Modifying Psychedelics to Capture Therapeutic Effects

Improving Treatment Outcomes in OCD

MAGAZINE

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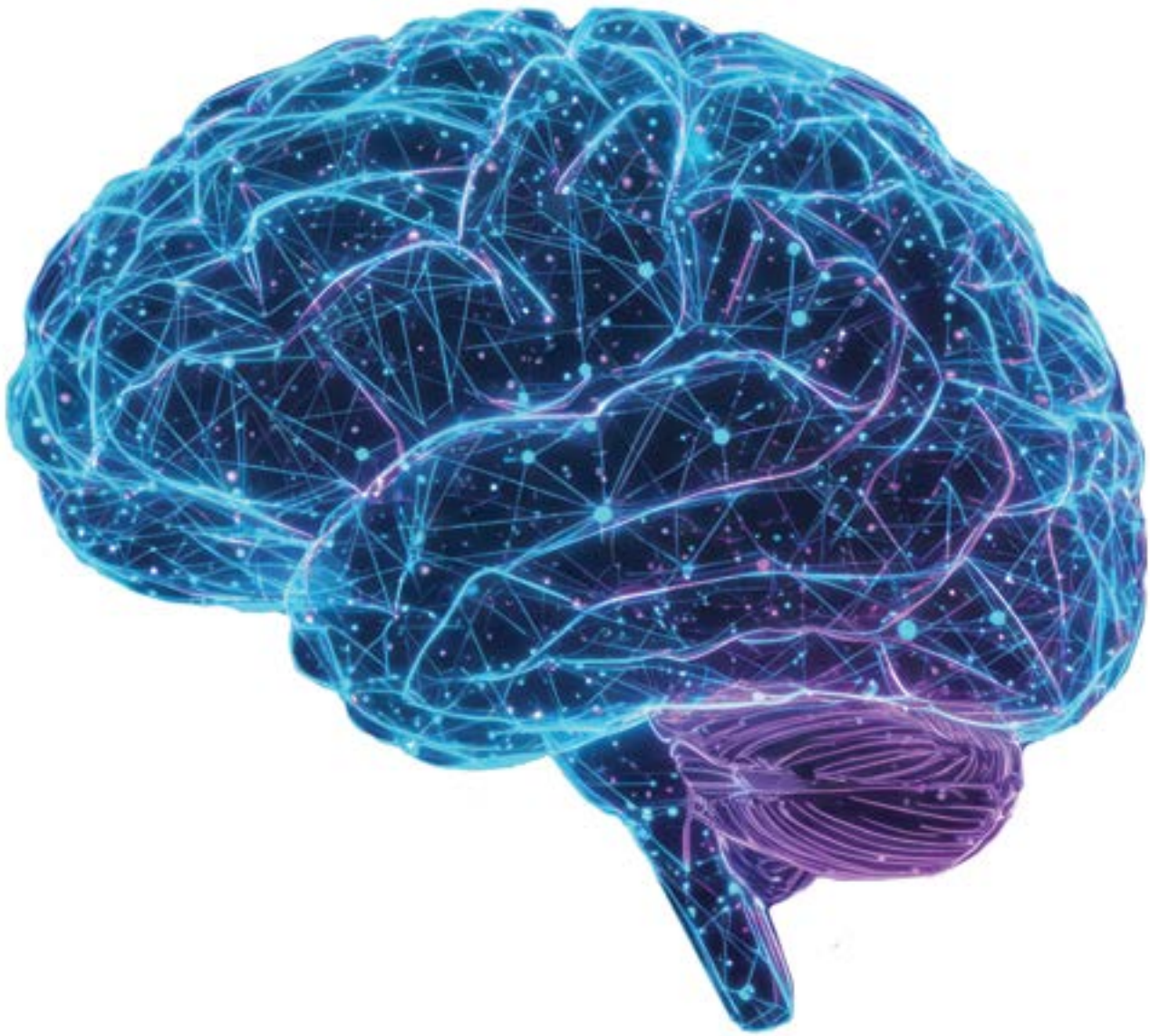
WINTER 2026



How the Search for Genes Involved in Mental Illness Has Led to Key Insights About Reducing Medication Side Effects

PRESIDENT'S LETTER

Welcome to the Winter issue of *Brain & Behavior Magazine*.

Our **PATHWAYS TO THE FUTURE** story focuses on important contributions to mental health research made by James L. Kennedy, M.D. A five-time BBRF grantee, Dr. Kennedy, who is also a member of our Scientific Council, first set out to discover genes associated with schizophrenia, and was among those who realized that not one, but many different genes were playing a part in risk and causation. His experience treating schizophrenia patients led him to explore possible genetic vulnerabilities related to the tardive dyskinesia (TD) side effect of first-generation antipsychotics. This work was part of a process that culminated in the 2017 approval of Ingrezza, a medicine to treat TD. But Dr. Kennedy's contributions are much broader. We explain how he helped lay a foundation for the field of pharmacogenetics, which leverages information obtained from genetics studies to identify how individual DNA variations make some of us very good or rather poor candidates for specific medicines. Simple genetic tests he and others have created have the potential to match individual patients with the medicines most likely to help them.

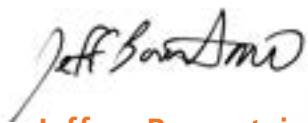
In **A RESEARCHER'S PERSPECTIVE**, Dr. Helen Blair Simpson, an expert on the treatment of OCD, discusses various forms of therapy and how they have fared in clinical trials. A form of CBT called exposure and response or ritual prevention therapy (EX-RP) generates a therapeutic response in about two-thirds of patients, with one third achieving a remission. Dr. Simpson discusses alternative treatment scenarios and explains how researchers are trying to develop better therapies for OCD.

Our **SCIENCE IN PROGRESS** story focuses on how psychedelic and other psychotropic drugs might be modified to treat psychiatric illness. We detail efforts by four research teams supported in part by BBRF grants to harness potentially therapeutic effects of specific drugs while minimizing or eliminating hallucinations and other unwanted side effects.

This issue also features summaries of BBRF's 2025 **EVENTS**—the BBRF Scientific Council Dinner where we presented the Klerman & Freedman Awards, and the International Mental Health Research Symposium and International Awards Dinner featuring winners of the BBRF Outstanding Achievement Prizes—the BBRF Lieber, Maltz, Colvin, Ruane, and Goldman Rakic prizes. The **AWARDS DINNER** story also provides details of the 2025 winners of the Pardes Humanitarian Prize in Mental Health.

As always, we report news of treatment advances for psychiatric conditions in our **THERAPY UPDATE**, and on important scientific advances moving the field forward in **RECENT RESEARCH DISCOVERIES**.

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



Jeffrey Borenstein, M.D.

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How the Search for Genes Involved in Mental Illness Has Led to Key Insights About Reducing Medication Side Effects

IN BRIEF
Recipient of 5 BBRF grants, Dr. James L. Kennedy first set out to find genes associated with schizophrenia and in so doing made discoveries that helped lead to a drug for tardive dyskinesia. His pioneering research linking common DNA variations with other medication side effects has provided a foundation for the field of pharmacogenetics, which matches patients with the medicines most likely to help them, based on DNA variants they carry.

People who are ill and those who love and care for them want medicines that work. This yearning provides a powerful fuel for researchers and clinicians the world over. Among them is **James L. Kennedy, M.D.**, a distinguished professor at the University of Toronto and its affiliated Centre for Addiction and Mental Health (CAMH). Dr. Kennedy is one of only two people with the distinction of having been awarded five BBRF grants (the other is **Flora Vaccarino, M.D.**, a pioneering neuroscientist in brain development at Yale University).

Dr. Kennedy, who, since 1996, has been a member of BBRF's Scientific Council, is keenly aware of the need for new and improved treatments. He was trained in clinical psychiatry and still treats patients, with a current focus on aging patients with schizophrenia. His attention to patients, and his personal connection to their problems and unfulfilled needs, provides a key link to the research activities to which he has devoted much of his professional life.

Dr. Kennedy has helped to build the scientific foundation for a field called **pharmacogenetics**. Its aim is to figure out how to optimally match individual patients with specific therapeutic medicines. Pharmacogenetics does this, as the name implies, by harvesting knowledge about the human genome—specifically, the individual DNA

variations that each of us has—and connecting it with biological understanding about how drugs are metabolized by the body, and how individual genetic variations make some of us very good or rather poor candidates for specific medicines. In recent years, the same idea that has animated pharmacogenetics has been popularized in the idea of "precision medicine."

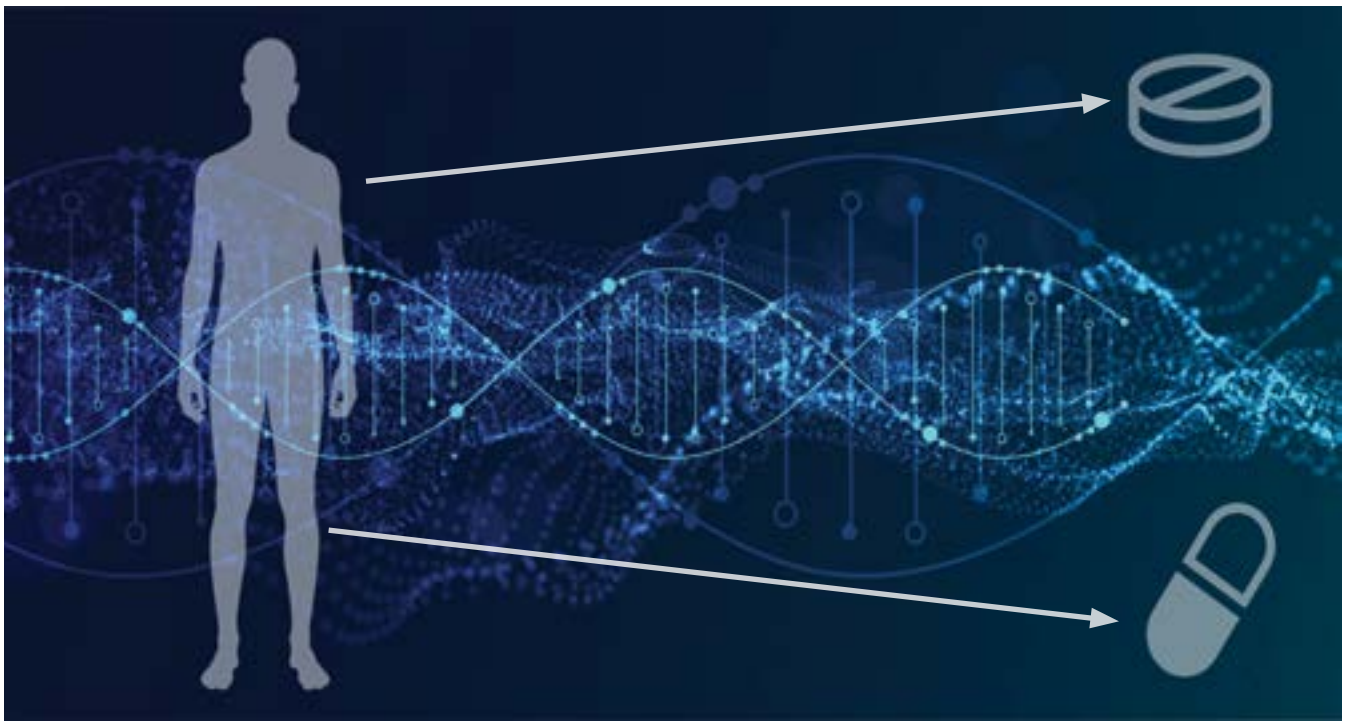
To paraphrase Dr. Kennedy, referring to the possibility of each of us knowing which drugs are most and least likely to help us: "Who wouldn't want to know *that?!*"

Remarkably, the field that his research helped to establish has already made this a possibility for a large number of people with psychiatric illnesses—as many as two-thirds of those taking medicines for schizophrenia, depression, bipolar disorder and other conditions. The opportunity presented by pharmacogenetics is the subject of the accompanying story [pp. 11–13]. In this story, we explore the career of Dr. Kennedy, focusing on the way in which his treatment of patients informed and encouraged his research activities, which began with a broad effort "to identify genes involved in mental illness." In this journey, in which BBRF has played an important part, one of the highlights, described here, was a genetics discovery that led to a new medicine for a motor disorder that has helped many thousands of people, including some who take antipsychotic medicines for schizophrenia.

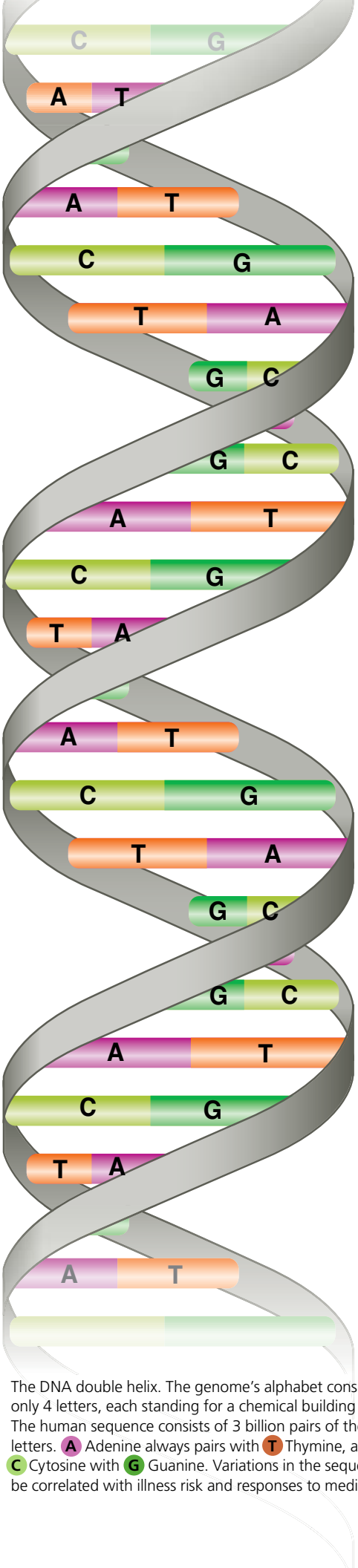
QUESTIONS WITH NO ANSWERS

Like many people who go on to careers in psychiatry and psychology, Dr. Kennedy, "a boy from a village of 200 people in rural Ontario," was fascinated at any early age with "a bunch of questions about human nature," questions which seemed to have "no satisfactory answers." As an undergrad he learned as much as he could about psychology and the biology of the brain (as it was understood at that time). For his master's degree, he had his first experience with research, working on a project exploring the biology behind the harmful behavioral impacts in children caused by exposure to lead. Wanting to continue with research, specifically in psychiatric disorders, he attended medical school at the University of Calgary, which offered such opportunities, and he led a project that in 1986 resulted in the first of Dr. Kennedy's published papers in psychiatry (there are now over 900). It showed how certain instinctual behaviors, including dominance displays and scapegoating, could impair group psychotherapy.

By the time Dr. Kennedy went to Yale University for his residency in psychiatry, in the mid-1980s, 30 years had passed since James Watson and Francis Crick first described the elegant double-helical structure of DNA, the genetic material. In this long intervening period, brilliant, difficult, and meticulous research had revealed how genetic information is copied and translated into the myriad proteins that give cells



DNA variations each of us carries can indicate how we metabolize various medications.



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 illness risk and responses to medicines.

and bodily organs their structure and enable them to perform highly specific functions. Insights afforded by genetics research were naturally also applied to human illness, and to processes in the body that go awry because of genetic mutations. But this was a difficult task a full decade before rapidly advancing technologies were brought to bear upon the grand-challenge task of sequencing, i.e., "spelling out," the full human genome, work that was not completed until after the year 2000.

In psychiatry, an era of "biological psychiatry" was blossoming, with an explosion of interest in studying underlying biological processes in the brain that might help explain the behavioral patterns long associated with specific illnesses. Dr. Kennedy was right in the middle of the action, involving himself in research at Yale on the genetics of schizophrenia—even as he performed his work as a clinician, treating patients with schizophrenia and other illnesses.

This was right around the time that BBRF and its Scientific Council were formed by a group led by the late **Herbert Pardes, M.D.** Then called NARSAD (the National Alliance for Research on Schizophrenia and Depression), the organization in 1987 had just awarded its first 10 grants. Early the following year, Dr. Kennedy applied for what would be the second round of BBRF grants. "I had a project on the genetics of schizophrenia, using a very large pedigree," he remembers. His project proposal bore the provocative title, "Is There a Gene for Schizophrenia?"

Knowing what we know today, it is easy to dismiss the idea that a single gene would account, by itself, for the many and varied symptoms of the illness, and even less probably, in every patient. But it was definitely a question worth asking: it had recently been discovered that mutations in a single location ("locus") of the genome on chromosome 4, and perhaps a single gene *within* that location, was responsible for the pathology that generated Huntington's Disease, which, like schizophrenia, has a diversity of symptoms. The techniques making the discovery of the Huntington's gene possible were ingenious and painstaking; it had taken years to find the genetic culprit. In addition to advances in technology, the discovery was possible because Huntington's researchers had access to a large and unique group of patients from the same family with the illness—a "large pedigree."

TRANSFORMATIONAL FIRST GRANTS

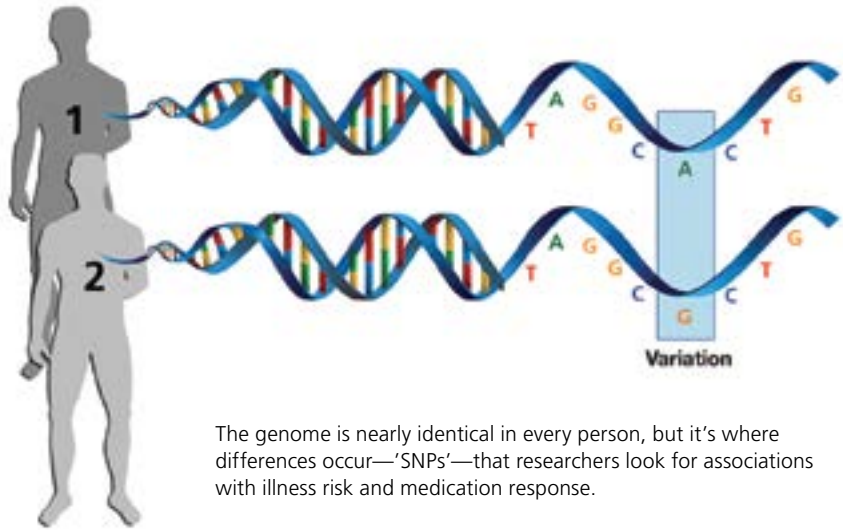
Dr. Kennedy's 1988 bid for a first BBRF grant involved exploring whether a similar strategy might reveal "a gene for schizophrenia." The young researcher was awarded the grant by the fledgling Foundation, and, as he tells the story, it had a "transformational" impact on his career. Modestly, he says that without the grant he would have "fallen upon the rocks, I would have struggled." His subsequent success gives us reason to doubt this. But it is certainly true that, as he puts it, this early-career vote of confidence from BBRF was what enabled his career to "explode."

During the year of that first grant (BBRF grants were then funded for a single year; today, Young Investigators receive 2 years of support) Dr. Kennedy was the lead author of a paper appearing in the prestigious scientific journal *Nature*. The paper was about well-documented

efforts to link DNA "markers" on chromosome 5 with schizophrenia. The techniques used in making this linkage were of the same type used in the Huntington's gene research. In their paper, Dr. Kennedy and colleagues expressed optimism about the value of the method, but made the important point that results in the large cohort of Swedish patients showing a schizophrenia linkage on chromosome 5 were not replicated in similar studies using different patient cohorts.

Presciently, given the state of the science at that point, Dr. Kennedy and colleagues ventured that additional research would ultimately show that "the genetic factors underlying schizophrenia are heterogeneous," i.e., not limited to a single location on a single chromosome. In other words, they were suggesting that, unlike in Huntington's, a "single gene" for schizophrenia would most likely not materialize. (Today, using much more sophisticated technologies and with full knowledge of the human genome sequence, several hundred genome variations have been associated with risk for schizophrenia: see illustration, next page.)

