

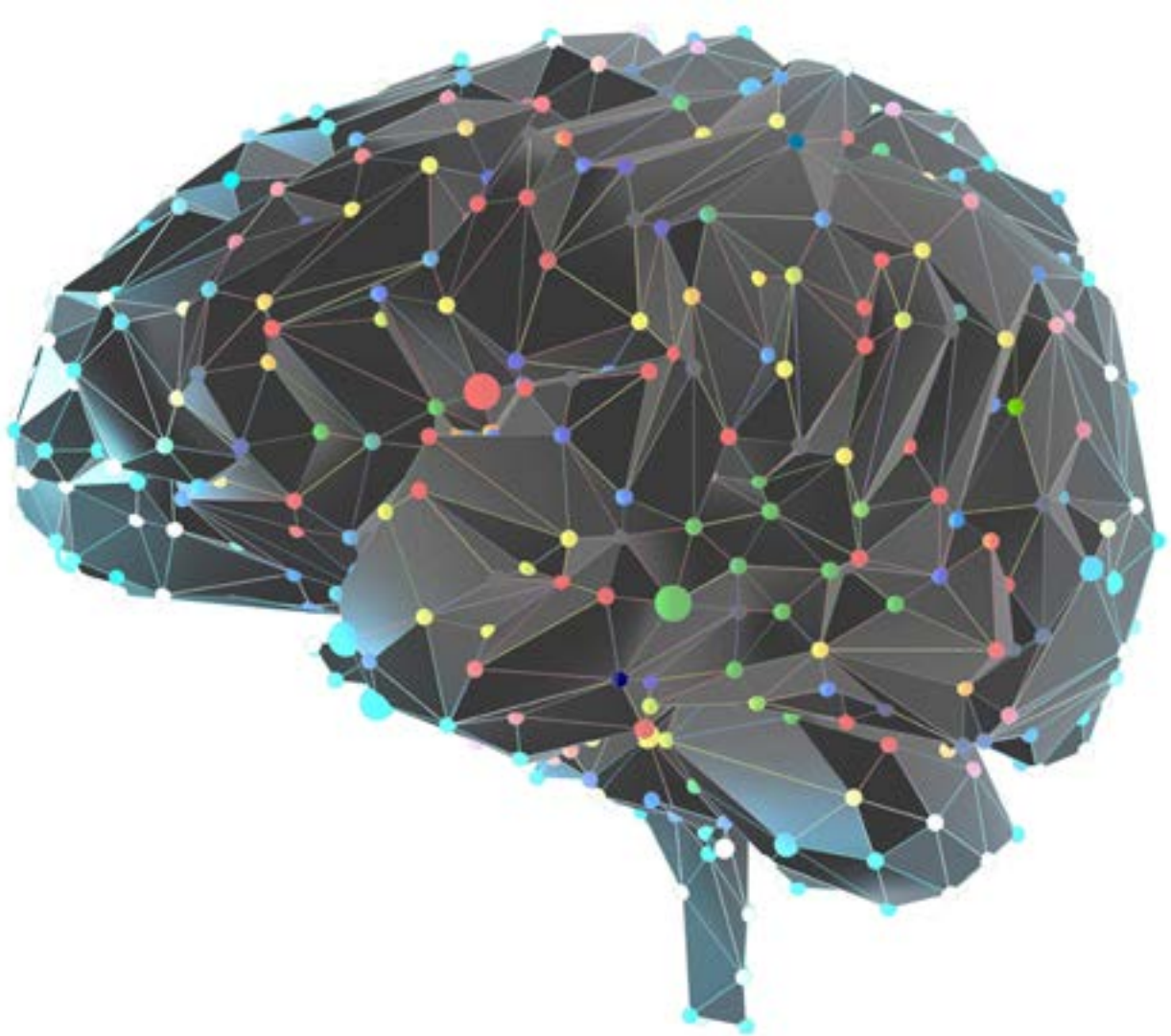
Understanding Brain Development
in Pediatric Anxiety

When Medication Isn't Enough
in Treating Schizophrenia

Brain & Behavior

M A G A Z I N E

APRIL 2023



Harnessing Memory's Malleability to
'Rewrite' Trauma

PRESIDENT'S LETTER



This issue of *Brain & Behavior Magazine* focuses on research that hopes to leverage the brain's remarkable plasticity for therapeutic purposes. Our **PATHWAYS TO THE FUTURE** story describes the research of 2016 BBRF Young Investigator Dr. Steve Ramirez of Boston University. Dr. Ramirez and colleagues have identified the location of individual memories in the rodent brain, both positive and negative, and have artificially activated such individual memories. They have also succeeded in taking advantage of a window of opportunity that opens in the brain when a memory is recalled. During this interval, in rodents, they have modified negative memories in ways that they hope can inform the development of new therapies in people for memory-based illnesses such as post-traumatic stress disorder.

The **SCIENCE IN PROGRESS** story summarizes the research of Dr. Chad Sylvester, a 2017 BBRF Young Investigator at Washington University, St. Louis.

Dr. Sylvester is trying to link pediatric anxiety disorders with specific forms of atypical brain development. His search for new therapies focuses on a window of great environmental sensitivity that opens in brain development in the early years of life.

In **A RESEARCHER'S PERSPECTIVE**, Dr. Dawn Velligan, a three-time BBRF grantee at The University of Texas Health Science Center at San Antonio, describes some of the approaches she uses in the clinic to help schizophrenia patients better cope with their symptoms. She describes ways of helping patients with persistent positive symptoms come up with alternate explanations for their perceptions. She also addresses a range of strategies to help patients cope with negative symptoms, which include flat affect, low motivation, anhedonia, and difficulty speaking. The overall aim is to help patients to more effectively function in society.

This issue also highlights our **2022 International Mental Health Research Symposium**, the **International Awards Dinner** and the winners of the **2022 Pardes Humanitarian Prize for Mental Health**. We also feature recent news on treatments for psychiatric conditions in our **THERAPY UPDATE** and important research advances that are moving the field forward in **RECENT RESEARCH DISCOVERIES**.

I continue to be inspired by the magnitude and scope of the discoveries that are being made by the scientists we fund together and appreciate your ongoing support. We have received an **exciting \$1 Million Challenge Match** for 2023 from two very generous family foundations that are passionate about BBRF's vital mission. The goal of the match is to accelerate the momentum in brain research as further breakthroughs are still needed. We hope you will join us. Donor contributions will be matched dollar-for-dollar if they're from:

- a new donor to BBRF
- a former BBRF donor who's lapsed, but makes a new 2023 contribution
- a current BBRF donor who increases their 2023 contribution (the increased amount is matched)

Together we will continue to fund innovative and impactful research that is making a difference in the lives of those living with brain and behavior disorders.

Sincerely,

A handwritten signature in black ink that reads "Jeff Borenstein M.D." in a cursive style.

Jeffrey Borenstein, M.D.

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

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Harnessing Memory's Malleability to 'Rewrite' Fear and Other Negative Memories



Steve Ramirez, Ph.D.

Assistant Professor of Psychological and Brain Sciences
Boston University

2016 BBRF Young Investigator

IN BRIEF

Dr. Ramirez and colleagues have identified the location of individual memories in the rodent brain, both positive and negative, and have artificially activated such individual memories. Remarkably, they have also succeeded in modifying negative memories in ways that they hope can inform the development of new therapies in people for memory-based illnesses such as post-traumatic stress disorder.

Even before Dr. Steve Ramirez begins to tell you about the experiments his team has conducted in the last few years—remarkable experiments that he acknowledges sound to some like the stuff of science fiction—he has a winning way of drawing you into the subject he's spent his career studying.

"I gently poke fun at my physicist friends," he says, "by reminding them that each of us, between our ears, has the one thing that *they* tell us we cannot have. We each possess a time machine that can instantly transport us to the past. All you have to do is close your eyes and think about something as simple as what you had for breakfast today, or as complex as how you felt when you visited your grandmother's house when you were a child. That's it! In the blink of an eye, you've time-traveled back to a moment in your past, without breaking a sweat. It's impressive the brain can do that!"

A 2016 BBRF Young Investigator, Dr. Ramirez, who earned his neuroscience doctorate at MIT, is a faculty member at Boston University and a member of BU's Center for Systems Neuroscience. It is the goal of his lab to reveal the neural-circuit mechanisms of memory storage and retrieval, and to artificially modulate memories in ways that might relieve the

grip that an illness like PTSD has on those who have experienced severe trauma, or to enhance the recall ability of people with memory impairment.

Over the last decade, Dr. Ramirez and colleagues have published a series of research papers in leading scientific journals including *Neuron*, *Nature*, and *Science* describing their successful attempts to identify the location of individual memories in the rodent

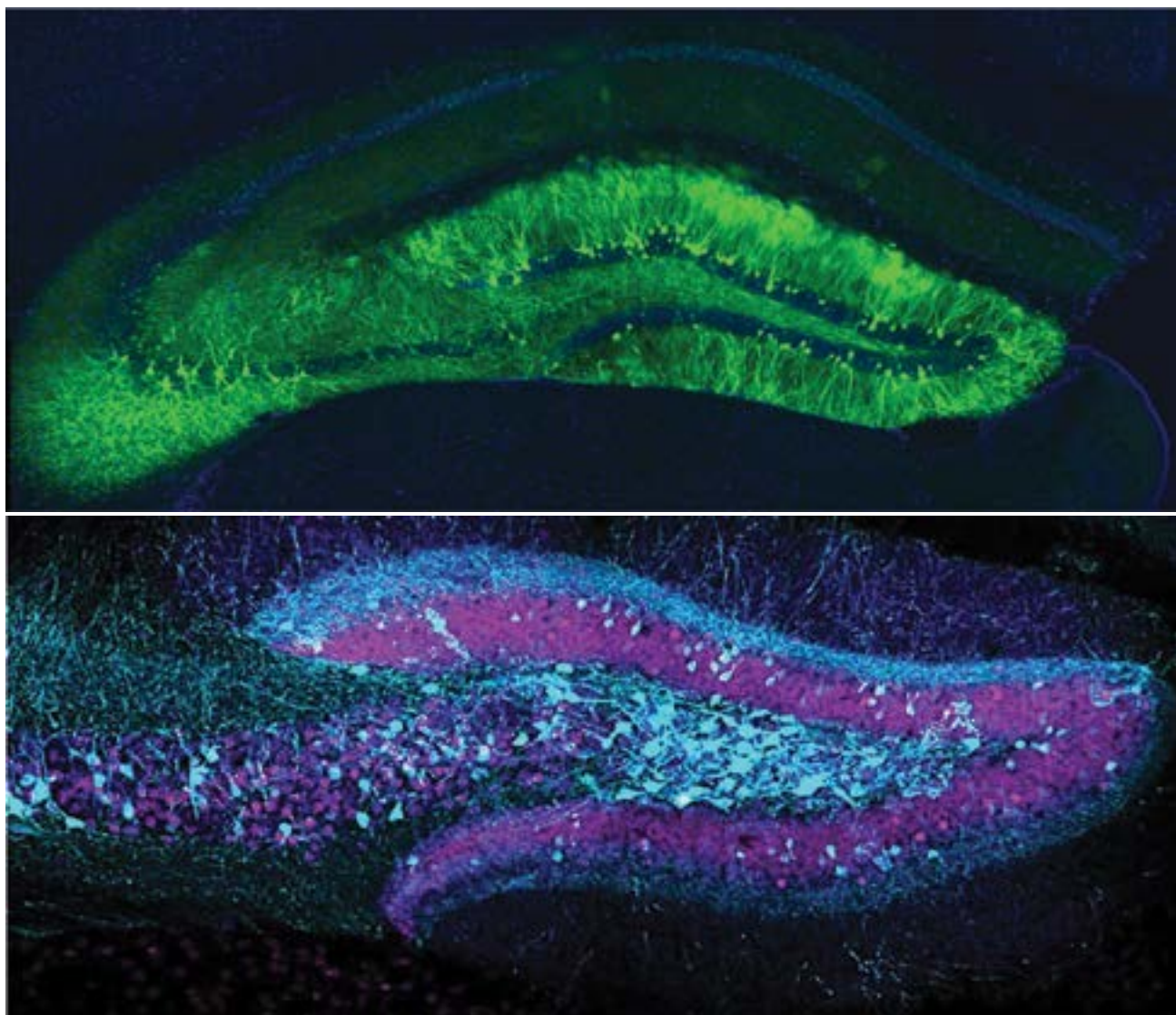
brain, to artificially activate such individual memories, and perhaps most remarkably, to modify them in ways they hope can inform the development of new therapies for memory-based illnesses in people.

“When you’re absorbed by a memory, when it’s good, it can feel great, and when it’s bad it can be pretty debilitating,” Dr. Ramirez notes. “So memory has this kind of bi-directional

power to put us in an unbelievably positive head-space or put us in the darker corners of what past experiences have left us with in terms of the marks they make in our brain.”

WHERE DO MEMORIES LIVE?

Before he could seriously contemplate the prospect of therapeutically modifying memories, Dr. Ramirez’s first goal was to work on a problem



“This is one of my favorite images that I’ve ever taken as a scientist,” Dr. Ramirez says. These are cross-sections of the mouse hippocampus. Cells that show up as green dots in the top image are thought to hold on to a negative memory (a mild foot shock); those glowing in blue, below, hold a positive memory (a pleasurable social encounter).



Dr. Ramirez says: “We each possess a time machine that can instantly transport us to the past. In the blink of an eye, your memory can send you back—to a moment that occurred this morning or one that happened 30 years ago. That’s impressive!”

that many others in the field have worked on, including his mentor at MIT, Dr. Susumu Tonegawa. Where exactly are memories located in the brain? Can we figure out a way to visualize a memory as it is being formed?

Dr. Ramirez’s general approach to the problem, he explains, was a bit like trying to figure out from across the street who is working at night in an office building. Your attention is directed to the offices in which the lights are on, where there appears to be activity. Reduced to its fundamentals, this is what he and his colleagues did with mice. At moments in time when it was reasonable to assume a mouse was forming new memories, the team looked into the brain to see which neurons were being activated or whose level of activity was elevated relative to other neurons in their neighborhood.

