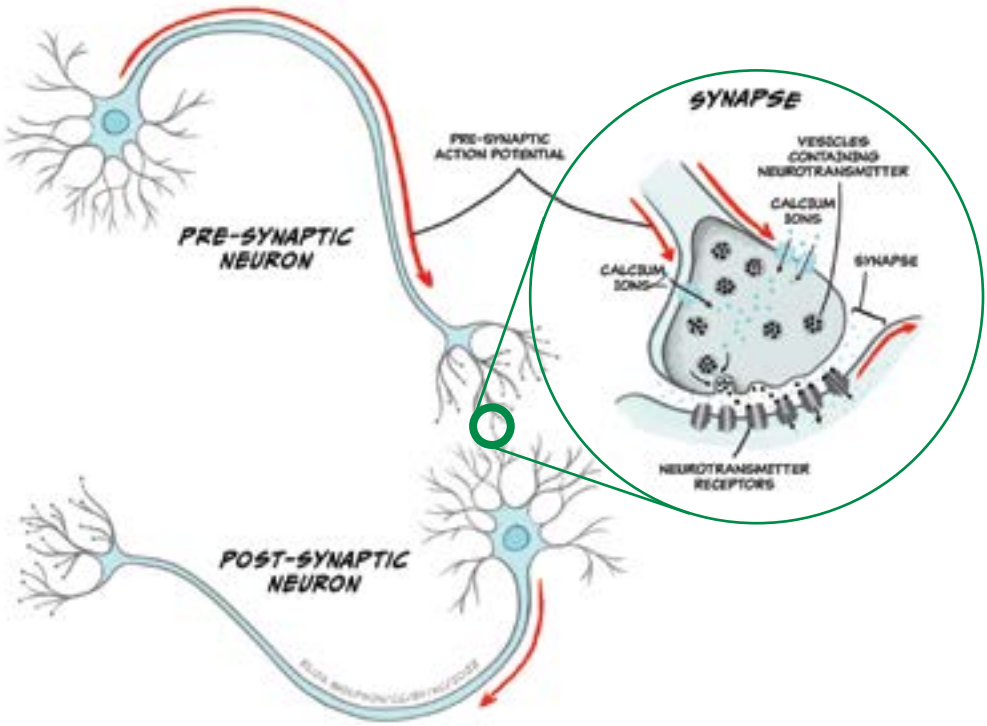
has sought to discover as its safety profile has been steadily improved.

Before tackling this subject, Dr. Lisanby makes a point about stigma. She stresses that "the stigma surrounding ECT isn't just unfortunate. It is deadly. Stigma can prevent people from getting life-saving treatments." Or as she put it on another occasion: "Depression kills, while ECT saves lives." This should hit home with particular force, she says, in the context of current trends in suicide. Just shy of 50,000 Americans ended their lives by suicide in 2022 according to statistics just released by the National Center for Health Statistics. There is no question that ECT is among the most effective treatments in addressing suicidal crisis in inpatient settings. "So I think it's really important to de-stigmatize, to call this out" she says.

"We need to think about 'the body electric': our brains are electric. But so are our hearts and muscles. Without electricity in our bodies, we wouldn't be able to walk and our hearts would not beat. And we wouldn't be able to think. When you get an EKG, you are seeing an electrical rendering of how your heart works; and when the heart gets an arrythmia, the normal rhythm can be restored using electricity in the form of a pacemaker. When a life-threatening ventricular fibrillation occurs, you give a defibrillation with paddles to normalize the rhythm—and that's using electricity, applied to the chest."

'IS IT THE ELECTRICITY—OR THE SEIZURE?'

Few people think twice about these applications of electrical energy to save lives in other medical contexts. As a psychiatric resident at Duke, Dr. Lisanby did not think twice about using ECT in the context of serious brain-based illnesses after she witnessed that it too can save lives. After her residency, she earned a fellowship at the New York State Psychiatric Institute (NYSPI), affiliated with the Department of Psychiatry at Columbia University. The year was 1995, the same year she and others read the first published study about a then-new technology called TMS (transcranial magnetic stimulation). Unlike ECT, in which electricity is delivered into the brain via electrodes placed on the scalp, TMS involves placing a magnetic coil above the scalp to generate magnetic fields that penetrate the brain and induce an electrical current to which the neurons in



Neurons communicate via electrical events called "action potentials" and chemical neurotransmitters. At the synapse or gap separating two neurons (green circle), an action potential causes the sending neuron to release a chemical neurotransmitter ("SYNAPSE" close-up). It can excite or inhibit the receiving neuron, whose response is determined by the balance of many excitatory and inhibitory inputs.

the brain respond. It is a way of using magnetism from outside the brain to alter electrical activity within it.

TMS was specifically designed to modify electrical activity in the areas just beneath the scalp—outer layers of the prefrontal cortex that lay just beneath—but not to cause a seizure. In ECT, when the brain experiences a brief seizure, it is because the electricity delivered is above the excitation threshold of most neuronal tissue. This results in activation of essentially the entire brain, and this universal activation causes the brain to seize for some seconds. (Seizures induced in this way end, it is thought, because of the action of inhibitory neurotransmitters, which are released across the brain during the seizure.)

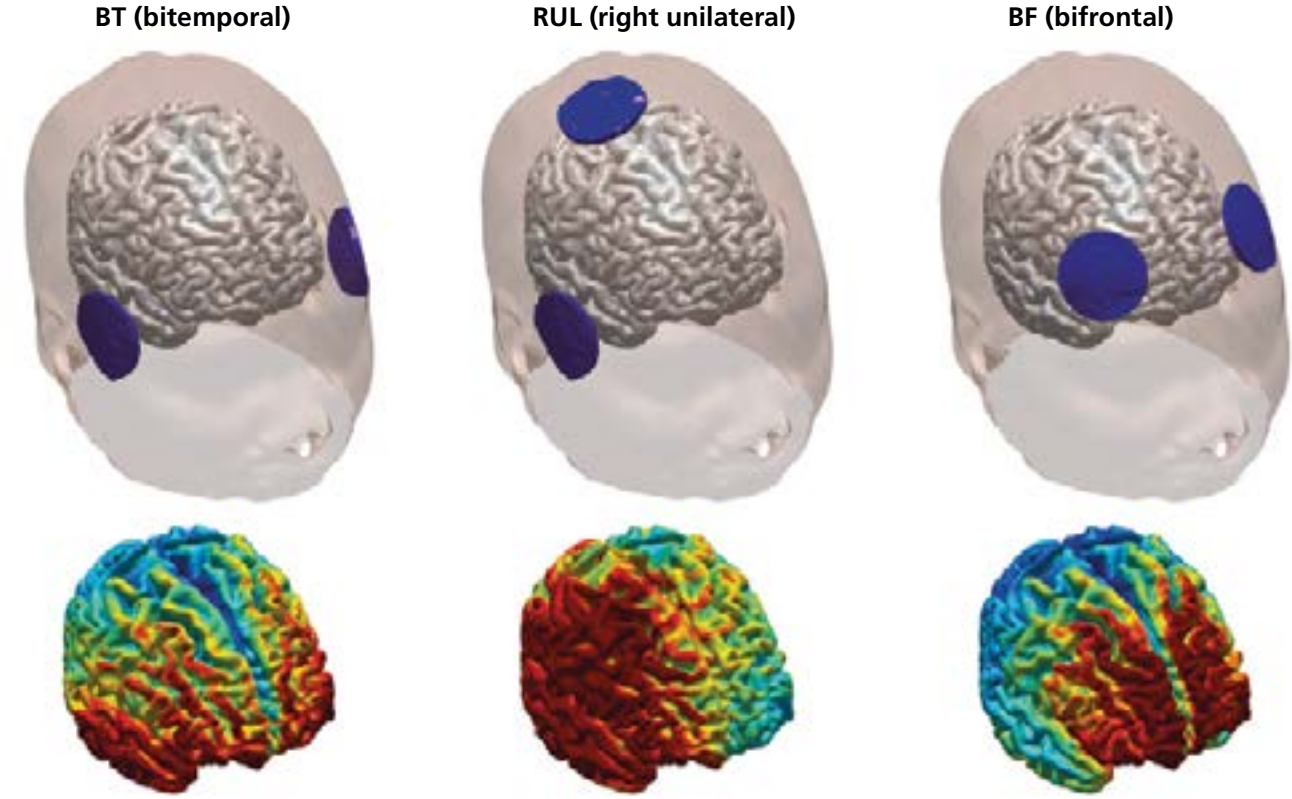
"The dogma of the day," says Dr. Lisanby, thinking back to the mid-1990s, "was that you've got to induce a seizure" to get a therapeutic effect—whether in treatment-resistant depression or refractory psychosis or catatonia. "I approached this question as a scientist and a pragmatist." It was the ostensible aim of her fellowship project to bring TMS to Columbia and to learn about how it works. "But the idea was also to understand seizures better. There was a lot of skepticism about whether TMS could work or not because it did not induce a seizure."

Ultimately, the big question about electrically altering brain activity to generate a therapeutic effect continues to be, in Dr. Lisanby's words, "is it the electricity or is it the seizure, or is it both?" The question is still under study, although it has long been clear that TMS and other therapies that do not induce seizures can have important therapeutic effects. The question now is whether the efficacy of ECT depends upon the induced seizure.

While learning about TMS at Columbia and using TMS, in effect, to study ECT, Dr. Lisanby developed a novel technology that was neither ECT nor TMS—a neuromodulation technology that her name is today perhaps most closely associated with: magnetic seizure therapy, or MST. It utilizes more powerful magnetic fields than are used in TMS to induce electrical activity in the brain that are just sufficient to cause a brief seizure. "We wondered: could we induce a seizure with very little electricity? It might be a way to try to understand what the seizure itself is doing without the overlay of the stronger electric field that's used with ECT." There was also the possibility that a seizure induced with MST might help improve the safety of ECT, perhaps in part by minimizing or eliminating memory loss.

In the early 2000s, Dr. Lisanby's collaborations with MST pioneers in Wales, UK and Bern, Switzerland led to the first tests of MST in humans. "The first [depressed] person we treated, in Bern, got better, and that gave us the signal that we might be on to something," she remembers. A first clinical test in the U.S., led by Dr. Lisanby at Columbia/NSYPI, provided a first indication that MST might indeed be safer than ECT in terms of its cognitive side effects. But at that time, it was not yet clear if MST was as effective as ECT in reducing symptoms of major depression. Both the side effects and efficacy of the two methods have been the subject of research ever since, as improvements have been made in both approaches.

"There's nothing more rewarding than seeing a person respond—going from the depths of depression, hopelessness, even having thoughts of wanting to end their life—and have that melt away and have them return to the person they were before the serious disease of depression affected them."



The spatial specificity of brain stimulation is important in understanding how modern ECT has improved over previous versions. By moving from the old standard "BT" electrode placement (bitemporal ECT) to "RUL" (right unilateral) and "BF" (bifrontal) configurations, electrodes have been repositioned with the aim of reducing cognitive side effects, while maintaining the largest amount of therapeutic efficacy. "We're sculpting where the electric field is going in the space of the brain," Dr. Lisanby says. Intensity of the induced electric field is shown in color-code from red (stronger) to blue (weaker).

In 2005 Dr. Lisanby's innovation and leadership in neuromodulation was recognized by Columbia, where she became founding director of the Division of Brain Stimulation.

In 2010 she was recruited back to Duke University where, in the department of Psychiatry and Behavioral Sciences, which she chaired, she founded the Duke Division of Brain Stimulation. Five years after that she was recruited by the director of the National Institute of Mental Health, Dr. Thomas Insel, to lead research on neuromodulation therapies in the intramural research program at the Institute, as well as the Division of Translational Research on the extramural side of NIMH. She was founding director of the Noninvasive Neuromodulation Unit in the NIMH Intramural Research Program and co-led the NIH BRAIN Initiative Team focused on development of large-scale neural recording and modulation devices.

BRAIN STIMULATION VS. DRUG TREATMENTS

Today, more than two decades after Dr. Lisanby began learning about, testing, improving, and developing new neuromodulatory approaches, a great deal is known about them that was not known then. TMS is the technology that has gained the widest acceptance and now is used to treat many thousands of people annually with depression and OCD, and to a lesser extent, other neuropsychiatric conditions. TMS has evolved over these years, as has been reported in this magazine, but so have ECT and MST, the two methods that were the initial focus of Dr. Lisanby's research.

All forms of neuromodulation used today are in basic ways unlike currently used drug therapies to treat psychiatric illnesses. Some of those differences are potential advantages. Dr. Lisanby and two co-authors, **William T. Regenold, M.D.** (a 2010 BBRF Independent Investigator and 2000 Young Investigator) and **Zhi-De Deng, Ph.D.** (a 2017 BBRF Young Investigator), talk about this in a "Review Article" published in 2021.

"As a family of interventions," they note, "neuromodulation devices are distinct from pharmacological therapies in several respects." Therapeutic medicines target receptors in cells, where they bind, causing a cascade of "downstream" effects which impact a range of biological functions. In contrast, devices that use magnetism or electricity to modulate the brain target the electrical properties of neurons and the axons and dendrites that connect them. Medications, when

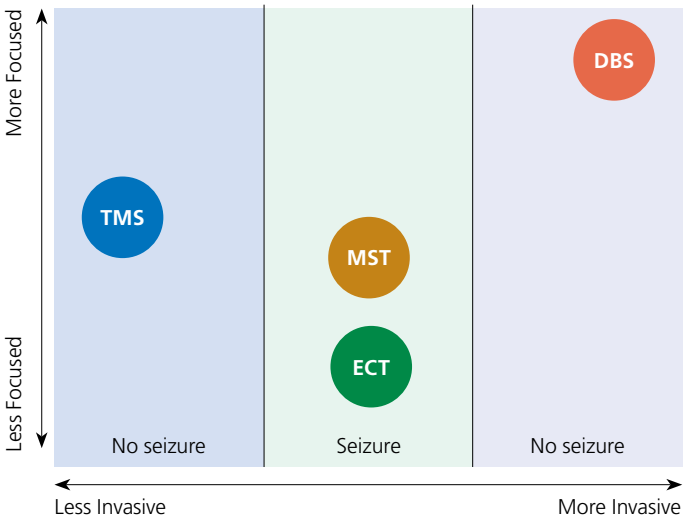
ingested, are distributed throughout the body (and brain, when they can penetrate the blood-brain barrier), while neuromodulation devices directly apply electric fields to brain structures—sometimes with great specificity (it depends in part on the device). Also, unlike medicines, which reach a "steady-state" level in the blood and then decay over varying periods of time, neuromodulatory devices can apply stimulation to neurons, brain circuits, and brain regions at specific times relative to ongoing neural activity—which can be monitored in real time, via functional brain imaging.

In sum: there are ways in which brain stimulation can do things that drugs cannot. The spatial specificity of brain stimulation is especially important in understanding how modern ECT has improved over previous iterations of the technology. Making ECT safer with respect to cognitive side effects has been the product of experimentation involving different ways of placing the electrodes on the scalp that deliver electrical energy to the brain.