Two additional Young Investigator grants were secured by Dr. Kennedy in the subsequent 2 years, as he began to follow up on this notion of "genetic heterogeneity" in schizophrenia. Some of the work sought to identify **single-nucleotide polymorphisms, or SNPs** (pronounced "snips")—single DNA "letters" among the 3 billion pairs of letters comprising the human genome (each letter standing for one of the four chemical DNA "bases") that vary between individuals. In some genome locations, single DNA letters differ in people with schizophrenia compared with people without the illness. The hypothesis was that these DNA variations in patients were in some way related to elevated risk for the illness.



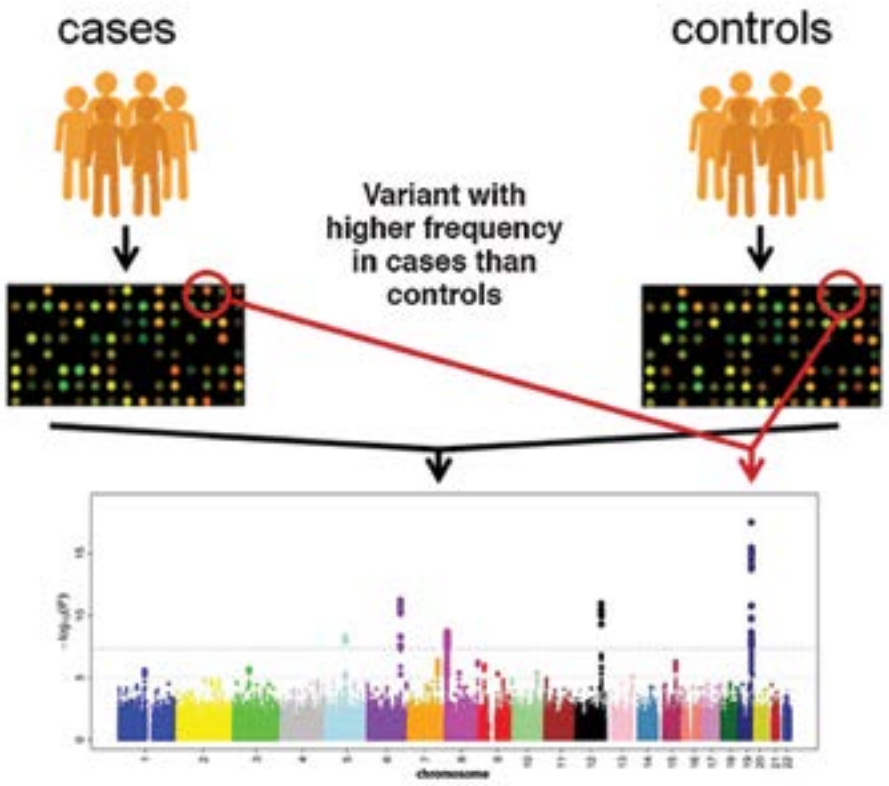
The genome is nearly identical in every person, but it's where differences occur—'SNPs'—that researchers look for associations with illness risk and medication response.

Research would eventually show that there are millions of SNPs in the human genome, and each of our genomes is studded with them. Most SNPs, it turns out, are part of normal genetic variation and have no effect whatever on our health. But in the context of serious illness, the critical question initially was: do certain SNPs occur consistently, or with above-average frequency, in significant numbers of patients with specific illnesses?

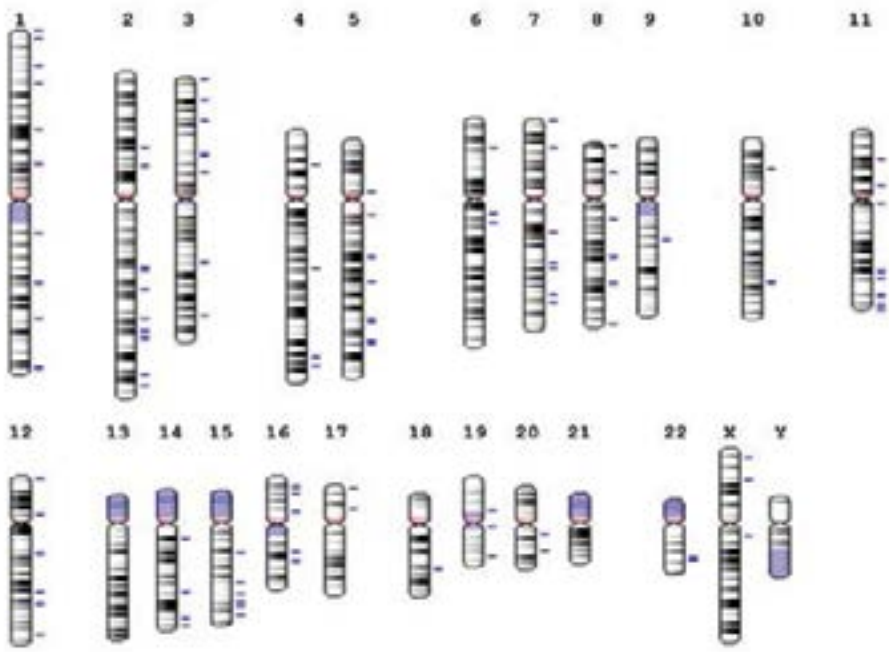
If so, were these DNA variations related to biological factors that helped cause the illness or raised the risk of having it? Perhaps the illness-related variations in schizophrenia patients in some way impaired the function of genes essential in prenatal brain development or postnatal brain function. These questions are still in play, although the consensus is that most illness-linked SNPs, considered alone, raise illness risk (in schizophrenia and other common disorders) by a tiny amount. It is thought that having multiple illness-associated SNPs, or particular constellations of them, in some cases in concert with specific environmental factors, is what can alter biology and raise the risk that a particular individual will develop the illness.

Other kinds of genetic variations—deletions or multiplications of certain DNA sequences, for example, or deletion or rearrangement of a part of a chromosome—can have catastrophic biological impacts and by themselves cause an illness like schizophrenia. These insights were still years away in 1990 when Dr. Kennedy received his third BBRF grant, to study the "molecular genetics of schizophrenia."

Years before a drug was successfully tested to treat tardive dyskinesia, Dr. Kennedy had been collecting data on schizophrenia patients in his Toronto clinic, and asking the question: "How might genetic variations dispose some patients to this and other side effects?"



ABOVE: Large genome studies comparing people with a particular illness ("cases") and healthy controls can identify places in the genome where DNA variations occur more often in patients. These are plotted on a graph showing which variations generate the strongest associations with the illness (vertical lines marking the highest 'peaks'). **BELOW:** this data is displayed to show where, in schizophrenia studies, the risk locations are located along the 24 human chromosomes (tiny ticks long the right edge of each chromosome).



In retrospect, we can say that he was among the generation of researchers who, in Dr. Kennedy's words, "had the right skills at the right time" to forge the research path and step by step make the key discoveries that have since revealed much (but far from all) about the association of schizophrenia and other illnesses to genetic variations.

RELATING VARIATIONS TO MEDICATION SIDE EFFECTS

One near-term impact of having received three early-career BBRF grants was that Dr. Kennedy found himself in considerable demand. In 1991, he moved to the University of Toronto, where "a great genetics lab had been established." Genetics research on schizophrenia was moving away from large-pedigree family studies to studies analyzing patterns of genetic variation in large numbers of people with the illness—people who were unrelated—and comparing them with large numbers of people without the illness ("controls"). These were precursors of what became the standard tool for such investigation, called **genome-wide association studies (GWAS)**, which sought to find statistically significant correlations between individual SNPs and illness risk.

While these seminal developments in genetics were under way, Dr. Kennedy at the same time was establishing a clinical practice at Toronto focusing on treating people with schizophrenia. This would have a crucial impact on his genetics research.

While treating patients, he remembers, "it hit me how inaccurate, imprecise—we could even say clumsy and blunt—our antipsychotic medications were." It so happened that a colleague at the University of Toronto had established a clinic specifically to investigate tardive dyskinesia (TD), a disorder that involves involuntary repetitive movements affecting the face, mouth, or other

parts of the body. TD was among the more serious side effects of first-generation antipsychotic medicines, and one that Dr. Kennedy had begun to study from a genetics perspective. Might there be variations in specific human genes that predispose certain individuals to develop TD? "I was very focused on that, as well as the much more complicated question of predicting who would and would not respond to antipsychotic medicines."

In a good illustration of how BBRF has made a tangible impact on the course of brain and behavior research, Dr. Kennedy's connections with the Foundation, already strong after receiving three grants, "put me in touch with **Dr. Herbert Meltzer,** who headed the Young Investigator grant program for many years." Dr. Meltzer, who, like Dr. Kennedy, was among those who received grants in the Foundation's second year of existence, was in close touch with those then conducting clinical trials of clozapine. That drug would become the first of the "second generation" of antipsychotic medicines to be approved by the FDA. Dr. Meltzer went on to perform research demonstrating clozapine's great value in reducing suicide risk in schizophrenia patients.

Most medicines have side effects. Clozapine proved highly effective in reducing hallucinations and delusions in schizophrenia (it did this as well and often better than first-generation antipsychotics, especially in treatment-resistant patients). But, it proved to be linked with side effects of its own, including significant weight gain followed by diabetes in some patients.

Dr. Meltzer and others sent blood samples and information from the clozapine clinical trials to Dr. Kennedy, who was able to extract DNA and study possible genetic factors related to the weight-gain side effect of this new class of antipsychotics, adding it to his ongoing study of the tardive dyskinesia side effect from first-generation medications. In parallel with these side-effect investigations, he continued to work on the question of who would and would not respond to these medicines, or, to put it differently, the problem of treatment resistance in schizophrenia.

In the 2000s, with the advent of the powerful GWAS approach, Dr. Kennedy and **Dr. Anil Malhotra**, a more recent BBRF grantee (now, as is Dr. Meltzer, a BBRF Scientific Council member) performed important studies that led to the discovery of variations in a gene called MCR4 which was linked with weight gain in schizophrenia patients taking clozapine or olanzapine, both second-generation antipsychotics.

"It was thrilling, absolutely thrilling!" Dr. Kennedy well remembers, referring to his presentation with Dr. Malhotra of this result to colleagues in 2012. Soon thereafter, further probing by Dr. Kennedy enabled him to flag another gene responsible for encoding three proteins that had a direct impact on weight-gain risk. That gene, he notes in passing, is called GLP-1—the gene that encodes a receptor that is the target of diabetes and weight-loss drugs like Ozempic and Wegovy that have made so much news in recent years.

'FROM GENE TO TREATMENT'

In the meantime, other research was beginning to shed new light on the original side-effects question pursued by Dr. Kennedy, that of a possible genetic factor disposing some who took antipsychotics to tardive dyskinesia. In the early 2000s, another early BBRF grantee who would join the Scientific Council, **Dr. Jeffrey Lieberman** of Columbia University, led a team that performed the largest-ever randomized clinical trial of antipsychotics in schizophrenia patients. That study found that while all the

While treating patients, Dr. Kennedy remembers, "it hit me how inaccurate, imprecise—we could even say clumsy and blunt—our antipsychotic medications were."

tested antipsychotics were effective for treating the positive symptoms of schizophrenia (hallucinations and delusions), individual differences in side effects and tolerability led to high discontinuation rates. Following these important initial findings, an investigation of the DNA samples from the trial participants suggested the possible importance of several genes—including ones in the dopamine neurotransmitter system—that appeared to impact side-effect risk.

Two variants of the gene were examined. One version increased the amount of the VMAT transporter protein in the brain and the other variant decreased it. In 2013, Dr. Kennedy's team, in research led by **Dr. Clement Zai** and directly supported by his BBRF Young Investigator grant in 2012, published a paper stating that it was the version of the VMAT2 gene which caused an excess of the transporter protein in neurons that created a high risk for the tardive dyskinesia antipsychotic side effect.

'It was thrilling, absolutely thrilling!' Dr. Kennedy recalls, of the day his team announced discovery of gene variations linked with weight gain in schizophrenia patients taking second-generation antipsychotics.

This preliminary finding became important to Dr. Kennedy some years later, when he led "a very precise, precision-medicine study" with a cohort of schizophrenia patients that he and colleagues had been following in Toronto. "At that time, we probably had the world's largest sample, based on our clinic here, that was well characterized over time. We'd been collecting patients with the tardive dyskinesia side effect for 15 years at that point." This story illustrates how basic research and clinical research can come together to generate a finding of great import that could not have been anticipated in advance. "In 2013, we published a paper pointing to a key gene, out of all the dopamine system genes, that was predictive of risk for the tardive dyskinesia side effect in antipsychotics." It was a gene called VMAT2 that encodes a transporter protein that takes free-floating dopamine inside a cell and puts it into tiny balloon-like structures called storage vesicles.

The story has a remarkable coda—an unexpected major payoff.

"We had said that VMAT2 would be an important target for developing treatments for tardive dyskinesia, for which at that time there were no treatments at all," Dr. Kennedy remembers. "We said, further, that an excess of the transporter protein was the mechanism of risk, so it would make sense to try to develop an antagonist"—something that would reduce the excess.

A California company called Neurocrine Biosciences had been developing a candidate drug called valbenazine that targeted the VMAT2 protein. They had been hoping to use it to treat Huntington's disease. Among the symptoms of Huntington's is "chorea"—involuntary and uncontrollable bodily movements, a symptom similar to tardive dyskinesia. The company moved the drug into a series of clinical trials to treat tardive dyskinesia, and in Phase 3 its great effectiveness led the FDA to "fast-track" it. It was approved for treatment of tardive dyskinesia in April 2017, and marketed under the name Ingrezza. Today it is a drug with some $2.3 billion in annual sales (2024), and since 2023 it has also been indicated to treat Huntington's chorea.

Dr. Kennedy—who had no financial stake in this process, but did play an important role in validation of the science behind it—marvels about how research led "from gene to treatment." He means that at his end, in building upon basic pharmacology studies revealing the function of the VMAT2 transporter protein in relation to the dopamine system, his group "uniquely had the required skills and well-characterized patient DNA samples in place to demonstrate the association between the VMAT2 gene variant and the clinical side effect of tardive dyskinesia." They were also able to suggest what a potentially effective drug would have to do to correct the problem introduced by the VMAT2 gene variant. Separately, a company with a candidate drug meeting these criteria rapidly progressed to the clinic and demonstrated its efficacy.

But long before these developments, it is important to remember, was 15 years of work performed by Dr. Kennedy and colleagues treating schizophrenia patients in Toronto, some of whom had the tardive dyskinesia side effect when they took antipsychotics; and the fact that Dr. Kennedy had asked how genetics might dispose some patients to have the side effect. In short, the entire process might be said to encapsulate the power of basic clinical and molecular-genetic research to foster solutions for people who need better medicines.

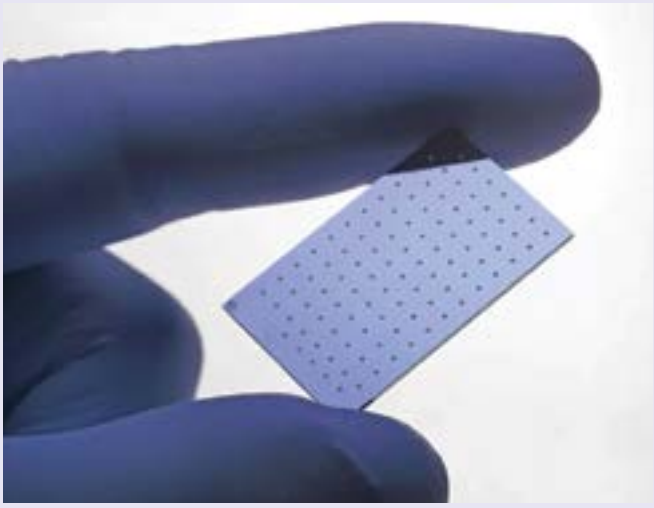
Dr. Kennedy reflects: "Funding this kind of research is the essence of the BBRF concept, as it was conceived from the Foundation's beginnings." ❖ **PETER TARR**

The Promise of Pharmacogenetics: How It Can Help Patients

In the period following their discovery of the VMAT2 gene association with tardive dyskinesia, and the identification of a treatment validated by that finding [detailed in the accompanying story], Dr. Kennedy and collaborators were meantime working on another track to "collect the top six gene variants associated with antipsychotic-induced weight gain," Dr. Kennedy says.

They patented that panel of genes, which included the MCR4 gene variant and the GLP-1 receptor variant [see p. 9]. The "panel" developed by Dr. Kennedy and colleagues is a small chip (like that pictured below) that harnesses genetics technology to determine, in a single low-cost lab test, how many risk variants an individual (who gives a saliva sample) carries across the multiple genetic variants that the panel targets. The risk score generated by the test will vary from one individual to the next, and this risk assessment can help a physician prescribe the optimal medication based on the higher versus lower side-effect risk scores. The panel also can be used, for instance, by pharmaceutical companies trying to develop new second-generation antipsychotics. In conducting a clinical trial for a new medication, one might want to screen for patients with genetic vulnerability to weight-gain, in order to more precisely define who will benefit most from the trial drug.

This idea of creating multi-gene "panels" that would test for specific gene variants associated with medication side-effect risks is fully amenable to patient-facing applications. Pharmacogenetics tests in theory can be used widely in different medical contexts and potentially have great value for millions of people taking medicines of many kinds for a wide variety of illnesses. The key has been to identify as many genetic variants as possible that expose those who carry them to significantly elevated side-effect risks.



Dr. Kennedy has played a pioneering role in the development of such broad-panel pharmacogenetic tests over the years. While research already described in this article was under way, he and other researchers with similar interests had been pursuing studies that led to the validation of a number of key gene variants with broad impact on the way most drugs are metabolized in the human system.

This effort, like most science, builds on basic-science findings made by earlier investigators. Beginning in the 1950s and '60s, research on the liver led to the discovery of enzymes that perform a wide range of essential functions, from detoxification to glucose regulation to the processing of nutrients from food. This work importantly revealed a number of liver enzymes that help process pharmaceuticals, among other molecules. They are members of an enzyme family called the cytochrome P450 family. A number of these enzymes have been found to be particularly important in metabolizing psychotropic drugs, including antipsychotics and antidepressants. Each of the key enzymes—called CYP2D6, CYP2C19, CYP2C9, CYP2B6, and CYP3A4—is encoded by a gene of the same name. Variations in the DNA "spelling-out" these genes are present in many of us. About three-quarters of the population will have at least one non-normal variant across these five genes, according to Dr. Kennedy. Having one or another of them, or several of them, can mean the difference between being someone who rapidly or slowly metabolizes medicines, relative to the average person. One's "metabolizer status" can be used to guide dosing strategies for specific medications in which these enzymes are implicated.

Other pharmacogenetic discoveries have identified gene variations affecting the way medications interact with the body, impacting the effect of specific drugs. As Dr. Kennedy and co-authors note in a 2025 review paper in *Psychiatric Clinics of North America*, pooled results from 13 clinical trials showed that those receiving pharmacogenetics-guided antidepressant treatment were 41% more likely to achieve symptom remission relative to patients who received treatment as usual. Further: "A recent study that included

patients with schizophrenia, major depression, and bipolar disorder showed that pharmacogenetics-guided treatment in psychiatry led to 34.1% fewer adverse drug reactions, 41.2% fewer hospitalizations, 40.5% fewer readmissions to hospital, and shorter duration of initial hospitalizations, compared to patients receiving treatment as usual."

At this point, about 35 drugs including antidepressants, antipsychotics, and anticonvulsants have pharmacogenetics-based guidelines for prescription, developed by expert groups such as the Clinical Pharmacogenetics Implementation Consortium. In some cases, the guidelines are mentioned in drug labeling by regulatory authorities including the FDA and Health Canada. According to Dr. Kennedy and colleagues in their 2025 review paper, 63% of these 35 drugs have guidelines related to gene variants for enzymes CYP2C19 or CYP2D6. People of different ethnic heritage will sometimes have different vulnerabilities to these key variants. But the variants are commonplace. For example, "depending on the population tested, 37% to 96% of people will carry at least one clinically actionable CYP2C19 genetic variant, for which a change in standard prescribing may be indicated; and 35%-73% will carry a CYP2D6 actionable variant," Dr. Kennedy and co-authors note.