They made these observations at specific moments—when, for example, a mouse was put in contact with a member of the opposite sex—typically, the basis for a positive memory. Or, they put the animal in a

special cage in which tiny shocks that feel like static electricity are randomly experienced. These are not painful but they are uncomfortable. When animals feel these little shocks, they freeze in place—a mark that they have been taken by surprise and have paused to contemplate how to protect themselves. This gets recorded as a negative memory.

The task of searching for specific neurons activated at such moments is very challenging, for many reasons. First, there are an estimated 70 million neurons in the mouse brain; large numbers of them are constantly being activated, for an enormous number of possible reasons. Many operations are going on at the same time. On the one hand, forming a new memory surely only occupies a small subset of brain cells. On the other hand, it is impossible to know, by simply observing them visually, which activated neurons at any given moment are being recruited for encoding a memory.

The task is somewhat more manageable if you concentrate on a brain structure already known from

past research to be central in memory formation, retention, and recall. The team focused on the hippocampus. The mouse brain, like that of humans, contains two, one on each side of the brain. They are crescent-shaped structures that are centrally involved in encoding memory. It’s long been known that if one disables or removes the hippocampus of an animal, or if the hippocampus is damaged, say, due to a brain injury, memory is severely impaired.

But the hippocampus is itself a complex structure, packed with neurons that are arrayed in multiple layers. What the Ramirez team did was figure out a way to use genetic footprints to identify which neurons have just been activated. Activation alters gene expression in particular ways, and researchers can see these in real-time by linking the gene changes with chemical tags that glow in fluorescent colors. It’s what Dr. Ramirez calls “a trick we use to get a read-out of which brain cells are active, specifically when animals are making or forming memories.”

Using fluorescent tags of neural activation at moments during which memories were being formed enabled the team to literally show what Dr. Ramirez calls “the crystallization of a memory.” He describes the picture shown on page 5: “This is one of my favorite images that I’ve ever taken as a scientist,” he says. “These are cross-sections of the hippocampus. The cells that show up as green dots in the top image are hippocampal cells that we believe are holding on to a negative memory.” These cells became illuminated while a caged rodent was experiencing mild foot shocks. Below, the cells that display a blue color “are the ones that we think are holding on to a positive memory”—for example, a pleasurable social encounter or food treat.

After he obtained these images, Dr. Ramirez paused to reflect. “Memory, as we experience it, is this ephemeral thing, this subjective thing—something that doesn’t seem like something you can reach out and touch.” And yet the images from the hippocampus speak to another thing we intuitively believe to be true: that memories must on some level be a physical phenomenon, that they must have some physical basis in the brain.

The physical manifestation of memory—the constellation of neurons that happens to be activated while a memory is being recorded and stored—is called an “engram” by scientists. No one knows how many neurons are recruited to form these constellations. And it is almost certain that individual neurons can be part of different engrams—they are part of multiple memories. Another

important fact about the physical manifestation of memories: according to Dr. Ramirez, they are “distributed” in the brain. The engrams representing positive and negative memories depicted on this page are located in the rodent hippocampus, but there are other dimensions of these and all memories that engage neurons in locations scattered across the brain. For example, we know that memories trigger our emotions; the portion of an engram that contains the memory’s emotional “coloring” involves a brain structure called the amygdala, which is also activated when the memory is encoded or subsequently recalled.

ARTIFICIALLY ACTIVATING A MEMORY

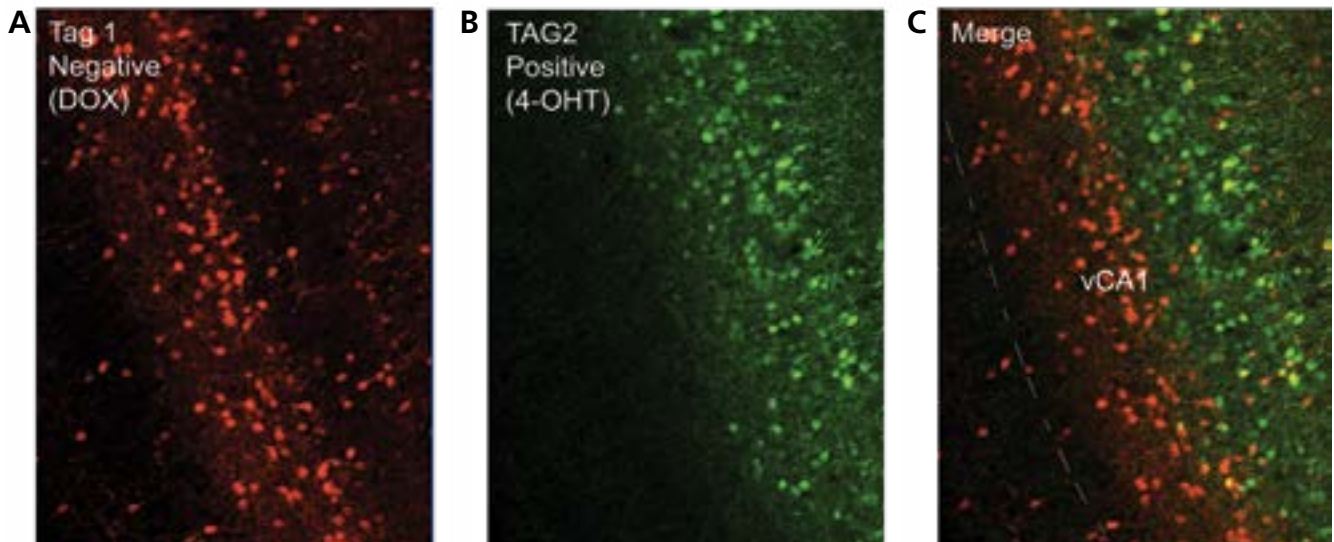
Once Dr. Ramirez and his team succeeded in visualizing specific memories in the mouse brain, the next step was to see whether they could artificially activate them. That is, when they wanted to, as opposed to when a rodent might just happen to recall the memory. To do this, they used a technology called optogenetics

co-developed at Stanford in the early 2000s by BBRF Scientific Council member, grantee, and prize-winner **Dr. Karl Deisseroth**, and colleagues. Optogenetics involves making specific neurons in the rodent brain sensitive to a particular wavelength of light. Threadlike fiberoptic wires are introduced into the animal’s brain to deliver the beams of light to the desired neurons. When the light is delivered, the neurons are activated.

The team performed a fascinating experiment with a mouse that had been allowed to explore a cage in which it experienced mild foot shocks, causing it to freeze in fear and thus forming a negative memory of that place. They identified the engram of that memory in the animal’s hippocampus. The next day, the same animal was placed in a cage with “a completely different environment, with completely different sights, sounds and smells associated with it.” The animal had no reason to be fearful of this second cage—nothing unpleasant occurred there.



This mouse’s brain is being activated optogenetically, even as it moves freely in its living space.



The cells glowing red on the far left **(A)** and those glowing green in the center **(B)** hold, respectively, negative and positive memories in the ventral hippocampus of a single mouse. When they merged the images **(C)**, the team discovered that positive and negative memories were physically segregated. This now opens investigation into whether there are differences between neurons holding each type of memory.

Then what Dr. Ramirez calls “the million-dollar experiment”: While the animal was in the “safe” cage, they used optogenetics to activate the cells holding the negative memory formed the day before in the first cage. Result: the animal “almost immediately goes into a freezing posture” even though it was under no threat at all.

This was a proof-of-principle for the team “that really opened up the floodgates.” They now knew they could conduct experiments in rodents in which they could attempt to manipulate memories. One set of experiments could test, for example, whether artificially activating the “fear” memory when the animal was in a variety of different environments always generated the same freezing behavior. Or might that behavior change in some environments?

In fact, when they placed a rodent like the one described above in a very large, open box, much larger

and less confining than a cage, it did not freeze at all, but rather seemed to look for ways to escape. It’s analogous, says Dr. Ramirez, to a person who sees a grizzly bear at close quarters in the woods compared with on the far side of a broad, fast-flowing river. The context does affect one’s response.

This brings to mind another important fact about memory that previous research has firmly established. We know that memories are constantly being modified and updated with new information. Put another way: we know from experience that memory is malleable. This can be a good thing or a bad thing, depending on the circumstances. It’s good in the sense that all memory involves an act of learning. The brain is taking in information about an event from the senses, remembering all sorts of things about the context, and laying down memories for subsequent retrieval. This is how memory can be considered

among the most important “adaptive” capabilities of the brain, in the evolutionary sense; we remember what we have enjoyed and benefited from, and we remember what has given us pain and put us in harm’s way.

At the same time, memory can make us virtual prisoners of our past. For example, the soldier who has experienced trauma or the child who has been physically abused. In PTSD, memories of the trauma intrude upon consciousness, and can paralyze the individual.

REWRITING MEMORIES

The question that really intrigued Dr. Ramirez was: “Can we leverage memory’s malleability? Is it possible that we could utilize the malleability of memory in a therapeutic way?” An important existing therapy for PTSD does try to do that. In exposure therapy, the doctor, under controlled conditions, works with the

traumatized patient to expose them to a stimulus that causes fear, but in a safe environment. When this works, the patient gradually learns to avoid being triggered by the stimulus.

Dr. Ramirez, working with rodents, wanted to explore a very different approach. He knew that he could identify specific memory traces in the brain and that he could activate them artificially. The next question was: could the team actually modify an already-formed memory in the rodent brain? They set out to create what they called a “false memory.”

This involved taking advantage of the process through which a memory is updated. Researchers call this process “reconsolidation.” Every time we recall a memory, it can and often is altered in some way to reflect new information or the context in which it has just been recalled. It is thought, incidentally, that this naturally occurring process of memory modification is what can make some memories unreliable or unfaithful to

the original context in which they were formed.

The intervention designed by Dr. Ramirez’s team involved taking an animal that had formed a neutral memory of a safe environment and then activating the engram associated with that memory precisely when the same animal was subjected to some unpleasant foot shocks. “We wanted to know if their memory of the safe environment and the experience of getting those shocks could become linked or connected at the biological level,” Dr. Ramirez explains.

“The pretty remarkable thing was that when we put the animal back in a safe environment, now it seemed to be afraid of it. Absolutely nothing bad had happened to it there, but we had effectively updated the memory of that safe place with the memory of getting the foot shock.” In a sense, the animal now had a “false memory” of the safe place, associating it now with danger.

The physical manifestation of memory—the constellation of neurons that happens to be activated while a memory’s being recorded and stored—is called an “engram.”



Mice enjoying a food treat can be expected to form a positive memory, linked to the place where it occurred; mice encountering something unpleasant, like a mild static-like shock to the feet, form a negative memory, also linked to the place it occurred. “False memories” can be created by artificially activating a negative memory when an animal is in a “neutral” environment. Nothing adverse has occurred in that space, but activation of the negative memory causes the animal to freeze in fear.

During the ‘window of reconsolidation’ when a fear memory was being recalled, if the team artificially activated a competing positive memory, the animals’ conditioned fear behavior virtually disappeared.

There were other experiments. In one paper, the team described activating a positive memory in animals that had been conditioned to experience chronic stress. Activation of the positive memory tended to diminish the behaviors in the animals that are associated with depressive behavior. “This is a case where we apply what we know from humans to what we see in the animal experiments,” Dr. Ramirez says. “There are a whole host of human studies suggesting that recalling positive memories can buffer the effects of stress. It can reduce levels of stress-associated markers in the blood or get heart rate back to baseline, or even activate the brain’s reward circuitry so that things feel good.”

Drugs can be given to stimulate the reward system to alleviate the negative effects of stress. Dr. Ramirez hopes to find a way to use memory, in this sense, as a drug, perhaps in lieu of administering drugs. A glimpse of this possibility is offered in a paper the team published in *Nature Communications* in September 2022.

They tagged neurons in a part of the mouse hippocampus called the dentate gyrus with fluorescent markers; these neurons were of three kinds: associated with positive, neutral and negative experiences. The animals underwent fear conditioning. Then, neurons encoding memories in each of the three groups were artificially activated via optogenetics, while fear memories were being recalled.

The team found that during the “window of reconsolidation” when the fear memory was being recalled, if the team artificially activated a competing positive memory, the

animals’ conditioned fear behavior virtually disappeared. In effect, the fear memory was overwritten, or rewritten in such a way that it was no longer a memory that triggered fearful behavior. Just as impressive, this modification appeared to be long-lasting, perhaps even permanent. The same animals were tested weeks later (a long time in the life of an animal that lives only 2 or 3 years) and the animals remained unafraid of what they previously had feared.

TRANSLATING TO PEOPLE

Since optogenetics can not be used in people, do these experiments have any application in the development of new therapies? Dr. Ramirez thinks they do.

The point he stresses is that we (obviously) cannot make suggestions to rodents when we want to trigger a specific memory they have formed. “But in people I don’t have to go in and optogenetically tinker with anything to get a memory to come online. I could just ask you.”

“We could either try to mimic the effects we saw in mice by giving certain drugs, or ask people to recall certain experiences in an attempt to try to get the brain to fix itself, so to speak. That is really the most exciting part of this work, for me. We showed we could artificially activate positive memories to alleviate aversive states in animals, but to do that in humans, in principle, is as straightforward as asking someone to mentally re-live one of their most cherished positive memories.”

Especially important, it seems, is the malleability of memory in the period of



Once a memory has been recalled, a window of reconsolidation opens, during which the memory is malleable and potentially modifiable. Dr. Ramirez thinks of it “as the brain’s window of opportunity for doing therapeutic things with a memory, full of untapped potential.”

reconsolidation, once the memory has been recalled. In people, this window opens within minutes of recall, and remains open for as long as 6 hours, Dr. Ramirez says. “I think of it as the brain’s window of opportunity for doing therapeutic things with a memory. I think it has tremendous untapped potential. We are learning through this research to take advantage of what we may have thought was one of the ‘bugs’ of memory—that it’s changeable, sometimes not reliable—and we’ve spun it into a ‘feature,’ something that we can leverage therapeutically for the good.”