By moving from the old standard "BT" configuration (bitemporal ECT) to "RUL" (right unilateral) and "BF" (bifrontal) configurations, electrodes have been repositioned [see illustration, facing page] with the aim of reducing cognitive side effects, while maintaining the largest amount of therapeutic efficacy. By directing electric fields generated by the electrodes away from the dominant temporal lobe of the brain, memory loss associated with the treatment has been significantly reduced. "We're sculpting where the electric field is going in the space of the brain," Dr. Lisanby says.

This improvement in the spatial dimension of the treatment has been accompanied by improvements that pertain to the temporal dimension. By literally changing the shape of the electrical waves being delivered by the electrodes, it has been possible to substantially improve safety. "Shortening the duration of the electrical pulses also dramatically reduced cognitive side effects," Dr. Lisanby explains. "Brief pulse" ECT was developed, and then "ultrabrief pulse," which, when used in combination with right unilateral placement of electrodes (RUL), offers the safest form of ECT yet used in the clinic. The changes were of sufficient magnitude to lead the FDA to reclassify ECT in 2018 as a "moderate risk" class II medical device (it had formerly been rated "higher risk.") The new classification applies to the use of ECT specifically in individuals age 13 and above with catatonia or a severe major depressive episode associated with major depressive disorder or bipolar disorder. ECT is also used to treat manic and mixed episodes of bipolar disorder, schizoaffective disorder, treatment-resistant schizophrenia, and a kind of treatment-resistant epilepsy that features long-lasting seizures (status epilepticus).

There is still considerable mystery surrounding exactly how ECT delivers major reductions in a variety of psychiatric symptoms. When all of the cells of the brain are firing together, inducing a seizure, says Dr. Lisanby, "it powerfully releases all of the neurotransmitters that the brain runs on, and it induces neuroplastic changes [changes in the strength of connections between neurons] that last beyond the seizure itself and that convey powerful antidepressant effects and antipsychotic effects, among other changes that are helpful clinically in a number of severe disorders." In



Comparing 4 kinds of neuromodulation. TMS and DBS do not induce a seizure, but differ in focus and invasiveness (DBS involves brain surgery and implantation of electrodes; TMS, delivered in a medical office, is non-invasive and patients continue normal routine following a session). MST and ECT induce seizures, with MST being more focused than ECT. Both are non-invasive and are delivered painlessly under anesthesia while the patient sleeps.

major depression, ECT needs to be given periodically, with the benefits from treatment often lasting half a year, or more in some cases. Longer lasting remission can be achieved by using a relapse prevention strategy, such as continuation ECT and combination pharmacotherapy.

PROGRESS WITH MST

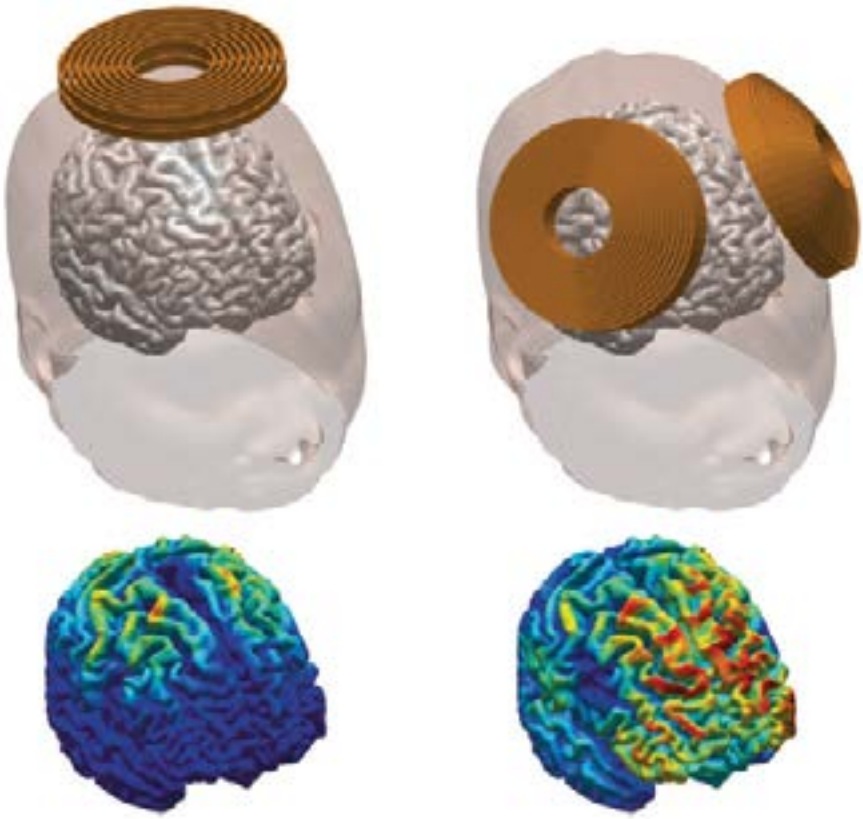
"If it is the seizure that is driving the therapeutic benefit of ECT, and if it is the electricity that is driving the side effects, then inducing a seizure with a minimum of electricity could be a way of maintaining the antidepressant effects of ECT without the cognitive side-effect burden," Dr. Lisanby reasons.

"Our studies and those of others suggest MST can have comparable antidepressant effects as ECT—and that MST carries less cognitive side effects. That's our goal: we want to have the benefit of the seizures without the downside of the memory loss."

In an important paper appearing in *JAMA Psychiatry* in December 2023, Dr. Lisanby and colleagues compared MST and ECT in 73 "severely ill" patients with refractory depression in a double-blinded, randomized clinical trial conducted at three academic hospital locations. A typical participant, about 48 years old, was in the third year of a current major depressive episode; 10 were suffering from bipolar depression. Thirty-five participants were treated with MST and 38 with what is considered the safest version of ECT yet employed (ultrabrief pulse right unilateral [RUL] ECT). Patients received three treatments per week until they either reached remission (60% or greater reduction in symptoms) or a "plateau" response.

The trial provided evidence "for substantial advantages" of MST relative to a version of ECT. "Both MST and ECT demonstrated clinically meaningful antidepressant effects. There was no significant difference between ECT and MST for either response or remission rates," the team reported. "Both MST and ECT showed a sustained benefit over a 6-month follow-up period, again with no significant difference between them."

MST and ECT results differed in two respects. One was that it took, on average, 2 or 3 more MST sessions for patients to achieve remission compared with ECT. The other had to do with what researchers call "time to orientation." This is the amount of time it takes patients to reacclimate after awakening from anesthesia. A longer time to orientation is a predictor of the severity of post-treatment amnesia—the memory loss that is associated with ECT, but, so far, not MST. In this trial, MST patients reoriented in a few minutes, compared with about a 20-minute period, on average, for ECT patients. This result is "consistent with previous reports on MST that found that cognitive adverse effects are negligible." In fact, MST patients "exhibited superior performance on both autobiographical memory recall and specificity," the team noted. MST patients "also reported significantly fewer subjective adverse effects," including fewer



Two ways of delivering MST, differing in number and placement of magnetic coils above the head. Induced electrical fields in the brain are compared below, from red (stronger) to blue (weaker).

physical adverse effects such as headache, nausea, and muscle pain, in addition to less post-treatment confusion or disorientation."

What do these results mean to Dr. Lisanby? "I think they justify further work. What we aim for is real-world impact. To have treatments that are clinically available that are really helpful to people who are suffering with severe conditions means that MST will need FDA approval. The next step is a noninferiority trial, a larger trial that is adequately powered to test whether MST is truly non-inferior to ECT. If the FDA were to find MST safe and effective it could potentially be cleared for clinical use in the future." The NIMH is supporting such a trial, which is called the Confirmatory Efficacy and Safety Trial of Magnetic Seizure Therapy for Depression (CREST-MST) study, and it is now enrolling patients.

"We look at the national suicide rates. We need to do something about that. We already know that ECT is powerfully effective and rapidly acting at preventing suicide, and yet it is underutilized. And so anything we can do to get the benefits of ECT without the barriers, like the risk of memory loss, into the hands of people who need it—this is our goal."

MORE RESEARCH, MORE OPTIONS

Recent variations of rTMS therapy such as SAINT, the protocol involving a 5-day course of accelerated brain stimulation therapy, developed at Stanford University by two-time BBRF Young Investigator and Klerman Prize winner **Nolan R. Williams, M.D.**, and colleagues, is rapid acting and shows considerable promise for addressing patients in suicidal crisis. So does inpatient administration of the experimental drug ketamine or its FDA-approved derivative, esketamine. Yet while these drugs have benefits that can be dramatic, it is not yet known how long-lasting they are, especially when compared with the duration of ECT and MST benefits as demonstrated in the newly published study.

Dr. Lisanby directs an NIMH division that is charged with furthering therapies of many kinds, including neuromodulatory interventions. As director of her lab and division, it is her goal "to provide clinicians with more options." That means the NIMH is sponsoring clinical trials not only to test MST but a wide range of other potential neuromodulatory therapy approaches. One trial under way

"Dr. Lisanby has done groundbreaking work in neurostimulation. She's taken a 20th-century treatment, ECT, and brought it into the 21st century, using modern neuroscience."

—Dr. Matthew Rudorfer,
Assoc. Director, Treatment Research, NIMH

in her lab, called iLAST (individualized low-amplitude seizure therapy) seeks to generate MST-like effectiveness using an ECT device that employs less electricity and five small closely spaced electrodes rather than two in most ECT and MST applications. The idea here is to more narrowly and precisely focus the electric field in the brain, with the aim of further reducing cognitive and other side effects.

Another NIMH-backed trial in her lab called TEST (transcranial electric stimulation therapy) involves delivering brain stimulation with an ECT device operating below the seizure threshold. It's applied exactly as standard ECT, and under anesthesia, but in doing so without causing a seizure, it is hoped that TEST may generate efficacy with a minimum of cognitive side effects.

Efforts are also under way to achieve greater personalization of TMS and related brain stimulation approaches. This involves improving targeting and experimenting with ways to reach areas deep in the brain that were once thought inaccessible to the superficial penetration of electromagnetic waves generated by TMS and related technologies. An example of this is using neuroimaging to target the brain's subgenual cingulate cortex (sgACC) "transsynaptically," via TMS, in a study that was also supported by BBRF.

Finally, says Dr Lisanby, there are a number of completely new technologies whose development is supported by the NIH's Brain Initiative. Two such technologies involve the use of light and sound waves, as opposed to electricity or magnetism, to alter the function of brain circuits implicated in psychiatric illnesses.

"We are on the frontier of figuring out how to harness different forms of energy to influence brain function and study and promote brain health," says Dr. Lisanby. "It's a pretty exciting time." ❖ **BY PETER TARR**

On Fentanyl, the Opioid Crisis, Psychedelics, and Cannabis Risk

A Q&A With Nora Volkow, M.D.

Nora Volkow, M.D.

Director of the National Institute on Drug Abuse (NIDA)

A pioneer in brain imaging with "PET" technology (Positron Emission Tomography), Dr. Volkow is one of the world's leading experts on the biological basis of addiction, an active researcher, and a longtime member of BBRF's Scientific Council.

IN BRIEF

Dr. Volkow, a world expert on substance use and the science of addiction, explains the origins of the fentanyl crisis, the particular challenges of treating overdoses, and offers her assessment of what we know and don't yet know about the risks of using psychedelics as therapies for psychiatric illness, as well as current evidence on the dangers of regular cannabis use for a subset of young people.

Editor's Note:

For the benefit of our readers, a few basic facts about opioids and the system in the human body with which they interact. Opioid drugs exert their effects by stimulating opioid receptors in the body. These receptors are part of what is called the endogenous, or "naturally occurring," opioid system. Why do we have this system in the body? Endogenous opioids such as enkephalins, endorphins, and dynorphins, have roles in regulating reward, mood, motivation, learning, and memory. They also have a role in relieving pain. Opioid receptors are present in abundance throughout the brain and central and peripheral nervous systems as well as the gastrointestinal tract.

Natural opioids are naturally occurring substances extracted from the seed pods of poppy plants that interact with the endogenous opioid receptors. Synthetic opioids, which are manufactured in the laboratory, also act on the endogenous opioid system. They are used as anesthetics and as pain relievers. Some synthetic opioids, including methadone and fentanyl, have been approved for medical use. In addition to being 50 to 100 times more potent than morphine, fentanyl is often made illegally, and cannot be seen, tasted or smelled when mixed with other drugs, including other less potent opioids. Illicitly manufactured fentanyl and other synthetic opioids are the most common drugs involved in drug overdose deaths.

Poppy-based opium has been used for medical, recreational, and religious purposes for millennia. Morphine and codeine have been used since the 19th century. Diamorphine, or heroin, was first synthesized in the late 1800s. Opioid prescribing began to increase significantly in the 1990s.

Dr. Volkow, in a recent paper in the *American Journal of Psychiatry*, you and a co-author noted that the increased prevalence of more powerful opioids and drug mixtures in the illicit market has led to an unprecedented number of deaths and overdoses. When did this all start? What are the roots of this phenomenon? Why are opioids more powerful and more dangerous these days?

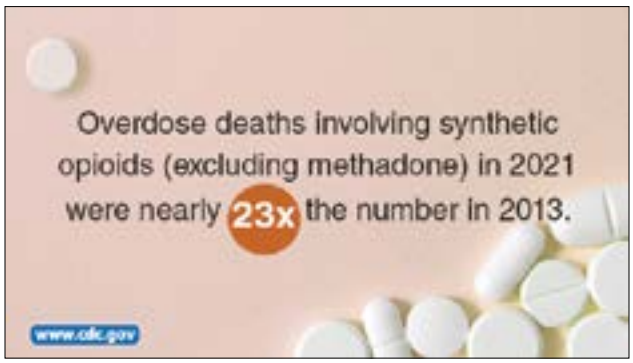
To be honest, I think it is a combination of innovation and greed. Innovation in terms of the ability to generate increasingly more powerful chemicals and the ability to synthesize them in ways that are quite simple, so that they can be synthesized rapidly without the need for advanced technologies. Greed, because manufacturing extremely potent synthetic opioids like fentanyl enables illegal drug manufacturers and dealers to maximize their profits.

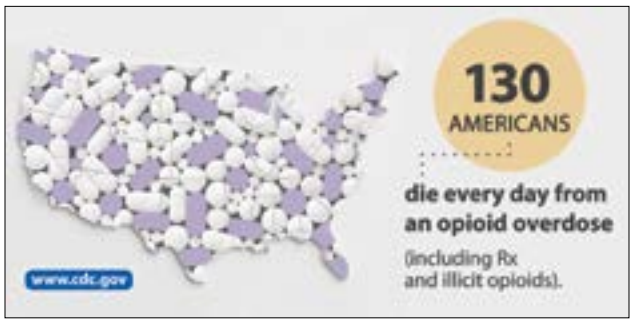
Part of this, then, is the fact that it's easier than ever to illegally manufacture extremely powerful synthetic opioids, much more potent than previously popular opioid drugs.