Five genes (CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A4) and 2 human leukocyte antigen genes (HLA-A, HLA-B) are implicated in these guidelines affecting 25 psychotropic drugs. Panels or "gene chips" have been created to enable doctors to have patients tested for these genetic variants. This capability exists today.

Dr. Kennedy estimates from 1/2 to 2/3 of treatment-resistant schizophrenia patients "will have an improved course if they have the test done." Of the 30% of depression patients who don't respond to SSRIs, "easily half can significantly improve clinically with medication type or dosage changes following the pharmacogenetic test."

Professional scientific organizations currently have **pharmacogenetics-based prescribing guidelines** for:

13 antidepressants: amitriptyline, citalopram, clomipramine, desipramine, doxepin, escitalopram, fluvoxamine, imipramine, nortriptyline, paroxetine, sertraline, trimipramine, venlafaxine);
7 antipsychotics: aripiprazole, brexpiprazole, haloperidol, pimozide, quetiapine, risperidone, zuclopenthixol),
4 anticonvulsants: carbamazepine, oxcarbazepine, phenytoin, fosphenytoin), and the ADHD medication atomoxetine.

BARRIERS TO ADOPTION

Why, then, have the tests not yet become a standard part of patient evaluation when a medicine is going to be prescribed? Dr. Kennedy and colleagues explored "barriers to clinical adoption" in a 2021 paper in *Translational Psychiatry*. The answers, in brief, are that various powerful entities, perhaps most important among them payers in various healthcare systems, have claimed that the evidence for the clinical utility and economic value of the tests has not yet been sufficiently proven. Another important factor is lack of awareness on the part of some physicians as to how (or which) of the tests can help with specific classes of patients, and the medicines for which guidelines currently exist.

The latter barrier is arguably solvable via physician education. But the arguments about clinical and economic utility have been hard to counter. In the most optimistic way of thinking—Dr. Kennedy is an optimist, but also realistic about the state of the healthcare systems of Canda and the U.S.—clinical effectiveness will become harder and harder to deny as pharmacogenetics research continues to advance and be published.

Dr. Kennedy has received strong support from Larry Tanenbaum, owner of the Toronto Maple Leafs and Raptors professional sports teams. He has funded the Tanenbaum Pharmacogenetics Center at the Centre for Addiction and Mental Health, University of Toronto, which Dr. Kennedy heads. "The research is rapidly progressing," Dr. Kennedy says. "But it takes a long time to do clinical trials that are large and statistically powerful, and they are very expensive."

The research he is able to perform makes him confident that the argument for pharmacogenetics will win out in the end. After noting that the Canadian government healthcare system had raised the question of proof of effectiveness—"they didn't feel the clinical impact was proven beyond the shadow of a doubt"—Dr. Kennedy noted that since that time, a number of

additional randomized controlled trials of pharmacogenetic testing have been published. In these trials, some patients get a pharmacogenetics test and they are compared with people whose doctors dispense medication in their usual way—"treatment as usual." The results can be eye-popping. A study Dr. Kennedy and colleagues in Toronto published in 2022, involving 370 depression patients, "showed an 88% increase in the number of patients who made it all the way to remission after receiving the test."

This kind of information, Dr. Kennedy says, "empowers the patient to make the best informed decision about which medication to take for their psychiatric disorder." Because results are better, "it helps the doctor-patient relationship." Having a medicine that you can expect to respond to also encourages better adherence to medication programs. This is especially important in an illness like schizophrenia, where a significant percentage of patients discontinue antipsychotic medicines, often due to side effects. This applies to both first- and second-generation antipsychotics, and helps us better understand why, from the beginning of his career, Dr. Kennedy has been working to find genetic factors that might help deal with the phenomenon of treatment resistance. By definition, the work on pharmacogenetics is one way of dealing with the problem: some patients for whom a medicine does not work get much better results when a pharmacogenetics test shows that they have a gene that, for example, makes them excrete a drug too rapidly, or have a drug in their system for too long a time.

One other hesitation about pharmacogenetics has been addressed in recent years. Discovery of the key liver enzyme genes regulating drug metabolism was based on research mainly involving White, Euro-American populations. More recent research has made sure to include people of diverse ethnicities, from all of over the world, and has added significantly to the sensitivity and utility of the tests.

Dr. Kennedy and others are working to develop more sophisticated pharmacogenetics tests. Their most comprehensive one is built into a gene "chip" that uses a saliva sample or single drop of blood to test for a total of 60 medication-related genetic variations in 22 genes. This test, which he and colleagues hope to be able to study in a clinical trial, includes variations pertaining to eight liver enzymes affecting drug metabolism.

With respect just to these eight enzymes, "what are the chances that an individual will have none of them—no variations that result in fast or slow drug metabolism?" Dr. Kennedy asks. "If we think across all the medications a patient may take, across disorders, only 22% would not have a benefit from the test. Conversely, 78% will have at least one of these variants, and therefore will get some benefit" based on the liver enzyme variants alone."

The tests will continue to improve, as they reflect new knowledge about individual vulnerability to factors affecting drug metabolism and effects. Factors still to be incorporated which could add considerable fine detail to an individual's pharmacogenetic profile include polygenic risk scores, a statistical estimate of an individual's genetic predisposition to a particular trait or illness based on the collective influence of many genetic variants; and so-called "omics" research, which adds highly detailed information from vast genomic databases about gene activation, epigenetics, protein dynamics, and RNA biology.

In the end, pharmacogenetic testing may eventually prevail because it makes good sense. "When you think about these liver enzyme genes, the case is pretty simple" Dr. Kennedy says. "They either increase the breakdown of a drug, which makes its level low in the bloodstream, which causes lack of response; or it blocks the breakdown of the drug which causes the drug to accumulate in the bloodstream, causing all kinds of side effects and toxicity."

"It's just unquestionably a good idea for patients, but also for doctors, using their powerful prescription pad to order a foreign chemical to go into a patient's body. It's dangerous if the doctor does not know whether this patient is among the subgroup who cannot break the drug down. So, the drug accumulates to very high levels and becomes toxic and has side effects. Why would a doctor not want to know that?"

❖ **PETER TARR**

2025 INTERNATIONAL MENTAL HEALTH RESEARCH SYMPOSIUM

Joseph LeDoux, Ph.D., Antigona Martinez, Ph.D., Daniel C. Javitt, M.D., Ph.D., Jeffrey Borenstein, M.D., Nur Yanayirah, Ole A. Andreassen M.D., Ph.D., Luis Augusto Paim Rohde, M.D., Ph.D., and Geoffrey Simon, BBRF Board Chairman.

On Friday, October 24, 2025 BBRF hosted its International Mental Health Symposium at the Kaufman Music Center in New York City, which was simultaneously live-streamed.

Later that same evening at its International Awards Dinner, BBRF presented the Outstanding Achievement Prizes in Mental Health to five scientists 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 195 mental health experts across disciplines in brain and behavior illnesses.

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.

Daniel C. Javitt, M.D., Ph.D., opened the symposium with his presentation entitled, *Listening to Schizophrenia: How Modern Neuroscience Explains the Subjective Experience of Schizophrenia and Points to New Treatment and Remediation Approaches*. Dr. Javitt is Professor and Director, Division of Experimental Therapeutics at Columbia University Medical Center, and Director, Schizophrenia Research Division at the Nathan S. Kline Institute for Psychiatric Research. He is also a member of the BBRF Scientific Council, a 1995 BBRF Independent Investigator, and a 1990 BBRF Young Investigator.

Early in his career, Dr. Javitt demonstrated that PCP induces its clinical effects by blocking neurotransmission at the N-methyl-D-aspartate (NMDA) receptor. In 1991, he proposed a neurochemical model of schizophrenia based on the effects of PCP on NMDA receptors. This theory has since been extensively supported in pharmacological, immunological, and genetic research.

Dr. Javitt's recent research focuses on the role of basic auditory and visual processing deficits as drivers of cognitive impairment in schizophrenia and targets for treatment development. He calls attention to how EEG- and fMRI-based imaging measures can be used to isolate the source of cognitive deficits on an individual level, and seeks to show how targeted cognitive remediation, combined with non-invasive neuromodulatory approaches, can be developed to develop personalize intervention strategies targeting key bottlenecks to functional recovery.

In his presentation Dr. Javitt focused on the brain mechanisms that underlie persistent cognitive deficits and clinical symptoms in schizophrenia with a particular emphasis on low-level auditory and visual deficits that undermine basic aspects of instrumental and social function. Specific examples include impairments in tone-matching ability that contribute to impairments in processes such as auditory verbal learning, auditory emotion recognition and phonological processing; and deficits in visual integration and motion processing that lead to impairments in rapid stimulus detection, face emotion recognition and reading.

Antigona Martinez, Ph.D. discussed *Targeting Brain Circuits to Improve Emotion Recognition in Schizophrenia*. Dr. Martinez is a Research Scientist at the Nathan S. Kline Institute for Psychiatric Research at Columbia University. She is also a 2005 BBRF Young Investigator.

A cognitive neuroscientist with a background in the neural basis of visual processing in humans, Dr. Martinez recently has focused on identifying the neural mechanisms that contribute to social cognitive impairments in schizophrenia, a major driver of long-term disability that currently lacks targeted treatments. She uses advanced brain imaging tools, including EEG and MRI, alongside non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS), to examine how deficits in early visual processing cascade into higher-order social cognitive dysfunction and poor functional outcomes. A central goal of this work is to

2025 PRIZEWINNERS

LIEBER PRIZE FOR OUTSTANDING ACHIEVEMENT IN SCHIZOPHRENIA RESEARCH

Daniel C. Javitt, M.D., Ph.D.
Columbia University Medical Center
Nathan S. Kline Institute for Psychiatric Research

MALTZ PRIZE FOR INNOVATIVE & PROMISING SCHIZOPHRENIA RESEARCH

Antigona Martinez, Ph.D.
Columbia University Medical Center
Nathan S. Kline Institute for Psychiatric Research

COLVIN PRIZE FOR OUTSTANDING ACHIEVEMENT IN MOOD DISORDERS RESEARCH

Ole A. Andreassen, M.D., Ph.D.
University of Oslo and Oslo University Hospital

RUANE PRIZE FOR OUTSTANDING ACHIEVEMENT IN CHILD & ADOLESCENT PSYCHIATRIC RESEARCH

Luis Augusto Paim Rohde, M.D., Ph.D.
Hospital de Clínicas de Porto Alegre
Federal University of Rio Grande do Sul, Brazil

GOLDMAN-RAKIC PRIZE FOR OUTSTANDING ACHIEVEMENT IN COGNITIVE NEUROSCIENCE RESEARCH

Joseph LeDoux, Ph.D.
New York University
NYU Langone Medical School

develop neuroscience-based, personalized interventions to improve social functioning and quality of life for individuals living with schizophrenia.

People with schizophrenia often struggle to recognize facial emotions, making social interactions more difficult and isolating. Dr. Martinez' presentation explored how non-invasive brain stimulation, specifically, transcranial direct current stimulation (tDCS), may enhance the brain's ability to process facial emotions. By combining tDCS with brain imaging tools such as EEG and MRI, she explained how her team examined how specific neural circuits contribute to emotion recognition and how they can be individually targeted to improve social functioning. This work lays the foundation for future interventions that go beyond symptom management and aim to enhance real-world social engagement and quality of life.

Ole A. Andreassen, M.D., Ph.D., presented *Genetic Analyses Yield Biological Insights Into Bipolar Disorder With Potential Clinical Relevance*. Dr. Andreassen is a Professor at the University of Oslo and Oslo University Hospital and Director of the Centre for Precision Psychiatry in Norway.

His research is translational, combining clinical, neurocognitive, and brain imaging methods with molecular genetics to identify causes and underlying pathophysiology of bipolar disorder and related mental and somatic disorders. He has initiated large, longitudinal cohorts in mental disorders building on Nordic populations and biobanks, and developed new analytical tools for big data to translate findings to the clinical setting to implement precision medicine tools. Heritable factors are involved in the development of bipolar disorder, but the specific mechanisms remain mainly unknown.

Thank you to our Bronze Sponsor, Simon & Associates Wealth Management of Raymond James, and our Benefactor Sponsor, Miriam E. Katowitz.

In his talk, Dr. Andreassen explained that in a series of genetic studies of bipolar disorder, most recently including more than 2.9 million participants, he and colleagues increased genetic discovery to nearly 300 genetic variants. These genetic findings improved their understanding of the underlying biological mechanisms in the illness. Applying advanced analytical tools, the team showed that the genetic signal of bipolar disorders was related to specific brain cell types and molecular biological mechanisms. They identified differences in the genetic signal of bipolar disorder based on recruitment from hospital wards or from the community. They also found different genetic signals between bipolar subtypes I and II. Dr. Andreassen said that this suggests differences in molecular biology, and can form the basis of future opportunities for new treatment development, and more precise and personalized treatment options.

In his presentation, **Luis Augusto Paim Rohde, M.D., Ph.D.,** discussed *What Can a Research Center in Brazil Tell Us About ADHD?* Dr. Rohde is the Director of the Hospital De Clínicas De Porto Alegre and a Professor at the Federal University of Rio Grande do Sul in Brazil.

Dr. Rhode has participated in the working group to define the diagnostic criteria for ADHD and Disruptive Behavior Disorders in the DSM-5 manual for the American Psychiatric Association and has been president of the World Federation of ADHD. He has published more than 500 scientific articles, 50 book chapters or editorials, and is the organizer or editor of nine books on the mental health of children and adolescents in Brazil, England, Germany, and the USA. Between 2020 and 2023, he was among the researchers most influential in the fields of psychology and psychiatry (top 1%) for the last decade, according to Clarivate (Web of Science). Among various awards, he has received the ADHD Lifetime Achievement from the World Federation of ADHD.

During his presentation, Dr. Rhode discussed relevant contributions from work at his research center to improve the understanding of ADHD, pertaining to epidemiology, a possible late-onset trajectory, and the predictability of adult ADHD, based on data from childhood, new non-pharmacological treatments, and scientific data that have had an impact upon national policies in Brazil. He also underlined some key concepts learned on how to build a research center in a developing country, making it part of the international research effort in child and adolescent mental health.

In his symposium talk, **Joseph LeDoux, Ph.D.,** presented *What Happened to the "Mental" in "Mental Disorders"?* Dr. Ledoux is Professor of Neural Science and Psychology at New York University and Professor of Psychiatry and Child & Adolescent Psychiatry at NYU Langone Medical School.

Dr. LeDoux has focused on the topics of emotion, memory, and consciousness, and their interaction in the brain. He is the author of several books, including *The Emotional Brain, Synaptic Self, Anxious, The Deep History of Ourselves,* and *The Four Realms of Existence*. Forthcoming is his memoir, *Starting Over: Tales from an Accidental Neuroscientist*. He is also a renowned musician in the New York City band The Amygdaloids. Dr. LeDoux's research has shed light on how the brain detects and responds to threats, and how memories about such experiences are formed and stored through cellular, synaptic, and molecular changes in the amygdala. In his presentation, Dr. LeDoux observed that while people often seek help for mental problems because they are suffering subjectively, for decades the subjective experience of patients has been marginalized. He suggested that this is in part due to the dominant medical model of mental illness, which has tended to treat subjective experience as a relic of a scientifically less enlightened time. To the extent that subjective symptoms are related to the underlying problem, it is often assumed that they will be taken care of if the more objective symptoms, such as behavioral and physiological responses, are treated. Given that "mental" disorders are named for, and defined by, their subjective mental qualities, Dr. LeDoux suggested that it is perhaps not surprising, in retrospect, that treatments that have sidelined mental qualities have been disappointing, at best. Negative views about subjective experience took root in psychiatry and allied fields decades ago, he noted, when there were few avenues for rigorously studying subjective experience.

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

It is his view that today, however, research on consciousness is thriving, and offers a viable scientific approach that could help achieve a deeper understanding of mental disorders and their treatment.

The BBRF International Mental Health Symposium also featured a presentation from **Nur Yanayirah,** Founder of **MotherHope Indonesia**, the winner of the 2025 Pardes Humanitarian Prize in Mental Health. Ms. Yanayirah's presentation, *Empowering Maternal Voices Through Peer Support and Advocacy*, explored the challenges of living through postpartum depression in Indonesia's unique cultural context.

She discussed her personal journey of hope and resilience, which began when she gave birth to a stillborn baby in 2011 and experienced postpartum depression (PPD) with her second child. Ms. Yanayirah overcame these challenges and recovered from PPD. In 2015, she was trained by Postpartum Support International (PSI) and founded MotherHope Indonesia. She dedicates herself to providing support for women and families with similar experiences. She discussed how she and her team advocate for influencing policy changes in the medical system as well as seeking to raise awareness of maternal mental health and women's rights. ❖ **LAUREN DURAN**

2025 International Awards Dinner

The BBRF International Awards Dinner was held on Friday, October 24, 2025 at The Pierre Hotel in New York City. The event celebrated the progress being made in neuropsychiatric 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 (see pages 14–17).

(Names in each picture listed L–R):
1. Dr. Antigona Martinez
2. Dr. Jeffrey Borenstein and Dr. Luis Rohde
3. Marla Press and Ken Harrison
4. Geoffrey Simon, BBRF Board Chaiman
5. Steven Greenbaum, Dr. Judith Genshaft, and Holly Duncan


1


2


3


4


5

6. Andrea Simon, Janice Lieber, and Geoffrey Simon
7. Dr. Joshua Gordon, Jennifer Greenfeld, and Geoffrey Simon
8. Janie and Martin Borell
9. Dr. Jeffrey Borenstein and Dr. Daniel Javitt
10. Dr. Joseph LeDoux
11. Dr. Judith Ford and Dr. John Krystal
12. Dr. Ole Andreassen and Dr. Jeffrey Borenstein
13. Scott Shimberg, Mary Pat and John Osterhaus, Heidi Shimberg
14. Dr. Helen Mayberg and Dr. Daniel Weinberger

PHOTOS BY CHAD DAVID KRAUS

2025 Pardes Humanitarian Prize in Mental Health

Awarded to MotherHope Indonesia and Tamar and Milton Maltz

Dr. Jeffrey Borenstein, President & CEO of BBRF and Nur Yanayirah, Founder of MotherHope Indonesia

On Friday, October 24, 2025 at The Pierre Hotel in New York City, BBRF presented the 2025 Pardes Humanitarian Prize in Mental Health at its International Awards Dinner.

MotherHope Indonesia, a pioneering voice in Asia for maternal mental health, received the 2025 Pardes Humanitarian Prize in Mental Health. Through advocacy, peer support, education, and collaborations with health professionals, MotherHope Indonesia is transforming public attitudes and access to care. The Prize was accepted by the founder of MotherHope Indonesia, Nur Yanayirah, who experienced postpartum depression. The organization provides compassionate support and safe spaces for women and families affected by perinatal mood and anxiety disorders and promotes perinatal mental health literacy, connects families to professionals, and advocates for integrating mental health into maternal health systems.

"MotherHope Indonesia demonstrates the profound impact that a grassroots movement can have in breaking stigma and providing hope for families living with mental illness," said Jeffrey Borenstein, M.D., President & CEO of the Brain & Behavior Research Foundation. "Their pioneering work in maternal mental health in Indonesia is a model of compassion, resilience, and community-based leadership that is changing lives."

The Pardes Humanitarian Prize in Mental Health is awarded annually to recognize an individual or organization 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 the late Herbert Pardes, M.D., the internationally renowned psychiatrist, outspoken advocate for the mentally ill, and the award's first recipient.

The 2025 Honorary Pardes Humanitarian Prize in Mental Health was awarded to **Milton & Tamar Maltz,** whose visionary philanthropic leadership has advanced groundbreaking mental health research and advocacy.

Dr. Borenstein noted that "Tamar and Milton Maltz are an exceptional choice to receive the Honorary Pardes Humanitarian Prize in Mental Health for their efforts to make the world a better place and for their unparalleled leadership in advancing mental health research and increasing understanding and acceptance of people living with mental illness. We are especially proud to recognize them not only for being generous philanthropists to humanity, but also as valued members of the BBRF Board of Directors."