In their recent paper on rewriting a fear memory in rodents, Dr. Ramirez and colleagues made a potentially very important observation. They found that they could therapeutically modify a fear memory not only by activating a specific memory engram, but also when they used optogenetics to randomly stimulate neurons in a patch of the dentate gyrus of the hippocampus.

One of the possible implications is that it may be possible to stimulate,

for example, positive memories while negative memories are being recalled via currently existing methods of brain stimulation, provided they were focused in the right place and can reach that far into the brain. It might be tested in animals using deep-brain stimulation, Dr. Ramirez says. But that is an invasive procedure and cannot be a typical therapeutic approach for people with PTSD, for example. It is possible, however, that non-invasive brain stimulation methods like TMS (transcranial magnetic stimulation)—now being given to many thousands of patients worldwide to treat depression and several other psychiatric disorders—could be used to stimulate carefully targeted areas that might activate positive memories during fear-memory reconsolidation.

Referring to the success they had in randomly stimulating dentate gyrus neurons to rewrite a fear memory, the team noted: “We believe this manipulation...may work similarly to other stimulation-based protocols associated with neuroplasticity, such as electroconvulsive therapy, deep-

brain stimulation, and transcranial magnetic stimulation. We think activating a large set of randomly labeled dentate gyrus cells may perturb the system in a way that provides a ‘reset signal.’”

The team will continue to study in rodents the cellular mechanisms that are engaged when memories are reconsolidated and modifiable. Dr. Ramirez explains: “Is there activity in other brain areas that is changing? Changing in what specific ways? Are there certain receptors in brain cells that are being recruited or blocked, and do we have drugs available that can modify those receptors? That is the kind of conceptual scaffold that this work sets up. The more futuristic approaches we think about would be guided interventions in the brain, whether via stimulation or drugs, but with the aim of jump-starting processes that can produce therapeutic effects in illnesses affecting memory.” ❖ **PETER TARR**

In Search of New Therapies, Studying the Neurobiology of Brain Development in Pediatric Anxiety



Chad M. Sylvester, M.D., Ph.D.

Associate Professor of Psychiatry (Child)
Washington University, St. Louis
2017 BBRF Young Investigator

IN BRIEF

Anxiety disorders are the most common type of pediatric psychiatric illness, affecting up to 30% of all youths and severely impairing an estimated 10%. They place affected children at significantly elevated risk for anxiety, depression, and substance-use disorders later in life. Dr. Sylvester is trying to link pediatric anxiety disorders with specific forms of atypical brain development, and focuses his search for new therapies on a window of great environmental sensitivity that opens in brain development in the early years of life.



Anxiety disorders are the most common class of pediatric psychiatric illness,” notes Dr. Chad Sylvester. They affect up to 30% of all youths under 18 years of age and severely impair an estimated 10%, he says. In the U.S. alone, that means impairment due to anxiety in some 7 million children.

Just as worrisome, pediatric anxiety disorders “can place affected children at significantly elevated risk for anxiety, depression, and substance-use disorders later in life,” Dr. Sylvester noted in a 2018 editorial published in the *Journal of the American Academy of Child & Adolescent Psychiatry*.

Perhaps in part this is because as many as 50% of anxious children remain symptomatic “even with the best available treatment,” Dr. Sylvester has also pointed out. This, he stresses, “makes pediatric anxiety disorders a major public health problem.”

Another factor possibly contributing to the levels of impairment and difficulty in successfully treating childhood anxiety disorders is the time lag that often occurs between the time when symptoms or their precursors are thought to first manifest and the time, often years later, when a young person receives a diagnosis.

This helps explain the focus of research conducted by Dr. Sylvester and his team at Washington University. They are trying to establish a base of scientific evidence that would link pediatric anxiety disorders with specific forms of atypical brain development—processes that likely begin very early in life, even in infancy.

Dr. Sylvester is called “a star” by BBRF Scientific Council member **Daniel S. Pine, M.D.**, a National Institutes of Health Distinguished Investigator and Chief of the Section on Development and Affective Neuroscience, who praises him for his abilities as both a doctor and researcher. The two have collaborated on several published papers. For his part, Dr. Sylvester



Childhood anxiety disorders may have their origin in atypical trajectories of brain development that begin very early in life.

humbly states that “I really like being a child psychiatrist.” Being a medical doctor is part of the story, but it is linked to the fact that he also has a doctorate in neuroscience. His young and rising career is an example of how medical training with a focus on psychiatry plus training in the sciences can combine to motivate and shape a career.

Dr. Sylvester finds being a doctor immensely satisfying. “I really enjoy working with children and families. I like hearing people’s stories and thinking about how they think and feel—and thinking about these things in the context of how the brain develops.”

The salient point is this, he says: “If we can intervene during the early years in life when anxiety or other pediatric psychiatric disorders develop, then we may be able to prevent lifelong morbidity associated with those illnesses. This kind of research could have the highest impact, from a human and public-health point of view.”

FINALLY RECOGNIZING CHILDHOOD ILLNESSES

Research programs like that of Dr. Sylvester mark the great distance science has come in very recent times. Less than 20 years ago, the notion of a child, particularly a preschooler, having a diagnosable depression or anxiety disorder was not taken seriously by many in medicine.

Asked about this, Dr. Sylvester speaks about one of the senior members of the faculty at Washington University, **Dr. Joan Luby**. Dr. Luby is a BBRF Scientific Council member, three-time recipient of BBRF grants, and winner of BBRF’s Ruane and Klerman prizes in 2020 and 2004, respectively.

“You have to give great credit to Joan,” Dr. Sylvester says. “She really had to fight tooth-and-nail to get people to believe that someone so young could be depressed.” Dr. Luby’s pathbreaking research has

focused on the characterization of early childhood psychopathology, early behavioral and biological markers of risk, and associated alterations in brain and emotional development in early childhood. Her contributions include establishing criteria for identification, validation, and early intervention in depressive syndromes in preschoolers. She also conducted studies, some with **Dr. Deanna Barch**, a Washington University colleague, BBRF Scientific Council member and four-time BBRF grantee, showing the effect of parental nurturance and early experiences of poverty on brain

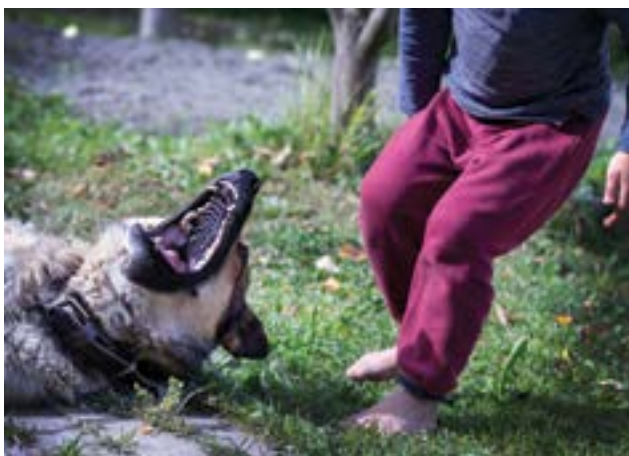
development. Dr. Luby has also developed and tested an early psychotherapeutic intervention for preschool depression called Parent-Child Interactive Therapy.

Dr. Sylvester points out that the research of Drs. Luby, Barch, and others did much to change

minds of the skeptics. “It showed that preschoolers have depressive symptoms, that they can exhibit low mood, lack of interest, irritability, etc. For many kids like this, it’s not a



Dr. Joan Luby



It's perfectly normal for a young child to fear an aggressive dog; but checking the front door every few minutes when no threat is present is a possible sign of an anxiety disorder.

momentary phenomenon. And these symptoms really do predict that kids with these emotional problems when they're younger also have emotional problems when they're older. I think these findings are part of what has forced people to take these symptoms in preschool and childhood more seriously."

NORMAL VS. ABNORMAL FEAR

When is fear or anxiety abnormal? Every parent knows that every child expresses fears. Anxiety about strangers is common to see within half a year of birth, and can continue until about age 2. It's part of the normal process of the child learning to be at home in the environment that extends beyond the parent-child dyad. There's an even deeper reason that traces to evolution. "Even single-cell organisms have avoidance responses to things that are dangerous," Dr. Sylvester points out. "There's a long evolutionary history of response to threat. Of course it's fundamentally important that people have fear in particular instances. It's when fear gets hijacked in situations where a person is actually safe that problems arise." There are several reasons. For one thing, the fear response can generalize to other situations, without warrant; or it can be too intense, given the level of threat; or, it can get to the point of impairing a person's ability to function.

"In the first couple of years of life, your brain is learning what you can expect from the environment; what you have to do for yourself versus what you can depend on from others; whether or not the environment is safe versus dangerous.



And there's evidence that the plasticity of the brain when these things are being learned is especially sensitive to the environment."

Developmental plasticity can be thought of in two very different ways. On the one hand, malleability of connections between neurons is what enables us to learn and remember—to instinctually recoil from perceived threats, but also to learn to know that some novel exposures pose no threat. At the same time, if a very young child has stressful or otherwise unusual exposures, unusual challenges in their environment, or if their brain circuitry underlying the response to novelty, for example, is following an atypical trajectory, there is the possibility patterns will be established that not only generate psychiatric symptoms in early life, but patterns that may be increasingly difficult to modify as the child ages.

But Dr. Sylvester stresses: "'Difficult to change' does not necessarily mean it will be impossible to modify a particular brain circuit" underlying, for example, an inordinate feeling of threat or anxiety about unfamiliar things in the environment. "It just may take some work to change it."

"This prospect is one of the reasons I went into child psychiatry," he explains. It's where the observation of early childhood anxiety intersects with research the team is performing on how brain circuits develop.

"One thing our lab is focusing on is to examine different brain circuits that respond to things related to attention, paying attention to things that are unexpected or new or different.

We refer to the ‘oddball response’—the brain’s response to novelty. How does that circuit develop? How does variation among individuals affect how that circuit responds? And how does this relate to different levels of individual risk?”

The lab’s studies of attention and brain responses to novelty span a wide range of ages—from infancy to ages 10-12. This has led to the development and testing of methods to train the attention of young people. The general idea is that “we test how readily attention in children is grabbed involuntarily by things that are unexpected or different,” Dr. Sylvester explains. “In older kids we measure that by showing flashes of light on a screen and measuring how those flashes distract kids from a task that we instruct them to perform. We’ve found that anxious kids have increased distractibility—their attention network in the brain responds more strongly to the flashes on the screen than that of kids who are not anxious.

The attention-training program we’re working on teaches kids to stay focused on the task, even when flashes come up all the time.”

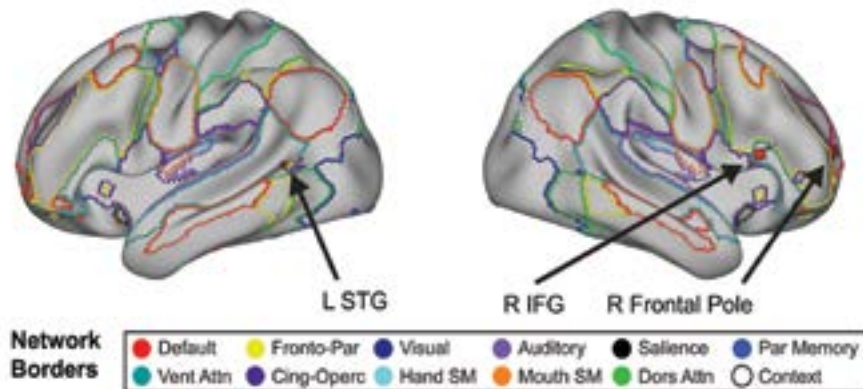
To the extent young people can be trained to “get used” to the flashes and persist in their assigned task, the question is how this relates to activity levels in parts of the brain that process the distracting flashes. “We hope to leverage what we’re finding out about how these brain circuits function differently at higher and lower levels of attention paid to the ‘distractions.’ We hope that can become a basis for developing new treatments,” Dr. Sylvester says.

EARLY WINDOW OF SENSITIVITY

It all relates to the window of great environmental sensitivity that opens in brain development in the early years of life—and trying to find ways to take advantage of the plasticity that underlies that sensitivity in kids who

Dr. Sylvester and colleagues are trying to establish a base of scientific evidence that would link pediatric anxiety disorders with specific forms of atypical brain development—processes that likely begin very early in life, even in infancy.

Anxiety Related Activity Change During Attention Capture



The team used functional whole-brain scanning to study the relation between anxiety and brain activity while children were given a task that required them to pay attention. They observed three clusters: (1) in the left superior temporal gyrus (L STG); (2) near the right inferior frontal gyrus (R IFG), and (3) in the R frontal pole (part of the default mode network). In each case, higher anxiety was associated with higher regional brain activity.

are overreacting to distractions or novelty. “We’re trying to see if we can retrain them.”

Adaptive behavior includes being able to act on new, salient stimuli that are appropriate under the circumstances, without over-reacting any time a new stimulus appears, but also not under-reacting and ignoring new, important stimuli. Dr. Sylvester’s hypothesis is that anxiety, in terms of attention, can be thought of as at the opposite end of a spectrum whose other extreme is attention-deficit hyperactivity disorder (ADHD). The anxious child is hypervigilant, to the point of being thrown off by almost any new or unusual stimuli; the child with ADHD is under-vigilant, not paying attention even to important new stimuli (e.g., their name being called).

“The goal is to have an optimal balance between, ‘Yes, I need to detect new things as they happen’ and ‘no, I mustn’t get jumpy and overreact to any new stimulus,’” Dr. Sylvester says.



When a child is hypervigilant or excessively concerned with making an error, it is likely to impair normal function—for instance, in taking a test at school.