Yes, and the other part is that compounds like fentanyl also generate much greater returns on investments for drug dealers and manufacturers than heroin or cocaine. Those crop-derived drugs require cultivation, which is costly. And in the case of heroin, there is the extra step of extracting morphine from the crop and transforming it into heroin.

With fentanyl and other synthetic opioids, the combination of simple synthesis and the increased revenue from sales is driving widespread prevalence. A key point is that because fentanyl is so extraordinarily potent, you need to manufacture much smaller volumes of it. Also, most illicit drugs are brought into this country from abroad. It's much easier to smuggle smaller volumes without being detected than bringing in pounds and pounds of drugs like cocaine or heroin.

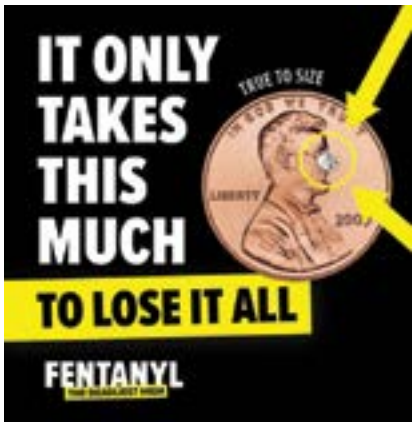
Fentanyl is highly addictive. Many people initially get exposed to it, unknowingly, because it is mixed into other drugs, such as heroin. And because fentanyl is so potent, sometimes 50 times more potent than heroin, someone who uses fentanyl rapidly becomes tolerant to heroin (or other drugs) that don't contain fentanyl. For such people, fentanyl-free heroin doesn't do the trick anymore. They then seek out increasingly more powerful drugs such as fentanyl or drugs laced with it.





Fentanyl, being an opioid, interacts with the endogenous opioid receptors found in large numbers all throughout the body, including the brain. So they're interacting with the same receptors as the "older opioids," right?

Correct. Exactly the same receptors. The differences rely on two factors. First, fentanyl is an incredibly potent drug. Meaning, you don't need to use a lot of fentanyl to experience significant effects. A very small amount of fentanyl has a massive effect. In addition to potency, the second important factor is affinity. Some drugs bind with



higher affinity to cellular receptors than others. When they bind with higher affinity, there is a greater probability that the drugs "stick" to the binding site. Fentanyl has both extremely high affinity for the receptors and extremely high intrinsic efficacy. So it activates, and it activates maximally. Other powerful drugs, such as heroin, do not have the same efficacy or affinity as fentanyl.

What is the half-life of fentanyl in the body compared to other opioids? In other words, does it linger?

Fentanyl has a relatively short half-life, around 60 minutes. But fentanyl accumulates in the fat tissues. So if you use fentanyl regularly, you end up having a "depot" of fentanyl in your body. And so when you take fentanyl [if you've taken it regularly], the effects are much longer lasting because you you're not starting from zero. You're starting from a slow-release compartment, the fat "depot."

The other characteristic that makes fentanyl so addictive is that it gets into the brain very rapidly. We just discussed how drugs may have higher or lower affinity for receptors and greater or lower potency. However, drugs also differ in the speed with which they get into the brain.

Fentanyl gets into the brain rapidly. The faster a drug gets into the brain, the more rewarding it is, and the quicker it is likely that someone may feel the untoward effects. Respiratory depression is an effect of opioid use, and in the case of fentanyl it appears extremely fast. This is challenging because even though we have a medication that's very effective for reversing overdoses—naloxone (marketed as Narcan)—we need to administer it much faster for fentanyl than for heroin. The window for saving the overdosed person is much shorter than with heroin. You have to intervene right away.

Stimulation of one class of endogenous opioid receptors—mu-opioid receptors—in cells in the brainstem inhibits breathing and is the mechanism that drives opioid overdoes.

Yes. And if you suspect someone has overdosed on fentanyl, and you give them naloxone, they may start breathing again and become conscious. However, multiple healthcare providers have documented that due to the "depot effect," after a person becomes conscious, they may lose consciousness again and stop breathing. This is called re-narcotization.

In other words: the beneficial effects of Narcan are shorter-lasting than the duration of the respiratory depressant effect of fentanyl. With less potent opioids naloxone can cover someone for 60 minutes. But someone with a depot supply of fentanyl can re-narcotize several times. In order to protect that person from overdosing, we need to give higher doses of naloxone or alternatively repeat the doses every 60 minutes. It's easier to repeat if you are in the ER or the hospital. However, if repeated doses are not possible, you want to give the person a higher dose of naloxone because it prolongs the concentration of naloxone in the blood.

What is NIDA's priority regarding the crisis with high-potency opioids like fentanyl? You're not the federal drug enforcement agency, so arresting manufacturers or dealers is not your mission. But what can your agency do, and what are you trying to do with respect to the fentanyl, and more broadly, the opioid crisis?

First of all, NIDA needs to come up with tools and strategies for a person who gets exposed to fentanyl, knowingly or not. We need to discover interventions to reverse those overdoses.

We do research to develop tools like Narcan, and now we've also developed tools that can get into the brain faster than naloxone/Narcan and that can have a longer duration of effect. We need other strategies that stimulate respiration and medications that help people with substance use disorders control their cravings and withdrawal and can protect them from overdosing.

We are also developing therapeutics for addiction to cocaine, methamphetamine, and prescription drugs. People have a higher risk of overdosing because cocaine, methamphetamine, and illicitly manufactured prescription medications are being contaminated with fentanyl.

Protecting people goes beyond doing research on how to treat them. For example, say you have a young person who occasionally consumes simulant drugs to prepare for a college exam or uses medications for the reward, i.e., the "high," and you want to protect them from overdosing. What types of interventions should one develop to prevent people who are at an extremely high risk of being contaminated with fentanyl from starting to take drugs—the kind of drugs that can kill them after a single exposure?

That's one avenue of research. There are other areas of research about how to deploy interventions that we know work. Medications that treat opioid addiction and overdose, although effective, are often not being given to people who actually need them. Our research looks into how we can change that.

The medicines that treat opioid use disorder have been around, the three very effective ones—methadone, buprenorphine and naltrexone—for a long time. But the percentage of people who seek treatment themselves is extremely low, less than 20%. So this is a real social problem.

The drugs work, but there are many impediments to people seeking treatment. There is just a tremendous stigma against people who take drugs. If I am a person taking drugs and I'm mistreated when I go to my provider, I'm not going to bring it up.

But there are other issues around the medications we use to treat opioid addiction. You've heard it many times—the incorrect idea that "methadone is just exchanging one [opioid] drug for another." That's an incorrect, yet common, belief. There are many programs, like Narcotics Anonymous, that provide help to people, but many of these programs are unwilling to accept someone who is being treated with methadone or buprenorphine. These issues interfere with the proper deployment of therapeutics.

There are 3 very effective drugs to treat opioid use disorder and overdose, but less than 20% of those addicted seek treatment.

Another aspect that makes addiction a stigmatized condition is that many psychiatrists or other healthcare providers don't want to treat people with opioid addiction because the reimbursement that they get is not sufficient.

Why is someone treating Alzheimer's getting a higher reimbursement than someone treating addiction? This is not justified by the level of clinician involvement. That's why I say stigma plays an extremely important role, and the stigma also has driven the lack of priority given to education in healthcare systems. Whether you are in medical school or in nursing or in other specialties, addiction is not deemed to be a condition that is the responsibility of healthcare providers. So healthcare professionals are not prepared for it or not prepared to do it.

Again, knowing this, what is NIDA's approach?

What do we do as an agency is to fund research documenting the benefits of education and treatment. We seek to provide evidence that employing and engaging nurses, emergency department physicians, infectious disease doctors, primary care physicians, has specific benefits. We have also been extremely proactive on doing research on how addiction and overdose brings justice settings into the picture.

Recently, evidence from research has started to change the culture, as we see more of those in the justice system willing and open to consider treatments. The research has shown it's very effective. The rise of telehealth has made it easier, for example, to deliver treatments in jails and prisons, which in the past was not possible because of the lack of in-person clinicians.

One other component I want to highlight is prevention.

I always ask: why are we in the current situation? What has made us so vulnerable as a country that we're taking these drugs? Why is it that we have such a big problem with drugs in the United States?

This is a key question that we need to ask ourselves. Then we can target prevention to address that vulnerability.

This gets at the classic [2015] paper by Case and Deaton about the "deaths of despair" in America, many of which are deaths due to opioid misuse and overdose.

I suppose it's so much larger than the question of science alone. It goes far beyond science into the social fabric and how people feel about their lives.

But we need to tackle it! It's part of the science in my view. We now have tools that allow us to start to address the questions that we've known all along. For example, we know in the field of addiction that individuals who have had adverse childhood experiences are at much higher risk of developing addiction. What are these adverse childhood experiences doing to the human brain and physiological organs that ultimately drive these behaviors?

Also, it is possible to study how discrimination, neglect, poverty, and other socioeconomic factors affect the brain throughout the lifespan, most importantly in the transition from childhood into adulthood. What are these structural factors that influence our brains and our wellbeing?

Many BBRF grants are exploring this really important question of what happens to the brain when a child is abused or neglected or

exposed to violence—these terrible things that clearly perturb brain biology.

They do perturb brain biology. Researchers are starting to identify how impactful these factors are in brain development. Among the areas of research, for example, it has become clear how underrepresented groups that have been discriminated against, like Black Americans or Native Americans, are negatively influenced by the social determinants of health.

So we've generated a system that is putting underrepresented groups at a tremendous disadvantage that starts to impact their brain development. We're focusing on brain, but I'm sure that other NIH Institutes are addressing the issues in the heart and the immune system, and other parts of the body.

In a "Viewpoint" article for *JAMA Psychiatry* this past October, you and Dr. Josh Gordon, the Director of the National Institute of Mental Health and a fellow BBRF Scientific Council member and former grantee, wrote about the prospect of psychedelics as therapeutics for psychiatric disorders.

In that piece you wrote that "it is clear that psychedelics are not wonder drugs," and noted that "the hype has gotten ahead of the science." You say that this is reminiscent of what happened with medical cannabis.

Yes, there is a similarity in the response to renewed interest in psychedelics to treat psychiatric disorders. We love fairy tales. We all want happy endings.

The hype comes from two sides. As an investor you say, "This looks very promising." And you want to get ahead of the curve. Your cognitive appraisal will go toward exaggerating and believing the positives more than the negatives. We all do that.

If you are a patient, you're going to gravitate toward stories that tell you that there is a solution. We all have the cognitive dissonance that if we see something that is potentially desirable, like a treatment that could be a cure, our cognitive ability shuts down the critical aspects of cognition.

When you put together the opportunity for investors to make money, the desperation of patients, and the lack of regulation of how these messages are communicated, you generate the hype we are observing right now. Just as we saw for medical cannabis, we see a lot of people exposing themselves to treatments with psychedelics for which there is at present no conclusive evidence.

For the benefit of our readers: in your "Viewpoint" article you and Dr. Gordon note that one important research question that needs to be explored is whether the positive subjective experiences that some people report with psychedelic drug use "are intrinsic to or separable from" the putative therapeutic effects of these drugs. Does the benefit, when there is one, come from the drug or the talk therapy that follows the experience? How are the two related? You also note the need to study the "contextual factors" which may impact people's experiences. There is as yet "no standard protocol" for administration of drugs such as psilocybin, yet it is widely thought that support during a psychedelic drug experience may have a great deal to do with what someone who uses these drugs may gain afterward from the experience.

Our position has been that right now, there is not sufficient evidence to show that psychedelics are beneficial. On the other hand, there may be evidence—depending on the condition—that other [non-psychedelic] medications are beneficial. It makes sense to actually opt for a therapeutic that is shown to work as opposed to one for which there is a lot of hype.

We are the evidence-based agency. We're funding researchers to evaluate the potential benefits, for example, that psilocybin may have for the treatment of depression or addiction. Or the potential that MDMA may have for the treatment of PTSD.

The same applies to cannabis. We are predominantly funding research as it relates to its potential benefits for pain and addiction. Other NIH Institutes hopefully are going to start funding more research as it pertains to other reasons why people are using it.

"The hype has gotten ahead of the science regarding the possible therapeutic uses of psychedelic drugs."

In recent years we have reported on a number of papers, including one that you and others published this past May in *Psychological Medicine*. In that paper you showed that in a sample of nearly 7 million people born in Denmark in the last 50 years, young males "might be particularly susceptible to the effects of cannabis." You estimated that one-fifth of over 45,000 schizophrenia cases among young males in that sample of 7 million people might have been prevented if those who did develop schizophrenia had not had cannabis use disorder.

How worried are you about this?

I'm definitely worried because the concern is that more and more people are using cannabis. Cannabis use in young people has been pretty stable. Regular use in the U.S. is close to 6%. ("Regular use" means almost every day.) But the transition period from adolescence to adulthood is one of a very high rate of use of cannabis. And in that transition, we're seeing what appear to be very negative effects. One that has attracted a lot of attention for many decades is schizophrenia-related psychosis.

The other thing we need to keep our eye on is that in people with suicidal behaviors, the prevalence of cannabis use is much higher than in those that without suicidal behaviors. Independent studies show that there appears to be a higher association of suicidal thinking and behaviors among people that consume cannabis, and it's even higher among those with cannabis use disorder.

This doesn't mean that there is a causal linkage. But the association is there, and it's strong. We need to determine if people are using cannabis to medicate suicidal thinking or whether cannabis could trigger suicidal behaviors. We need to understand those dynamics. NIDA and others have a mission to research these important questions.

❖ **INTERVIEW BY PETER TARR**

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What Genetics Is Telling Us About Substance Use Disorders

By Sandra Sanchez-Roige, Ph.D.

Department of Psychiatry, School of Medicine
University of California, San Diego

2018 BBRF Young Investigator

The following is based on a BBRF webinar presentation Dr. Sanchez-Roige made on July 11, 2023.

IN BRIEF
Dr. Sanchez-Roige explains how large-scale studies of genome variations have identified risk locations for substance-use disorders. She also discusses the importance of converting these signals from the genome into biological understanding of mechanisms and vulnerabilities which may provide a path forward for the development of novel treatments.

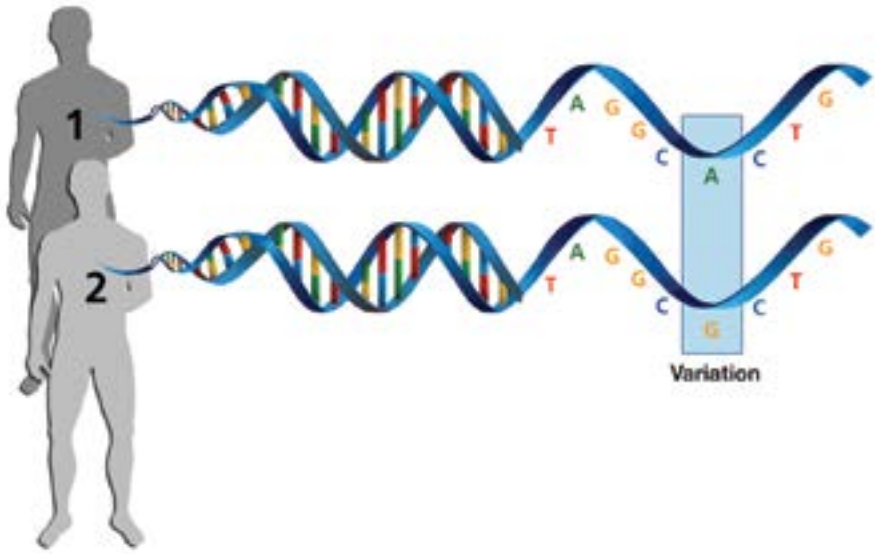
What have studies of the genetics of substance-use disorder so far uncovered? How can we transform these discoveries into concrete actions, effective interventions, and bring hope to those in need?