THE PRIZEWINNERS

2025 PARDES HUMANITARIAN PRIZE RECIPIENT

MOTHERHOPE INDONESIA

Founded in 2015, **MotherHope Indonesia** aims to promote perinatal mental health and enable support for mothers and families affected by perinatal mood and anxiety disorders. It acts in various ways, face-to-face and digital, in an environment where there is otherwise limited support for the mental health and wellbeing of women and families in adversity. MotherHope Indonesia aims to become a social, community, and health institution which is trusted and contributes to improving the health of women and mothers.

Its specific missions, with a focus on depression, anxiety, and stress-related disorders, are to: increase maternal mental health literacy; increase access to communication, information, and education about mothers' mental health; increase community empowerment in preventive mental health; and grow the network of various maternal mental health support, stakeholders, professional organizations, academics, non-governmental organizations, and community and donor agencies, at the national, regional, and international levels.

2025 PARDES HONORARY PRIZE RECIPIENT

TAMAR & MILTON MALTZ

Tamar and Milton Maltz are generous philanthropists whose vision and leadership have strengthened the global mental health ecosystem. Their longstanding leadership and generous support of the Brain & Behavior Research Foundation have helped advance critical research and accelerate progress in understanding and treating mental illness.

They were instrumental in founding the Lieber Institute for Brain Development/Maltz Research Laboratories, advancing discovery and treatment, and have long fostered opportunities and inclusion for people living with mental illness.

Over the years, they have championed initiatives that reduce stigma, expand access to care, and create supportive communities for individuals and families affected by mental illness. Through the Maltz Family Foundation, they have also supported education, arts, and cultural institutions, extending the reach of their impact beyond science to strengthen resilience and understanding in society. ❖ **LAUREN DURAN**

To watch the video honoring the Maltzes please visit:
https://bbrfoundation.org/grants-prizes/pardes-humanitarian-prize-mental-health

PAST PARDES PRIZE WINNERS

2024
Franca Ma-ih Sulem Yong
Honorary Tribute:
Graham Boeckh Foundation

2023
Special Olympics International
Honorary Tribute: Henry Jarecki, M.D.

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.

Improving Treatment Outcomes for People with OCD

By Helen Blair Simpson, M.D., Ph.D.

Professor of Psychiatry,
Columbia University Irving Medical College (CUIMC)

Director, Center for Obsessive-Compulsive & Related Disorders,
CUIMC & New York State Psychiatric Institute

President,
Anxiety and Depression Association of America (2024–2025)

2010 BBRF Independent Investigator
2005 BBRF Young Investigator

This article is adapted from a BBRF webinar with Dr. Simpson held on July 8, 2025

IN BRIEF
Stressing the import of early diagnosis in OCD, Dr. Simpson discusses various forms of therapy and how they have fared in clinical trials. A form of CBT called exposure and response or ritual prevention therapy (EX-RP), given over 17 weeks alongside an SRI medicine, generates a therapeutic response in about two-thirds of patients, with one-third achieving a remission. Dr. Simpson discusses alternative treatment scenarios, and how researchers are trying to develop better therapies for OCD.

WHAT IS OCD—AND HOW DO WE TREAT IT TODAY?

The hallmarks of OCD are in the name: Obsessive Compulsive Disorder. Its core features are obsessions, which are repetitive thoughts, images, or urges that a person finds intrusive and distressing; and compulsions, which are repetitive behaviors or mental acts.

These obsessions and compulsions are not simple one-minute problems. They are highly distressing, time-consuming, and impairing. I have patients with obsessive and compulsive behaviors that go on for hours, if not all day. And you can imagine that if you're doing that, it can really interfere with your ability to function socially and emotionally, as well as with your family and at work.

While all patients with OCD have obsessions and compulsions, what makes one OCD patient different from another are what I call "associated features." First, patients differ in the content of their obsessions and compulsions and their associated fears. In the field, we call these "symptom dimensions." For example, one patient might have concerns about contamination, and intrusive thoughts about getting ill with a lot of washing compulsions. Another might have intrusive fears about harm befalling themselves or someone else with a lot of checking rituals. Other patients can be very concerned with symmetry and exactness and they're trying to set things in order all day long. It isn't that you can only have one type of symptom. Many patients have symptoms across multiple symptom dimensions.

OCD patients can also experience different affects. While many have intense anxiety and panic and can even have panic attacks, other OCD patients might have a sense that "it just doesn't feel right" or even a strong sense of disgust.

Another thing that distinguishes OCD patients from each other is their varying degrees of insight about their condition. Some patients say, "I know that these washing rituals don't make any sense. I know this is irrational, but I can't stop," but others really believe that if they don't do that washing ritual, they might die. It's also true that insight can vary over the course of the illness. A lot of times, kids with OCD may not know what's real and what's not real, and they might believe that their intrusive thoughts (such as that they can harm someone just by thinking) are real and it's only with treatment or growing up that they realize it's OCD.

It's also important to note that while OCD can occur on its own, it often co-occurs with other disorders. In adults, the most common co-occurring disorders are other anxiety disorders or depressive disorders. Those with eating disorders also often have OCD. In kids, you can see a triad of attention deficit hyperactivity disorder (ADHD), tic disorders, and OCD. It's important for people who are working with patients with schizophrenia to know that up to a quarter of patients with the illness will have OCD symptoms. All of this clinical heterogeneity sometimes can make it difficult for people to recognize and treat OCD.

The other thing I like to emphasize is how disabling OCD can be without treatment. Its affects 2% of the global population (about 160 million people). Half the cases start by age 19, and a quarter will start by age 14. Typically, when people start having symptoms and they meet the diagnostic criteria, the course of their OCD is chronic, with waxing and waning if not treated. Epidemiological studies show that if you have OCD, chances are you're going to have moderate to serious symptoms. So, if you add this all up—the prevalence, the age of onset, the chronic course, and the moderate to severe symptoms—this is what makes OCD disabling.

TREATMENTS, AND HOW WE KNOW THEY WORK

The good news is we have two first-line treatments that we know work from clinical trials. One is a class of medications that we call serotonin reuptake inhibitors (SRIs), and they include clomipramine, which is an old-fashioned tricyclic antidepressant, but has very strong serotonin reuptake inhibition. And then we have clinical trials showing that selective SRIs such as fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram also work. *[These medicines, widely prescribed for depression, are also known as SSRIs, and have trade names such as Prozac, Paxil, Zoloft, Lexapro*--editor].




"Obsessions and compulsions are not simple one-minute problems. They are highly distressing, time-consuming, and impairing… [and] interfere with your ability to function."

The other first-line treatment is a form of psychotherapy called cognitive behavioral therapy (CBT). In OCD, we use a particular form called **exposure and response or ritual prevention (EX/RP)**. This is the therapy with the best evidence, and I'll discuss it here in some detail.

First, what does a therapist do? They make a list with you of the types of situations or objects that trigger your OCD and ask you to rank how anxious or distressing these triggers are (rank them from 0 to 100). Then in a very focused and structured way, the therapist and patient collaboratively work to expose the patient to these triggers, going up the hierarchy of fears till they get to the top. During and after this exposure, the patient is trying not to perform their usual rituals. The goal of the therapy is to disconfirm the patient's fears, to learn distress tolerance, and to break the habit of ritualizing. For example, if you have contamination concerns and don't want to touch an ordinary item, for instance a trash can, disconfirming that might involve touching a trash can without ritualizing and realizing that a life-threatening illness does not follow. This is a way of challenging the distorted belief about the risk, developing distress tolerance, and breaking the habit of ritualizing and avoiding. The overall goal is to improve functioning and quality of life.

A well-studied standard format of EX/RP is two sessions where you plan the treatment with your therapist, followed by 15 structured exposure sessions. We like to do it at least twice a week or more for a better outcome than just once weekly. A key part of this treatment is the daily homework, in which the therapist asks you to practice exposures in your home environment, to do your best to stop ritualizing, and to monitor your success. The therapist may also do home visits to promote generalization of the skills, because the goal is that the patient learns the skills and can use them in everyday life.

We know the effectiveness of this format from clinical trials, which are one major form of patient-oriented research. They test what treatments work.

When I first came to Columbia University as a postdoctoral researcher, I was able to work on an important study led by Dr. Edna Foa, of the University of Pennsylvania, and Dr. Mike Liebowitz, who was my research mentor. The question they asked was simple: What's the best treatment for OCD? In the study, they recruited 100 adults with OCD, and randomly assigned one group to a tricyclic antidepressant (the SRI medication clomipramine); a second group to receive CBT (the EX/RP form); a third group to receive a combination of the two; and a fourth group to receive placebo pill.

The group that received placebo over the 12 weeks of the trial had little change in symptoms. The group that was randomly assigned to the active SRI medication had a gradual decrease in symptoms over the 12 weeks. But the two groups that received the CBT, with or without the medication, had a higher and quicker decrease in symptoms than those taking the medication alone (see graph, facing page). This study really showed the power of CBT for the treatment of primary OCD. But back then, and still today, most people get medication first, mostly because it's easier to take a pill than to commit to a course of in-person therapy.

Two subsequent clinical trials extended these results, in different ways. In one study, we asked if adding EX/RP to a stable dose of medication was better than accompanying SRI medication with a therapy that focused on teaching stress reduction and relaxation skills and did not specifically address the symptoms of OCD. This latter served as

a control. We wanted to see if it was the specific skills learned by the patient in EX/RP that matter. The other possibility was that maybe all one needed for OCD to get better was meeting face-to-face with a caring, thoughtful therapist, i.e., there might be little or no extra benefit from doing EX/RP.

Another subsequent study, 5 years later, studied whether adding EX/RP to medication is better than adding an antipsychotic medication instead of an SRI. And why did we do that trial? Because in actual medical practice, that's what psychiatrists typically did. If SRIs didn't lead to enough symptom reduction—and most of the time, they don't—psychiatrists would add an antipsychotic because clinical trials had shown that it worked.

WHAT THE TRIALS TAUGHT US

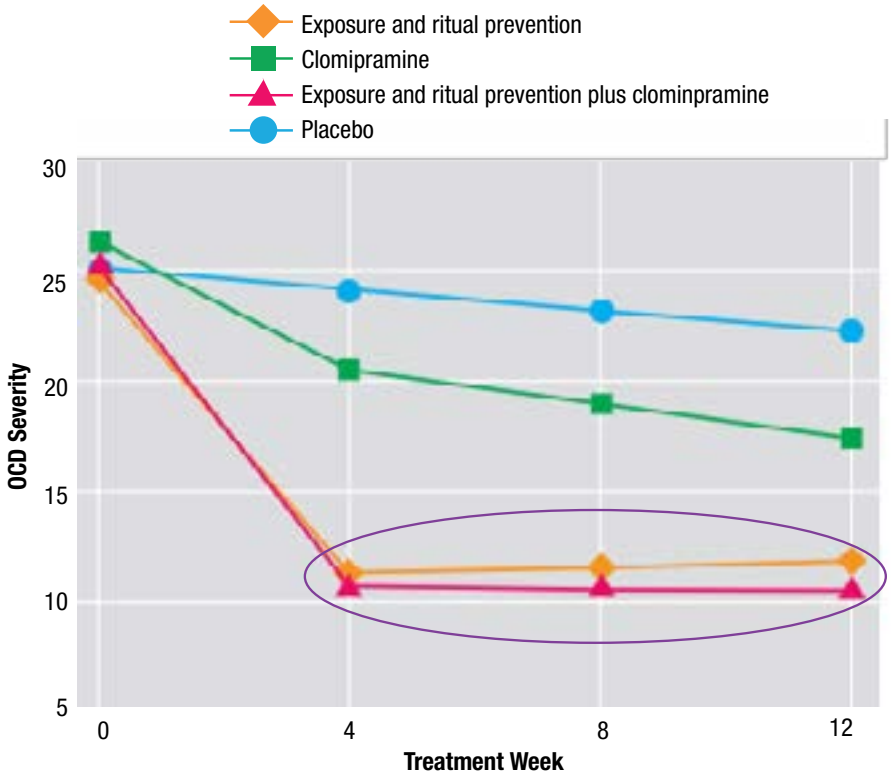
What we learned from both of these subsequent trials was that for OCD patients on SRIs who still have ongoing OCD symptoms, adding EX/RP to the SRI medication for adults with OCD was much better than adding the non-specific control therapy; and it was also better than adding an antipsychotic medication to SRI treatment. Across both studies, done years apart with completely different patients and different therapists, ***we found that about two-thirds of people who received EX/RP in addition to their SRI medication got better, and about one-third reported minimal symptoms after the trial.*** In a subsequent study we showed that if you went beyond the standard 17 sessions of EX/RP, increasing the number of sessions to 25, you could get two-thirds of people "well," by which I mean having no or minimal symptoms.

What's the take home message from not only this series of trials, but trials others have conducted? SRIs are effective for some, but response is usually partial. (In OCD, partial response is considered a good response). We don't know why, but that's the result. And what do we know from the clinical trials involving EX/RP? We learned that EX/RP is effective for more people than medication, but a key thing here is patient adherence. Patient adherence to EX/RP predicts outcome 6 months after the start of treatment, and, in particular, early adherence to the therapy can forecast how you're going to do.

This means a therapist can have a good idea of how you're going to do by the end of the second week of EX/RP therapy—just by knowing how quickly you start to adhere.

At the same time, from yet another clinical trial, we know that if you combine these two treatments (SRI medication and EX/RP), and optimize both, up to two-thirds of patients can attain minimal symptoms. That is a pretty incredible outcome for such a disabling disorder.

What is the Best Treatment for Adults for Adults with OCD?



The 2 groups receiving CBT, with or without the medication, had far superior outcomes (oval).

ALTERNATE TREATMENT SCENARIOS

But what if somebody, because of their symptoms, has a hard time doing the CBT treatment (i.e., EX/RP)? One strategy is to stop the treatment and focus in on the obstacles that are getting in the way. Are the exposures too hard? Is the ritual prevention or the demands too high? Can you tailor the treatment at the beginning to get the patient to see that it will work, but start a bit more gently?

One way to approach this is to focus on medication. Sometimes a patient's symptoms are so severe that it's really hard for them to focus on the therapy. By putting them on medication first—maybe even just for enough time for it to reduce symptoms to some degree—the patient may then be able to adhere to the EX/RP.

Another strategy is that of support and trying to make sure the patient has an environment, whether it's the family or the work environment, that supports their adherence to the treatment. We also sometimes use more frequent sessions or even residential treatment, for a 24/7 therapeutic environment.

Having said that, I have seen people who don't want to do EX/RP, and I believe patients should have choice, as long as they know it's one of the most effective treatments we have. If they then choose not to do it, I honor that decision. What's interesting is that I've had patients come back a year later, two years later, and say they're now ready. This is often because SRIs, while usually well tolerated, can have side effects. It's hard to take SRIs for the rest of your life. So sometimes, it's about people, as they try to function in their lives, finding the motivation to take on EX/RP.

Therapist and patient collaboratively work to expose the patient to triggers. The goal is to disconfirm the patient's fears, learn distress tolerance, and break the habit of ritualizing.

And this leads us to another question that patients ask us: If they're on an SRI, and get the addition of EX/RP and they start feeling much better, can they then stop their SRI? What we discovered in the trial I mentioned earlier involving combining and optimizing treatments, is that on average, there is not a significant difference in symptoms of OCD or depression 6 months later between those who stayed on their SRI and those who were tapered off. However, after 6 months, 45% of those who tapered off were rated by their clinician (who did not know which group they were in) as clinically worse. Thus, if you are on SRIs for OCD and have minimal symptoms and are considering tapering off your medication, speak to your prescriber first and only taper off under close supervision.

These are the first-line treatment options for adults. Similar clinical trials have been done for kids, and the results similarly demonstrate the power of EX/RP for the treatment of OCD in kids, as well as the typical partial response to medication, and that the combination of both is sometimes what works best.

THE IMPORTANCE OF EARLY DIAGNOSIS

As I noted earlier, half of OCD cases start by age 19 and a quarter of cases by age 14. So I've become a real proponent of early diagnosis and intervention, to prevent patients going through years and years of needless suffering.

Parents and teachers can and should look out for early signs in adolescents or even younger children. Avoidance is a pretty important sign. Sometimes in life it's healthy to avoid difficult people or dangerous places. I'm not talking about that type of avoidance. But if you start seeing your kid not wanting to go to school or avoiding certain situations, that should be a red flag.

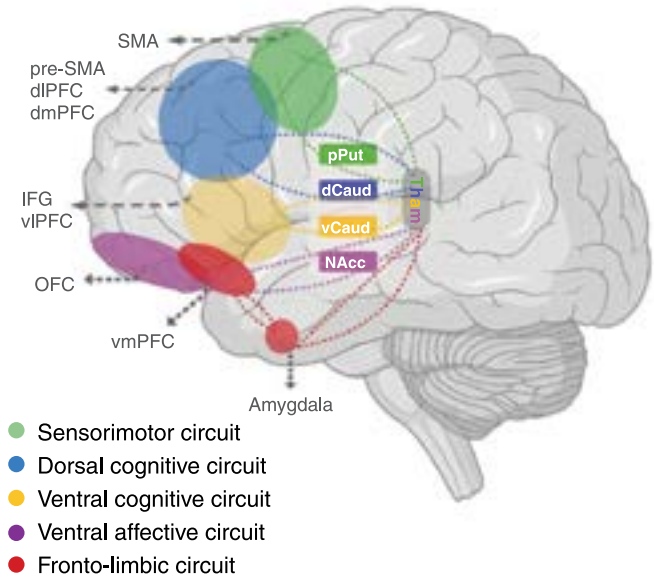
I'm a big believer that it's better to get someone evaluated sooner rather than later because in the field of anxiety and OCD, we're lucky. We have powerful psychotherapies that can help people. In fact, the first-line treatment for anxiety and OCD in young people is CBT. And frankly, they're a skill set for life: to strategically expose yourself to what you fear and learn to master those fears. The more someone does this, the more resilience they build. Life has all sorts of disruptors for all of us, and

skills learned from EX/RP can also help someone deal with the general ups and downs of life.

EX/RP is arguably the most effective treatment we have. And when you get the standard dose, which is 17 sessions, and it's not enough, we increase the dose, giving people another eight sessions. Given the data we have, we really focus on enhancing patient adherence. Or if somebody is on a low dose of medication and is not experiencing side effects, we could increase the dose. For some people, that's all they need to get a reduction in symptoms.

But sometimes, the first-line treatments (i.e., EX/RP and SRI medication) don't work. Clinical trials are looking at second-line treatments in case patients don't have a medication response at all or have a partial medication response. There are ongoing trials of ketamine, cannabinoids, anti-inflammatories, and psilocybin, among others. People are also studying how to improve EX/RP by increasing technology and access, enhancing learning, implementing intensive formats, as well as testing new therapies. And there's a lot of work going on with transcranial magnetic stimulation, a non-invasive way of stimulating the brain to alter neural activity to reduce symptoms. All of the trials that are in progress are listed on clinicaltrials.gov. If you're eligible, participating in these trials can be a great way to try something new while also helping to advance the science.

Multiple Brain Circuits Implicated in OCD



"Half of OCD cases start by age 19 and a quarter of cases by age 14. So I've become a real proponent of early diagnosis and intervention, to prevent patients going through years and years of needless suffering."

CONTINUING CHALLENGES

This leads me to two outstanding challenges in the field. The first is that most people with OCD don't receive first-line treatments. And why is that? Sometimes the problem is that the patient doesn't know they have OCD, so they don't know how to ask for help. Further, in many parts of the world, stigma is a real issue and coming in for treatment is really hard. Even when a patient comes in, the clinician may not recognize the patient's symptoms as OCD or may misdiagnose it or may not know the right dose of medication or the right therapy to deliver. Sometimes, the system of care doesn't offer evidence-based treatment or insurance policies don't cover those treatments.

To address this issue, we use a different type of patient-oriented research than clinical trials: we use "implementation science." In implementation science studies, we figure out how to bring evidence-based care to real-world clinical practice. We are working to bring evidence-based care to New Yorkers through an initiative called IMPACT-OCD (https://practiceinnovations.org/initiatives/impact-ocd/overview). This is a partnership between my Center for OCD and Related Disorders, the Center for Practice Intevention, and the New York State Office of Mental Health. If you are eager to learn more about OCD, there are public-facing resources there for both clinicians and families and those with lived experience.