Being overly vigilant is not just an inconvenience; it can really impair a child’s function. “If, every time they hear some sound, some noise, some movement, they become anxious, because they think it’s the signal of danger, that child is not going to be able to concentrate, won’t do as well on their test in school. Kids who are trying to sleep who react to every bump in the night—they are not going to get their sleep.

“On the one hand, we don’t want to take away vigilance—we all need to be able to detect danger. But hypervigilance is a problem. We want the child to strike the optimal balance.”

Hypervigilance is only one symptom of anxiety in young children. There are others—for example, anxiety about making a mistake, or overreacting when one has made an error. In children who develop anxiety, Dr. Sylvester hypothesizes it’s possible that symptoms won’t be apparent until there are disruptions in multiple relevant brain circuits. Oversensitivity to errors points to increased activity in brain areas that respond to errors, such as the dorsal anterior cingulate and the anterior insula, he notes. It may be that disruptions in multiple circuits—for example, those that are overactive in response to novelty in addition to those involved in error oversensitivity—may need to co-occur before anxiety symptoms become noticeable.

The challenge is to be able to detect anomalies in circuit development in those developmentally sensitive windows of time when they may

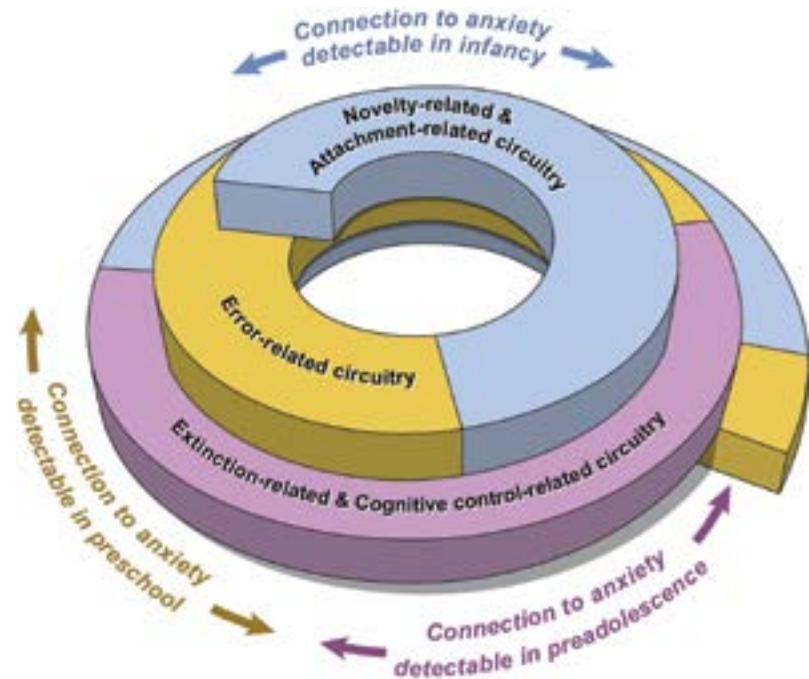
be most amenable to therapeutic modification, say, via behavioral training.

“Each of these circuits that we think are perturbed in children on a path to anxiety is developing on its own schedule, and each has its own developmental window. We propose that it’s the interaction among these developing circuits, each on its own trajectory, that is ultimately related to a child’s risk for anxiety as the brain develops,” Dr. Sylvester says. “It’s possible that each of the anomalies builds upon the others, ultimately leading to a disorder.”

STUDYING NEWBORNS

With the earliest phases of circuit development in mind, Dr. Sylvester and colleagues have been performing remarkable brain-imaging studies of newborns. He credits their ability to gather important information to “our really amazing staff” who care for the infants and their mothers.

“The babies are fed immediately before we put them into the scanner. We have an ICU nurse there who wraps the babies up in blankets and rocks them to sleep. Then we put them in something that looks like a papoose that makes them feel snug. And then we put them in the scanner. We don’t give them any medicine or sedatives. They fall asleep and usually they’ll stay asleep for an hour or two. We have a success rate of about 95%—a testament to the staff. They’re just incredible at what they do.”



A layering of psychological processes and associated neural circuitry relevant to anxiety is the result of a developmental process that occurs step-wise over time. Dr. Sylvester and colleagues propose that processes at the top of the spiral manifest relations with anxiety earlier than processes at lower levels in the spiral. Layering may result when late-maturing processes influence threat responding in tandem with early-maturing processes.

While the babies are being prepared, they are fitted with ear protector pads that block the sound of the scanner. They also wear noise-cancelling headphones. Those headphones also deliver the auditory stimulus that the team is trying to measure the brain’s response to. Unexpected little bits of static are piped through the headphones while the babies sleep and the brain’s response is recorded by the scanner. This data enables the team to gauge how circuits respond to novelty—in this case, unexpected sounds—in the youngest children.

It is laying the groundwork for attaining the therapeutic goals the team shares. “We don’t know as much as we’d like about the basic functional architecture and organization of the neonatal brain,” Dr. Sylvester says. “In order to be able

to describe how a circuit develops and changes during development, and how that’s related to psychiatric risk, we begin by looking at the brain in newborns. What do the networks look like at this initial stage? Where are they? And then, thinking of psychiatric disorders, can we determine what’s the developmental norm?”

Knowing the normal pattern could provide a basis for being able to determine very early in life which children are already on a path to being at risk for developing anxiety or other early-childhood psychiatric disorders. “The younger we can intervene,” reasons Dr. Sylvester, “the larger the impact we can have.” ❖ **PETER TARR**



\$1 MILLION CHALLENGE MATCH

Goal: To accelerate momentum in brain research as further advancements are still needed.

Contributions will be matched from:

- New Donors
- Former Donors who have lapsed, but make a 2023 contribution
- Current Donors who increase their 2023 contribution (the increase amount is matched)



As you plan your 2023 charitable donations, we hope you will help us successfully reach this generous \$1 Million Challenge Match. The cutting-edge mental health breakthroughs of BBRF grantees depends on you, so please consider making a gift this year to advance our vital research.

This match is made possible by two very generous family foundations that are passionate about BBRF's vital mission.

EVENTS

2022 INTERNATIONAL MENTAL HEALTH RESEARCH SYMPOSIUM

On Friday, October 28, 2022, BBRF hosted its 2022 International Mental Health Symposium at the Kaufman Music Center in New York City, which was simultaneously live-streamed.



Dr. Robert Hirschfeld

Later that same evening BBRF presented the Outstanding Achievement Prizes in Mental Health to five scientists at the International Awards Dinner for their extraordinary work in advancing psychiatric research, and also presented the Pardes Humanitarian Prize in Mental Health to two extraordinary mental health advocates.

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 are recognized for their research achievements in schizophrenia, suicidal behavior in bipolar disorder, pediatric mood and anxiety disorders, and cognitive neuroscience.

In a press release, **Dr. Herbert Pardes**, President of the Brain & Behavior Research Foundation's Scientific Council noted, "The 2022 Outstanding Achievement Prizes are awarded to exceptional scientists for their groundbreaking research in brain and behavior research. Because of their important work, we are making great progress in our understanding of the brain and how to treat and potentially cure psychiatric illnesses."

Dr. Jeffrey Borenstein, BBRF's President & CEO, opened the Symposium with a welcome to all attendees and noted "We celebrate the prizewinners and acknowledge the importance of neuroscience and psychiatric research in transforming the lives of people living with mental illness. These extraordinary scientists are profoundly helping the world gain new insights and advancing the development of new treatments, cures, and methods of prevention for mental illness."

Dr. Robert Hirschfeld, a BBRF Scientific Council member, once again served as the moderator at the Symposium and has done so since its inception more than 30 years ago. (Sadly, Dr. Hirschfeld passed away in February 2023; see p. 23.)



Dr. Jeffrey Borenstein

The Symposium featured presentations by the prize-winning scientists and the two winners of the Pardes Humanitarian Prize in Mental Health, each speaking for about 20 minutes as they took the audience through slide presentations explaining their work. In the pages that follow, we summarize the subjects covered in each Symposium talk.



Robert Schwarcz, Ph.D., delivered a Symposium talk entitled *From Obscurity to Hot Topic: The Kynurenic Acid Story*. Dr. Schwarcz is a Professor of Psychiatry, Pharmacology and Pediatrics, University of Maryland School of Medicine, and Foreign Adjunct Professor (elected) of Physiology and Pharmacology, Karolinska Institute. He is also a member of the BBRF Scientific Council and a 2002 BBRF Distinguished Investigator.

In the early 1980s, work in Dr. Schwarcz's laboratory began to focus on the neurobiology of kynurenines, metabolites of the essential amino acid tryptophan. Using a combination of biochemical, histological, electrophysiological and genetic approaches, he and colleagues elaborated many of the fundamental characteristics and control mechanisms which govern the function of these compounds in the mammalian brain, and examined adverse consequences when these functions are impaired.

In his presentation, he discussed studies which increasingly indicated that one of the tryptophan metabolites, kynurenic acid (KYNA), is an important endogenous regulator of the function of two major neurotransmitters which play critical roles in cognitive processes in health and disease—glutamate and acetylcholine. Abnormally elevated levels of KYNA in the brain are now considered to be causally related to cognitive impairments seen in people with schizophrenia. He described ongoing efforts to reduce/normalize KYNA levels in the human brain. This new pharmacological approach may provide benefits to persons who experience cognitive impairments in conjunction with psychiatric diseases like schizophrenia and may also improve cognition in healthy individuals.



Symposium speaker **Sophie Erhardt, Ph.D.**, discussed *New Evidence for Translationally Relevant Roles of Kynurenic Acid in Schizophrenia*. Dr. Erhardt is a Professor of Experimental Psychiatry and the Chair, Department of Physiology and Pharmacology, at the Karolinska Institute.

Dr. Erhardt's research has focused on the idea that abnormal tryptophan degradation along the kynurenine pathway leads to increased brain levels of the metabolite kynurenic acid (KYNA), and related inhibition of NMDA and alpha7 nicotinic receptor function. She believes this is of pathophysiological significance for the psychotic symptoms and cognitive impairments in people with schizophrenia. By conducting a creative mix of electrophysiological, biochemical, pharmacological and imaging experiments in laboratory animals, she has provided fundamentally new insights into the mechanisms by which elevations in brain KYNA impair the function of dopamine and glutamate, neurotransmitters that are widely believed to play key roles in schizophrenia etiology.



J. John Mann, M.D., spoke about *Unlocking the Mysteries of Mood Disorders by Science Instead Of Guesswork*. Dr. Mann serves as Professor of Translational Neuroscience in Psychiatry and Radiology; Director, Molecular Imaging and Neuropathology Division; Co-Director, Columbia Center for Prevention and Treatment of Depression at Columbia University / New York State Psychiatric Institute. He is also a member of the BBRF Scientific Council and a 2008 BBRF Distinguished Investigator.

Dr. Mann's clinical work has turned suicide prevention into a scientific endeavor. In a series of studies, he identified a systemic serotonin-related series of abnormalities present in suicide attempters compared with controls and the degree of abnormality correlated with lethality of future suicidal behavior. He found that there is over-expression of inhibitory serotonin 5-HT1A auto-receptors in major depression and in bipolar disorders, indicating a common biological phenotype related to the depressive episodes that characterize both disorders.

He later turned his attention to the clinical and biologic predictors of suicidal behavior in bipolar disorders, showing that bipolar disorders share many suicide risk factors with major depression, with important differences. In other studies, he also found human neurogenesis is present in the human brain undiminished into the eighth decade of life and may play a role in depression. He and his colleagues discovered that the rapid onset of antidepressant effect of intravenous ketamine is dose-dependent and that this dose effect is mediated by the degree to which ketamine reduces stress-related increases in brain glutamate.



Boris Birmaher, M.D., addressed *Who Is at Risk to Develop Bipolar Disorder* in his Symposium presentation. Dr. Birmaher is Distinguished Professor of Psychiatry, Endowed Chair in Early Onset Bipolar Disorder and Director of the Child and Adolescent Bipolar Spectrum Services at the University of Pittsburgh Medical Center and Western Psychiatric Institute. In 2013 he won the BBRF Colvin Prize for Outstanding Achievement in Mood Disorders Research.

Dr. Birmaher has made fundamental contributions to virtually all aspects of clinical and translational pediatric psychopathology. His most significant impact is in pediatric mood and anxiety disorders. He created many of the standard tools used for assessment and diagnosis of these conditions. He was fundamental in defining familial and longitudinal relations among these conditions, and he has led some of the most impactful treatment studies in this area. Our current understanding of pediatric mood and anxiety disorders rests heavily on his accomplishments.

2022 PRIZEWINNERS

LIEBER PRIZE FOR OUTSTANDING ACHIEVEMENT IN SCHIZOPHRENIA RESEARCH

Robert Schwarcz, Ph.D.
*University of Maryland School of Medicine
 Karolinska Institute, Stockholm*

MALTZ PRIZE FOR INNOVATIVE & PROMISING SCHIZOPHRENIA RESEARCH

Sophie Erhardt, Ph.D.
Karolinska Institute

COLVIN PRIZE FOR OUTSTANDING ACHIEVEMENT IN MOOD DISORDERS RESEARCH

J. John Mann, M.D.
*Columbia University
 New York State Psychiatric Institute*

RUANE PRIZE FOR OUTSTANDING ACHIEVEMENT IN CHILD & ADOLESCENT PSYCHIATRIC RESEARCH

Boris Birmaher, M.D.
*University of Pittsburgh Medical Center
 Western Psychiatric Institute*

GOLDMAN-RAKIC PRIZE FOR OUTSTANDING ACHIEVEMENT IN COGNITIVE NEUROSCIENCE

Peter L. Strick, Ph.D.
University of Pittsburgh School of Medicine

In his presentation, Dr. Birmaher noted that bipolar disorder is an illness that affects about 2% to 3% of children and adolescents. Untreated, it affects the normal development of the child and is associated with social, family, academic, and work difficulties. Moreover, it significantly increases the risk for substance abuse, legal problems, and suicidal behaviors. This is why he believes that it is important to identify who is at risk to develop bipolar disorder and to develop strategies to delay, and in the best of cases, prevent the onset of this disorder. Dr. Birmaher discussed the Pittsburgh Bipolar Offspring Study (BIOS), which seeks to identify the symptoms and other factors associated with increased risk to develop bipolar disorder. His presentation showed that offspring of parents with bipolar disorder are at specific high risk to develop bipolar disorder. Also, he discussed the symptoms and the genes associated with increased risk to develop bipolar disorder.