Substance use disorders have been my focus throughout my career. They are among the most common psychiatric conditions. Causation is complex—embedded in a web of environmental and genetic factors. Prevention, diagnosis, and treatments remain limited.

Over the past 6 years, there has been an explosion of large studies aimed at finding the genetic factors that may be associated with substance use disorders. These studies are vital, because they can reveal biological mechanisms of substance use disorders that can be targeted for new interventions, and thus make a significant impact in people's lives. This fuels my research.

It has been inspiring to see the progress in human genetics. At the forefront have been genome-wide association studies, or GWAS. These studies are designed to scan across our human genome in search of genomic regions that may be associated with a trait like problematic drinking.

Your genome is the complete sequence of DNA that you have in all the cells in your body that is used as the blueprint to build all the parts of the body. A DNA strand is made up of a sequence of DNA "letters"—abbreviated as G, C, T, and A. Although much of the genome (around 3 billion pairs of DNA letters) is the same in all humans, some letters can



The genome is nearly identical in every person, but it's where differences occur that researchers look for associations with illness. In most cases, a single-"letter" variation in DNA between 2 people won't affect health. But if the change prevents a critical gene from functioning properly, it could help cause or raise risk for one or more illnesses

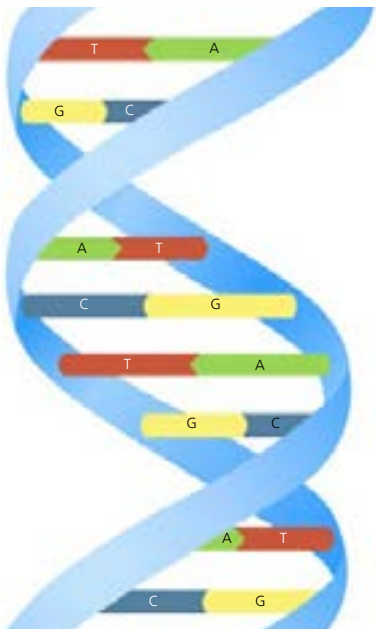
be different between individuals. For example, at a particular spot in the genome, you might have an A, whereas someone else has a G.

An individual's unique configuration of genetic variation across the genome is called their "genotype." A GWAS measures millions of these genomic variants and correlates each one with the trait that is being studied. Alcohol dependence is an example of a trait we can study with GWAS. Scientists often call them "phenotypes," but I am going to use the friendlier term "trait" in this article.

GWAS have proved to be extremely successful tools, but in order to obtain meaningful results, we've learned that we need extremely large sample sizes—hundreds of thousands of people whose genomes we have received permission to scan (anonymously, of course—a process called "de-identification"). We must also have data about an individual's traits. For example, in order to conduct GWAS of alcohol dependence we must have a way to identify those who have an alcohol dependence diagnosis and contrast their genomes with those who do not. Computational methods to analyze the vast amounts of data from these huge cohorts have become more refined over the years.

How do we measure substance use disorders? Doctors can very accurately measure our blood pressure; they have very precise instruments for that. But when we go to a psychiatrist's or a psychologist's office, they will ask us a series of questions to determine whether we meet certain criteria for a disorder diagnosis. And if we carry two or more of the symptoms outlined in the DSM-V diagnostic manual, we would be diagnosed with a substance use disorder. [see illustration, next page]

Using the diagnosis as defined in the DSM, we could recruit lots of people with or without a diagnosis of alcohol use disorder and perform a GWAS. I have been part of major efforts of this kind led by the largest international consortium on psychiatric genetics, the Substance Use Disorder Workgroup of the Psychiatric Genomics Consortium. One of the landmark papers by this group, published in 2018, focused on assembling multiple cohorts to get a sample large enough to perform a statistically meaningful GWAS of alcohol dependence. In this study, our subjects were identified according to the diagnostic criteria of the DSM manual.



The DNA double helix. The genome's alphabet consists of only 4 letters, each standing for a chemical building block. The human sequence consists of 3 billion pairs of these letters. A Adenine always pairs with T Thymine, and C Cytosine with G Guanine. Variations in the sequence can be correlated with increased illness risk.

Substance Use Disorder (DSM-5)

1 Larger amounts or longer than intended

2 Unsuccessful efforts to cut down

3 Excessive time to obtain, use, or recover

4 Craving or strong desire to use

5 Failure to fulfill role obligations

6 Continued use despite recurrent problems

7 Important activities reduced due to use

8 Hazardous use

9 Continued use due to a problem caused by the substance

10 Tolerance

11 Withdrawal

Mild 2–3 symptoms **Moderate** 4–5 symptoms **Severe** 6 or more symptoms

After much rigor and effort, this study was able to reveal only one locus—one location in the human genome—with a statistically significant association with alcohol use disorder. This area contains one of the genes that regulates how ethanol is metabolized in the body. We realized that much larger sample sizes would be needed to achieve the statistical power to find other risk locations in the genome related to this particular trait.

HOW TO GET BIGGER AND BETTER SAMPLES

Over time, research began to reveal that substance use disorders, like all complex traits, are highly polygenic. This means that many genetic risk variants—hundreds or even thousands—are involved in vulnerability for the trait. Commonly occurring risk variants are thought to each have a very small impact on total risk for the trait (here, alcohol dependence).

Yet we realized that in our GWAS cohorts we may be including high levels of heterogeneity—differences between people who display the trait we are looking at. For example, there are over 2,000 unique combinations of the DSM diagnostic criteria that can result in a substance use disorder diagnosis. That means two people can be given the same diagnosis, yet exhibit the substance use disorder in very different ways.

To complicate things even further, substance use disorders develop over time, starting with experimental use, leading to regular use, compulsive use, then, often, cessation, and also, often, relapse. It is possible that different genes may impact or have a different role at different stages of substance use disorders. If we're not careful in assembling our study populations, we may inadvertently obscure signals from the genome that may be relevant to *each of these stages*, signals which could potentially have enormous therapeutic value.

Back in 2016, I joined **Dr. Abraham's Palmer** laboratory as a postdoc. Dr. Palmer is a 2006 and 2003 BBRF Young Investigator. The challenge we wanted to solve was related to the difficulties of putting together samples to perform GWAS. We asked, "where can we get high volumes of good data that may be relevant to substance use disorders?" The answer was: with a consumer genetics company, 23andMe, Inc. The beauty of working with them is that they have already genotyped millions of people.

We paid 23andMe to deploy an online survey capturing different aspects of substance use that we compiled with

AUDIT-C

1 How often do you have a drink containing alcohol?

2 How many drinks containing alcohol do you have on a typical day when you are drinking?

3 How often do you have six or more drinks on one occasion?

AUDIT-P

4 How often have you found that you were not able to stop drinking once you had started?

5 How often have you failed to do what was expected from you because of drinking?

6 How often have you needed a first drink in the morning to get yourself going after a heavy drinking session?

7 How often have you had a feeling of guilt or remorse after drinking?

8 How often have you been unable to remember what happened the night before because you had been drinking?

9 Have you or someone else been injured as a result of your drinking?

10 Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?

input from psychologists. 23andMe users who participate in the company's genome research efforts were asked to fill out the survey. This was completely voluntary with informed consent.

This survey included a 10-item questionnaire, called the Alcohol Use Disorder Identification Test (or "AUDIT") that measures past-year alcohol use. We collected 25,000 AUDIT responses from 23andMe research participants. We then combined this data with additional AUDIT data from another population-based cohort, the UK Biobank, which has genotype and trait data for half a million participants.

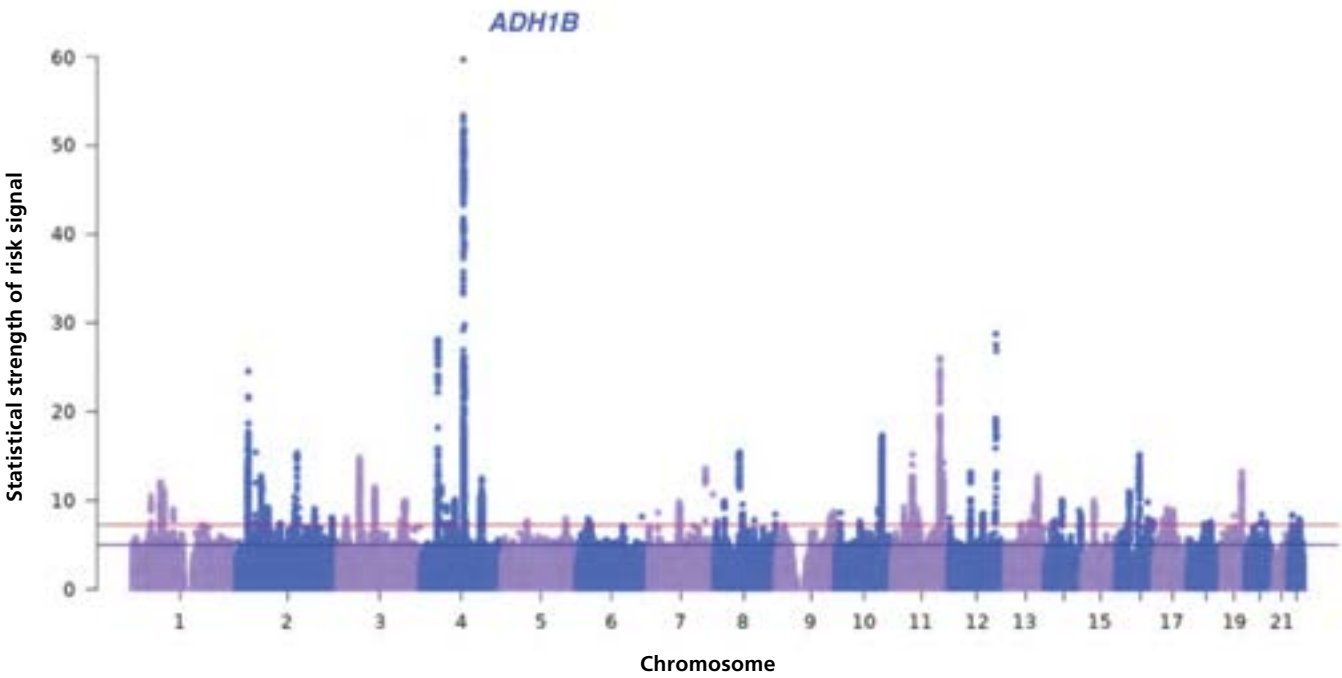
We aggregated the data from these two datasets and performed a GWAS, which uncovered 10 genome locations associated with elevated risk for problematic alcohol use, nine more than the inaugural 2018 GWAS of alcohol dependence that I mentioned. It was reassuring to learn that among the 10 risk locations identified in this GWAS, one was the location that we identified previously, which included the gene for an enzyme that metabolizes ethanol.

The beauty of the AUDIT questionnaire is that it can distinguish alcohol use from misuse. For example, the first three items measure aspects of consumption, such as the frequency of drinking, quantity of drinking, and patterns of binge drinking (drinking too much over a short time period). We called this version of the questionnaire AUDIT-C. Another variation measuring problematic consequences of alcohol use, such as causing injury to oneself or others as a consequence of drinking, we named AUDIT-P.

We performed two separate GWAS based on responses to AUDIT-C and AUDIT-P. It was clear that some genome risk locations, or "loci," consistently appeared (for example, the ethanol-metabolizing enzyme genes I've mentioned, which are on chromosome 4). But we also saw that the overlap was incomplete, suggesting that the genetic architecture of alcohol *use* is not the same as the genetic architecture of alcohol *misuse*. This is important; it calls attention to the need to distinguish these two core aspects relevant to alcohol use disorder.

How closely related were these various AUDIT traits to clinically defined alcohol dependence (i.e., based on the DSM criteria)? We used a revolutionary statistical method to perform genetic correlations, which allowed us to estimate the *genetic factors shared between two traits*. The uniqueness of this method is that unlike "trait" correlations, which are performed using the same individuals, genetic correlations can be performed across pairs of traits that are measured in independent cohorts.

We performed genetic correlations between AUDIT-C and AUDIT-P and alcohol dependence, and we identified very strong, significant genetic correlations between the traits. These



Correlating results from AUDIT-C and AUDIT-P revealed 110 risk locations in the genome associated with problematic alcohol use. Locations associated with elevated risk across the 23 chromosomes (left to right) are those which rise above the red line. The height of each individual "spike" indicates its relative statistical significance. The strongest corresponds with the gene *ADH1B*, which encodes an enzyme that metabolizes ethanol.

findings, to my view, are extremely important, because they illustrate that we could *combine* clinical traits and reach unprecedented sample sizes. Thanks to support from BBRF, **Dr. Hang Zhou**, a 2018 BBRF Young Investigator, combined clinical data with AUDIT data, revealing 110 risk locations in the genome associated with problematic alcohol use, a dramatic increase from our original study back in 2018. [see illustration above]

So, to sum up so far: Using AUDIT, we have shown that alcohol use and misuse have a different genetic basis, and we have uncovered hundreds of novel genes associated with problematic alcohol use. I've also told you that we've begun to stiudy the genetic underpinnings of the different addiction stages.

We have also learned that alcohol use disorders, like all complex conditions, are not single-gene disorders and that *hundreds to thousands* of commonly occurring genetic variants, each likely with small impact on total risk, are involved in the condition.

"HAVE YOU EVER MISUSED AN OPIOID?"

Another study I'd like to discuss pertains to aspects of prescription opioid use. The metrics for the current opioid epidemic in the U.S. are shocking. Almost 130 people die every day from opioid overdose. The majority of opioid users initiate with prescription pain relievers. Because prescription opioids are widespread in medical settings, we believe that prescription opioid misuse is be a trait that could be captured in, for example, the 23andMe population.

In 2018, we extended our 23andMe survey to 125,000 people, and one of the added questions pertained to taking prescription painkillers not as prescribed. To our surprise, 20% of the 23andMe research participants reported having at least once taken opioids not as prescribed. We wondered if a trait like this could generate a genetic signature that is highly correlated with opioid use disorder.

We performed a GWAS and identified two significant risk loci. The strongest signal was with variants in the gene *KDM4A*, which, intriguingly, was recently associated with opioid use disorder as diagnosed by clinicians in an independent study.