Another challenge is that we have treatments that can help half of people. Why don't our treatments work for most everyone? We don't know yet. And that really leads to the fundamental question of what causes OCD. If we better understood the causes, we could perhaps understand why our treatments work for some but not all, and we could develop even better treatments.

What causes OCD? I think about this is two ways. First, what doctors call pathophysiology. How does the brain produce obsessions and compulsions? The working model we have is that specific brain circuits aren't functioning properly. Frankly,

that's the working model we have for all psychiatric diseases. We know from a huge body of literature that there are neurocognitive and neurobehavioral alterations in people with OCD when you compare them to healthy volunteers. That can include alterations in how they process threat or extinguish fear. This can alter the balance between goal-directed and habitual behavior. It can impair their ability to inhibit responses or have cognitive control over their thoughts.

But pathophysiology is distinct from what we call etiology. Etiology is how did the brain develop those alterations in the first place? And that's a different question. We know from past research that there is genetic risk for OCD, and we see this, in particular, in studies of identical twins. There also are cases of new-onset OCD after exposure to infectious agents, and there's a hypothesis around autoimmune mechanisms. There have also been new-onset cases of people in their 50s or 60s after neurological insults and also after severe trauma. These suggest OCD in some cases may have an environmental cause. We also know from a huge body of brain imaging studies that there are alterations in multiple brain circuits in people with OCD.

"Neurocognitive and neurobehavioral alterations in people with OCD can include alterations in how they process threat or extinguish fear. This can alter the balance between goal-directed and habitual behavior and impair one's ability to inhibit responses or have cognitive control over one's thoughts."

But neuroimaging studies are a snapshot in time. Ideally, we want to know what's the cause and what's the effect? If you see an alteration in the brain, is it the symptoms causing the alteration or is the brain alteration causing the symptoms? And there's another question I think about a lot. Do I think all of my OCD patients have exactly the same brain dysfunction? No. There's some difference between patients in their clinical presentation, and I'll bet at the end of the day when we really understand this, we're going to see corresponding heterogeneity in the brain alterations involved in their symptoms.

A final thing to consider is whether neuroimaging findings are robust and reproducible. That's a really important point because if you're going to use a brain-imaging finding as a target for new treatment development, you want to know that you're going to find that same target robustly and in a reproducible way. In own studies, we have sought to identify robust signatures in the brains of OCD patients. The idea of this research is to see if different brain alterations in different patients explain some of the different clinical presentations. Such information could help tailor treatments to different people for better outcomes. This is a move toward precision psychiatry.

As someone who's been in the field of OCD research for over two decades, I've seen with my own eyes how research conducted in patients (including clinical trials, implementation science, and neuroimaging studies) has led to a better understanding of what causes OCD as well as to improved outcomes for OCD patients, and I see very exciting developments on the horizon. Thus, I ask all who are reading this: if you care about OCD and better treatments tomorrow than we have today, please join me in advocating for patient-oriented research. This is the research that can translate basic-science discoveries to clinical practice. ❖

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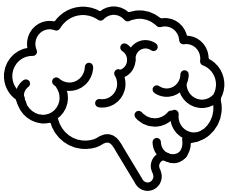

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Awarding **NARSAD** Grants

Harnessing Potentially Therapeutic Properties of Psychedelics While Eliminating Hallucinations and Other Unwanted Effects

IN BRIEF
We detail efforts by 4 research teams supported in part by BBRF grants to find ways of harnessing potentially therapeutic effects of psychedelic drugs while minimizing or eliminating hallucinations and other unwanted side effects. These methods include modifying molecular structure; using molecular variants of the primary molecule; redirecting the molecule to engage alternate cellular receptors; and selectively activating circuitry contributing to therapeutic effects.

Considerable effort has been made in recent years to evaluate—or in some cases, reevaluate—psychedelic drugs for potential use as therapeutics to treat psychiatric disorders such as PTSD, depression, and anxiety.

None of this research so far has led to approval by the U.S. Food and Drug Administration of any "classical" psychedelic drug (such as LSD, psilocybin, or DMT) for any medical purpose, despite a number of clinical trials suggesting promise in specific applications and under specific conditions of administration. Among the lingering concerns are those relating to the hallucinogenic properties and abuse potential of these drugs, which continue to be listed by the U.S. government as prohibited Schedule I substances.

Even as clinical testing of psychedelics continues, these issues have inspired research on other tracks. In this article we will explore recent efforts by several BBRF grant recipients who are interested in some—but not all—of the properties of psychedelic drugs to treat psychiatric disorders. Our focus is on researchers who are not administering psychedelic compounds to patients, but instead are trying to isolate and capture some of their potentially therapeutic effects.

Some advocates of psychedelics in psychiatry have suggested that the "trip"—the subjective, perception- and consciousness-altering experience induced by these drugs—is an essential part of what makes them powerfully therapeutic. But this issue has not yet been addressed

in a rigorous way by evidence-based scientific research. It's a difficult thing to study, in part because the experience one has while under the influence of hallucinogens is not only subjective, but may even be uniquely personal.

Past research has succeeded in establishing some basic facts about the complex pharmacology of psychedelics. Among other impacts, they are known to act upon the **serotonin neurotransmitter system**, which plays an important role in mood regulation.

Psilocybin, for instance, has been shown to stimulate several types of serotonin receptors in nerve cells, especially the serotonin 2A receptor. Such stimulation has a wide range of "downstream" pharmacologic effects in the brain and body, which remain poorly understood but could impact symptoms of mood disorders such as depression and anxiety. Animal studies have shown that MDMA, an amphetamine-based stimulant known on the street as "molly" and "escstacy," which has a distinct mechanism of action, induces serotonin release by binding to serotonin transporter proteins. There is some evidence the drug may enhance the extinction of fear memories and modulate fear memory reconsolidation and thus it too holds promise in treating PTSD and anxiety.

As noted, it is not known whether or how the "psychedelic experience"—the subjective experience the user has after ingesting a psychedelic drug—may be related to therapeutic effects reported by users in the aftermath of the experience. But the experience of users varies widely. While some report life-altering insights or revelations while under the influence, others have described very difficult, emotionally painful, even harrowing experiences.

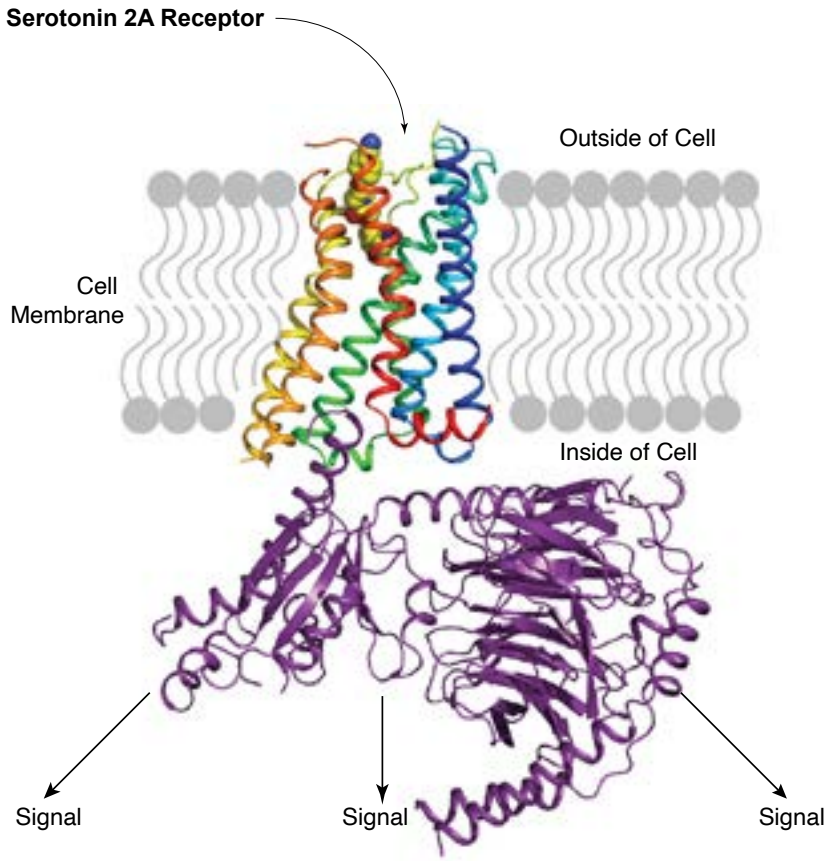
Alongside, but separate from what might be called applied research that explores how psychedelic compounds influence behavior in people, the disciplines of pharmacology, structural biology, and medicinal chemistry each and in combination provide pathways for learning more about the compounds themselves, their intrinsic properties which follow from their physical structure and interactions with other molecules as well as brain cells and circuits. These disciplines have provided the pathways taken by the grantees whose work we will now describe, which take four distinct approaches.

1. MODIFY THE MOLECULE'S STRUCTURE

For various reasons, the hallucinogenic properties of psychedelic drugs make these drugs particularly inappropriate and dangerous for people with schizophrenia and other disorders involving psychosis, which involve distortions of reality and difficulty distinguishing what is real and what is not.

But researchers also have recognized the power of some of these same substances to promote neuronal growth. Specifically, some psychedelic compounds have been shown to be powerful promoters of growth in atrophied cortical neurons, a fact that has intrigued researchers interested in addressing one of the hallmark pathologies associated with schizophrenia. Analysis of postmortem brains of people who suffered from the illness have revealed decreased branching of the dendrites that bring signals from other neurons into nerve cells in the cortex; reduced density of dendritic spines, the tiny bump-like protrusions along dendrites that are the points of contact for axons projected by neighboring neurons (see illustration, p. 33); and abnormally low levels of the proteins that form synapses in cortical tissue. All are manifestations of cortical atrophy.

Users report a wide range of experiences after taking hallucinogens, from life-affirming to emotionally harrowing.



Like LSD, the synthetic analogue called JRT, while apparently not hallucinogenic, specifically engages with the serotonin 2A receptor, one of many serotonin receptor types in the body. It likely interacts with the receptor differently than does LSD. Any molecule docking at the portion of the receptor that protrudes just above the cell membrane (top curving arrow) activates the complex, which extends below the membrane in structures (purple) that transmit signals within the cell. These initiate the train of events which causes a drug to have various effects. Different engagement with the receptor can lead to different effects.

It is inconceivable to contemplate treating schizophrenia with psychedelics, yet the problem of cortical atrophy has inspired some researchers to search for ways to modify psychedelics so as to retain their potentially therapeutic neuronal growth-promoting properties while reducing or eliminating their hallucinogenic ones.

In 2025, a team led by David E. Olson, Ph.D., at the Institute for Psychedelics and Neurotherapeutics at the University of California, Davis, reported in *Proceedings of the National Academy of Sciences (PNAS)* that they have modified the LSD molecule—a very powerful hallucinogen— to create a drug dubbed JRT. The new drug proved in a range of experiments to be "an exceptionally potent analogue of LSD," yet with much lower hallucinogenic potential. The new drug appears to have "the ability to produce a wide range of therapeutic effects." A powerful promoter of growth among cortical neurons, JRT also had strong antidepressant properties in animal tests and showed potential to address the negative and cognitive symptoms of schizophrenia.

The research team included three BBRF grantees: **William A. Carlezon Jr., Ph.D**., a 2007 and 2005 BBRF Independent Investigator and 1999 Young Investigator; **Conor Liston, M.D, Ph.D.**, a 2013 BBRF Young Investigator; and **Alex S. Nord, Ph.D**., a 2015 BBRF Young Investigator. Drs. Carlezon and Liston are members of the BBRF Scientific Council.

The researchers performed a remarkably simple modification of the LSD molecule, swapping the positions of just two atoms to create JRT. Like LSD, the new drug specifically spurs activity at **serotonin 2A receptors**. But the structural tweak that generated JRT also reduced its potential to generate hallucinations, as both test tube-based and mouse-based experiments indicated.

"What I think is so interesting about this work is that JRT and LSD have essentially the same molecular shape and weight, yet they have distinct pharmacology thanks to the transposition of those two atoms," Dr. Olsen says.

JRT proves to be a partial agonist, or stimulator, of the serotonin 2A receptor, as compared with LSD, which is a powerful agonist of the same receptor. This fact may explain JRT's ability to promote cortical neuron growth with much lower hallucinogenic potential. In the team's mouse experiments, JRT failed to cause behaviors that indicate hallucinogenic impact. In rodents, such behaviors include head-twitching behavior, hyperlocomotion, and deficits in prepulse inhibition, a measure of the brain's ability to filter out irrelevant sensory information.

"Despite its lower hallucinogenic potential," JRT in head-to-head comparisons with LSD and the antipsychotic clozapine "demonstrated superior effects on cortical neuron growth, [and] moreover produced a remarkable 46% increase in dendritic spine density" in living mice. Other experiments showed it "completely rescued cortical atrophy" in a particular layer of neurons in the mouse cortex.

"These changes in structural plasticity were accompanied by robust antidepressant-like properties and pro-cognitive effects," in tests that included measuring active coping strategies in response to an unavoidable stressor. When mice were subjected to chronic

"social-defeat" stress, the drug reversed anhedonia-like behaviors (inability to seek pleasure). JRT also "promoted cognitive flexibility" in mice performing a "reversal learning task," a test in which an individual learns to abandon a previously learned behavior and adopt a new one.

The researchers believe their experiments highlight the potential of modifying the chemical structures of some psychedelics "to produce analogues with improved efficacy and safety profiles," as in this case they appeared to have discovered a non-hallucinogenic stimulator of cortical plasticity and growth with potential to treat illnesses that cannot be addressed by psychedelics including schizophrenia, psychosis, and bipolar disorder with psychotic episodes.

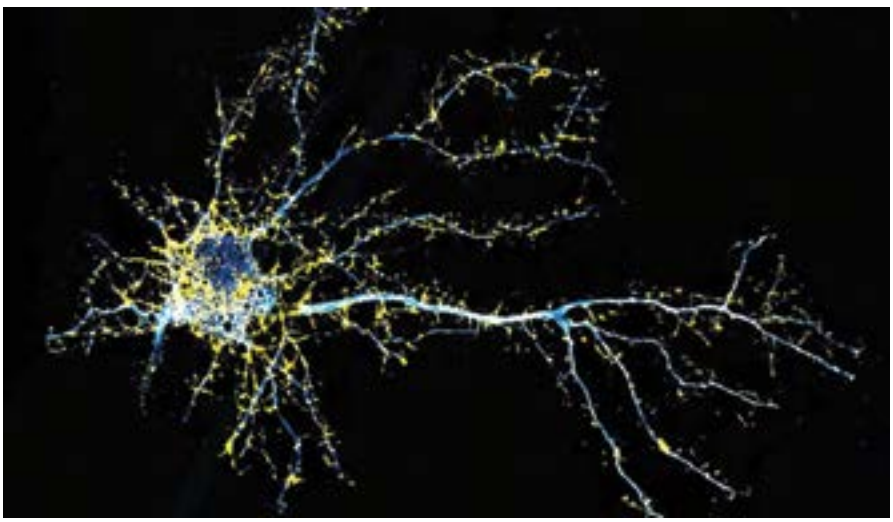
The research on JRT continues. Dr. Olson, who is a co-founder and head of the scientific advisory board of Delix Therapeutics, the developer of the drug, continue to test it as a possible schizophrenia treatment.

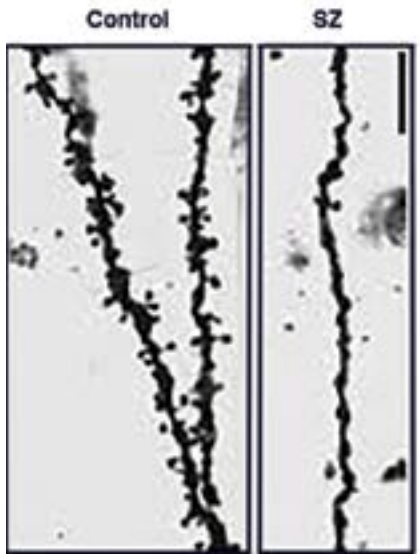
2. ALTER THE MOLECULE TO TARGET A DIFFERENT RECEPTOR

It has been suggested that LSD, psilocybin, and other psychedelics called tryptamine hallucinogens exert *both* their hallucinogenic and therapeutic effects when they bind at the serotonin 2A receptor. But those and some other psychedelic compounds also engage with a variety of other receptors, including the serotonin 1A receptor. In such cases, what roles do the various receptor targets play in the drugs' effects?

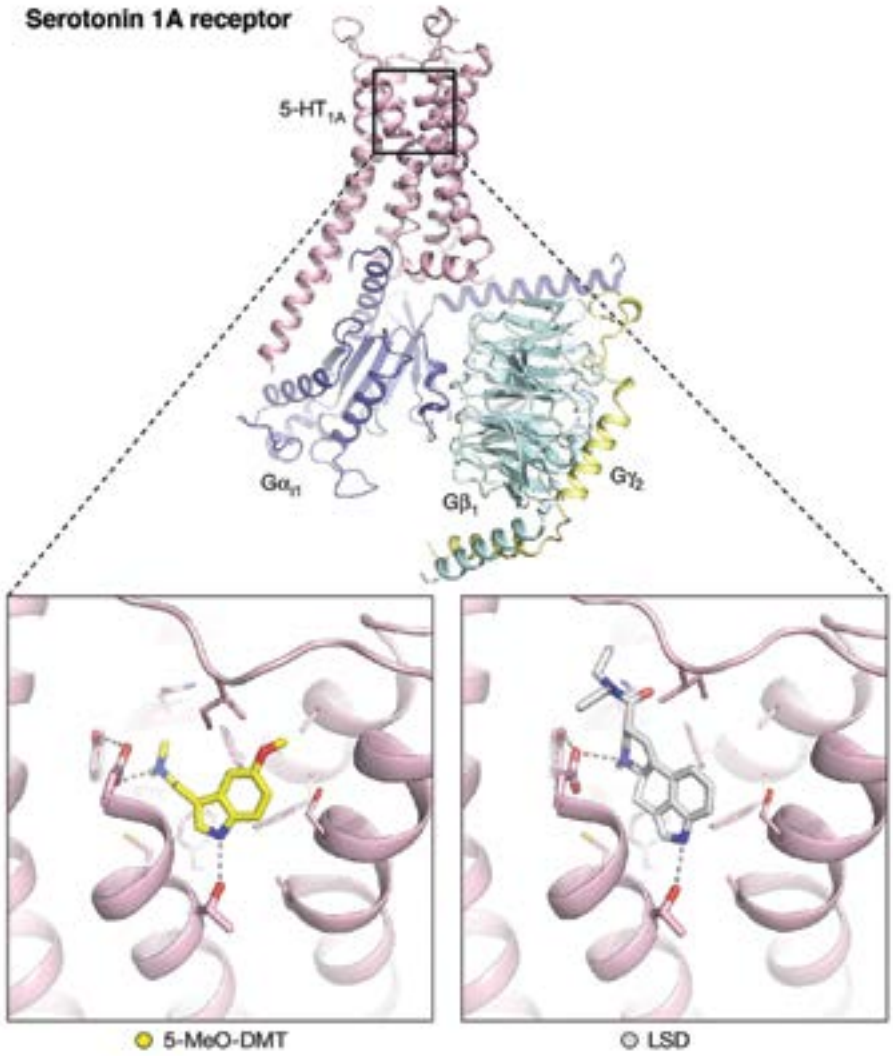
One psychedelic that engages both the 1A and 2A serotonin receptors is 5-MeO-DMT (sometimes called "five methoxy," "bufo," or "toad venom"), a toxin found in the glands of a toad found along the Colorado River. It's very similar to the powerful psychedelic DMT (the active ingredient in ayahuasca), and like it and others, is being considered for possible use in certain psychiatric conditions. A small study conducted recently in Mexico with U.S. Special Forces Veterans tested 5-MeO-DMT in concert with the psychedelic ibogaine for relief of acute PTSD and depression. Both are Schedule I substances currently banned for human use in the U.S.

Researchers believe their experiments highlight the potential of modifying the chemical structures of some psychedelics to produce analogues with improved efficacy and safety profiles.