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



In his symposium presentation, **Peter L. Strick, Ph.D.**, discussed *Solutions to the Brain-Body Problem: Neural Substrates for Psycho-somatic Disease*. Dr. Strick is the Detre Professor & Chair of Neurobiology, the Scientific Director of the University of Pittsburgh Brain Institute, and Director, Systems Neuroscience Center and Co-Director, Center for Neuroscience at the University of Pittsburgh. He is also a 1995 BBRF Distinguished Investigator.

In his presentation he noted that modern medicine has generally viewed the concept of “psycho-somatic” disease with suspicion, partly because no neural networks were known for the “mind,” conceptually associated with the cerebral cortex, to influence autonomic and endocrine systems that control internal organs. He also explained how his team has used a unique tracing method to identify the areas of the cerebral cortex in the monkey that communicate through multi-synaptic connections with the adrenal medulla. He discussed the results and their implications, among other things, in the control of stress, and for understanding stress disorders and depression. One of the insights from his lab’s work is that there is a concrete anatomical basis for psychosomatic illness where mental states can alter organ function.

Dr. Strick’s research focuses on four major areas: 1) the generation and control of voluntary movement by the motor areas of the cerebral cortex; 2) the motor, cognitive and affective functions of the basal ganglia and cerebellum; 3) the neural basis for the mind-body connection; and 4) unraveling complex neural networks in the central nervous system. His lab is using modern neuroanatomical, physiological, and functional imaging techniques to determine how each of the cortical motor areas differentially contributes to the generation and control of voluntary movement. He is also investigating the role of the premotor areas in the recovery of motor function that can occur following damage to the primary motor cortex or its connections, as in spinal cord injury or strokes.

The 2022 International Mental Health Research Symposium was sponsored by:

- Geoffrey Simon/Raymond James
- Miriam Katowitz
- Rogers Behavioral Health



2022 BBRF Symposium Speakers. From L to R: Dr. J. John Mann, Dr. Sophie Erhardt, Dr. Robert Schwarcz, Dr. Robert Hirschfeld, Dr. Altha Stewart, Dr. Jeffrey Borenstein, Dr. Peter Strick, Dr. Robert van Voren, and Dr. Boris Birmaher.



The BBRF Mental Health Symposium also featured presentations from the two winners of the 2022 Pardes Humanitarian Prize in Mental Health, **Altha J. Stewart, M.D.**, and **Robert van Voren, FRCPsych (HON)**.

Dr. Stewart's presentation, *Recommendations for Addressing Mental Health Disparities Through Research*, addressed disparities in the prevalence and outcomes of mental health disorders that are well recognized in the U.S. in racialized and underserved communities. Factors ranging from limited access to services, challenges in finding culturally competent providers, and navigating systems that are structurally incompetent, present barriers to care and continue practices that do not fully address the needs of many communities. Dr. Stewart spoke about the need for more research to improve care and reduce the structural determinants of mental health in diverse populations. She also talked about the need to establish priorities, engage community stakeholders, and collaborate with communities on research to develop and test effective interventions to reduce these disparities.



Dr. van Voren spoke about *Providing Psychological Support to Victims of State Repression and War*. During his presentation he discussed efforts to provide psychological support to victims of state repression in Belarus and victims of war in Ukraine. He spoke about several programs that were developed over the past 2 years to deal with the psychological distress caused by mass arrests of human right defenders and others, and, subsequently, the war that was unleashed on Ukraine in which over 10 million people were displaced, tens of thousands of people were killed

and many more were subjected to the horrors of war.

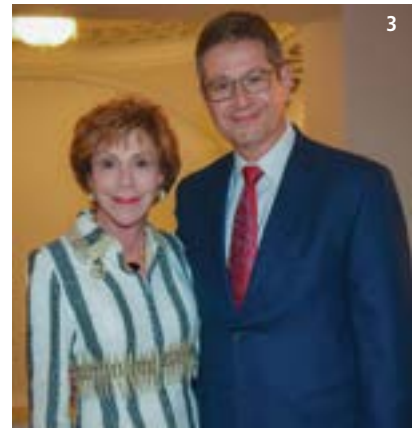
A full story about the winners of the Pardes Humanitarian Prize in Mental Health can be found on pages 25–27. ❖ **LAUREN DURAN**

**In Memory:
Robert M. A. Hirschfeld, M.D.**

Robert M. A. Hirschfeld, M.D., passed away on Feb. 10, 2023. Dr. Hirschfeld was a member of the BBRF Scientific Council and served as moderator of BBRF's annual research symposium since its inception. He was awarded the Foundation's Falcone (now Colvin) Prize in 2003 for Outstanding Achievement in Affective Disorders Research, and was a 2002 BBRF Distinguished Investigator. Dr. Hirschfeld's research significantly contributed to classifications of depression and bipolar disorders—their clinical course, their relationship to personality and personality disorders, and their treatment with medication and psychotherapy. He and colleagues developed the Mood Disorder Questionnaire, a widely used screening instrument for bipolar disorder. The author of over 200 research papers, Dr. Hirschfeld for 25 years was Chairman of Psychiatry at the University of Texas Medical Branch in Galveston. He also served for 18 years as Chief of the Mood, Anxiety and Personality Disorders Research Branch at the National Institute of Mental Health. BBRF is grateful for his many contributions to the Foundation's programs and mission and is deeply saddened by his passing.

2022 International Awards Dinner

The BBRF International Awards Dinner was celebrated on Friday, October 28, 2022, at The Pierre hotel in New York City. The event celebrated the progress being made in brain and behavior research. This event honored the winners of the Pardes Humanitarian Prize in Mental Health and the five Outstanding Achievement Prizewinners who spoke earlier in the day at the BBRF Symposium.



CLOCKWISE FROM TOP LEFT:

1. Dr. Jeffrey Borenstein and Dr. Altha Stewart
2. Geoffrey Simon, BBRF Board Chair
3. Dr. Judy Genshaft, BBRF Board member and her husband, Steven Greenbaum
4. Dr. Sophie Erhardt
5. Dr. Peter Strick and Dr. Jeffrey Borenstein
6. Dr. J. John Mann
7. Dr. Boris Birmaher
8. Dr. Jeffrey Borenstein and Dr. Robert Schwarcz
9. John Osterhaus, BBRF Board Secretary and Dr. Carol Tamminga, BBRF Scientific Council

EVENTS

2022 Pardes Humanitarian Prize in Mental Health Awarded to Pioneers Expanding Access to Care for People Impacted by Structural Racism and Lack of Human Rights

On Friday, October 28, 2022, at The Pierre Hotel in New York City, BBRF presented the 2022 Pardes Humanitarian Prize in Mental Health at its International Awards Dinner.

The Pardes Humanitarian Prize in Mental Health, which carries an honorarium of \$150,000, is awarded annually to recognize individuals whose contributions have made a profound and lasting impact in advancing the

understanding of mental health and improving the lives of people who are living with mental illness. It focuses public attention on the burden mental illness places on individuals and society and the urgent need to expand mental health services globally. Established in 2014, the Pardes Prize is named in honor of Herbert Pardes, M.D., the internationally renowned psychiatrist, outspoken advocate for the mentally ill, and the award's first recipient.

“The 2022 Pardes Prize recipients personify the deep knowledge and understanding of human behavior and the compassion for people suffering from mental illness with limited access to needed services. We applaud their groundbreaking work and honor their service.” noted Dr. Pardes, President of the Brain & Behavior Research Foundation’s Scientific Council.



The 2022 Pardes Humanitarian Prizewinners and Honorary Prizewinners with Dr. Borenstein

THE PRIZEWINNERS



PAST PARDES PRIZE WINNERS

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.

PARDES HUMANITARIAN PRIZE RECIPIENT

ALTHA J. STEWART, M.D.



Dr. Altha J. Stewart has dedicated her career to helping the most disadvantaged and underserved people in our society who are living with serious mental illnesses.

A pioneering voice in America on structural racism and its impact on mental health treatment for people of color, Dr. Stewart combines her formidable leadership skills with her fierce sense of fairness and decency. She used her presidency of the American Psychiatric Association to eliminate barriers for

the most vulnerable and address systematic racial inequities that often make it difficult for people of color to access mental health treatment. She has also authored numerous publications on the determinants of disparities in mental health treatment.

Dr. Stewart is a longtime advocate for better behavioral and mental health services for young people. Her work with the Center for Youth Advocacy and Well-Being aims to promote a trauma-informed culture that focuses on preventing violence and trauma to children, providing help to children exposed to violence, offering peaceful options for resolving conflict, and creating a climate that supports children and fosters collaboration among service providers.

PARDES HUMANITARIAN PRIZE RECIPIENT

ROBERT VAN VOREN, FRCPSYCH (HON)



Robert van Voren has dedicated his life to the cause of human rights and mental health. For 45 years his dynamic leadership and global efforts have provided direction and practical support for making human rights a strong pillar of how societies deal with people living with mental illness. Over the years, he has protested injustices faced by patients, sided with those who fight for human rights, and exposed systematic abuse of psychiatry, at a substantial risk of harm to himself.

During this time of humanitarian emergency work in Eastern Europe, Professor van Voren's zeal is evidenced by his efforts in Ukraine and neighboring countries, where he has organized mental health services for people impacted by the war and supplied essential medicines and supplies to institutions that house persons with mental disorders.

As a leader and professor, he has also created countless initiatives and activities for schools, workshops, training seminars and advocacy campaigns. He has established and restructured mental health services, documented human rights abuses, and has given voice to people with mental illnesses.

2022 PARDES HONORARY PRIZE RECIPIENT
CLUBHOUSE INTERNATIONAL



For more than 25 years, Clubhouse International has pioneered the recovery concept for people living with mental illness, putting into practice their active participation in their own recovery process, a model

that has been endorsed by governments, civil society, and professionals globally.

Built upon the belief that every member has the potential to recover from the effects of mental illness and lead a personally satisfying life as an integrated member of society, Clubhouses, now numbering 320, are comprised of communities of people who are dedicated to one another's success, no matter how long it takes or how difficult it is. Clubhouse offers people living with mental illness opportunities for friendship, employment, housing, education, and access to medical and psychiatric services in a single caring and safe environment. This social and economic inclusion is a model of care that helps lower trends of higher suicide, hospitalization and incarceration rates associated with mental illness.

2022 PARDES HONORARY PRIZE RECIPIENT
SEAN MAYBERRY



While working in Africa implementing HIV/AIDS and malaria programs, Sean Mayberry, a former diplomat and social marketer, saw firsthand the challenges of millions of women with mental illness. He was determined to find a solution. In 2013, he came across a Johns Hopkins University study that showed remarkable

success in treating depression in individuals in Uganda using Group Interpersonal Psychotherapy (IPT-G), facilitated by lay community health workers. The potential of this simple, low-cost intervention inspired Sean to quit his job and start a new organization called StrongMinds, to provide depression treatment to women in Africa, most with no access to effective treatment.

Since its founding, StrongMinds has treated depression in 150,000 women and adolescents in Uganda and Zambia. On average, over 80% are depression-free following therapy. Through Sean's inspirational vision, StrongMinds has proven that IPT-G is a simple, cost-effective way to scale access to depression treatment for underserved populations. IPT is now a WHO- recommended first-line intervention and is being delivered in many countries.

"These talented and accomplished leaders are striving to expand the reach of mental illness treatment here in the U.S. and around the globe. They serve as extraordinary advocates for mental health and inspire us all to use our knowledge toward the greater good for all humanity," said Jeffrey Borenstein, M.D., President & CEO of the Brain & Behavior Research Foundation. ❖ **LAUREN DURAN**

What Can We Do When Medicine is Not Enough in the Treatment of Schizophrenia?



By Dawn I. Velligan, Ph.D.

Henry B. Dielmann Chair, Department of Psychiatry
Director, Division of Community Recovery, Research, and Training
Department of Psychiatry and Behavioral Sciences
The University of Texas Health Science Center at San Antonio

2016 BBRF Distinguished Investigator
2002 BBRF Independent Investigator
1997 BBRF Young Investigator

IN BRIEF

When people use antipsychotic medicines, Dr. Velligan notes, they can go longer without a relapse. Yet only half of medications prescribed are taken by patients. She describes ways of helping patients with persistent positive symptoms come up with alternate explanations for their perceptions. She also discusses ways of helping patients cope with cognitive difficulties which impact the ability to plan, use judgment, and carry out goal-directed activity; and to work through negative symptoms such as anhedonia and low motivation.

Schizophrenia is a common illness, and one with serious impacts that often disable or greatly impair the lives of individuals with this diagnosis. Somewhere between half a percent and one percent of American adults have schizophrenia, according to the most recent studies. It therefore affects over a million American adults, and possibly two or more million.