We found that the *KDM4A* gene interacted with multiple drugs, including serotonin reuptake inhibitors (SSRI antidepressants) as well as disulfiram (used to treat chronic alcoholism), medicines often

prescribed for disorders known to co-occur with opioid use disorder. We also found interaction with drugs affecting the dopamine system that are known to influence neural circuits associated with reward and reinforcement—which are critical in substance use disorders.

Even more important, the trait of opioid prescription misuse shows strong genetic correlations with results of the largest available GWAS of opioid use disorders. We also identified strong genetic correlations with over 200 other outcomes, particularly other substance-use traits, pain, pain medications, as well as associations with risky behaviors.

We were concerned that maybe we were just picking up on a signal that had little to do with opioid misuse, but more to do with risky behaviors—people who may be inclined to misuse opioids may also be inclined to risky behavior in general. We used statistical tools that suggest the signal we captured is primarily specific to opioids and not merely risk-taking.

So here again, by asking a single simple question in a cost-effective way—as we did when we asked 23andMe research participants about whether they had ever misused an opioid—we were able to help discover something of broad importance about the genetic basis of opioid use disorders.

Encouraged by these findings, my lab, in collaboration with Dr. Palmer and 23andMe, have launched what we call the Prescription Opioid Genetics Study in a cohort of half a million people from multiple ancestries. This survey has already been deployed and we are in the process of collecting data. All subjects in the cohort have a history of using prescription opioids at least once in their life. We will incorporate data on pain, trauma, and other conditions that are known to intersect with opioid use.

We hope this will further our understanding of opioid use disorder as well as our understanding of the intricate relationships between prescription opioid use and misuse and the relationship with mental and physical health. We hope to finish assembling this data set in 2024.

HOW IMPULSIVITY CONTRIBUTES TO SUBSTANCE MISUSE

Let's turn now to another trait, impulsivity: thoughts or actions that are poorly conceived, prematurely expressed, and that often result in undesirable consequences.

Many neuropsychiatric disorders are associated with impulsivity, including substance use disorders. Impulsivity is involved at multiple stages of vulnerability for substance use disorder, including the transition from regular to harmful use, as well as in relapse. By studying the fundamental nature of this trait of impulsivity, which is present in each one of us at a higher or lower level, it is our hope to learn more about the biology underpinning multiple conditions characterized by excessive impulsivity levels, including substance use disorders.

As part of our collaboration with 23andMe, our survey included several well-established questions that capture different facets of impulsivity. For example, we asked respondents to assess themselves on the statement: "I quite enjoy taking risks." We also asked people to respond to the statement: "I do things without thinking."

We collected 150,000 responses on eight impulsive personality traits and we performed independent GWAS studies of *each* of these traits. We learned that *impulsivity is heritable*, which means that the extent to which we are more or less impulsive, or the way that we responded to the previous questions, can be attributed, in part, to genetic factors. We found a heritability of 10% for impulsivity.

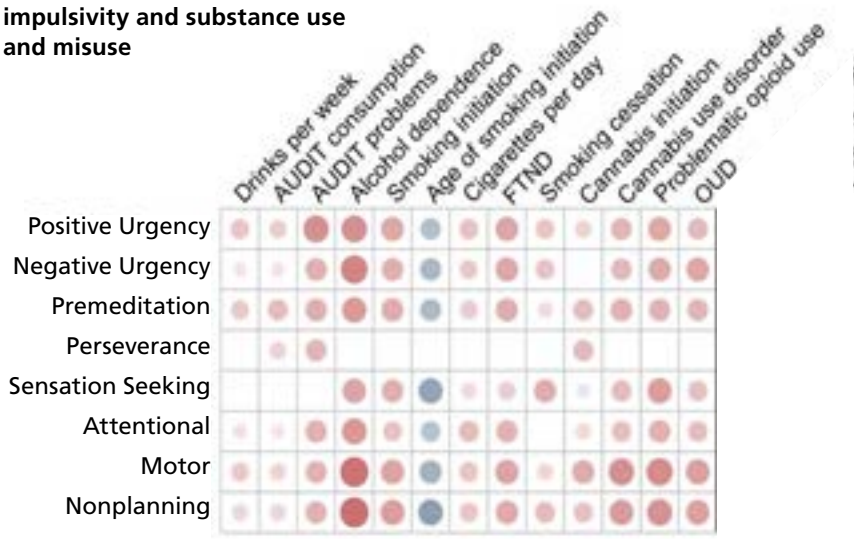
This means that only about 10% of impulsivity can be explained by genetic factors. And this suggests that even though we, as geneticists, are interested in finding biological causes that contribute to behavior, *the environment* plays an equally or even more important role in shaping how we feel and how we act.

We also learned that the impulsivity-related traits are genetically correlated, but that the overlap is incomplete, emphasizing what has been known in neuroscience for a long time: each impulsivity trait is governed by different biological mechanisms. These *impulsivity traits are also genetically correlated with substance use traits*, traits spanning nicotine dependence, and alcohol, cannabis, and

opioid use disorders. The challenge for future studies is to disentangle the nature of this complex web of correlations. [see chart below]

The GWAS for the eight impulsivity traits we measured identified 16 genomic regions associated with impulsivity. The frustration all geneticists share is that GWAS are correlation studies and can only point to regions in the genome that are associated with a trait. The variations we find in these locations do not cause impulsivity [chart, facing page]. They don't even indicate what we call the "directionality" of the association.

Genetic correlations between impulsivity and substance use and misuse

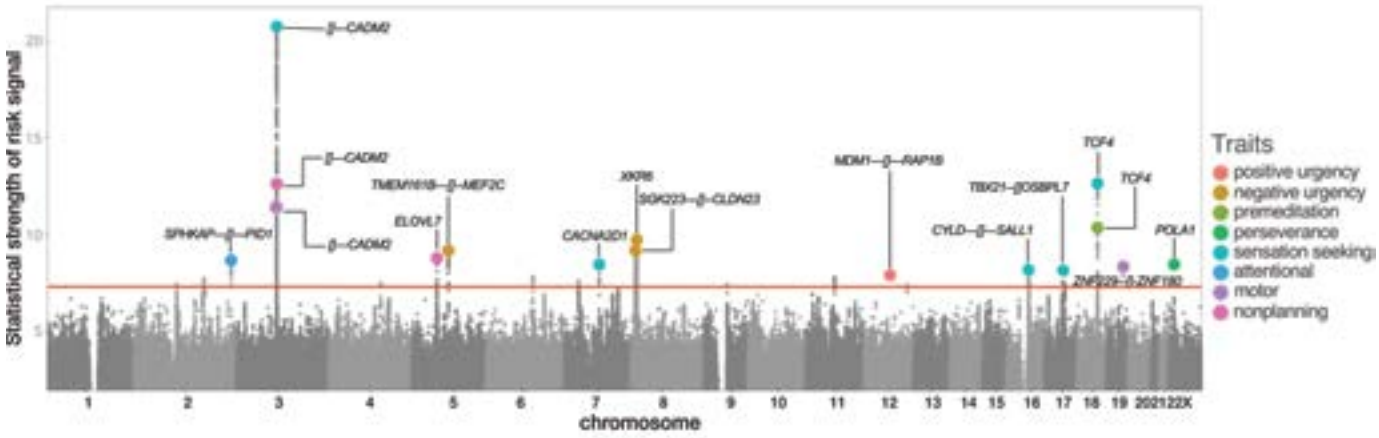


Impulsivity-related traits (listed top to bottom, left side) are genetically correlated. They are also correlated with substance use traits (top left to right), and span nicotine dependence, and alcohol, cannabis, and opioid use disorders. Future studies will attempt to disentangle this complex web of correlations. Intensity of correlations is color-coded, ranging from greater correlation (red) to anti-correlation (blue).

For example, even though we and others have robustly established that variations in the gene *CADM2* are associated with impulsivity, we still have little understanding about the mechanisms in the brain through which this gene influences behavior. My BBRF Research Partners grant (supported by **Families for Borderline Personality Disorder Research**) enabled us to produce mice with the variation in the mouse version of this gene, called *Cadm2*. (Borderline Personality Disorder is also characterized, in part, by impulsive behavior). In the genome there are two copies of each gene, and in mice we can selectively remove or deactivate one or both genes to directly test how it impacts behavior. Using mice with manipulated *Cadm2*, we tested how this gene contributes to performance in a broad battery of behavioral tasks that included measures of impulsivity.

In one test that measures "risky" responses in mice, we found that mice lacking one functional copy of the *Cadm2* gene showed less risky behavior. This is an indication, in one case, of the direction in which a specific genome variation affects a given trait—in this case impulsivity.

We also measured other facets of impulsivity. Loss of both functional copies of the *Cadm2* gene in mice resulted in less impulsive responding to a task. Beyond impulsivity measures, we did not observe deficits in tasks we had the mice perform to measure anxiety-like behavior. This showed that this gene, *Cadm2*, at least in the ways we were able to assess in our study, seems to be specific to impulsivity and not general aspects of behavior.



The GWAS for 8 impulsivity traits (color-coded, far right) identified 16 genome locations associated with impulsivity. These are spikes that rise above the red line of "statistical significance." Their corresponding locations on the 23 human chromosomes are found on the left-to-right axis, bottom.

TURNING SIGNALS OF RISK INTO BIOLOGICAL KNOWLEDGE

Our knowledge of the genetic underpinnings of traits such as impulsivity or problematic substance use are not meant to replace clinical diagnosis of substance use disorders. But they do allow us to dissect, in this case, substance use disorders; they provide a more granular biological understanding of them, which enables us to move toward translational research in years to come.

GWAS have been tremendously successful. And with the availability of newer, larger-scale data sets (one is called All of Us), or other academic initiatives such as the PsycheMERGE consortium (with access to longitudinal data from millions of individuals), it is almost certain that the number of risk loci associated with substance use disorders will continue to grow.

But: is increasing sample sizes for GWAS—with the hope of identifying more risk locations in the genome—all we should be doing? When we perform such studies, moreover, what are we going to do with all the newly identified risk loci in the genome?

In other words, how are we going to turn these statistical signals of risk into biological knowledge?

If we can do this, it is quite possible that we will find better targets that could have treatment and prevention value. We are working now on developing new methods that go beyond identifying risk genes like *CADM2*. We seek to generate 3D high-resolution maps of where and when such genes impact operations of the brain.

We must increase the diversity of the population samples whose genomes form the basis for our research. Most of the studies that I have presented here are dominated by one group of genetically similar individuals, namely individuals of shared European ancestry. Some of us are working on translating and integrating research findings across ancestries to enable equitable health research and therapeutic innovations.

It is going to be very exciting to see the impact upon our knowledge of substance use disorders moving forward. Our ultimate goal is to translate some of the most promising findings to the clinic to provide relief to those who suffer from substance use disorders.

A final appeal to those struggling with this condition or to those who have a family member or a beloved friend who does. If you think, "How can I help genetic studies?" please know that it is very important that we increase community participation.

We encourage others to become involved. These studies are very costly, not only in terms of funding, but also because it is incredibly challenging to reach the large sample sizes that make our studies statistically robust and thus meaningful to the discovery of new therapies. We need help from the public.

As some of the work I've presented here suggests, we can learn a lot about substance use disorders by learning about people who do not, in fact, have substance use disorders. For example, there is much to be gleaned by studying how impulsive a person is, or how a person responded to opioids the first time they used one. There is a great deal we have already learned by asking questions like these of anyone who wants to help. ❖

2023 INTERNATIONAL MENTAL HEALTH RESEARCH SYMPOSIUM

Dr. Jeffrey Borenstein

Dr. Carol Tamminga

On Friday, October 27, 2023, BBRF hosted its International Mental Health Virtual & In-Person Symposium at the Kaufman Music Center in New York City, which was simultaneously live-streamed.

Later that same evening BBRF presented the Outstanding Achievement Prizes in Mental Health to five scientists at the International Awards Dinner for their extraordinary work in advancing psychiatric research.

The BBRF Outstanding Achievement Prizes acknowledge and celebrate the power and importance of neuroscience and psychiatric research in transforming the lives of people living with mental illness. The recipients of this year's awards were recognized for their research achievements in schizophrenia, bipolar disorder, pediatric mood and anxiety disorders, and cognitive neuroscience. The Outstanding Achievement Prizewinners were selected by special committees of the Foundation's Scientific Council, a volunteer group of 193 mental health experts across disciplines in brain and behavior illnesses.

Dr. Jeffrey Borenstein, BBRF's President & CEO, opened the Symposium with a welcome to all attendees, and noted, "We applaud the Outstanding Achievement Prizewinners for their extraordinary contributions to advancing the development of new treatments, cures, and methods of prevention for mental illness. In celebrating these excellent scientists, we acknowledge the significance of neuroscience and psychiatric research in transforming the lives of people living with mental illness."

Carol Tamminga, M.D., served as the Symposium moderator. The program featured presentations by the prize-winning scientists and the winner of the Pardes Humanitarian Prize in Mental Health, each speaking for about 20 minutes. In the pages that follow, we summarize the subjects covered in each Symposium talk.

Philip D. Harvey, Ph.D., gave a talk entitled *Self-knowledge in Schizophrenia: Importance, Characteristics, and Treatment*. Dr. Harvey is the Leonard M. Miller Professor of Psychiatry and Behavioral Sciences & Senior Health Research Scientist at the Leonard M. Miller School of Medicine, at the University of Miami. He also serves as Senior Health Research Scientist, VA Medical Center, Miami, and is a member of the BBRF Scientific Council.

Dr. Harvey's research has focused on reducing the disability associated with schizophrenia by trying to advance the assessment and treatment of cognitive impairments, functional skills, and negative symptoms. He leads a large-scale initiative to understand the genomic underpinnings of cognition and disability, in a collaborative study funded by the U.S. Department of Veterans Affairs. An additional focus of his recent research has been on challenges in self-assessment in schizophrenia.

In his presentation Dr. Harvey noted that many of the symptoms of schizophrenia arise from misperception—hearing voices that are not actually there and believing things that cannot possibly be true. A critical related area is mis-estimation of cognitive and functional abilities. This domain of misperception has important implications for everyday functioning: those unable to judge their abilities can underestimate, concluding that things within their grasp are impossible, or overestimate, having extraordinary confidence in their skills and declining assistance. Both can lead to a mismatch between self-perceptions and real potential. This is not due to random responding, lack of motivation to accurately self-assess, or inability to remember, Dr. Harvey says. People with schizophrenia have an extraordinary ability to remember information that is self-generated, hence the tenacity of delusional beliefs. He mentioned his recently developed smartphone application targeting self-assessment and an increased focus on strategies aimed at increasing both accuracy in self-assessment and better task performance.

Symposium speaker **Amy E. Pinkham, Ph.D.**, Professor of Psychology at The University of Texas at Dallas, discussed *Social Cognition and Social Difficulties in Schizophrenia*.