RIGHT: In people with schizophrenia, dendritic spines, or contact points for communication among neurons, are greatly reduced relative to healthy controls—an example of cortical atrophy. **LEFT:** Treatment with the LSD analogue JRT in mice resulted in a strengthening of dendrites and proliferation of dendritic spines.



Researchers use x-ray-based technology to carefully scan biomolecules in crystalline form, including cellular receptors. Here, the technology enables investigators to picture at the atomic level precisely how the LSD molecule engages with the main docking site of the serotonin 1A receptor (detail, below right) compared with how 5-MeO-DMT docks at the same receptor (below left). This is a basis for understanding the effects of both drugs and for designing other molecules that might engage the receptor to generate different effects.

The type 1A serotonin receptor is a validated target of several FDA-approved drugs, including anti-anxiety and anti-depressant agents (buspirone and vilazodone). Yet, say a team of researchers led by Daniel Wacker, Ph.D., of the Icahn School of Medicine at Mount Sinai, and Dalibor Sames, Ph.D., of Columbia University, "little is known about how psychedelics engage it, and which of their effects are mediated by this receptor." They recently published results of a study in which they and colleagues performed a detailed structural and functional exploration of the mechanisms through which several "classical" tryptamine psychedelics as well as 5-MeO-DMT and several prescription drugs bind to and activate the 1A serotonin receptor at the molecular and atomic levels. **Scott J. Russo, Ph.D.**, a member of BBRF's Scientific Council and a 2008 and 2006 BBRF Young Investigator, and **Lyonna F. Parise, Ph.D.**, a 2022 BBRF Young Investigator, and were members of the research team.

In a mouse model of depression, they also tested a compound different but structurally analogous to 5-MeO-DMT that selectively targets the **serotonin 1A receptor**. One of the implicit questions they sought to shed light on was whether a drug targeting the 1A receptor alone, i.e., one that did not engage the 2A receptor, might still generate psychedelic effects, and whether it would still generate therapeutic effects (lowering anxiety and depression) ascribed to some psychedelics that bind primarily at the 2A receptor.

The team tested the 5-MeO-DMT analogue drug in mice subjected to social-defeat stress, which ordinarily leads the animals to avoid social interaction and to cease caring about seeking treats (similar to anhedonia in people). The analogue drug, which other experiments showed was a highly selective agonist of the serotonin type 1A receptor, "rescued" these deficits, the team reported, a finding with "potential implications for the therapeutic effects" of 5-MeO- class compounds in treating human psychiatric illnesses perhaps including depression, anxiety, and PTSD.

Other parts of the study generated data supporting the idea that both the 1A and 2A serotonin receptors are involved in stress-coping mechanisms on both a psychological and cellular level; the role of the 1A receptor in stress resilience; and the previously reported antidepressant effect of drugs that specifically target the 1A receptor in animals.

There was also preliminary evidence that the 5-MeO-DMT analogue targeting the serotonin 1A receptor

that was tested in mice "lacked the preclinical indications of classical psychedelic effects [e.g., the "head-twitch response"], which suggests that some of these compounds may not be hallucinogenic while retaining therapeutic effects."

The team described how the configuration of tiny three-dimensional spaces within cellular receptors called subpockets—in this case, highly specific to type 1A vs. 2A serotonin receptors—"determine both the potency and efficacy" of tryptamine hallucinogens at both receptors. This, they said, "provides a structure-guided framework that enables the development" of tryptamine psychedelic analogues "with finely tuned pharmacological activities and varying degrees of selectivity" for 1A and 2A serotonin receptor binding. Synthesizing and testing such compounds will be the subject of future studies.

Importantly, the team also suggested that FDA-approved medicines buspirone, vilazodone, and the antipsychotic aripiprazole, all of which target the serotonin type 1A receptor, engage with it differently than 5-MeO-DMT, generating signaling that is distinct from that produced when the psychedelic docks at the receptor to generate signaling outputs. These differences, as well as engagement of other receptor targets, probably accounts for the different effects of these medicines compared with the 5-MeO-DMT analogue tested in the socially defeated mice, the researchers said.

3. TARGET SPECIFIC CIRCUITS WITH NON-PSYCHEDELIC DRUGS

Another approach is to closely investigate the neural and circuit mechanisms though which psychedelics exert their effects. The hope is to see whether the brain cells and circuits that drive hallucinogenic effects are perhaps distinct from those that drive specific therapeutic effects.

New research of this kind, reported in 2024 in the journal *Science*, was led by 2021 BBRF Young Investigator **Christina K. Kim, Ph.D.**, a UC Davis collaborator of Dr. Olson, mentioned earlier. A co-author of the new paper, Dr. Olson said the idea of decoupling putative beneficial effects of psychedelics from their hallucinogenic effects is not, in this research, "a matter of chemical compound design," as it is in Method 1, described on pages 31–33. "Rather, it's a matter of targeting neural circuity."

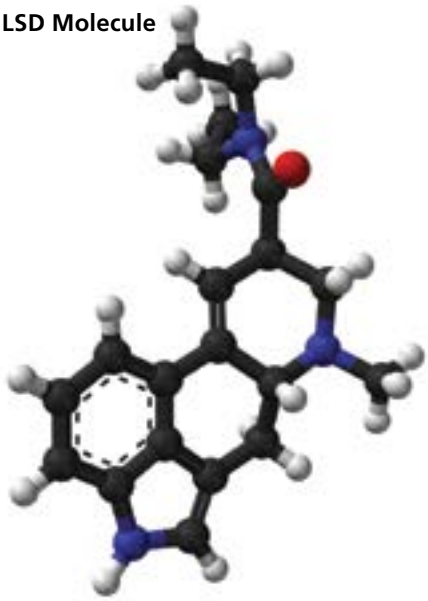
Drs. Kim, Olson and colleagues used a sophisticated technology in mice to apply genetics-based tags to neurons in the brain's medial prefrontal cortex (mPFC). This is an area where psychedelics engage the serotonin system, generating powerful "plasticity" effects. The psychedelic drug the team administered to their mouse-subjects is called DOI, a well-studied compound that targets, as many other psychedelics do, the serotonin 2A receptor.

In the minutes immediately following DOI administration, while mice were experiencing hallucinogenic effects (evident in their head-twitching behavior), the team used a technology called scFLARE2 to tag neurons in the mPFC that had been activated by the drug. These tags could be "placed" in the very short time window in which the drug is most active—a matter of minutes.

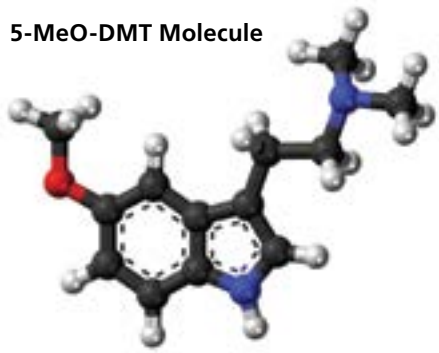
The tags enabled the researchers to molecularly profile the activated neurons, and also, in subsequent experiments, to selectively manipulate their firing using optogenetics, a technology co-developed by BBRF Scientific Council member **Karl Deisseroth, M.D., Ph.D.**, and colleagues that renders specific neurons sensitive to activation with laser light of a specific color.

Serotonin Molecule

LSD Molecule

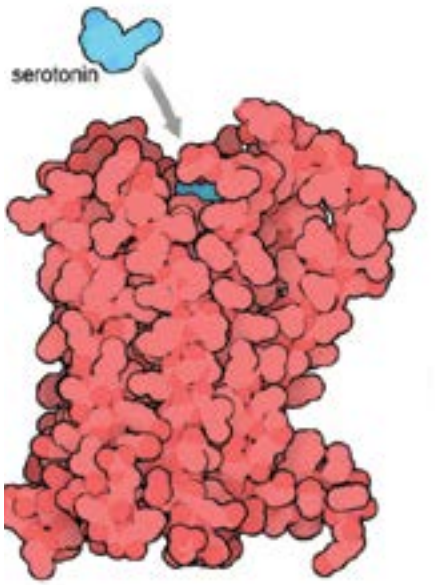


5-MeO-DMT Molecule



The precise shapes of these molecules are part of what determines whether they can engage with specific receptor types as well as what effects they generate once engaged.

The experiments revealed a psychedelic-responsive network of neurons in the mouse mPFC that included many neurons expressing the serotonin 2A receptor, but, importantly, not only these cells; the network extended beyond the population of cells bearing the receptor. This was a crucial discovery that helped the team determine that the hallucinogenic effects of the drug and capacity to reduce anxiety-like behaviors are not inextricably bound together but may in fact be distinct, in terms of neural circuity.



In a major reward center of the brain called the nucleus accumbens (NAc), serotonin release appeared to account for MDMA's prosocial effects in mouse experiments. This prosocial effect was the result of an interaction between MDMA and the serotonin transporter protein, called SERT, seen here, and subsequent activation of one of the many receptors for serotonin in the brain—the serotonin 1B receptor, in cells in the NAc.

Long after the hallucinogenic effects of DOI administration had ended in the mouse-subjects, the team found it was possible to use optogenetics to reactivate the neural network initially activated by the drug and associated with anti-anxiety effects, and in so doing, restore the anxiety-reducing effect of the drug when it was originally administered. This reactivation of tagged neurons, in fact, took place a full day after the drug had been administered and had long cleared the body.

"We thought that if we could identify which neurons activated by DOI were responsible for reducing anxiety, then we might be able to reactivate them at a later time to mimic those anti-anxiety-like effects," Dr. Kim says.

The team noted that while DOI is a potent psychedelic, it is not being considered as a potential therapeutic in the clinic. The point of the study was to dissect the basic circuit mechanisms that enable one psychedelic to exert both hallucinogenic but also anti-anxiety effects. Discovering circuity that specifically mediates the anti-anxiety effect in the case of DOI may be possible to extend to studies of other drugs and other impacts—for example, the anti-depressive or fear-extinguishing impact that some psychedelics have been reported to have in clinical tests. These potentially could reveal circuitry that might be specifically targeted in future therapies.

4. DISTINGUISH HOW PSYCHEDELCIS INTERACT WITH DIFFERENT NEUROTRANSMITTER SYSTEMS

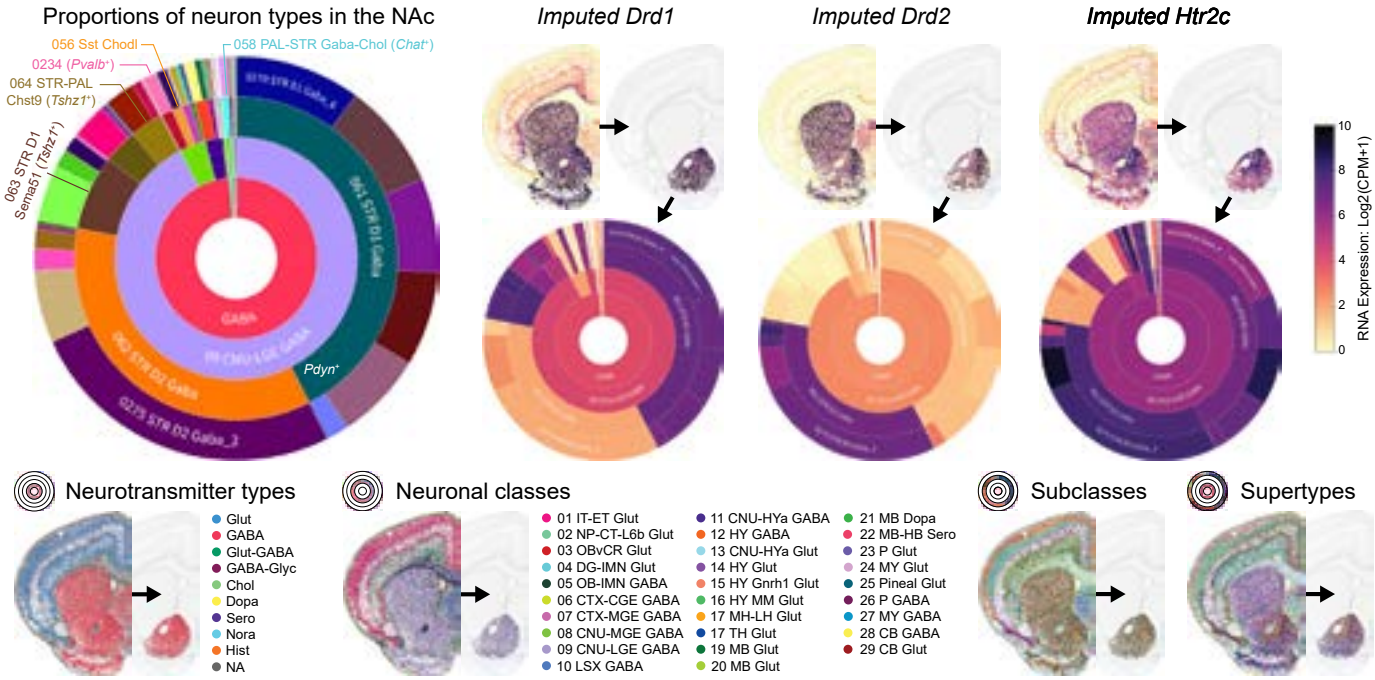
For several years, **Robert C. Malenka, M.D., Ph.D.**, a BBRF Scientific Council member and a 3-time BBRF grantee and prizewinner, along with some of his Stanford University colleagues, have been pursuing what they call a "circuits-first approach" to research aimed at better understanding psychedelic and other consciousness-altering drugs and their potential to be useful in the treatment of psychiatric illnesses. They have urged that by using modern neuroscience tools to "define the [brain-]circuit adaptations that contribute to a drug's behavioral and therapeutic effects, studies can be conducted to reveal new molecular targets in brain cells or circuits" which might be used as a basis for developing novel versions of psychedelic drugs that have maximum therapeutic impact and cause fewer side effects.

In a paper published this past July in *Molecular Psychiatry*, Dr. Malenka, along with senior collaborator Boris D. Heifets, M.D., Ph.D., and a team that included 2023 and 2020 BBRF Young Investigator **Neir Eshel M.D., Ph.D.**, show some of the fruits of the "circuits-first" approach. They closely studied how the drug MDMA exerts its principal effects—some undesirable, some potentially therapeutic—and found separate mechanisms that appear to be responsible for each. Taken together, the results suggest how and why MDMA appears to have lower abuse potential than some other psychotropic drugs, and may have potential for use as an "enactogen," a drug that induces feelings of empathy and emotional openness.

MDMA is not a "classical psychedelic," although it can have weak psychedelic effects. The behavioral effects of MDMA in assisted therapy applications tested in small trials in people with PTSD have indicated its characteristic properties: an enhanced sense of emotional connectedness and empathy, along with reduced fear when confronted with aversive stimuli like traumatic memories. But MDMA, an amphetamine, is prone to misuse and abuse, which, the team notes, is "an important risk consideration for treating patients with PTSD, many of whom have comorbid substance use disorders."

At the same time, MDMA is not as widely abused as closely related amphetamine drugs, such as methamphetamine. The question the researchers explored was whether MDMA's reduced abuse potential is mechanistically linked to its therapeutic behavioral effects. Prior work by the team indicated that MDMA has a molecular affinity for the protein that transports dopamine molecules in the brain, called the dopamine transporter (DAT). Like all amphetamines, MDMA amplifies dopamine release in the brain, which generates an intensely rewarding feeling—and is also the reason it can be addictive.

Serotonin 2C Receptor Expression Across Neuron Types in Nucleus Accumbens



Mouse experiments revealed that R-MDMA's activation of a specific receptor for serotonin in the NAc—the serotonin 2C receptor—actively suppressed dopamine release in that brain structure. This action, the team proposed, may account for MDMA's lower addictive potential. These graphics, generated by the team, are part of their effort to identify which neuronal types in the NAc and related regions bear the serotonin 2C receptors responsible for this important effect.

But unlike meth, MDMA also has a high affinity for the protein that transports serotonin in the brain, called the serotonin transporter (SERT), the new research indicated. In a major reward center of the brain called the nucleus accumbens (NAc), serotonin release appeared to account for MDMA's prosocial effects in various mouse experiments. This prosocial effect was the result of an interaction between MDMA and SERT, and subsequent activation of one of the many receptors for serotonin in the brain—the serotonin 1B receptor, in cells in the NAc.

In contrast, the nonsocial drug reward evoked by meth—as well as high doses of MDMA—appear to be traceable to dopamine release, in the same brain structure, the NAc. This raises the question of whether and how the specific dopamine- and serotonin-enhancing effects of MDMA in the NAc might be mechanistically related.

The form of MDMA administered in the experiments at various dosages (from low to high), called R-MDMA, is a version with a structural configuration that gives it distinct properties compared to conventional MDMA. Multiple structural forms of MDMA were administered for comparison purposes, as well as methamphetamine and cocaine. Tests were performed revealing the addictive properties of the drugs based on conditioned expectation of reward, as well as tests in which the social behavior of the animals could be closely observed before and after drug administration, including in animals with transporters for serotonin or dopamine genetically deleted.

One finding was that serotonin released after R-MDMA administration had the effect of *limiting the release of dopamine*, via activity observed in the NAc.

Further experiments revealed that R-MDMA's activation of a specific receptor for serotonin in the NAc—the **serotonin 2C receptor**—actively suppressed dopamine release in that brain structure. This action, the team suggested, may account for MDMA's lower addictive potential.

Other experiments provided evidence for the possible source of MDMA's prosocial effects. The form being tested as a potential therapeutic, R-MDMA, appears to have prosocial effects because it is more active at serotonin transporter molecules (SERTs) than at transporters for dopamine (DATs), especially in comparison with the standard form of MDMA, which affects these transporter molecules more evenly.

Importantly, the precise cellular location of the serotonin 2-C receptors in the NAc linked with the drug's limitation of dopamine release and thus its lower abuse potential is still unclear, and should be taken up in subsequent research, the team said.

Results of their study provide, they said, reason to continue exploring the use of R-MDMA (at low doses) in the clinic for therapeutic purposes in patients with illnesses like PTSD that often do not respond satisfactorily, or over the long-term, to current treatments. ❖ **PETER TARR**

The 2025 BBRF Klerman and Freedman Prize Winners

Six Young Investigators received the annual Klerman and Freedman Prizes on Friday, July 25th in New York City, in recognition of their exceptional research.

These two prizes pay tribute to Drs. Gerald L. Klerman, M.D. and Daniel X. Freedman, M.D., whose legacies as researchers, teachers, physicians, and administrators have indelibly influenced neuropsychiatry. These prizes recognize exceptional clinical and basic research by young scientists who have been supported with BBRF Young Investigator Grants—our hallmark program which enables aspiring young scientists with innovative ideas to garner the pilot data needed to often go on to receive further funding once they have "proof of concept" for their work.

The prizewinners are selected by committees of the Foundation's Scientific Council, an all-volunteer group of 195 distinguished scientists across brain and behavior research disciplines. This early recognition of their work by the Foundation's Scientific Council often serves as a precursor to further accomplishments, awards, and prizes.

1. Dr. John Krystal, Dr. Amy Arnsten, Geoffrey Simon, Dr. Judith Ford, and Dr. Helen Mayberg
2. Dr. Nathaniel Harnett
3. Dr. Joseph Taylor and Dr. Jeffrey Borenstein
4. Dr. Zachary Pennington
5. Dr. Jeffrey Borenstein and Dr. Joshua Gordon

2025 Klerman Prize

The Klerman Prize was established in 1994 by BBRF Scientific Council Member Myrna Weissman, Ph.D., in memory of her late husband, Gerald Klerman, M.D.

The **Selection Committee for the Prize** was **chaired by Karen Dineen Wagner, M.D., Ph.D.** Other members included: Anissa Abi-Dargham, M.D.; Zafiris J. Daskalakis, M.D., Ph.D.; Martin B. Keller, M.D.; Cecile D. Ladouceur, Ph.D.; Dost Ongur, M.D., Ph.D. and Nina R. Schooler, Ph.D.

2025 Klerman Prizewinner for Exceptional Clinical Research

Joseph J. Taylor, M.D., Ph.D.

Mass General Brigham
Harvard Medical School

2022 BBRF Young Investigator

"The BBRF Young Investigator Grant allowed me to zero in on a critical scientific question. Without it, I would have been unable to run the study or collect pilot data for my first R01 application."