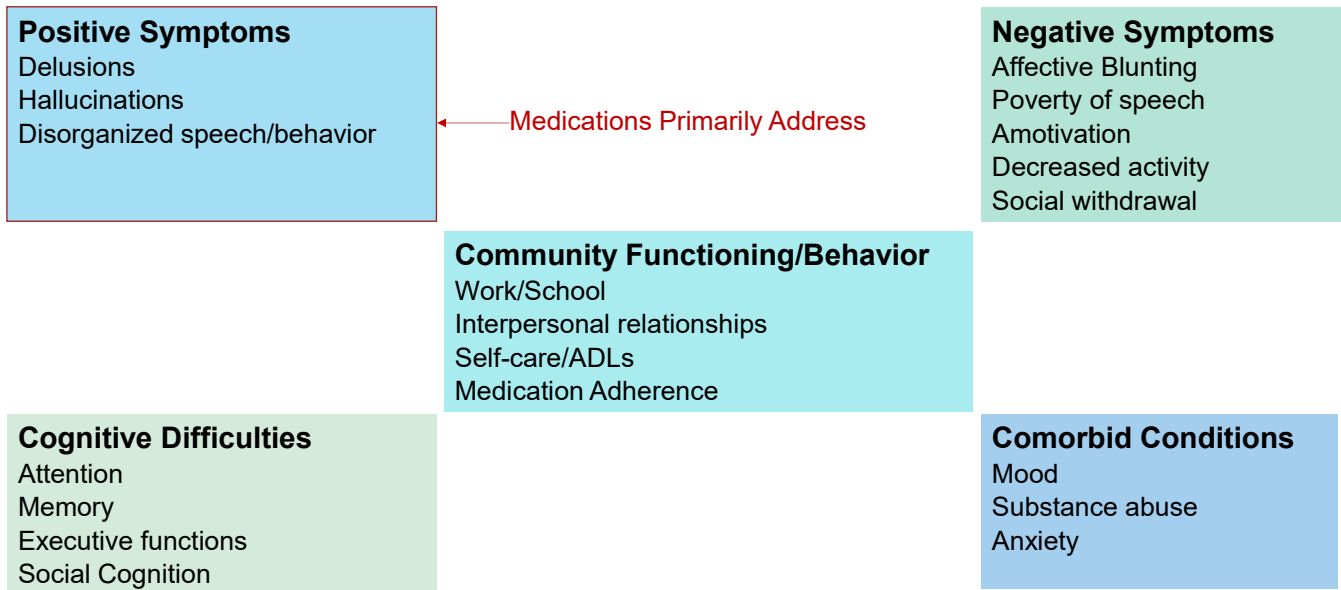
The illness can be thought of as a constellation of multiple signs and symptoms. First of all, there are what we call the “positive symptoms:” delusions, hallucinations (aspects of psychosis), and disorganized speech and behavior. These are the symptoms that medications are designed to target.

Then there are the symptoms we call “negative symptoms:”, which include the blunting of affect, problems with speech and movement, and trouble with motivation. Importantly, we don’t have good medication choices for negative symptoms.

In addition, there are cognitive impairments in attention, memory, and planning that are present even prior to the positive symptoms of the disorder.

In schizophrenia there are also comorbid conditions involving mood regulation, substance use, and anxiety, all of which need to be addressed when they are identified. Together, all of these symptoms impact how people with schizophrenia get along in the community, how they work and go to school, the kinds of interpersonal relationships they can have, their independent living skills, and whether or not they are going to follow through with medication.

Schizophrenia: Signs and symptoms related to outcome



THE USES — AND LIMITS — OF MEDICATION

Let's start with the role of medication, which is important. When people use antipsychotic medicines, they survive longer in the community without a relapse. This is compared with when they discontinue those medications or may be taking a placebo in the context of a clinical trial. We also know that if you don't take antipsychotic medicine for 11 days, that doubles the risk of hospitalization.

What are the limitations? For one thing, only half of the medications that are prescribed are ever taken by patients. And on average, individuals with schizophrenia have eight to nine relapses in a given 5-year period. Medication follow-through is arguably one of the most modifiable obstacles to clinical stability and relapse prevention. And so it's something that we often target in our psychosocial treatments and education. Additionally, medications have side effects and are often intolerable for patients, and help explain why adherence is a problem in some cases. Furthermore, while antipsychotic medication might quiet things down, sometimes it doesn't take everything away. Many individuals on antipsychotics continue to experience delusions or hallucinations. So it's

important to reduce those persistent symptoms and the distress that goes along with them.

THE ROLE OF COGNITIVE BEHAVIORAL THERAPY

For many years, cognitive behavior therapy (CBT) has been an evidence-based treatment for persistent positive symptoms. Some people can hear voices but remain able to do many things. Other people with this problem find it's very difficult to function. CBT is focused on helping the person come up with **alternate explanations** for their symptoms. This can help reduce the impact of those symptoms on their behavior.

We also want to focus on **changing underlying beliefs**. Many people with psychosis develop a worldview while they are growing up that later predisposes them to certain kinds of psychosis. The first thing we do in CBT is to try to normalize the experiences that people have. Addressing distressing or problematic beliefs has to be done carefully. Individuals are used to defending their ideas or being patronized. Confronting them can cause them to have greater conviction in their beliefs. But, it's important not to agree with these statements. We therapists don't say things like, "Yeah, I saw the FBI

“Addressing problematic beliefs has to be done carefully. People are used to defending their ideas or being patronized. Confronting them can cause them to have greater conviction. But, it’s important not to agree with these statements.”

following you, too.” We want to find a fine line in the middle where we’re choosing our words very carefully and really attempting to understand. “Why would the FBI want to follow you? What’s so important or what’s so special about you? I’m confused about that. Do they do this to everyone?” We’re trying to expand the patient’s thinking here. We also want to investigate evidence with the patient. We might ask: How much does it really cost to surveil someone? How big of a team do you need? What kind of devices do you need? And when people realize what it takes, sometimes they begin to have a teeny bit of doubt.

Many famous and successful people have heard voices. Anthony Hopkins. Sigmund Freud. Winston Churchill. It’s important for people to keep in mind that their life is not over because they’re having these experiences.

There’s an organization called voicehearers.org which offers a poster that I give out. The poster summarizes skills for coping with auditory hallucinations. There’s really two basic strategies. One: **distracting yourself**. For example, wearing earphones that play music that competes with the voices; getting away from things, like going on a picnic. The second method is **focusing**. You focus on the voices, listen to them, negotiate with them. We encourage people to try a variety of approaches.

A meta-analysis—a study of multiple studies on a topic—that assessed 19 CBT studies for psychosis showed that most of the studies achieved at least a small effect positive impact, and 32% achieved a moderate impact. Does that mean CBT is for everybody? Maybe not, but maybe certain CBT techniques can help many people a least a little bit.

THE CHALLENGE OF COGNITIVE PROBLEMS

But as I said at the beginning, there’s more to schizophrenia than positive symptoms. There can also be cognitive difficulties in memory, information processing speed, and executive function. This means that individuals have trouble planning, using judgment, and carrying out goal-directed activity. There are also difficulties in social cognition. These faculties underlie our abilities to perceive, interpret, and respond to other people in the world. So if you can’t assess the emotional states of other people, if you can’t understand facial expression and voice tone well, that can cause problems in social relationships. These cognitive difficulties predict how people are going to function socially and at work and to what extent they can live independently.

There are different ways to intervene. One is to directly target cognitive problems such as attention and memory and the ability to plan with cognitive practice. With drills and practice, either on a computer or using pen and paper, you can improve people’s cognitive functioning. This hasn’t been well integrated into clinical treatment overall, and it works best if it’s part of a multimodal program.

There are also a number of programs that look at how to improve cognition in the context of vocational functioning. It’s been found that people in cognitive remediation tend to work longer hours and make more money than people who don’t get





Happy; angry; confused; concerned; sad: many people who are diagnosed with schizophrenia have difficulty accurately reading facial expressions. This, in addition to low motivation and difficulty putting thoughts into words, makes it hard to function in society.

cognitive remediation. What you're expecting here is that cognitive gains are going to generalize into the real world in terms of functional outcomes.

OPTIMIZING THE SURROUNDINGS

Cognitive Adaptation Training (CAT) was developed at my institution, the University of Texas, decades ago, and we're still using it to help people to stay out of the hospital and to develop good social and community relationships. CAT relies on what are called automatic processes. Most of what we do every day is automatic. If we paid attention to absolutely everything, it would be impossible, and we wouldn't get anything done. Environmental cues get us ready to act. Cues are easier to follow than they are to resist. Cues also increase the experience of fluency: they make behavior feel easy to do. Your phone rings, you answer it.

In our practice, we look closely at how people's environment is set up. Are things set up safely? Are they set up for that fluency, that ease of use? We help patients reorganize belongings in their apartments to decrease the number of steps that it requires to do things.

I do home visits. I see so much clutter that you can't do anything. Can you imagine trying to get ready for a doctor's appointment when you open a drawer and there's SSI papers and potato chips and underwear? Every time you have to do something, there's a chance that it's going to take forever. Or, if you do go to the doctor and do pick up your prescription, and then you put your prescription on the dresser, chances are you may not even see it, or you might put the hat on top of it or it might fall somewhere because there's so much stuff laying around.

So we try to organize things, and then we remind patients where those things are by labeling. I recall a patient who kept their toothbrush and toothpaste in the bottom dresser drawer. Under those circumstances, it's really unlikely they're going to use it. So we moved it out of there and we put it in the bathroom where they can see it.

It's one of the things we do for people whose negative symptoms include apathy, those who have trouble starting things. They're laying in bed, thinking, "Oh man, I got to get up. I got to walk all the way over there and get my clothes. I got to do this, I got to do that." And pretty soon it's too much. So we put a clothing rack at the foot of the bed. And then on every hangar there's a shirt, pants, underwear, and socks. I try to reduce the number of steps. Everything is right there. We set this up together. Next, you can set an alarm that says, in effect, that it is time to get dressed.

Dr. Velligan has had success with patients by helping them to plan in advance, reduce clutter, and organize important daily activities such as taking medicines.



Whatever the person's recovery goal, you can tie that to how important it is to get dressed. You try to make this automatic, something you do every day.

REPETITION, ORGANIZING, MAKING THINGS HABITUAL

Repetition with verbal and visual cues also increases familiarity. For example, you have a voice alarm that tells you it's two o'clock, it's time to take my medicine. And that happens every day at two, it starts to have that sense of truth. If you repeat the same behavior at the same time every day it starts to become automatic.

For problems with memory and organization, we use a huge calendar. We put it on the wall and attach a sharpie marker with yarn. If we don't attach a sharpie marker, nothing ever gets written on the calendar. A lot of people forget to check their phone but if they can see the calendar from across the room, they know that their next appointment is going to be in

a day or two. We teach patients to check every day off, so they always know what day it is.

Similarly, if you put a sign on your door, you will not be able to leave your house without taking your medication. And that will work for a while. And then we can change the color or the wording or whatever is going to capture that person's attention over and over.

We also use pill containers. For people who take more pills than they need, we'll pack them in separate compartments representing the days of the week so that there's no cue to open extra compartments. We also put bottles of water and the medicine for evening by the bed, so that all one has to do is reach over. Again, it's decreasing number of steps, making things easier. We use a lot of checklists. People feel good when they check things off.

In addition to calendars, we also use blank daily schedules. Tell me how you



spend your day. For people with negative symptoms, this is really a visual aid. The truth is, if you spend all the week not focusing on how you spend the hours, some people will say that's fine, that's what they want. But then, we tell them, if you don't do anything different this week, next week is going to be the same and the week after that. Is this how you want things to be next year or in five years? Because if we don't do something different today, there's not as much hope that things are going to change. So we try and we're a little bit pushy. We often do things and engage in activities to get people going and doing.

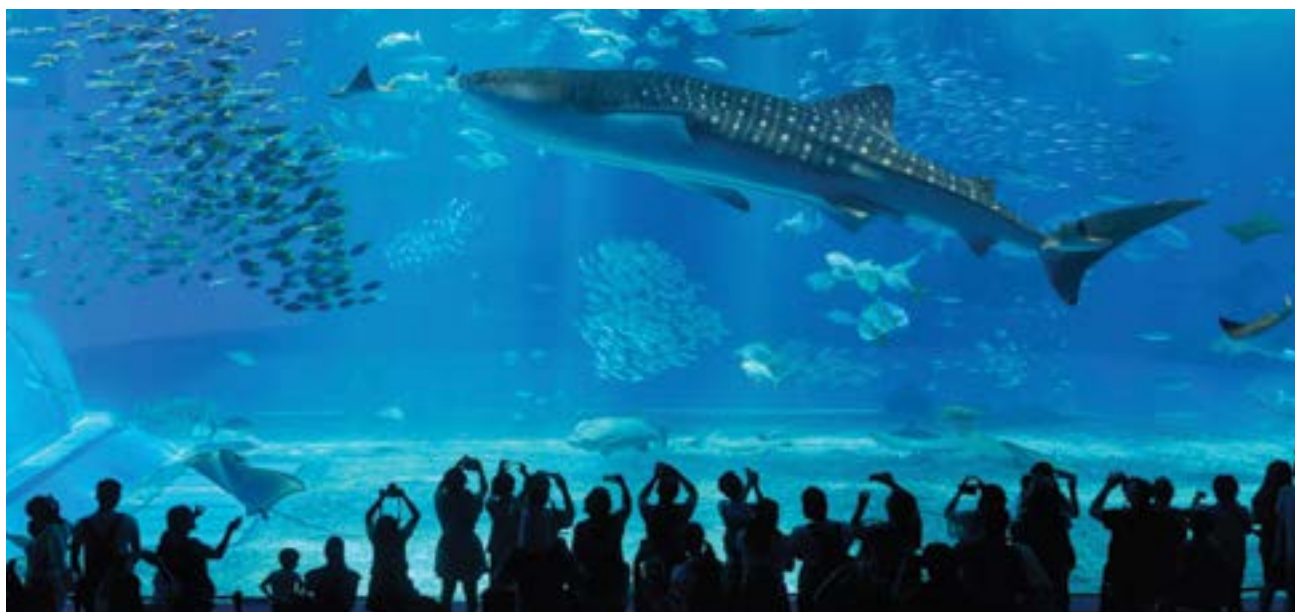
We find that there are pretty good outcomes with cognitive adaptation training. In a study that tested PharmCAT, which is CAT that focuses on taking medicine and making it to your doctor's appointments and treatment, and compared it with what happens when patients are not in such a program, we found people were only taking about 60% of their medication unless they were in CAT and PharmCAT. We also found that when we stopped making weekly home visits, the habit that we created continued.

People function at a much higher level when they have full CAT. The full CAT program is really necessary to get enough of a boost that it makes a difference in your social and occupational functioning. And you can see that without booster sessions, functioning starts to decline. We also find that people in PharmCAT and CAT were able to stay out of the hospital for longer periods of time.