In her talk, Dr. Pinkham explained that social cognition is a broad construct encompassing the ways in which individuals perceive, process, and use information about other people. She defined social cognition and reviewed what we know about social cognitive impairments in schizophrenia spectrum illnesses. She placed emphasis on evidence demonstrating that social cognition is a critical contributor to functional outcomes. She also discussed potential neural mechanisms of social cognitive impairment in schizophrenia.

2023 PRIZEWINNERS

LIEBER PRIZE FOR OUTSTANDING ACHIEVEMENT IN SCHIZOPHRENIA RESEARCH

Philip D. Harvey, Ph.D.
Leonard M. Miller School of Medicine, University of Miami
VA Medical Center, Miami

MALTZ PRIZE FOR INNOVATIVE & PROMISING SCHIZOPHRENIA RESEARCH

Amy E. Pinkham, Ph.D.
The University of Texas at Dallas

COLVIN PRIZE FOR OUTSTANDING ACHIEVEMENT IN MOOD DISORDERS RESEARCH

Roger S. McIntyre, M.D., FRCPC
University of Toronto

RUANE PRIZE FOR OUTSTANDING ACHIEVEMENT IN CHILD & ADOLESCENT PSYCHIATRIC RESEARCH

Katie McLaughlin, Ph.D.
University of Oregon

GOLDMAN-RAKIC PRIZE FOR OUTSTANDING ACHIEVEMENT IN COGNITIVE NEUROSCIENCE

Elizabeth A. Phelps, Ph.D.
Harvard University

Many people with schizophrenia experience significant social difficulties. Dr. Pinkham's work attempts to identify factors that contribute to these social problems, focusing on social cognition, or how we think about other people. Her work demonstrates that individuals with schizophrenia display deficits or biases in multiple domains of social cognition and that abnormal functioning of the brain networks that support social cognitive processing likely contribute to these deficits. Her work has consistently shown that social cognition is an independent contributor to social dysfunction in schizophrenia, validating it as a promising treatment target.

Roger S. McIntyre, M.D., FRCPC, discussed *Does Obesity Metastasize to the Brain? Implications for Clinical Care and Identifying the Causes and Cures for Persons Living with Bipolar Disorder.* Dr. McIntyre is Professor of Psychiatry and Pharmacology at the University of Toronto, Canada, and Chairman & Executive Director of the Brain and Cognition Discovery Foundation in Toronto. He also serves as a Professor at Guangzhou Medical University, China and was a 2007 BBRF Independent Investigator.

Dr. McIntyre is involved in multiple research endeavors which primarily aim to characterize the phenomenology and neurobiology of mood disorders, and to develop novel therapeutics. He has been especially interested in identifying innovative, rapid-acting psychotropic treatments. Dr. McIntyre's research has also extended into public health and implementation research at the population-based level.

In his talk Dr. McIntyre noted that people who are living with bipolar disorder are more likely to be affected by Type II Diabetes, obesity, and heart disease when compared to persons in the general population. This happens for many reasons, including research suggesting that the underlying cause of bipolar disorder may overlap with the causes of these medical conditions. He suggested that from a clinical perspective, it is important to prevent and treat these conditions as they are the single largest cause of loss of life in persons living with bipolar disorder. Research conducted during the past two decades suggests that abnormalities in insulin signaling and inflammation, contributory to metabolic problems and heart disease, may also contribute to causation in bipolar disorder. Such findings may indicate a new way to treat and prevent the illness.

Katie McLaughlin, Ph.D., spoke about *The Long Shadow of Childhood Adversity: Implications for Children's Brain and Behavioral Development*. Dr. McLaughlin is the Executive Director, Ballmer Institute, and the Knight Chair and Professor of Psychology at the University of Oregon. She is also the 2016 BBRF Klerman Prizewinner for Exceptional Clinical Research and a 2013 BBRF Young Investigator.

Dr. McLaughlin is a clinical psychologist with interest in how environmental experience influences brain and behavioral development in children and adolescents. Her research examines how adverse environmental experiences shape emotional, cognitive, and neurobiological development throughout childhood and adolescence. Specifically, she seeks to understand how experiences of stress, trauma, and social disadvantage alter developmental processes in ways that increase risk for psychopathology.

In her presentation, Dr. McLaughlin explained that children who have experienced environmental adversity—such as abuse, neglect, community violence, or chronic poverty—are at markedly elevated risk for developing mental health problems. What is less clear is how and why adverse early experiences exert such a profound influence on children's mental health. Her symposium

talk summarized her program of research demonstrating that adversity can have a profound impact on brain development, particularly when these experiences occur during periods of heightened brain plasticity early in life when brain circuits are particularly likely to be sculpted by environmental experiences. She also shared recent findings suggesting that early-life adversity can accelerate the pace of biological aging across numerous bodily systems, contributing to elevated risk for a host of physical and mental health problems. She believes identifying developmental processes that are disrupted by adverse early environments is the key to developing better early interventions to prevent the onset of mental health problems in children who have experienced adversity.

In her symposium presentation, **Elizabeth A. Phelps, Ph.D.**, addressed *The Human Amygdala, Threat, and Anxiety: Translational Progress and Challenges*. Dr. Phelps is the Pershing Square Professor of Human Neuroscience, Department of Psychology at Harvard University.

Dr. Phelps' laboratory has earned acclaim for its groundbreaking research on the neurobiology of human emotion, critically extending animal models of threat learning to the neural systems of anxiety and related disorders. The primary inspiration behind their research is the observation that emotions color our lives, and even subtle, everyday variations in our emotional experience can alter our thoughts and actions. By uncovering the impact of emotion and affect on cognition, Dr. Phelps and colleagues aim to enhance our understanding of cognition broadly and provide insights into social processes and psychological disorders. Studies of the neurobiology of threat processing in rodents have formed the basis of our understanding of fear and anxiety in the human brain, and much of this research has focused on the central role of the amygdala.

The entire BBRF symposium is available to watch free On-Demand at: https://bbrfoundation.org/event/international-mental-health-research-symposium

Dr. Phelps highlighted the successes and failures in translating these neurobiological findings from animal models to humans. First, she presented research examining if findings from simple, associative threat learning in rodents translate to the complex learning situations typical of everyday human experience. Then she highlighted efforts and challenges in using insights from this research to inform novel treatments for anxiety-related disorders. She concluded by commenting on how we might more effectively build on neurobiological findings of threat processing in animal models to enhance the treatment of anxiety-related disorders.

The BBRF Mental Health Symposium also featured a presentation from **Károly Mirnics, M.D., Ph.D.,** entitled *Minds Matter: Mental Health and Intellectual Disabilities*. Dr. Mirnics spoke on behalf of the 2023 Pardes Humanitarian Prize in Mental Health winner, Special Olympics International. Dr. Mirnics is the Hattie B. Munroe Professor of Psychiatry, Biochemistry & Molecular Biology at the University of Nebraska Medical Center. He is also a member of the BBRF Scientific Council, a 2002 BBRF Young Investigator, and a Member, Board of Directors, of Special Olympics International.

In his presentation Dr. Mirnics noted that individuals with intellectual disabilities have a higher prevalence of mental health conditions when compared to the general population. Often overlooked, their challenges are compounded by limited access to appropriate care and resources. He suggested that activities by Special Olympics, especially through the Special Olympics Healthy Athletes program, are leading to improved mental health including, but not limited to, reduction in feelings of isolation, anxiety, and depression. ❖ **BY LAUREN DURAN**

A full story about the Pardes Humanitarian Prize in Mental Health can be found on pages 34–35.

2023 International Awards Dinner

The BBRF International Awards Dinner was held on Friday, October 27, 2023 at The Pierre Hotel in New York City. The event celebrated the progress being made in neuroscience research and honored the BBRF Outstanding Achievement Prizewinners and the winner and honorary winner of the Pardes Humanitarian Prize in Mental Health. Prizewinners spoke earlier in the day at the BBRF Symposium.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1. Geoffrey Simon, Dr. Roger McIntyre, Dr. Katie McLaughlin, Dr. Elizabeth Phelps, Dr. Amy Pinkham, Dr. Philip Harvey, Dr. Jeffrey Borenstein, and Dr. Carol Tamminga. **2.** Dr. Dimitri Christakis, Dr. Timothy Shriver, and Dr. Károly Mirnics – Special Olympics International **3**. Geoffrey Simon, BBRF Board Chairman **4.** Dr. Philip Harvey and Dr. Jeffrey Borenstein **5.** Dr. Jeffrey Borenstein and Dr. Katie McLaughlin **6.** Dr. Roger McIntyre and Dr. Jeffrey Borenstein **7**. Dr. Amy Pinkham and Dr. Jeffrey Borenstein **8**. Dr. Jeffrey Borenstein and Dr. Elizabeth Phelps **9**. Don and Jan Boardman and John and Mary-Pat Osterhaus **10**. Geoffrey Simon, Dr. Peg Brivanlou, Dr. Kenneth Sonnenfeld, and Andrea Simon **11.** Olivia Neu, Harvey and Carole Mallement, and Dr. Jeffrey Borenstein **12**. Dr. Judy Genshaft and Steve Greenbaum **13.** Geoffrey Simon, Janie and Marty Borell


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PHOTOS BY CHAD DAVID KRAUS

2023 Pardes Humanitarian Prize in Mental Health

Awarded to Special Olympics International and Henry Jarecki, M.D.

Dr. Károly Mirnics accepting the Pardes Humanitarian Prize in Mental Health Award on behalf of Special Olympics International from Dr. Jeffrey Borenstein.

On Friday, October 27, 2023, at The Pierre Hotel in New York City, BBRF presented the 2023 Pardes Humanitarian Prize in Mental Health at its International Awards Dinner.

Special Olympics International received the 2023 Pardes Humanitarian Prize in Mental Health for its lasting humanitarian impact around the world through sports training and athletic competition for adults and children with intellectual disabilities. The prize was accepted by Dr. Károly Mirnics, who serves as a Board Member of Special Olympics and is a BBRF Scientific Council Member.

The Pardes Humanitarian Prize in Mental Health, which carries an honorarium of $150,000, is awarded annually to recognize individuals or organizations whose contributions have made a profound and lasting impact in advancing the understanding of mental health and improving the lives of people who are living 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. Established in 2014, the Pardes Prize is named in honor of Herbert Pardes, M.D., president of the BBRF Scientific Council, outspoken advocate for the mentally ill, and the award's first recipient.

"Special Olympics International is being honored as a beacon of light and equality for its decades of service to adults and children with intellectual disabilities," said Jeffrey Borenstein, M.D., President & CEO of the Brain & Behavior Research Foundation.

The 2023 Honorary Pardes Humanitarian Prize in Mental Health was awarded to Henry Jarecki, M.D., for his important contributions to the field of psychiatry and his unique work to preserve academic and scientific freedom.

Dr. Borenstein noted that "BBRF also salutes Dr. Jarecki for his contributions to the field of psychiatry and his humanitarian efforts to protect scholars and scientists living under regimes that oppress people for their religious or ethnic backgrounds."

The 2023 Honorary Pardes Prizewinner Dr. Henry Jarecki with Dr. Borenstein

THE PRIZEWINNERS

PARDES HUMANITARIAN PRIZE RECIPIENT

SPECIAL OLYMPICS INTERNATIONAL

Special Olympics International is a leading advocate for the inclusion of people with disabilities and a powerful force in the efforts to reduce stigma and raise awareness about the mental health needs of individuals with intellectual disabilities.

Special Olympics International has had a profound and lasting humanitarian impact around the world through its dedication to providing year-round sports training and athletic competition for children and adults with intellectual disabilities. It is recognized for its global presence in making sports activities available to millions of children and adults worldwide.

Since its founding in 1968, Special Olympics International has understood that participation in sports training and competition can have impacts well beyond the physical health of athletes and can drive improvements in mental and emotional health.

The Special Olympics Healthy Athletes program provides free health screenings, including mental health assessments, to athletes to identify any issues or concerns and provide appropriate support and referrals. Titled "Strong Minds," the program began as an educational program that provides athletes with resources and training to help them build resilience, manage stress, and improve their overall mental health. Pilot data from Strong Minds events found that a large percentage of Special Olympics athletes in the U.S. face significant stresses daily but have access to only a few adaptive coping strategies. Special Olympics International inspires us all to use our knowledge toward the greater good of all humanity.

2023 PARDES HONORARY PRIZE RECIPIENT

HENRY JARECKI, M.D.

Dr. Henry Jarecki has had a profound humanitarian impact on the world through his unique and lasting contribution to preserving academic and scientific freedom, most notably in his role as the founding Chairman of the Scholar Rescue Fund of the Institute of International Education.

The Scholar Rescue Fund identifies scholars and scientists living in countries where their religious or ethnic background or their medical, scientific, or public activities have led to government reprisal. The organization relocates these individuals to settings where they are safe and can continue their important work.

Dr. Jarecki's lifelong commitment to social justice is an outgrowth of his personal experience growing up in a German Jewish family that fled Nazism, first to England and then to the United States. Building on his personal experience of political oppression, he first alleviated suffering through an illustrious career in psychiatry. He then broadened his focus to lead and support humanitarian and scientific initiatives around the world. In addition to founding the Scholar Rescue Fund, he co-founded a school in Cambodia, created the Youth Empowerment Project in the Caribbean country of Tortola, and funded the creation of a new campus at the University of Heidelberg. Dr. Jarecki inspires us all to use our knowledge toward the great good for all humanity. ❖ **BY LAUREN DURAN**

PAST PARDES PRIZE WINNERS

2022
Altha J. Stewart, M.D.
Robert van Voren, FRCPsych (HON)
Honorary Tribute:
Clubhouse International
Sean Mayberry

2021
Kay Redfield Jamison, Ph.D.
Elyn R. Saks, J.D., Ph.D.
Charlene Sunkel
Honorary Tribute:
John M. Davis, M.D.
Michael R. Phillips, M.D., MPH
Norman Sartorius, M.D., Ph.D.

2020
Myrna Weissman, Ph.D.
Sir Michael Rutter CBE
Honorary Tribute:
E. Fuller Torrey, M.D.

2019
William T. Carpenter, Jr., M.D.
Honorary Tribute:
Cynthia Germanotta &
Born This Way Foundation

2018
Judge Steven Leifman
Honorary Tribute:
Suzanne and Bob Wright

2017
Doctors Without Borders/
Médecins Sans Frontières
Honorary Tribute:
Constance E. Lieber

2016
Vikram Patel, Ph.D., F.Med.Sci. &
Charles F. Reynolds, III, M.D.
Honorary Tribute:
Senator Edward M. Kennedy

2015
Beatrix (Betty) A. Hamburg, M.D.
and David A. Hamburg, M.D.
Honorary Tribute:
Rosalynn Carter

2014
Herbert Pardes, M.D.

Recent Research Discoveries

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

"Still Depressed" or "Recovering"? Researchers Find Biomarker Signaling Recovery in Treatments for Severe Depression Using Deep Brain Stimulation

Researchers say they have identified an objective biomarker of recovery in major depression that in a small cohort of treatment-resistant patients was able (on an ongoing basis) to capture whether each patient was in a "depressed" or "stable response" state while being treated with deep-brain stimulation (DBS). Unlike some other proposed depression biomarkers, this one was found to be present in all of the patients analyzed; its detection does not require individualization from patient to patient.