Dr. Taylor was honored for his work on "The Role of Individualized Targeting in Accelerated Intermittent Theta-Burst for Depression."

Dr. Taylor serves as Medical Director of TMS and Director of Clinical Trials, at BWH Center for Brain Circuit Therapeutics; Assistant Program Director and Research Track Co-Director, at BWH Psychiatry Residency Program; and Director, BWH Interventional Psychiatry Research Program Assistant Professor of Psychiatry, at Harvard Medical School.

His research focuses on deriving and testing brain stimulation targets for psychiatric illness. He derives targets with network mapping, a method that leverages the human connectome (a wiring diagram of the human brain) to examine the connectivity patterns of brain lesion locations or brain stimulation coordinates that causally modify neuropsychiatric symptoms. Dr. Taylor tests these targets in clinical trials using invasive and non-invasive brain circuit interventions.

"The Klerman Prize is a celebration of community—of the family members, friends, colleagues, mentors, mentees, administrators, patients, study participants, and funders who play a role in good science. I am deeply humbled, and I can't wait to pay it forward."

2025 Klerman Prize Honorable Mentions

Ryan Thomas Ash, M.D., Ph.D.
Stanford University
University of California,
San Francisco

2022 BBRF Young Investigator

Dr. Ash was honored for his work on "Transcranial Ultrasound Neuromodulation of the Human Amygdala to Enhance Fear Extinction for Treatment of Anxiety and Post-Traumatic Stress Disorders."

Dr. Ash is a psychiatrist and clinician-scientist, whose primary current research goal is to help develop novel methods to rebalance neural circuit stability and plasticity in deep-brain areas to enhance recovery from neuropsychiatric illness. His work is grounded in the new field of transcranial ultrasound stimulation (TUS), a noninvasive technique that allows focal neuromodulation of the deep-brain areas like the amygdala, striatum, and hippocampus most implicated in psychiatric disease. He is well positioned to lead the translation of this technique into a new generation of circuit-based therapeutics. His clinical specialty is in functional neurological disorder (FND), and he currently directs a FND tertiary-referral practice in the Stanford Neuropsychiatry Clinic. He is starting his independent research lab in the UCSF Department of Psychiatry in Fall 2025.

"It is a distinct honor and pleasure to be recognized by the distinguished Klerman award committee. I'm so grateful for the work that BBRF does, and I sincerely hope that their investment in my growth will lead to better treatments for those who suffer with mental illness."

Nathaniel G. Harnett, Ph.D.
McLean Hospital
Harvard Medical School

2022 BBRF Young Investigator

Dr. Harnett was honored for his work on "Multimodal Fusion of Structure-Biochemical Neuroimaging Data to Understand PTSD Risk After Trauma."

Dr. Harnett is a neuroscientist whose research is focused on understanding the brain basis for why some people are more likely to develop stress-related disorders, such as post-traumatic stress disorder (PTSD), after trauma. His current work leverages magnetic resonance imaging (MRI) techniques—including functional MRI, structural MRI, and diffusion weighted imaging—to identify multimodal neural signatures of PTSD susceptibility in the acute aftermath of trauma exposure.

The overarching emphasis of Dr. Harnett's work is on elucidating neural circuitry linked to acute and long-term development of post-traumatic syndromes and identifying robust and generalizable neurobiological targets for early intervention and treatment. The goal of this research is to develop predictive and preventative neuroscience-based techniques to reduce the prevalence of trauma and stress-related disorders.

"The BBRF Young Investigator grant provided critical support at an early stage in my career to get our research, really focused on understanding PTSD vulnerability, off the ground; it serves as the foundation for all of the work we're doing going forward."

2025 Freedman Prize

The Freedman Prize was established in 1998 in honor of the late Daniel X. Freedman, M.D., a founding member of BBRF's Scientific Council.

The **Selection Committee for the Prize** was **chaired by Ariel Y. Deutch, Ph.D.** Other members included: Ted Abel, Ph.D.; Cecilia Flores, Ph.D.; Peter W. Kalivas, Ph.D.; Keri Martinowich, Ph.D.; Marina R. Picciotto, Ph.D., and Vikaas S. Sohal, M.D., Ph.D.

2025 Freedman Prizewinner for Exceptional Basic Research

Long Li, Ph.D.

Institute of Biophysics
Chinese Academy of Sciences

2021 BBRF Young Investigator

"The BBRF Young Investigator Grant represents far more than funding to me: First, personally, it gives me a lot of confidence in research; second, it's both an honor and a responsibility to translate this opportunity into meaningful advances for mental health."

Long Li, Ph.D. was honored for his work on "Circuit Mechanism of Social Reward Impairment in Depression Model."

Dr. Li's lab focuses on developing novel animal models for neuropsychiatric disorders, such as depression and PTSD, to uncover new molecular targets and therapeutic avenues. Specifically, they investigate neuronal molecular biomarkers modulated by innovative drugs for treating depression and anxiety, as well as seek to develop proactive coping strategies for stress. Their goal is to pinpoint which neurons and molecules can be targeted to alleviate disease symptoms. By elucidating the cellular mechanisms of therapeutic drugs in the brain, the lab aims to enhance drug specificity and minimize adverse effects. It is hoped that this foundational understanding will ultimately guide the design of optimized treatments with improved efficacy and tolerability.

"As a young investigator, I am incredibly honored to receive the Freedman Prize, and deeply motivated by the Foundation's commitment to supporting basic science that lays the groundwork for better treatments. This recognition reinforces our mission to uncover the neural and molecular underpinnings of depression and PTSD, with the ultimate goal of translating these insights into more precise and effective therapies."

2025 Freedman Prize Honorable Mentions

Hermany Munguba, Ph.D.
University College London

2022 BBRF Young Investigator

Dr. Munguba was honored for his work on "Circuit-Based Discovery of New Antidepressant Targets."

After completing his Ph.D. at the Karolinska Institute in Sweden, Dr. Munguba's curiosity about the brain evolved into a sense of urgency to understand the circuit basis of psychiatric disorders. During his postdoctoral training, Dr. Munguba's experience in neuronal cell diversity enabled him to merge his knowledge in circuit connectivity to his host lab's expertise in stress-related disorders and neuromodulation. Today, his research vision is to advance new discoveries at the intersection of basic and translational neuroscience, aiming to identify molecular, cellular, and circuit pathways involved in the onset and relief of symptoms common to major depressive disorder. His research aims to close the gaps between foundational neuroscience and clinical application, ultimately guiding the development of novel, disease-modifying treatments targeting cell types and circuits related to symptom-specific pathology.

"Receiving the Freedman Prize Honorable Mention is a very meaningful recognition of my research journey. It validates the persistence, curiosity, and efforts that went into my projects, and encourages me to keep pursuing rigorous and translationally guided research. I'm honored to be acknowledged alongside such talented peers and inspired to continue contributing to the academic community."

Zachary Pennington, Ph.D.
Icahn School of Medicine at Mount Sinai
University of British Columbia

2022 BBRF Young Investigator

Dr. Pennington was honored for his work on "Contributions of the Anterior Hypothalamic Nucleus to Post-Trauma Stress Sensitization."

Dr. Pennington's research focuses on understanding the alterations in brain function responsible for anxiety and stress-related disorders, with the ultimate goal of advancing novel treatments for these conditions. To pursue this goal, he uses cutting-edge tools for visualizing how neural circuits change in response to stressful life experiences and manipulating these circuits to modify their influence on behavior. The hope is that by identifying the specific brain circuits involved in anxiety and stress, more targeted treatments can be discovered. Dr. Pennington is also a contributor to several open-source projects, helping make modern scientific tools accessible to all. With the help of BBRF support, Dr. Pennington defined a novel brain region's role in vulnerability to stressful life events and is continuing to identify specific cell types within this brain region that might be targeted in conditions like PTSD. Dr. Pennington will be opening his own lab at the University of British Columbia in January 2026.

"I am immensely grateful to have been selected for a Freedman Prize Honorable Mention. Since the beginning of my training, my goal has been to advance our understanding of how changes in brain function influence mental health. To be selected for this distinction by a foundation that has made tremendous strides in this pursuit is a great honor. Moreover, as a young investigator just about to launch their own lab, this distinction is wonderful encouragement that I am on the right track."

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Recent Research Discoveries

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

Brain Changes Underlying PTSD Are Revealed in Detailed Analysis at the Single-Cell Level

A new study has provided what is likely the most detailed account to date of biological changes that take place in the brain when someone has post-traumatic stress disorder (PTSD). The findings shed light on PTSD pathology, identify specific and potentially targetable genetic, cell-type, and functional alterations, and also shed light on factors distinguishing brain changes in PTSD vs. major depressive disorder (MDD).

Led by **Matthew J. Girgenti, Ph.D.,** of Yale University, a two-time BBRF Young Investigator whose 2023 grant award helped support this research, a team that included 8 other recipients of BBRF grants examined a variety of changes at the single-cell level in 111 postmortem brains donated by people in three subgroups: those who had lived with PTSD, those diagnosed with MDD, and those who did not have a psychiatric diagnosis. Of the past BBRF grantees on the team, two are members of BBRF's Scientific Council: its Vice-President, **John H. Krystal, M.D.**, and **Kristen J. Brennand, Ph.D.**, both of Yale.

The data that contributed to the team's analysis was derived from over 2 million individual cells from the brain's dorsolateral prefrontal cortex (DLPFC), and specifically from the nuclei of those cells, which harbor the human genome and the regulatory elements that determine how and when genes are expressed. Until recently, it was not possible to study genetic variation in individuals affected by a given disorder at the level of individual cells in brain regions of interest like the DLPFC, which is part of the cerebral cortex and plays a major role in the regulation of emotions. "Advances in genome technologies now enable the study of chromatin assemblies in individual cells," the team noted, referring to the bundling of DNA in the cell nucleus that helps determine which of our ~21,000 genes can be activated and which cannot be at a given moment.

When combined with an analysis of which genes in a cell are being expressed, chromatin data can provide the resolution needed to identify how DNA variations associated with PTSD affect the process called transcription—the copying of genetic information to RNA—in individual cells. It is at this fine level of detail that progress can be made in learning how an illness like PTSD or depression alters neurons and the circuits they form, as well as other brain-cell types.

This new capability is especially significant in trying to understand the biological causes and effects of some psychiatric illnesses including PTSD and depression, which, unlike brain diseases like Alzheimer's, are not associated with large-scale pathologies like plaques that can be readily imaged.

"We annotated and censused all major [brain] cell types, including excitatory and inhibitory neurons and non-neuronal cell types," the team reported in the journal *Nature*. "We identified cell type-specific genes that were expressed differentially in PTSD and converging and diverging expression changes between PTSD and MDD." They also "constructed the regulatory landscape" impacting gene expression in PTSD. These and other analyses led to a number of major findings.

Among the postmortem brains with PTSD, the team's investigation revealed notable gene alterations in inhibitory neurons, which "fine-tune" excitatory brain circuits and in this way regulate them, among other things preventing them under normal conditions from firing too much. In brains affected by PTSD and MDD, the team observed a decrease in communication from inhibitory neurons—which may account for hyperexcitation in the prefrontal cortex. Following a traumatic experience, hyperexcitability might give rise to some of the symptoms seen in PTSD, such as hypervigilance or even nightmares.

The immune cells unique to the brain, microglia, were found to be overactive in the MDD brains and underactive in the PTSD brains. The apparent suppression of neuroimmune processes and microglial activity in the PTSD brains "is a finding that seems to differentiate MDD and PTSD," Dr. Girgenti noted, despite a number of previously noted genetic overlaps.

The PTSD brains were found to have genomic changes associated with dysregulation in endothelial cells, which line the blood vessels. This was an unexpected finding. It is known, however, that cortisol, the primary stress hormone, is paradoxically present at unusually low levels in PTSD brains. The team speculated that this previously unknown neurovascular dimension of PTSD, mirrored by high levels of activity in endothelial cells of a previously identified PTSD risk gene called FKBP5, may prove to be a mechanism to compensate for the unusually low cortisol levels.

Taken together, the study "enabled us to identify genes and pathways associated with PTSD pathology." These included stress hormones, immune, and neuroinflammatory mechanisms, in addition to the inhibitory neurotransmitter GABA.

About half of people with PTSD also suffer from MDD. The study helps identify "convergent and divergent molecular effects of both," the team said. ❖

Alcohol-Regulating Hormone Delivered in Combination With GLP-1 Drug Could Have Potential Application in Alcohol Use Disorder

Researchers led by a BBRF grantee report new research extending knowledge about how a naturally occurring hormone called FGF21 helps to regulate alcohol consumption. Using a synthetic analogue of the hormone, they showed in mouse experiments how it appears to impact behaviors relevant in alcohol consumption as well as how it impacts the activation of neurons involved in the initiation and termination of drinking.

The research is promising in part because FGF21 and the pathways it impacts are targets of interest in the development of new treatments for alcohol use disorder (AUD). A number of medications for AUD are in use today (naltrexone, nalmefene, acamprosate, and topiramate), but their effectiveness varies widely and the search for new treatments continues.

FGF21 is one of a number of peptides (protein fragments) that operate in the body as hormones and play key roles in metabolic health (glucose regulation, insulin sensitivity) and energy balance. These include GLP-1, produced in the gut and the target of weight-loss and diabetes medicines such as Ozempic and Mounjaro. FGF21 (fibroblast growth factor 21) is generated in the liver in response to various metabolic stressors, including alcohol.

In a paper appearing in *Neuropsychopharmacology*, a team led by 2020 BBRF Young Investigator **E. Zayra Millan, Ph.D.**, of the University of New South Wales, Sydney, Australia, point to three lines of evidence implicating FGF21 in the regulation of alcohol consumption. One is experiments in mice in which induced overexpression of FGF21 as well as pharmaceutical administration of an FGF21 analogue both lead to reduced preference for alcohol. Second, in large-scale genome studies

in people, DNA variations affecting the gene that encodes FGF21 and its cellular receptor are statistically associated with alcohol consumption and risk of AUD. Third, studies in which FGF21 signaling is disrupted or blocked result in increased alcohol consumption by laboratory mice.

The latter experiments serve to remind that FGF21 is involved in signaling that normally acts to curtail alcohol consumption. A pathway carrying this signal has been localized in mice, and involves neurons in the basolateral amygdala (BLA) that project to the nucleus accumbens (NAc). Stimulation of the relevant NAc neurons inhibits consumption, while a pause in activation of these neurons is required when an individual initiates and maintains alcohol consumption. How FGF21 affects these NAc neurons was unknown prior to the current study.

Dysregulation of FGF21's normal function could be one way of understanding how chronic and habitual alcohol consumption can lead to AUD. Mammals began consuming alcohol from fermented fruit long before humans developed methods to distill alcohol. It is therefore not surprising that multiple bodily systems in mammals, including humans, evolved over time to sense and regulate alcohol consumption. The prevalence of AUD in humans indirectly suggests that naturally evolved regulatory systems can become dysfunctional, removing the evolutionary "brake" on excessive or health-impairing alcohol intake.

In their newly reported research, Dr. Millan and colleagues used an FGF21 analogue called PF-05231023 to confirm FGF21's ability to reduce voluntary alcohol consumption and preference for alcohol (vs. other fluids offered—sweetened water, in the mouse experiments). But the results that are most notable concerned the influence of the FGF21 analogue on behaviors involving alcohol consumption. Notable among these are "approach behaviors," i.e., those an individual takes toward a stimulus perceived to be positive or rewarding. In alcohol consumption, a variety of cues, such as time of day, a specific activity, or suggestion by peers can trigger approach behaviors, i.e, actions required to obtain alcohol.

The team's experiments showed that the FGF21 analogue directly reduced alcohol consumption in male mice, but not females. The reason for the sex specificity is not clear and will be pursued in future studies. The team suggests the difference may be due to sex-specific metabolic effects of synthetic FGF21 (the analogue, as opposed to the naturally occurring hormone), and/or may be related to a difference in expression of FGF21 receptors in males and females or in liver status relative to diet.

In both sexes, the FGF21 analogue weakened the intensity of responses following the presentation of alcohol-related cues, and also reduced the motivation of individual animals to seek alcohol. Importantly, the drug did not affect the animals' pursuit of sugar when sucrose-related cues were given or when motivation to seek sucrose solution was tested. This is one of several pieces of evidence suggesting to the team that the FGF21 analogue's effects on consumption was reward-specific—it did not perturb the reward response globally.

The experiments also showed that the FGF21 analogue's impact on alcohol drinking in males appeared to be associated with "pre-ingestive evaluative processes and reward palatability." In other words, the hedonic, or pleasure-driven urge to consume alcohol appeared to be altered.

The team administered the FGF21 analogue in concert with a sub-therapeutic dose of a GLP-1 stimulating drug called Exendin-4, which targets signaling between the gut and brain to control metabolism. Their joint administration had the effect of augmenting the impact of the FGF21 analogue on alcohol-seeking behavior. Exendin-4, alone, had no such effect.

To the team, this was evidence of a "complementary and interdependent mechanism of action" in FGF21 and GLP-1. "Our findings suggest that combination agonist [i.e., hormone-stimulating] approaches may be of benefit in the treatment of AUD." Such an approach, they note, is already being tested in context of weight loss and insulin sensitivity. ❖

Addictive Use of Phones, Social Media, & Video Games Is "Common" in Young Adolescents and Linked to Mental Health Risks, Study Finds

Researchers using 4 years of interim data from a large, ongoing study of mental health and brain development in American children and adolescents have found that "high" or "increasing" addictive use of screen-based activities is not only commonplace, but is also associated with two to three times higher rates of suicidal ideation, suicidal behaviors, and other mental health problems, compared with those with "low" addictive or much weaker habitual screen use.

The new study, published in the *Journal of the American Medical Association (JAMA)*, is an important contribution to the vigorous debate about how the advent and ubiquitous use of social media, mobile phones, and video games is affecting young people.

Considerable past research has focused on the potential impact of total screen time on youth mental health. Results have been inconclusive. The new study, while including screen time in its analysis, finds that it is not, by itself, specifically associated with elevated risk for suicidal ideation or behavior or what psychiatrists call internalizing and externalizing behaviors. ("Internalizing" refers to inward-directed problems such as anxiety and depression; "externalizing" refers to problems directed at others, such as aggression or rule-breaking.) Rather, the study finds, it is the role that high or increasing addictive use trajectories of screen-based activities play in the lives of young people that can specifically be linked with adverse mental health outcomes, including those associated with suicide.

BBRF Scientific Council member **J. John Mann, M.D.**, a world authority on suicide at Columbia University and the New York State Psychiatric Institute, and the winner of 2022 BBRF Colvin Prize and a 2008 BBRF Distinguished Investigator, was senior member of the team.

The researchers based their study on the most recent release of data from the U.S. government-supported Adolescent Brain and Cognitive Development (ABCD) study, which has recruited over 11,000 youths ages 9 and 10 at 21 U.S. sites. These young people are being followed all the way through adolescence, to the transition to adulthood.

A total of 4,635 of the ABCD participants completed surveys at their 2-, 3- and 4-year follow-ups after joining the study. These follow-ups included self-reports of screen use and habits as

well as self- and parental reports of mental health. The cohort analyzed for the current study numbered 4,285 youths, who were 10 years old on average at the study's baseline and 14 at the 4th follow-up. About 59% were White, 19% Hispanic, 10% Black, and 2% Asian. Two-thirds of their parents had a college degree or higher and 73% were married. About 40% of participants' parents earned under $75,000 annually.

Establishing "addictive use" for the 3 screen-based modes—social media, mobile phones, and video games—was based on several self-report questionnaires, filled out annually over the 4-year interval monitored in the study. These included questions such as "I feel the need to use social media apps more and more" (1=never, 6=very often); "The thought of being without my phone makes me feel distressed" (1=strongly disagree, 7=strongly agree); and "I play video games so I can forget about my problems" (1=never, 6=very often). All of these have been shown to have high reliability in past studies.

Child and parent reports of suicidal behaviors and suicidal ideation over the prior year were assessed at year 4, using another well-validated questionnaire covering a spectrum of suicide-related outcomes. These included, for ideation: a "yes" reply to either: passive ideation; nonspecific active ideation; specific active ideation; active ideation with intent; or active

ideation with plan and intent. Suicidal behavior was indicated with a "yes" reply to any of the following: preparatory actions for imminent suicidal behavior; interrupted attempt; aborted attempt; or actual attempt.