WHEN NEGATIVE SYMPTOMS PERSIST

But what about when negative symptoms persist? Negative symptoms are defined as the absence or reduction of behaviors that are normally there. These include things like anhedonia, difficulty feeling pleasure. People don't socialize as much. They don't decide to do things, they don't plan things, they're not interested in social or work activities. Their affect can be blunted. They don't talk much.

At the onset and in the maintenance of negative symptoms, there is a neurodevelopmental issue, but there's also a protective issue. We see in a lot of early-onset psychosis that people shut down, they're overstimulated, they withdraw, and that's protective for them at the beginning of their psychosis. But this can lead to the development of negative symptoms. And it has consequences in the world. Such patients don't have as many activities or interests that they can discuss with others. So it affects how much others want to talk to them. There's also a lack of external positive reinforcement. They're not getting any goodies from the world because they've withdrawn from it, and they might lose skills that they used to have. If they were pretty decent conversationalists without practice, some of those skills can weaken. And then they don't plan things for tomorrow. So tomorrow looks just like today, and then this becomes a behavior pattern that repeats in a loop.



Patients often balk at invitations to participate in activities, anticipating they won't enjoy them. Going on an outing and having fun can then serve as an object lesson: "You didn't expect to have fun, but you say you did. What about joining us for dinner next week?"

“CATCH IT, CHECK IT, CHANGE IT” —AND OTHER TOOLS

With this problem in mind, we developed an approach we call MOVE, which is a kitchen-sink kind of approach. It involves five components of treatment, ideas we borrowed from others that have been shown to work, including the practices of CAT. We work on how to get people up, moving, doing. We use an intervention for anticipatory pleasure where we ask people, “All right, how fun do you think it’s going to be to go to the zoo?” And then we go to the zoo, have a good time, take pictures, and record their impressions. The next time someone mentions the zoo they might not anticipate that it might be fun. But if we can show them that it was, they can remember. And this is going to help them with anticipatory pleasure because research shows people with a psychotic illness have a capacity to enjoy things—it’s just that they don’t anticipate it.

We have patients do a lot of the training from SCIT, social cognition interaction training, where they look at certain parts of the face so they can identify emotions. And we have them practice things in front of a mirror and on a recorder so that they’re more likely to show affect in their voice and face.

The fourth component is CBT. People have these defeatist beliefs of how they’re going to do, “people aren’t going to like me,” etc. We borrow from one researcher a very simple approach when it comes to unhelpful thoughts: **catch it, check it, change it**. So you can take an unhelpful thought, look at the evidence, and then replace it with something more helpful.

We also use skill-building approaches such as social skills training and modeling. How do we cook healthy meals? How do we return a garment at a store? We send text messages while people are interacting to remind them to smile at other people and do other activities.



Flat affect is a common symptom of schizophrenia. But one can use a mirror to practice showing in one’s face the emotion that one feels inside.

In a study that was funded by BBRF and the NIH, we noted a moderate positive effect size on the negative symptoms scores with MOVE compared with treatment as usual. However, MOVE is labor intensive, requires knowledge of a lot of therapies, and is difficult to recruit therapists for.

There are many other evidence-based interventions for psychosis. Peer-to-peer programs are awesome. The clubhouse model where people come to the clubhouse to work and make their resumes is very helpful. We have one in San Antonio. Intensive care management is very effective. We have a number of programs where we work with “high utilizers,” individuals who go to the hospital a lot, and we work to keep them out using multiple approaches.



Learning how to prepare healthy meals is one of the life skills that can become a habit that improves quality of life, day to day.



Group therapy and peer-to-peer sessions have helped many patients work through issues and become more functional in the presence of others.

ADVICE FOR FAMILIES

As patients and families, you have to advocate for yourself and search for what's available. And unfortunately in some areas you have to pay for "extras," i.e., attention that involves more than "treatment as usual." We have really good programs here in the United States that I would encourage people to request their Managed Care Organizations to cover and reimburse for. We therapists only get paid if we keep people out of the hospital, and it's on the basis of the number of days we keep them out. We use that money flexibly to help people get engaged in activities in the community. That can really change

the face of treatment. Certainly, patients and their loved ones can talk to those working in mental health at universities. They would be the people who would most likely be doing studies or be aware of the best treatments and approaches. I urge you not to give up. Keep looking!

We want more people to take advantage of evidence-based interventions of the kind I have described here. They're not widely adopted a lot of times by agencies that see the greatest number of people with psychosis. We need to increase the first-episode of psychosis programs and recent schizophrenia-onset programs to keep people

working and in school, to prevent disability. Keeping people in their school and work life is the very best thing that we can do. We also need to ensure that these models are applied with fidelity. It's not enough to train people. You really need to make sure they're doing what they've been trained to do. And of course, we need to increase funding for mental health to ensure that these evidence-based programs are adopted alongside the best medical treatments. ❖

“Patients and families, you have to advocate for yourself and search for what's available. I urge you not to give up. Keep looking! ”

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

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



“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

Recent Research Discoveries

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

Does a Mother's COVID Infection During Pregnancy Raise Child's Neurodevelopmental Risk?

A preliminary study of thousands of children born during the pandemic has found that those whose mothers tested positive for COVID-19 during pregnancy had increased risk of a developmental disorder diagnosis during their first 12 months of life.

A team led by **Roy H. Perlis, M.D. M.Sc.**, a 2006 and 2001 BBRF Young Investigator at Massachusetts General Hospital, used electronic medical records covering births at six Massachusetts hospitals between March 2020 (soon after the pandemic began) and September 2020. The records captured 7,772 live births to 7,466 women, 222 of whom received a positive PCR test for COVID-19 during their pregnancy.



The mothers were in the early 30s, on average, and included women who identified as Hispanic (15%), Asian (10%), Black (8.4%), and White (69%). In all, 6.3%, or 14 of the 222 offspring whose mothers tested positive for COVID during pregnancy received a neurodevelopmental disorder diagnosis by age 12 months. This compared with 3%, or 227 of 7550 children born to mothers who did not receive a positive COVID test during pregnancy.

A wealth of data from epidemiologic studies has demonstrated over the years that maternal infection during pregnancy, including viral infection due to the flu, is associated with adverse neurodevelopmental outcomes in offspring. Risks for a wide range of disorders (autism spectrum disorder,

schizophrenia, cerebral palsy, cognitive dysfunction, bipolar disorder, anxiety, and depression) are thought to be elevated to varying degrees depending on a number of variables, including severity of the infection and possible comorbid health conditions in the mother.

While most of these disorders take years to become evident in a young person, some—including various kinds of cognitive dysfunction—can be detected in the first years of life. While the 12-month milestone is usually too early to detect, for example, autism spectrum disorders, precursor developmental signs are thought by some to indicate heightened risk in a child. The developmental diagnoses registered in the study by Dr. Perlis and colleagues were for the most part disorders of motor function and speech.

It is thought that the link between maternal infection during pregnancy and heightened neurodevelopmental risk in the child can be traced to inflammation caused by the mother's infection. Development of the fetal brain may be impacted by the mother's immune response to inflammation that can be communicated via the placenta.

Emerging evidence, Dr. Perlis' team notes, already suggests that COVID-19 infection may be associated with preterm delivery and possibly other birth complications. All of the specifically COVID-related studies including their own must be considered preliminary, however, since children born to mothers who were infected at the beginning of the pandemic are still only in their 3rd year of life. Data on the children born in the study by Dr. Perlis and colleagues also cannot reveal anything about differing levels of risk potentially corresponding with maternal infection by one of the more recent COVID variant strains.

Among the findings in the current study, it was clear that COVID infection during pregnancy was most likely to heighten the child's neurodevelopmental risk when the infection occurred in the 3rd trimester of gestation; and that mothers with COVID infection were significantly more likely to have given birth prematurely (14.4% vs. 8.7%).

Dr. Perlis' team as well as a commentator in the journal in which the study appeared, *JAMA Network Open*, noted that the results of this study were not designed to demonstrate a causal connection between maternal COVID infection and neurodevelopmental risk in the child, only an association.

This is among the reasons for the team's call to the research community to perform larger and longer-lasting follow-up studies investigating the impact of COVID infection during pregnancy on both mothers and their children. ❖

Long-Term Regular Cannabis Users Showed Cognitive Deficits at Midlife in 45-Year Study

The question of whether cannabis use causes cognitive deficits or structural changes in the brain is still an open one, and has mostly been tested in adolescents and young adults. There is good reason for this emphasis: the brain is vulnerable and continues to develop throughout the teen years and into the twenties, and those are typical ages when cannabis use is experimented with and can become chronic.

Several studies comparing cannabis use among young people with matched individuals who have not used cannabis have found evidence of subtle cognitive deficits and structural brain differences among the cannabis users. Various uncertainties remain controversial, including the potential importance of how frequently and for how many years cannabis is used and the potency of the cannabis used (in terms of THC content, the psychoactive component of cannabis).

The question of potential longer-term impact of chronic cannabis use was central to a team of investigators led by Madeline H. Meier, Ph.D., of Arizona State University, and **Terrie E. Moffitt, Ph.D.**, of Duke University. They have published results of a preliminary study on the question in the *American Journal of Psychiatry*. Dr. Moffitt is a 2010 BBRF Ruane Prize winner, as is another team member, **Avshalom Caspi, Ph.D.**; **Ahmad R. Hariri, Ph.D.**, a 2003 BBRF Young Investigator, was also a member of the team.

The researchers said the effects of long-term cannabis use upon brain function and structure in midlife and older users are especially pertinent with legalization of cannabis in many states, and increasing use of the drug among baby boomers (b. 1946-64), "a group that used cannabis at historically high rates as young adults and who now use cannabis at historically high rates as midlife and older adults."



Are all midlife and older adult cannabis users at risk? The team estimates that perhaps 10%-15% of users in this age range are dependent upon the drug. "Distinguishing problem and non-problem users is important," the researchers stressed, since those who use cannabis relatively infrequently in midlife without the problems associated with long-term use may not differ in risk from non-users. Another question the team asked: how do cognitive and other brain differences among chronic cannabis users, if they exist, compare with those seen in chronic alcohol or tobacco users in the same age group? Do differences, if any, persist after cessation of cannabis use? And finally: do structural brain differences among chronic cannabis users, if any, underlie cognitive deficits and do they predict higher risk for dementia later in life?

To study these questions, the team utilized a well-documented cohort of 1,037 individuals representative of people born in Dunedin, New Zealand in 1972 and 1973. 938 members of the group, followed through age 45, formed the basis for the analysis. Among a host of factors, cannabis use and dependence were assessed in members of the cohort at ages

18, 21, 26, 32, 38, and 45. The group was also tested for IQ at three points in childhood—ages 7, 9, and 11—and again at age 45. Specific neuropsychological functions and volume of the brain’s hippocampus were assessed at age 45.

Analysis of the New Zealand data revealed that long-term cannabis users showed a decline in IQ from childhood to midlife (typically by about 5.5 points), as well as deficits in their midlife learning ability and brain processing speed. Study participants’ friends and relatives also supplied information in response to questionnaires which indicated that chronic users were more likely to experience memory and attention problems.

“These deficits were specific to long-term cannabis users,” the team made clear. “They either were not present or were smaller among long-term tobacco users, long-term alcohol users, as well as those who used cannabis recreationally in midlife and those who stopped using cannabis altogether by midlife.” The team defined recreational users as those who used cannabis between 6 and 51 days a year (i.e., less than weekly) in midlife (ages 32, 38, or 45); “quitters” were defined as those who no longer used at age 45 but at one of the earlier time-points in the study had been diagnosed with cannabis dependence or used regularly, i.e., 4 or more times per week.

“Cognitive functioning among midlife recreational cannabis users was similar” to norms in the overall cohort of 938 people. “Quitters showed subtle cognitive deficits” of uncertain significance. Long-term chronic users of cannabis showed smaller hippocampal volume in 5 of 12 subregions of the hippocampus. However, the evidence did not support connecting smaller hippocampal volume with observed cognitive deficits. Such a connection may or may not exist. The team speculates that additional, more complex factors or processes may be involved in causing cognitive deficits among chronic life-long cannabis users; the nature of such mechanisms remains unclear.

The key question raised by the study, which merits continued exploration in this cohort and others, the team said, was whether midlife cognitive deficits in long-term cannabis users, to the extent they exist, raise risk or even predict dementia later in life. ❖

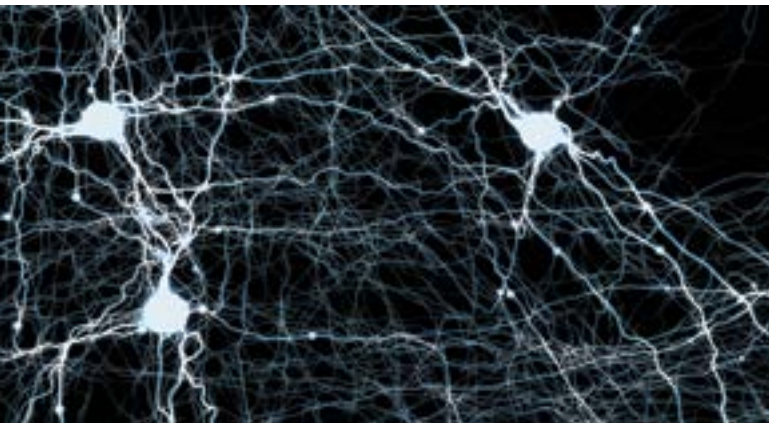
Lab-Grown Human Neurons Transplanted into the Rat Brain Grew, Connected, and Promise to Shed Light on Psychiatric Illness

During the last decade, neuroscientists have devised technologies that enable them to grow human brain cells under controlled conditions in the laboratory. A number of BBRF grantees and Scientific Council members have pioneered methods of directing human stem cells—the cells that are the “mothers” of all our cells—to specifically develop as neurons and other brain-cell types.