The result, which awaits validation in larger trials, would be a first, and could potentially have major implications for treating depressed patients, whose symptoms vary, often markedly, between individuals and also over time as treatments are being administered. The vast heterogeneity of depression often makes it hard for clinicians to know whether or how to adjust treatments over time—in the case of DBS, the level of current that is delivered by the pacemaker-like device implanted in the brain

DBS for treatment-resistant patients with severe major depression was pioneered in 2003–2005 by **Helen S. Mayberg, M.D.**, and colleagues in Toronto, research supported by Dr. Mayberg's 2002 BBRF Distinguished Investigator grant. It remains an experimental treatment for severe major depression that doesn't respond to conventional treatments. It involves the surgical implantation of electrodes in the brain's subcallosal cingulate, a small area behind and above the eyes which is also known as "area 25." Contacts from the electrodes are placed with great precision using individualized "tractography guidance" at the intersection of four white matter tracts—bundles of nerve fibers that enable neurons in different brain areas to communicate and which are implicated in depression. In 2019, Dr. Mayberg and colleagues published the results of multi-year follow-ups of 28 DBS patients. "Robust and sustained" antidepressant responses were achieved in 21 of the 28 cases, one of which at that point had extended over 18 years.

The new study, published in *Nature*, reports on a new cohort of patients receiving subcallosal cingulate DBS for treatment-resistant depression. It was co-led by Dr. Mayberg, Patricio Riva Posse, M.D., and Christopher Rozell, Ph.D. Dr. Mayberg, a neurologist who heads the Nash Family Center for Advanced Circuit Therapeutics at the Icahn School of Medicine at Mount Sinai, is a member of BBRF's Scientific Council, winner of the 2007 BBRF Falcone Prize for Outstanding Achievement in Affective Disorders Research, and the recipient of additional BBRF grants in 1995 and 1991. **Ki Sueng Choi, Ph.D.**, a 2016 BBRF Young Investigator, and **Allison C. Waters, Ph.D.**, a 2019 BBRF Young Investigator, were among members of the team.

Clinical management of DBS patients "is often complex," Dr. Mayberg and colleagues on the new paper point out. The progress of the antidepressant response is "non-linear and different for each individual," and commonly accompanied by periods of mood fluctuations despite overall improvement. "These intervals of transient but significant distress can be difficult for doctors to distinguish from the early return of depression symptoms," Dr. Mayberg notes. Without objective markers of depression severity, clinicians rely on patients' self-reports, questionnaire-based depression-score calculations, and their own clinical experience to decide whether to adjust the

device in the brain that delivers DBS stimulation—or to adopt a watchful waiting approach.

In the new study, the team took advantage of a new DBS device that in addition to delivering stimulation to area 25 also collected brainwave data saved to the implanted device, which could be downloaded by the researchers at weekly intervals over the first 6 months of treatment following the implant. The DBS device delivered no stimulation for the first several weeks, enabling the team to carefully collect data on each patient while in the "depressed" state. This data was compared with readings taken in the final 4 weeks of the 24-week trial period.

Using standard assessment tools for depression symptoms, at the 24-week point, 9 of the 10 patients had demonstrated a "robust clinical response," meaning a reduction in depression symptoms of at least 50%. Seven of the 10 had achieved a remission of symptoms—they no longer met the criteria for a depression diagnosis. Full data was obtained for 6 of the 10 participants. Five of those six had remissions; one, after responding for 4 months, then suffered a relapse.

Using artificial intelligence technology, the team was able to tease out subtle patterns in electrophysiological data which enabled them to discover a pattern in all six subjects that corresponded with positive response to the treatment. Interestingly, this response (as is vexingly typical in depression) occurred as early as the 8-week point for one participant and as late as the 20-week mark in another.

Just as important, the team was able to see a change in the "recovery" signal in the participant who relapsed. This signal, in fact, was found (in retrospective analysis) to have appeared a full month before the patient's relapse occurred. Although it will have to be replicated in many other patients, such a result would in theory provide doctors with an advance warning that a patient who was showing signs of stable recovery was regressing and thus a candidate for an adjustment of his or her DBS device.

The team's findings must be replicated. Dr. Mayberg and colleagues are already assessing results in another cohort of patients at Mount Sinai, again using a DBS system that can both deliver stimulation and sense signals such as the "depressed"/"recovery state" patterns reported in the current paper. The aim is to provide robust and reliable biomarker-based clinical-decision tools that can streamline and optimize DBS management and contribute to adoption of this treatment option in future.

There is also the possibility that the "recovery" signal found in the new research, if validated, could inform methods of treating depression that do not involve invasive surgery—such as TMS, or transcranial magnetic stimulation, in which magnets are used, non-invasively, to apply stimulation beneath the scalp in order to modify activity in underlying brain regions affected by depression pathology. ❖

Youths With Suicide- and Self Injury-Related Emergencies Are Often Missed by Standard Hospital Identification Methods

A study in a large hospital system in Southern California finds that common methods of tracking care in emergency settings are missing many children and adolescents with self-injurious thoughts and behaviors, hampering efforts to detect which youth are at elevated suicide risk. Current methods of tracking care, the study suggests, also may unintentionally be introducing biases as to which young people are recognized as being at risk.

A team led by 2020 BBRF Young Investigator **Juliet Edgcomb, M.D., Ph.D.**, the associate director of the Mental Health and Data Science (MINDS) hub at the University of California, Los Angeles, studied 600 emergency department visits for children ages 10-17 over a 4-year period to understand the performance of common ways of detecting suicide-related emergencies among children.

Two frequently used methods to track suicide-related visits include diagnostic codes, assigned by the care provider, and the patient's "chief complaint," or their stated reason for seeking care upon arriving to the emergency department. Dr. Edgcomb and colleagues looked at how well the two methods worked, separately and together, to detect which children experienced self-injurious thoughts or behaviors. The team

then developed and tested three different machine-learning algorithms to try to improve detection using available data from each patient's electronic health care record. To assemble the study cohort, the team applied a system of inclusion criteria that selected for children with mental health-related emergency department visits. Results of the study were published in *JMIR Mental Health*.

Measuring how well diagnostic codes and chief complaint captured visits related to suicide seemed all the more urgent to the researchers in light of a nationwide youth mental health crisis. In the U.S., suicide is the second leading cause of death among children aged 10–14, and recent data suggests 1 in 13 children attempts suicide before adulthood. Emergency departments are often the first point of access to mental health care, particularly care for suicidal thoughts and behaviors. Over 1.1 million pediatric emergency department visits each year are suicide-related—and visits for self-harm among children tripled between 2007 and 2016. During the pandemic, visits for suicide attempts increased further, especially among girls and older children.

Dr. Edgcomb's team, which reviewed clinical notes for 600 emergency department visits, found that diagnostic codes missed 29% of children presenting with self-injurious thoughts or behaviors. One reason for this, the team notes, is that codes classify the underlying or suspected mental health disorder, such as depression or anxiety, but may not specify that thinking or acting on self-injury or suicide was part of the picture. The analysis also showed that "chief complaint" missed 54% of such patients. Even when diagnostic codes and chief complaint notes were combined, 22% of children with thoughts or acts involving self-injury or suicide were still missed. Moreover, these two methods of classification were more likely to miss boys compared with girls; and missed disproportionately more preteens than teens. The researchers found a trend suggesting Black and Latino youth were more likely to be missed.

The team developed three machine learning-based algorithms to try to improve detection in the same dataset. The most comprehensive algorithm included 84 kinds of information available in the electronic medical record of each patient, including prior medical care, medications, demographics, and whether the child lived in a disadvantaged neighborhood, among others. A second model used only diagnostic codes, but included all mental health-related conditions. A third model used all of the non-diagnostic code data points, such as medications and laboratory tests.

All three machine learning algorithms were more sensitive in detecting children with self-injurious thoughts and behaviors compared with suicide-related diagnostic codes and chief complaint alone. The three algorithms performed similarly to one another, which to the team was good news, suggesting that health systems may be able to improve detection without having to build intricate models. "Adding more information helps," Dr. Edgcomb said, "but you don't necessarily need a bells-and-whistles approach to get better detection."

While they missed fewer kids with suicide-related visits, the machine learning algorithms did tend to generate more false positives—they sacrificed some specificity for greater sensitivity. In the context of potentially saving the lives of young people thinking or acting on suicidal thoughts, this may well be worth it, Dr. Edgcomb said. "It may be better to have some false positives and have a medical records analyst double-check charts that screen positive, than to falsely screen negative and entirely miss detecting a child who had presented for a suicide-related emergency."

The team will continue to work on developing algorithms to identify and predict youth at risk and is a now working on a model that would predict risk specifically in children of elementary school age. ❖

A Machine-Learning Tool That Predicts PTSD Risk Before Soldiers Are Deployed

Researchers have successfully tested a new method of predicting, prior to deployment, which soldiers serving in a combat zone are at greatest risk of developing PTSD in the months following their return home.

Gauging risk in advance of deployment could be valuable for several reasons. First, it is known that PTSD can become chronic if untreated and that it is strongly associated with various psychiatric comorbidities and suicide. Developers of the new predictive tool, in a paper reporting their results appearing in *JAMA Network Open*, suggest that "efficient assessment of PTSD risk may facilitate development of targeted preventive or early interventions that reduce individual suffering and societal costs."

The research team, led by BBRF Scientific Council member **Murray B. Stein, M.D., M.P.H.**, of the University of California, San Diego, and Santiago Papini, Ph.D., now at the University of Hawai'i at Manoa, used a dataset of 4,771 soldiers from three U.S. Army brigade combat teams based in different parts of the country who were about to be sent to Afghanistan in 2012. Participants were assessed 1–2 months prior to their departure and again, twice, 2–3 and 8–9 months after they returned home. They served in the combat zone for about 10 months.

Almost 95% of the cohort was male and 72% identified as White; the average age was about 27. Post-return assessments revealed that 15.4% of the cohort (746 soldiers) were suffering from PTSD. The question for the researchers was: which of several machine learning-based models of risk prediction that they had developed worked best to identify the soldiers who were diagnosed with PTSD following their return. The sole basis of the various models tested by the team was data collected in the initial assessment, made just before the soldiers deployed for Afghanistan.

The initial assessment, therefore, was critical. Participants completed a self-administered computerized assessment which included in all, some 801 potential pre-deployment predictors of vulnerability to trauma. Some of these factors, if considered alone, would be considered "weak predictors," although in the context of the full assessment may have had a strong predictive value. Questions asked of the participants pre-deployment included: assessment of symptoms of major depression, mania/hypomania, panic disorder, generalized anxiety disorder, ADHD, intermittent explosive disorder, and substance-use disorders. Suicidal thoughts and behavior were also assessed. Additional measures assessed childhood adversity and misconduct, lifetime trauma, six current and lifetime PTSD symptoms, previous deployment experiences, stress, coping styles, demographics, physical health, injuries, mental health treatment history, weapons ownership, social networks, religiosity or spirituality, and personality.

The machine-learning model ultimately chosen by the team was developed using data from members of two of the brigades within the total cohort and was tested on those in the third to provide an honest assessment of how well the model would perform with data that was not used to develop it. The post-deployment window of assessment, beginning at 2 months after return and ending 9 months after, was designed to rule out confusing early acute stress with PTSD, as well as to capture most delayed PTSD reactions.

The model ultimately chosen by the team used only 58 ("core predictors") of the 801 potential predictors in the

pre-deployment dataset, which was found to perform with accuracy comparable to a model that used all of the predictors as well as a model based on 196 of the potential predictors.

In the cohort that was used to test the final model, the 1/3 of soldiers with the highest predicted risk accounted for 62% of the PTSD cases actually diagnosed in the 9 months following their return from Afghanistan. While it is impossible to say that this prediction model would yield similar results in a future war involving other soldiers and a different combat zone and conditions, the team does believe the model "provides valuable information about which items may be most informative for predicting PTSD among soldiers who may be involved in future combat situations."

It will be important to test the model selected in this study with other cohorts of soldiers deployed to combat zones, particularly those with a larger fraction of female participants. The team also hopes that the cost-effectiveness of their approach will be studied in more detail, as well as the question of determining appropriate thresholds for targeted intervention among individual soldiers who are identified by the model to be most at risk prior to their deployment. ❖

Therapy Update

Recent news on treatments for psychiatric conditions

RAPID-ACTING PILL TO TREAT POSTPARTUM DEPRESSION IS APPROVED

Marlene Freeman, M.D.

On August 4th, the U.S. Food and Drug Administration (FDA) approved zuranolone, the first oral medication designed to treat postpartum depression (PPD) in adults. The drug, which is rapid-acting, was developed by Sage Therapeutics and Biogen, and will be marketed under the name Zurzuvae.

Because of its accessibility, zuranolone is an important advance. The first-ever rapid-acting medicine for postpartum depression, brexanolone, has been on the market since 2019. Brexanolone is administered via continuous infusion in a medical facility over a period of about 60 hours. While zuranolone, like brexanolone, can reduce symptoms of severe depression within 3 days of its administration, it is taken in pill form. The FDA recommended a dosage of 50mg for zuranolone, taken once daily for 14 days.

The efficacy of zuranolone for the treatment of PPD in adults was demonstrated in two randomized, double-blind, placebo-controlled, multicenter studies. The trial participants were women with PPD who met the Diagnostic and Statistical Manual of Mental Disorders ("DSM") criteria for a major depressive episode and whose symptoms began in the third trimester or within four weeks of delivery.

The results of one of those pivotal trials were published in the *American Journal of Psychiatry*. The research team was led by Kristina M. Deligiannidis, M.D., of Zucker Hillside Hospital/Northwell Health in New York. **Marlene Freeman, M.D.**, a 2000 and 1998 BBRF Young Investigator, of Massachusetts General Hospital and Harvard Medical School, was a member of the team.

The researchers noted that about 17% of women globally develop PPD either during pregnancy or following childbirth, and that the condition is generally underdiagnosed and often untreated, exposing mothers and their newborns to considerable health risks that in severe cases of PPD includes risk of suicide in affected mothers. Death from suicide accounts for about 20% of all postpartum maternal deaths. The risk of PPD is about twice as great in women with a family history of psychiatric illness, according to the researchers.

Knowledge about what causes PPD has grown markedly, thanks to basic research conducted over the last 25 years. **Cynthia Neill Epperson, M.D.**, who received three BBRF grants from 1995 to 2005, and others, revealed the possible role of the inhibitory neurotransmitter GABA in the illness. It is thought by many that depression occurring during the perinatal period is distinct in causation from depression at other times of life. Pronounced fluctuations in reproductive hormone concentrations—and the way in which some women respond to these—is thought to play a central role in onset. Notably, levels of the hormone allopregnanolone, which rise during pregnancy, peak in the 3rd trimester, then plummet following childbirth, appear to alter functional connectivity in the brain and may affect GABA-A receptors. Both brexanolone and zuranolone modulate the activity of these receptors.