"This study identified distinct trajectories of addictive use of social media, mobile phones, and video games from childhood to early adolescence, and found links to suicidal behaviors, suicidal ideation, and worse mental health outcomes," the team reported.

For both social media and mobile phones, addictive use trajectories followed 3 different patterns, "and a substantial proportion of youths had addictive use trajectories that increased over the 4 years of observation, starting at age 10," the team said. These patterns of increasing addictive use as the years passed, they noted, "would not have been predicted" based on assessments made at the beginning of the study, and were specifically associated with suicidal behaviors and ideation. "This underscores the potential importance of repeated assessment" of addictive screen use as children enter adolescence, they said.

Video game use was found to follow 2 trajectories, dubbed "high" and "low." These were stable over time, which to the team means that those most at risk might be identified early, without the need for repeated assessment.

Almost 1 in 2 youths had a high addictive use trajectory for mobile phones, and more than 40% had such a trajectory for video games. "Many others had increasing addictive use over the 4-year observation period which ended with high addictive use." Almost 1 in 3 had this "increasing addictive" trajectory for social media and 1 in 4 for mobile phones.

As for how these trajectories affected mental health risk: for social media and mobile phones, both the "high" and "increasing" addictive use paths were associated with 2 to 3 times greater risks of suicidal behaviors or ideation, compared with "low" addictive use trajectories (i.e., not all "addictive" use was linked with increased suicide risk—just "high" or "increasing" addictive use). Also, "high" and "increasing" addictive use of social media were found to be associated with higher internalizing and externalizing symptom scores compared with the "low" addictive use trajectory. The "high" addictive use path for video games was linked with higher risks of suicidal behaviors and ideation and higher internalizing symptoms compared with the "low" addictive use path.

Total screen time was not found in this study to be associated with suicide-related or mental health outcomes, nor did it alter the various findings regarding associations between addictive use trajectories and these outcomes. "Total screen time" and "addictive use" are likely two different constructs, the team said. This is not to say, however, that total screen time is not an important factor in mental health. For example, long periods on the phone or other screen activities are well understood to crowd out sleep, exercise, and face-to-face contact in many users—none of which are healthy. Both constructs are likely important, though in different ways.

The current study calls urgent attention to the issue of developing effective preventive and treatment approaches for those youth who do become addicted to their screens. ❖

Therapy Update

Recent news on treatments for psychiatric conditions

COMBINED tDCS BRAIN STIMULATION AND COGNITIVE REMEDIATION SLOWED COGNITIVE DECLINE IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT OR REMITTED MAJOR DEPRESSION

Tarek K. Rajji, M.D.

Older adults who have mild cognitive impairment (MCI) or past or present major depressive disorder (MDD) are at increased risk for cognitive decline and dementia.

The reasons are not clear, but some researchers suspect a main culprit is a loss of neural plasticity in the brain—the ability of neurons to change the strength of their connections (essential in learning and memory, among many other mental operations). Plasticity declines naturally with age, and perhaps at an accelerated pace when an older individual suffers (or has suffered) from depression, an illness which itself likely involves a loss of plasticity.

The relationship between major depression and cognitive decline in older people applies to those whose depression has been in remission for years or even decades, note a team of researchers who recently reported a clinical trial testing a potential approach for slowing cognitive decline in older individuals with remitted major depression (rMDD) or MCI.

The team, led by 2010 BBRF Young Investigator **Tarek K. Rajji, M.D.**, of the Centre for Addiction and Mental Health (CAMH) and the University of Toronto, Canada and now at the University of Texas Southwestern Medical Center, and Benoit H. Mulsant, M.D., of CAMH and the University of Toronto, Canada, included 10 recipients of BBRF grants, among them two members of BBRF's Scientific Council, **Zafris J. Daskalakis, M.D., Ph.D.**, and **Aristotle N. Voineskos, M.D., Ph.D.**

The team devised a treatment approach knowing that the prefrontal cortex (PFC) is overactive in healthy people who carry the APOe4 gene variant that raises risk for Alzheimer's disease, as well as in people with MCI. The PFC is underactive in adults with major depression when the brain is at rest, and either over- or underactive during executive function tasks.

Hoping to slow cognitive impairment in those at elevated risk due to remitted major depression or MCI, the team recruited people at five medical centers in Toronto, of whom 375 were included in the cohort that generated analyzable data. These 232 women and 143 men either had rMDD, MCI, or both. On average they were 72 years old and were followed up for up to 7 years (median 4 years). Depression ratings in the rMDD participants were low—the equivalent of "no or minimal active symptoms."

Randomly divided into two demographically comparable groups, the trial participants received either a combination "active treatment" consisting of cognitive remediation plus non-invasive tDCS sessions (transcranial direct current stimulation), 5 days a week for 8 weeks; or "sham," i.e., placebo versions of both cognitive remediation and tDCS over the same period. The follow-up period featured twice-yearly "booster" sessions of the active or sham treatments plus daily at-home computer-based cognitive remediation or a sham version throughout the study (i.e., up to 7 years). The follow-ups continued through the study's endpoint or the point at which a participant progressed from normal cognitive status to MCI or from MCI to full-blown dementia.

tDCS (active or sham) was delivered during the cognitive remediation sessions (active or sham). The non-active version of tDCS applied standard tDCS low-power current (2 milliamperes) to the scalp via electrodes for less than one minute, compared with the half-hour received by those in the active treatment group. The placebo version of cognitive remediation was designed, on its face, to be indistinguishable from the active version, although those who received the placebo were given less difficult tasks to complete and no coaching.

At the beginning of the trial and at all follow-ups (after the initial 8 weeks, and then yearly from baseline until the end of the study), depression symptoms were evaluated, and a neurocognitive battery of tests assessed 6 cognitive domains in each participant: processing speed, working memory, executive function, verbal memory, visual memory, and language.

The team reported results in *JAMA Psychiatry*. "Our results support the efficacy of cognitive remediation plus tDCS in slowing cognitive decline for up to 6 years in older adults with remitted major depression or mild cognitive impairment." Effects were more pronounced, they said, in executive function and verbal memory and in participants with rMDD, as well as in those at low genetic risk for Alzheimer's (i.e., participants who did not carry a high-risk gene variant of the APOe4 gene). In participants with MCI only, the active combined treatment had "limited acute [short-term] and long-term benefits."

The study was not designed to determine if cognitive remediation plus tDCS or either one alone was responsible for the beneficial effects that were seen in participants with rMDD. But noting "small and nonsignificant effects" of cognitive remediation alone on cognition in prior long-term studies, the team says their findings at least suggest that "pro-cognitive effects" are indeed present over the long term when tDCS is added to cognitive remediation in those with rMDD.

They believe further study to replicate or extend the results in this trial is warranted, using larger and more diverse participant populations. It would also be advantageous, they said, to conduct a trial with a comparison group that had neither remitted MDD nor mild cognitive impairment; in that way, it might be possible to determine if any observed cognitive benefits are specific to these high-risk conditions. ❖

NON-INVASIVE ULTRASOUND BRAIN MODULATION THERAPY SHOWS POTENTIAL TO TREAT MOOD DISORDERS, ANXIETY, TRAUMA, ACROSS DIAGNOSES IN PILOT TRIAL

Gregory A. Fonzo, Ph.D.

Over the last two decades, non-invasive brain stimulation, especially rTMS (repetitive transcranial magnetic stimulation), has become a widely used therapy for psychiatric disorders, most especially depression. In recent years, rapid-acting versions have been successfully introduced to treat severe, treatment-resistant major depressive disorder, while in other applications, non-invasive stimulation has been tested to address other conditions, including PTSD and OCD.

In a paper published in *Molecular Psychiatry*, researchers led by **Gregory A. Fonzo, Ph.D.**, a 2019 BBRF Young Investigator at the University of Texas at Austin Dell Medical School, report on a pilot study of low-intensity transcranial focused ultrasound (tFUS), which they tested for safety and therapeutic potential in 29 patients with a variety of mood, anxiety, and trauma-related disorders, as well as in 23 healthy controls.

While rTMS uses magnetic pulses to alter the activity of cortical cells just beneath the skull, tFUS uses focused high-frequency soundwaves to reach areas of the brain that lie beneath the cortex—so-called subcortical areas. rTMS can affect subcortical structures such as the amygdala and hippocampus, but only indirectly, via connections forged by stimulated cortical cells with those structures. In tFUS, there is no cortical intermediary; focused sound waves reach directly into the subcortical brain and can be targeted with considerable precision.

The study performed by Dr. Fonzo and colleagues, who included **Charles B. Nemeroff, M.D., Ph.D.**, a BBRF Scientific Council member, 1997 Selo Prize-winner, and two-time Distinguished Investigator (1996, 2003), focused

on tFUS's impact on the amygdala, a subcortical structure centrally involved in the processing of emotions. Hyperactivity in the amygdala is thought to be implicated in a range of psychiatric conditions.

The experiments, in addition to testing an application of tFUS technology, reflect an approach advanced at the National Institutes of Health that encourages researchers to think of psychiatric symptoms across diagnostic boundaries. Called RDoC, or Research Domain Criteria, it regards the amygdala, for example, as a key mediator of "all negative valence subdomains," i.e., brain areas involved in generating negative feelings that include perceptions of acute threat (fear), potential threat (anxiety), sustained threat, loss, and lack of reward. These constructs are interconnected and relate to responses to aversive situations or contexts, and some or all of them may be involved in various mood, anxiety, and trauma-related disorders.

The team's premise was: if tFUS is capable of safely and therapeutically modifying the amygdala, specifically in reducing hyperactivity in the structure, it could conceivably be used across diagnoses as a form of therapy. Current therapies including SSRI antidepressants and psychotherapy may act across diagnoses to some important extent. But many who receive these and other therapies don't respond or don't respond fully or in a durable way. Hence, the continuing search for new approaches.

A single application of focused ultrasound ("sonication") has been shown to alter neurobiological function in monkeys which can last over one hour. These and other tests indicate that tFUS alters neuroplasticity, i.e., the ability of neurons to change the strength of their connections, one of the mechanisms though which antidepressants are thought to deliver therapeutic results.

A test of tFUS to inhibit neural activation in the amygdala across a range of mood, anxiety and trauma-related disorders had not yet been attempted. Dr. Fonzo and colleagues recruited 29 patients with such disorders, as well as 23 healthy controls. They conducted a double-blinded, placebo-controlled "target engagement study" in the 52 participants, designed to test whether tFUS could indeed modulate activity in a targeted area, the left amygdala. Afterward, they conducted an unblinded pilot clinical trial in which the 29 participants with psychiatric diagnoses received daily repetitive tFUS (rtFUS) over 3 weeks (5 treatments per week) targeting the left amygdala.

The "target engagement" tests were successful. In two sessions separated by one week, patients and controls received an active tFUS session and a placebo, or "sham," version. The treatment was guided by MRI, and effects were observed when the participants were receiving a functional MRI scan. These experiments showed that active tFUS (versus "sham") reduced activation in the left amygdala, while modulating connectivity between that area and interconnected limbic and prefrontal circuitry. There was considerable variability in the magnitude of such reduction among recipients of tFUS, a result to be taken up in future studies. These tests also established to the team's satisfaction that tFUS as administered was safe and "feasible as an intervention approach." No serious adverse events were reported.

Of the 29 participants in the unblinded pilot clinical trial, most of them in the early 20s, diagnoses were overlapping: 16 had been diagnosed with major depression; 10 with bipolar disorder; 4 with alcohol use disorder; 2 with panic disorder; 23 with an anxiety disorder; and 10 with PTSD. The primary outcome measure was the Mood and Anxiety Symptom Questionnaire—General Distress (MASQ-GD) scale, on which the average participant had a score of about 30 prior to the 3 weeks of tFUS treatments, and 21 following the treatment course, a reduction, the team said, that was statistically significant, despite the small size of the cohort.

"The pilot trial provides initial evidence of safety, feasibility and possible utility of daily rtFUS as a transdiagnostic intervention," the team reported. "We observed a significant reduction in our primary outcome, a general measure of negative-affect symptoms" in the disorders affecting the participants. "Following the entire treatment course the effect size [of the benefit] was moderate-to-large for the primary outcome as well as for several secondary outcomes, including depression and PTSD symptom severity."

The researchers say these results justify a much larger, double-blinded "sham"-controlled clinical trial. Such a trial would not have the disadvantage of the current pilot of lacking a control group—which makes it difficult to assess the possible benefit of the tested rtFUS protocol. Future tests might also explore the dosing—whether sessions 5 days per week are optimal, or if fewer sessions or a different treatment duration might be advantageous. There is also no data yet on the durability of the therapeutic effects of rtFUS, another subject for exploration in future tests. ❖

COMBINED CBT AND DRUG THERAPY REDUCED BINGE EATING EPISODES IN PATIENTS WITH OBESITY BY 96%

Cenk Tek, M.D.

Researchers have reported a 12-week clinical test of a combination therapy that greatly reduced episodes of binge eating in people with binge-eating disorder (BED) and co-existing obesity.

BED is defined by recurrent binge eating—typically, eating unusually large quantities while experiencing loss of control—without accompanying behaviors such as purging to compensate for weight gain (which is seen in bulimia nervosa). BED is strongly associated with obesity, but has distinct psychological and neurobiological features, notes the team that conducted the newly reported trial. They also note that BED is highly persistent, and often goes undiagnosed and untreated. And "those who do seek help rarely receive the very few evidence-based treatments," they add.

Led by Carlos M. Grilo, Ph.D., of the Yale University School of Medicine, the team, which included **Cenk Tek, M.D.**, a 2009 and 2006 BBRF Young Investigator, recruited 141 people diagnosed with both BED and obesity. Of these, 83% were female, 76% were White, and 69% were college-educated; the average age was about 43.5 years, and the average BMI (body mass index) was 38.6 (obesity is defined as a score of 30 and above). The study appeared in the *American Journal of Psychiatry.*

Participants were randomly assigned to receive one of three treatments for 12 weeks (47 in each group). One group received cognitive behavioral therapy (CBT), a second group received the drug lisdexamfetamine (50-70mg/day), and the third group received both CBT and lisdexamfetamine.

Past trials have found that CBT for BED reliably results in roughly half of patients attaining a remission of binge-eating symptoms by posttreatment (i.e., zero episodes of binge eating over a month's time), along with significant improvements in associated eating-disorder psychopathology. In other research trials, CBT has demonstrated superiority for reducing binge eating compared to other treatments including behavioral weight-loss therapies and antidepressants. While reducing binge eating, CBT does not help with weight loss. Many people with BED do not have obesity, but, the researchers noted, "obesity and weight loss are frequent concerns and goals of most treatment-seeking patients with BED."

Lisdexamfetamine (LDX) is the sole pharmacological treatment approved by the FDA for treating BED. It is thought to impact the dopamine and norepinephrine neurotransmitter systems that play important roles in regulating eating and reward. Like CBT, LDX has been found in clinical trials to help roughly half of BED patients reduce binge eating episodes. But the medicine is approved only for those judged to have moderate-to-severe BED, and there remains uncertainty about the drug's effects on weight. It seemed logical to the team to test LDX in combination with CBT, in part because of preliminary evidence that LDX can reduce weight while limiting binge eating episodes.

In the 12-week trial, CBT was delivered in individual hourlong sessions by trained and supervised psychologists. In all three treatment groups, binge-eating episodes were significantly reduced. But the most important result of the trial was clear evidence that the combination of CBT and LDX yielded superior results. In fact, those taking LDX while receiving concurrent CBT had a 96% reduction in the frequency of binge-eating episodes, with 70% achieving remission (no episodes for the past month), assessed when treatments ended. The group receiving CBT alone reduced their binge eating episodes by an impressive 89%, with 45% achieving remission. Those in the LDX-only group had 80% fewer binge eating episodes with 40% achieving remission.

A significant factor in favor of combined treatment was the that CBT alone did not help patients reduce weight. When CBT was combined with LDX, an average weight loss of about 5% was attained, with 42% achieving a weight loss of 5% or greater. Weight loss in BED, particularly among those with obesity, is known to be difficult, the team noted, and this appears to be an important factor for patients and practitioners to consider regarding the relative value of the combined treatment, the researchers said.

One reason the team considers the superior results seen with this specific combination therapy to be important is that while a number of other combinations involving CBT and

medications have been previously tested, most have failed to find added benefits. Previously, one medication (topiramate) enhanced both binge eating and weight outcomes, but it could not be tolerated by a significant portion of patients, leading to high rates of treatment discontinuation.

The reason for the superiority of CBT plus LDX is not known, but the researchers suggested they likely operated via distinct mechanisms. CBT, they said, might be "reducing unhealthy restraint and unstructured eating, while addressing the core body-image disturbance," with LDX addressing "eating regulation and reward effects," perhaps helping to reduce impulsivity.

Future trials should test the combination therapy in more diverse populations, the team said, and in patients with BED who do not also have obesity. It is also unknown how long-lasting the benefits of the treatments are beyond the 12 weeks of observation in the current study. CBT benefits tend to be enduring, but the durability of LDX benefits is not yet fully known. ❖

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"Marla and I donate to the Brain & Behavior Research Foundation in support of science and the hope of finding better treatments for mental illness.

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

—Ken Harrison, Board Member

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

GLOSSARY

PHARMACOGENETICS (p. 4) Aims to figure out how to optimally match individual patients with specific therapeutic medicines. It does this by harvesting knowledge about the human genome—specifically, the individual DNA variations that each of us has—and connecting it with biological understanding about how drugs are metabolized by the body, and how individual genetic variations make some of us very good or rather poor candidates for specific medicines.

SNPs (Single Nucleotide Polymorphisms) (p. 6) Single DNA "letters" among the 3 billion pairs of letters comprising the human genome (each letter standing for one of the four chemical DNA "bases") that vary between individuals. Every individual has many such variations relative to a "consensus" human genome sequence, but most are harmless and only a small fraction affect risk for illnesses or factors like drug metabolism.

GENOME-WIDE ASSOCIATION STUDIES (GWAS) (p.8) Studies that seek to find statistically significant correlations between individual SNPs and factors such as illness risk or drug metabolism.

TARDIVE DYSKENESIA (p. 8) A disorder that involves involuntary repetitive movements affecting the face, mouth, or other parts of the body. It is among the more serious side effects of first-generation antipsychotic medicines.

BROAD-PANEL PHARMAGOGENETIC TESTS (p. 11) Simple genetic tests that analyze variations in multiple genes known to influence how individuals metabolize and respond to a variety of medications. These tests can help doctors prescribe medicines more likely to help a specific patient, or help the patient avoid taking medicines that will generate adverse drug reactions or other unwanted side effects. Dr. James Kennedy says that such tests can help many people taking medicines for psychiatric conditions.

EXPOSURE AND RESPONSE/RITUAL PREVENTION THERAPY (EX/RP) (p. 24) A type of cognitive behavioral therapy (CBT) found to be effective in many patients with OCD. The goal of EX-RP is to disconfirm the patient's fears, to learn distress tolerance, and to break the habit of ritualizing and avoiding. In clinical trials, about two-thirds of OCD patients who received EX/RP in addition to an SRI medication got better, with about one-third reporting negligible symptoms post-trial.

CORTICAL ATROPHY (p. 31) One of the hallmark pathologies associated with schizophrenia. Analysis of postmortem brains of schizophrenia patients have revealed decreased branching of the dendrites that bring signals from other neurons into nerve cells in the cortex; reduced density of dendritic spines, the tiny bump-like protrusions along dendrites that are the points of contact for axons projected by neighboring neurons; and abnormally low levels of the proteins that form synapses in cortical tissue. Some hallucinogens, including LSD, are powerful promoters of cortical growth, a fact that has spurred some investigators to try to tweak molecular structure or target in the brain to capture this therapeutic property while not generating hallucinations.

LOW-INTENSITY TRANSCRANIAL FOCUSED ULTRASOUND (tFUS) (p. 50) In contrast with TMS, which uses magnetic pulses to alter the activity of cortical cells just beneath the skull, tFUS uses focused high-frequency soundwaves to reach areas of the brain that lie beneath the cortex.

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