Dr. Deligiannidis and colleagues enrolled 196 patients with severe PPD (accompanied in many cases by moderate to severe anxiety) in their randomized, double-blinded clinical trial. Half received 50 mg/day of zuranolone over 14 days, and half a placebo. 170 completed the trial. The participants were about 30 years old, on average; 25% identified as Black or African American, 33% as Hispanic or Latina, and 69% as White. PPD onset was in the 3rd trimester for one-third of the women, while onset came within 4 weeks after childbirth for two-thirds. 82% never had PPD previously. About 15% continued to use standard antidepressant medicines during the trial, in addition to either zuranolone or placebo. The women were followed for 45 days from the beginning of the trial, although they were also assessed at days 3, 15, and 28.

"Women with PPD receiving zuranolone demonstrated statistically significant and clinically meaningful improvements in depressive symptoms at day 15 compared with the placebo group," the team reported. "The effects were rapid (by day 3), were sustained at all measured time points through day 45, and were observed across all measured [indices], reflecting a broad overall improvement in depressive symptoms. These benefits were mirrored in patients' self-reported assessments," the team noted. Clinically important symptoms of anxiety and insomnia also responded more to zuranolone than to placebo. The duration of the antidepressant impact of zuranolone beyond 45 days remains to be determined.

All adverse events related to the treatment were mild or moderate, and mostly involved sleepiness, dizziness or a sedative effect. The trial studied the drug only in women with severe PPD. Participants were not permitted to breastfeed during the trial, since there is as yet no conclusive data on potential impacts from zuranolone (this may be studied in future research). Also, there was a strong placebo effect in the trial, which was attributed by the team to the amount of attention given to each participant—8 visits from the clinical team over the 45 days of the trial. Such attention has been linked with the placebo effect in past trials of antidepressants.

Based on this trial and another Phase 3 trial which tested zuranolone at about 40mg/day for 14 days, the FDA approved the medicine—the first short-course, rapid-acting oral treatment for patients with PPD.

The trial was funded by Sage Therapeutics and Biogen. Nine of the 14 authors of the study paper are employees and may hold stock in the companies. Other team members reported research and/or advisory or consulting relationships with the companies. ❖

ANTI-INFLAMMATORY MEDICINE REDUCED POSITIVE SYMPTOM SEVERITY IN CHRONIC SCHIZOPHRENIA PATIENTS WITH ELEVATED INFLAMMATORY MARKERS

Thomas W. Weickert, Ph.D.

Cynthia Shannon Weickert, Ph.D.

In recent years, a steadily growing body of evidence has indicated an association between elevated levels of inflammation and psychiatric illness.

The word "association" is important: it means that, in schizophrenia, for example, some fraction of patients have significantly elevated markers of inflammation. But as to the key question of cause and effect, the jury is out. Does inflammation contribute to causation? Or does having the illness in some way cause inflammation levels to rise? Or are the two phenomena merely coincident?

A research team led by two BBRF grantees, **Thomas W. Weickert, Ph.D.**, and his wife, **Cynthia Shannon Weickert, Ph.D.**, has just reported in the journal *Brain, Behavior and Immunity* on the exploration of this specific question: in patients with schizophrenia with elevated levels of inflammation, would administering a drug to reduce the inflammation have any impact on reducing schizophrenia symptoms?

Dr. Thomas Weickert's 2016 BBRF Independent Investigator award was devoted to testing a new anti-inflammatory treatment in schizophrenia. Dr. Cynthia Weickert, a 2004 BBRF Independent Investigator and 2001 and 1999 BBRF Young Investigator, conducted work in schizophrenia patients that suggested elevated immune system activity.

The Weickerts are currently at SUNY Upstate Medical University and Neuroscience Research Australia. The team also included 2003 BBRF Young Investigator **Roshel Lenroot, M.D.**, and 2008 BBRF Young Investigator **Julia Lappin, MBChBN, MRCPsych**.

Drs. Weikert and colleagues point out that prior trials of anti-inflammatory medicines to help reduce symptoms in schizophrenia have been inconclusive. In their trial, Drs. Weickert and team exclusively recruited chronically ill schizophrenia patients with elevated markers of inflammation in their peripheral blood. It's possible that prior tests of anti-inflammatories didn't register significant positive results because many of the participants did not have elevated inflammation levels to begin with.

Twenty-seven patients were recruited for the study, which was conducted in Australia. To be included, a participant had to have at least two elevated markers of peripheral (bodily) inflammation, out of three such general markers tested. The markers indicated levels of: two cytokines (small proteins that help regulate immune system cells in the body), specifically, Interleukin 1-Beta (IL-1ß) and IL-6; high-sensitivity C-reactive protein (hsCRP), a protein whose level correlates with immune activation; and a marker called NLR that measures the ratio in the blood of neutrophils to lymphocytes (two types of white blood cells).

The cohort was composed of 12 females and 15 males with a diagnosis of schizophrenia (18) or schizoaffective disorder (9). The average age was late-thirties; the average duration of illness was about 12 years; the typical participant had been hospitalized three times over the course of their illness, and was moderately overweight (BMI ~ 32). Fourteen participants were assigned to receive a single injection under the skin of an approved medicine called canakinumab, a monoclonal antibody that blocks the activity of IL-1ß. Thirteen participants received a placebo injection. All 27 continued to take the antipsychotic medicines they had been taking before the start of the trial.

Why the focus on blocking the activity of IL-1ß? Levels of IL-1ß are known to be elevated in a "substantial subgroup" of chronically ill schizophrenia patients, as evidenced in blood, cerebrospinal fluid, and brain tissue. Past studies have shown that elevated peripheral IL-1ß levels correlate with impairment in attention, working memory, language, and episodic memory in schizophrenia patients. The Weickerts have previously found, moreover, elevated IL-1ß expression in white blood cells in 40% of patents with chronic schizophrenia, as well as higher levels of IL-1ß expression in cells of the prefrontal cortex in regions where new neurons are generated, and in the midbrain, in about an equal fraction of patients. The C-reactive protein marker was chosen because its level is elevated in 60% of patients admitted to hospital for a psychotic episode and 40% of chronically ill schizophrenia patients.

Results of the trial, based on comparisons between the two groups of inflammatory marker levels in peripheral blood and symptom severity at baseline and at 4 and 8 weeks post-injection, showed that a single injection of the drug (150mg) "was effective in reducing a peripheral marker of inflammation [CRP]." Levels of CRP declined continuously for the first 4 weeks post-injection and were significantly reduced at all times through 8 weeks relative to baseline levels.

Markers of inflammation were lower; but did this correlate with a reduction in the severity of symptoms? Negative symptoms—various cognitive impairments experienced by all schizophrenia patients—were not impacted by canakinumab or by the placebo. But the drug did have an impact described as "statistically significant" on schizophrenia's positive symptoms—hallucinations, delusions, and odd or intrusive thoughts.

Those in the canakinumab group "had a significant reduction in positive symptom severity score 8 weeks following the injection," the team reported. While "the magnitude of the reduction would not generally be considered clinically robust," they added, "it is important to note that most novel treatments do not reduce" these symptoms, particularly if the patients, as in this trial, continue to take their regular antipsychotic medicine throughout the trial. The team found that in the canakinumab group, reduction in CRP levels at week 4 predicted the degree to which a patient's positive symptoms would be reduced in severity at week 8. Reductions in CRP levels are also considered positive for general health, as elevated levels are strongly linked with heart disease.

Future trials to confirm or extend the team's results will need to include many more patients with elevated inflammation markers, including those at earlier stages of schizophrenia and psychotic disorders. To be truly meaningful, any benefit in reducing symptoms would need to be sustained for much longer than the 8 weeks tested in this trial. To that end, the

team hopes to test canakinumab in inflammation-affected patients with higher dosages of the medicine, and with longer treatment administration, including "top-up" or additional injections over time. Also, they noted, "treating people closer to the onset of the illness when inflammation has not been present for a long time may have the potential to show larger effects." ❖

TWO FORMS OF NON-DRUG THERAPY HELPED REDUCE IMPULSIVE AGGRESSION IN SCHIZOPHRENIA

Anthony O. Ahmed, Ph.D.

People with schizophrenia often show deficits in neurocognitive and social cognitive abilities. Neurocognitive abilities include processing speed, attention/vigilance, reasoning/problem solving, learning and memory, and working memory, a form of short-term memory for tasks immediately at hand. Social cognition refers to cognitive abilities specifically deployed in social interactions including perceiving and interpreting others' emotions, intentions, and behaviors.

These deficits can contribute to difficulties that schizophrenia patients have in the social domain—being able to accurately assess facial and verbal expressions of other people, being able to verbally communicate, and being able to monitor their emotions and negotiate interpersonally stressful situations.

In contrast with "positive symptoms" of schizophrenia—phenomena such as unusual thoughts, hallucinations, and delusions, which can be controlled with antipsychotic medications—there are no drug therapies for cognitive and social cognition deficits. Cognitive remediation is a form of non-drug therapy that can help lessen the burden of cognitive dysfunction in many patients, when it is available.

A team of investigators led by 2015 BBRF Young Investigator **Anthony O. Ahmed, Ph.D.**, of Weill Cornell Medical Center, recently published results of a study that Dr. Ahmed's BBRF grant helped to support. Their focus was to compare two types of cognitive remediation therapies for chronic schizophrenia patients (and those with schizoaffective disorder) with a history of aggressive behavior, and specifically, impulsive aggression. They reported on their results in *Schizophrenia Research*. The team also included **Matthew J. Hoptman Ph.D.**, a 1999 BBRF Young Investigator.

Most patients with psychotic disorders including schizophrenia do not manifest aggressive behaviors. But for those that do, such behaviors can contribute to adverse consequences, including involvement with the criminal justice system and frequent hospitalization in psychiatric and forensic facilities, as well as stigmatization.

In prior research, Dr. Ahmed and colleagues demonstrated that after taking part in cognitive remediation training (CRT), individuals with schizophrenia "experienced decreased hostility and agitation" and fewer incidents of verbal and physical aggression. In Dr. Ahmed's view, neurocognitive deficits experienced by patients are likely background risk factors for impulsive aggression, but "social cognitive deficits may be day-to-day contributors to aggression in patients with schizophrenia."

In their clinical trial, Dr. Ahmed and colleagues compared CRT treatment for schizophrenia patients with a history of aggression with a combination treatment in which CRT was paired with what the team called "social cognition training" (SCT). They recruited 130 chronic schizophrenia patients (average age 35; 84% male) with history of impulsive aggression, who were randomly assigned to two groups. One group received both CRT and SCT over 14 weeks; the other group received CRT plus a placebo version of SCT that served as a control. In the CRT + SCT group, 24 sessions of CRT were given over 14 weeks, along with 12 sessions of computer-delivered SCT training. In the CRT + placebo group, there were 24 CRT sessions over 14 weeks and 12 sessions of computer-delivered video games that involved no social cognitive training.

The CRT therapy used was called BrainHQ, a commercially available program that involves auditory and visual-based cognitive activities that allow patients to improve their

auditory and visual information processing skills. Those who received SCT received it via both BrainHQ and MRIGE, an interactive computer program in which one practices recognition of hundreds of emotions and mental states in video presentations. Those who received the placebo version of SCT instead played computer games such as solitaire, checkers, and dominoes.

Both CRT and SCT were found to "significantly reduce" impulsive aggression, measured in several different ways. The combination of CRT and SCT therapies was not more effective than CRT + placebo in this regard. Both interventions also enabled participants to significantly improve their overall cognitive functions, in all measured cognitive domains. But here, those who received the combined therapy of CRT and SCT did notably better. The combined intervention (but not CRT + placebo) was also associated with significant improvement in "general cognition"—measures of emotion recognition and mentalizing (the capacity to reflect on and interpret one's own behavior and that of others).

The particular advantages of CRT + SCT suggested to the team that there is a "close relationship" between neurocognition and social cognition. Specifically, they noted, providing training in social cognition "imparted additional benefits to neurocognitive functioning." When patients were trained to correctly recognize emotion expression in others, they likely had to draw upon cognitive skills such as processing speed, attention, and visual learning, the team said. At the same time, neurocognitive training may have improved patients' ability to apply lessons learned in social cognitive training "via improved memory to recall strategies as well as enhanced executive function to apply skills flexibly."

The team noted their trial involved chronic patients with considerable impairment ("moderate to marked"). For this reason, it is not known if the positive results of this trial will apply equally to higher-functioning patients with less pronounced cognitive deficits. This might be studied in future research, as well as the idea of supplying more intensive and more targeted social cognition training in combination with CRT. ❖

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GLOSSARY

NEUROMODULATION (p. 4) A range of technologies that involve applying energy to the brain to therapeutically alter the activity of brain cells, circuits, and networks. Some, like electroconvulsive therapy (ECT) apply electricity directly to the brain via electrodes placed on the scalp. Deep-brain stimulation (DBS) applies electrical pulses via electrodes surgically implanted within the brain. Other modes, like transcranial magnetic stimulation (TMS) and magnetic seizure therapy (MST), use magnetic fields applied from above the scalp to alter electrical activity within the brain. New technologies now in development seek to alter patterns of electrical activation in the brain with sound and light energy rather than electricity or magnetism.

ENDOGENOUS OPIOID SYSTEM (p. 12) A system native to the human body that has roles in regulating reward, mood, motivation, learning and memory, and the relief of pain. Endogenous opioids include enkephalins, endorphins, and dynorphins. Receptors for these molecules are present in abundance throughout the brain and central and peripheral nervous systems as well as the gastrointestinal tract. The system is dysregulated when an individual regularly or habitually takes natural (i.e. plant-based) or synthetic opioids, effects of which are mediated via endogenous opioid receptors. This often leads not only to addiction but also grave health risks including risk of death due to overdose.

SYNTHETIC OPIOIDS (p. 12) Products manufactured in the laboratory that interact with the body's endogenous opioid system.

"DEPOT EFFECT" (p. 14) Reserves of opioids that build up with regular use in fat tissues. An especially serious problem with fentanyl; slow release due to the depot effect can extend the duration of a fentanyl high and greatly increase the risk of overdose and death due to overdose. (See "re-narcotization," below.)

NALOXONE (p. 14) Also known by its commercial name, Narcan, naloxone, often given nasally, is an effective treatment for opioid overdose if given promptly. Repeated doses and/or higher doses are often needed in the case of fentanyl overdose, as the remedy's beneficial effect is often shorter in duration than fentanyl's power to depress the respiratory system. In such instances, **re-narcotization** can occur—after the patient becomes conscious, they may lose consciousness again and stop breathing.

GWAS (p. 20) Genome-wide association study. Used in genetics research, GWAS scan across the human genome in search of genomic regions that may be associated with a trait like problematic drinking. This is done by comparing the genotypes (unique genome sequences) of tens to hundreds of thousands of individuals—some who have the condition or trait under study, and many more who do not. DNA variations commonly seen in those with the trait or affected by the illness but not seen in healthy controls are then subjected to rigorous statistical analysis. Those exceeding a statistical threshold of "significance" are considered candidate risk loci, or locations, for the trait or illness.

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