This remarkable ability, seemingly out of the pages of science fiction, has opened up new possibilities for studying the roots of psychiatric (and other) illnesses. It is possible to direct stem cells to mature, for example, as brain cells, which are not normally accessible in ways that the cells of other bodily organs are. Perhaps even more remarkable is

the ability of neuroscientists to harmlessly sample skin cells from an individual suffering from a poorly understood illness with genetic roots, such as autism spectrum disorder or schizophrenia, and to re-program that person’s cells back to a stem cell-like state, and then to redevelop them in the lab as brain cells. This enables researchers to watch the cells as they mature, and potentially to observe problems at the cellular level that mark the beginning or early stages of the disease process.

As exciting as these advances have been, they have proven to have limitations. For example, while human neurons grown in a lab dish can form connections with one another, they don’t mature to stages seen in the living human brain. In the



developing brain, in particular—the stage when pathologies in illnesses like autism and schizophrenia likely begin—newly born neurons and other brain cell types receive a wide variety of signals that can't be mimicked in a lab dish. Among other things, neurons and emerging circuitry directly respond to experience: sights, smells, sounds that a newborn detects and tries to make sense of.

For the last 13 years, **Sergiu P. Pasca, M.D.**, of Stanford University, a 2017 BBRF Independent Investigator and 2012 BBRF Young Investigator, has devoted his efforts to developing and improving ways of growing human brain cells in the lab, and to finding ways of using them more effectively in disease research. In the journal *Nature*, he and colleagues now report that they have taken a major step forward.

Dr. Pasca's team has succeeded in taking organoids composed of human cortical cells and transplanting them into the cortex of rats in their first week of life. Cortical organoids are clumps of neurons grown in a dish from human stem-cell precursors.

Dr. Pasca's aim was to see if transplanted organoids composed of excitatory neurons found in the human cortex would survive in the rodent brain, and if they did, whether the neurons within the organoids would mature and integrate with neurons in the rodent brain, as the host animals matured. The answer to both questions was yes.

In fact, the transplanted organoids grew within 8 months to 9 times their pre-transplantation volume, and, as revealed by MRI, came to occupy about one-third of a hemisphere of the rat brain. Not only were the transplanted neurons larger; they also formed more complex branching connections with other brain cells than did neurons grown in organoids that were not transplanted and continued to be raised in the lab.

Amazingly, this occupation of the rat brain by human cells did not appear to impact the host brain's workings. The rat brain's contents were displaced but not disabled. As the researchers had hoped, human neurons within the organoids integrated steadily over time with cells in the rat brain, and in ways more complex than when single human neurons have been implanted in the rodent brain. The rodent hosts receiving the organoid transplants, accommodatingly, steadily supplied the human neurons with nutrients and electrical inputs.

Dr. Pasca's team targeted the organoids for transplantation into the portion of the rat brain that processes sensory information—the somatosensory cortex. The team conducted experiments demonstrating that the human neurons began to respond to inputs the rats were receiving from their whiskers. In other words, the human cells were integrating functionally into the rat brain and could receive sensory stimulation.

The team went a step further. By conditioning the rats to associate a reward with stimulation of their transplanted human neurons, the rats then began to seek the reward when the team stimulated the human neurons within the rodent brains using optogenetics technology. (Optogenetics employs beams of colored light conducted via a threadlike fiber to active specific neurons.)

In what might be their most consequential success, the team studied cells donated by patients with a rare neuropsychiatric illness called Timothy Syndrome. When transplanted into the rat brain, cortical organoids grown from these cells developed and integrated with the host brain in ways that clearly revealed pathologies consistent with Timothy Syndrome (some of whose symptoms overlap with those of autism spectrum disorder).

This suggests the potential of the cortical transplantation technology to enable researchers to explore pathologies in cells and circuits in a range of psychiatric illnesses with suspected origins in the early phases of life—not only autism, but also schizophrenia, epilepsy and intellectual disability, Dr. Pasca says. ❖

The team included **Karl Deisseroth, M.D., Ph.D.**, of Stanford, a BBRF Scientific Council member, 2013 Goldman-Rakic Prize winner, and 2-time grantee, as well as **Felicity Gore, Ph.D.**, a 2019 BBRF Young Investigator, and **Neal D. Amin, M.D., Ph.D.**, a 2021 BBRF Young Investigator. Dr. Gore was a co-first author of the team's paper.

Therapy Update

Recent news on treatments for psychiatric conditions

FOLIC ACID SUPPLEMENTS WERE ASSOCIATED WITH LOWER SUICIDALITY IN LARGE DATABASE STUDY



J. John Mann, M.D.

The annual number of U.S. suicides exceeds 45,000, according to the CDC, an increase of 36% compared with the number in the year 2000. Moreover, the CDC estimates that over 12 million adults gave serious thought to suicide in 2020; over 3 million made a plan; and 1.2 million made a suicide attempt. Thus, nonfatal suicide attempts clearly are also a major public health problem. Even as social scientists seek reasons that may help account for the

trend, psychiatric researchers have been looking for concrete ways to reduce rates of suicidal behavior.

One approach is to develop better ways of predicting suicidal behavior, for example through analysis of behavioral patterns indicating imminent risk, or via discovery of genetic and biological markers of risk traits. Another approach is to develop preventive measures—interventions, including behavioral and pharmacologic, which might be tested in those who are considered at high risk.

A promising lead in prevention has now emerged from research led by Robert D. Gibbons, Ph.D., of the University of Chicago, and **J. John Mann, M.D.**, of Columbia University, a BBRF Scientific Council member, 2022 BBRF Colvin Prize winner, and 2008 BBRF Distinguished Investigator. The research was reported in *JAMA Psychiatry*.

Following up on a clue from past research, the team sought to discover whether taking folic acid supplements might be related to lower rates of suicidal behavior. Folate, sometimes called vitamin B9, for years has been recommended in the form of folic acid supplements for pregnant women. Higher

maternal folic acid levels are associated with lower risk of neural-tube and heart defects in the fetus.

In prior research, Drs. Gibbons, Mann and colleagues developed a drug-safety algorithm, in which they examined associations between suicide attempts and 922 drugs on the U.S. market in 2014 that had been prescribed more than 3,000 times. Ten drugs were associated with increased suicide risk; 44 with decreased risk. One of 5 drugs with the strongest association with decreased risk was folic acid—and this was a surprise to the team.

Analysis revealed that over half of patients receiving prescriptions for folic acid (which is more often purchased over the counter) had a pain diagnosis; and 31% who were prescribed folic acid also filled a prescription for the drug methotrexate, which is often given to those suffering from rheumatoid arthritis. Methotrexate is known to deplete folate, explaining why folic acid is often co-prescribed to such patients.

The team hypothesized that low folate levels produced by methotrexate may increase suicide risk, which is then decreased after folic acid supplementation. A similar pattern was postulated for two other drugs that records showed were prescribed, for different reasons, in the year before folic acid was prescribed in the same patients. The team identified folic acid as having potential benefit in terms of lowering suicide attempt risk.

To put this idea to the test, the team made use of large databases which registered inpatient, outpatient, and prescription claims from over 100 insurers. The researchers singled out individuals aged 18 or over who filled a folic acid prescription between 2012 and 2017. Using the database, the team could cross-reference which of these individuals either attempted suicide or intentionally harmed themselves in the same years. They also looked to flag other diagnoses such as depression and anxiety, relevant for suicide risk; conditions such as arthritis which are linked to folate deficiency; and drugs like methotrexate that reduce folate.

The investigators identified a cohort of over 866,000 individuals that formed the basis of their analysis, which compared months in which these individuals filled folic acid prescriptions with months in which they did not. The same analysis was repeated with another vitamin supplement, vitamin B12, with no known relationship to suicidality, in a sample of over 259,000 individuals drawn from the same databases.

In the cohort that was prescribed folic acid over the 5-year period, there were 261 “suicidal events” (suicide attempts and intentional self-harm) specifically during times when folic acid was being taken. There were 895 such events recorded when folic acid was not being taken by the same individuals. When adjusted for various statistical factors, this worked out to a 44% lower rate of suicidal events while folic acid was being taken—in most cases, at the dosage of 1mg/day, which is typical and considered the “upper tolerable limit.” As expected, no association was found between the taking of vitamin B12 and suicidal events.

Importantly, the team was able to calculate that for every additional month of folic acid treatment, those prescribed had a 5% reduction in the rate of suicidal events.

The team found the same folic acid/suicide reduction linkage in men and women, as well as across all age groups, indicating that the effect was not restricted to pregnant women.

These results, the team concluded, “warrant conducting a randomized controlled trial” focusing on suicidal ideation and behavior. “If confirmed, folic acid may be a safe, inexpensive, and widely available treatment for suicidal ideation and behavior.” ❖

CLINICAL TRIAL COMPARED DIFFERENT FORMS OF EXPOSURE AND DRUG THERAPY IN COMBAT VETERANS WITH PTSD



Francis S. Lee, M.D., Ph.D.

After analyzing data compiled in a clinical trial conducted over 7 years with Iraq and Afghanistan combat veterans diagnosed with PTSD, a research team reports progress in efforts to match specific patients with specific forms of therapy.

Efforts like this one to realize the promise of “precision medicine” are fueled by steadily accumulating evidence from research indicating that across

psychiatric illnesses, individuals receiving the same diagnosis not only report a variety of symptoms but that these symptoms are likely caused by varying combinations of psycho-biological factors. One urgent question is whether, and if so, how, these factors affect treatment results.

JoAnn Difede, Ph.D., a Professor of Psychology in Psychiatry at Weill Cornell Medicine, led a team that set out to conduct a randomized, placebo-controlled trial testing two forms of exposure therapy in combat vets with PTSD, and to further determine the impact, if any, of adding a drug known to enhance aspects of cognition. **Francis S. Lee, M.D., Ph.D.**, Chair of Psychiatry at Weill Cornell Medicine, was a co-author on the paper. He is a member of BBRF’s Scientific Council, the recipient of a BBRF Independent Investigator grant in 2010, and Young Investigator grants in 2005 and 2002. Five other BBRF grantees were members of the research team.

The team studied military personnel treated between 2011 and 2018 at three sites. A cohort of 192 patients made up the group that was ultimately analyzed. The subjects were randomized into groups that received different forms of treatment. Half were assigned to receive a virtual reality exposure therapy (VRE); the other half received prolonged imaginal exposure (PE), another kind of exposure therapy.

VRE and PE call for patients to systematically confront their fears in a safe environment, the aim being to habituate to feared stimuli, thus retraining the brain to learn that the multi-sensory cues to fear that were learned during the trauma are now safe, and not signals that the feared event is happening again.

The study subjects were further randomized: groups receiving VRE and PE were divided into those who would take a drug, D-cycloserine (DCS), an antibiotic repurposed as a cognitive enhancer, 30 minutes before receiving exposure therapy, and those who would receive a placebo pill instead of active DCS.

DCS is a cognitive-enhancing drug that prior research shows to moderately stimulate NMDA receptors found in abundance in excitatory neurons. This is potentially useful in treating PTSD since fear extinction has been shown in animal studies to be inhibited by drugs that block the NMDA receptor. The hope is that DCS might overcome this blockage and thus enhance patients' ability to extinguish traumatic fears.

Two types of criteria were at the focus of an effort to analyze subsets of study participants. One was whether or not a subject was also diagnosed with major depressive disorder. The other was whether a subject was a carrier of either of two common genetic variants linked in past research with fear extinction.

The study's results were reported in the journal *Translational Psychiatry*. Perhaps the most important conclusion was that both VRE and PE enabled combat veterans to reduce their PTSD symptom scores, and by almost exactly the same amount (on average, about 20 points on a 136-point symptom severity scale). Both were administered a total of nine times over an average of 16 weeks, in 90-minute sessions. In PE, patients are instructed to close their eyes, imagine the scene of their trauma, and repeatedly recount it—"vividly, aloud, and in the present tense." In VRE, patients wear virtual reality headgear which exposes them to simulations of common combat scenarios while they recount their own trauma. The simulations are controlled by a therapist via a computer console.

While overall there was no significant statistical difference in therapeutic benefit in the two groups, there was one important exception: participants who also suffered from major depression were helped more by VRE. The team speculates the "immersion" effect of virtual reality might help overcome alterations in reward processing experienced by depressed individuals. The analysis also showed that participants who were not depressed did better, on average, with PE.

Another result of the study was that adding DCS to exposure therapy of either type provided no significant advantage vs. placebo.

A final set of results concerns the question of whether study participants bearing either of the two genetic variants potentially affecting fear memory processing may have shown distinct responses to the various forms of therapy given in the trial. The answer was yes, although the number of individuals in the trial who carried either of the mutations was not large enough to support firm conclusions. ❖

The research team included: **Barbara O. Rothbaum, Ph.D.**, a 2012 BBRF Distinguished Investigator; **Christopher Reist, M.D.**, a 1996 and 1993 BBRF Young Investigator; **Tanja Jovanovic, Ph.D.**, a 2015 BBRF Independent Investigator and 2010 Young Investigator; **Seth D. Norholm, Ph.D.**, a 2002 BBRF Young Investigator; and **Charles E. Glatt, M.D., Ph.D.**, a 2003 and 2001 BBRF Young Investigator.

HOME-BASED tDCS BRAIN STIMULATION TREATMENTS REDUCED INATTENTION IN ADULTS WITH ADHD



Douglas Teixeira Leffa, M.D., Ph.D.

Researchers have obtained promising results in a clinical trial of a home-based non-invasive brain stimulation treatment for adults with ADHD.

Douglas Teixeira Leffa, M.D., Ph.D., of the Universidade Federal do Rio Grande do Sul in Brazil, was first author of the paper reporting the results in *JAMA Psychiatry*. Dr. Leffa's 2020 BBRF Young Investigator project was devoted to performing the study.

The study was motivated by several factors. One is that long-term adherence to stimulant medicines, which are the first-line treatment for people with ADHD, is often low. A form of non-invasive brain stimulation called transcranial direct current stimulation (tDCS) has been tested on a pilot basis in ADHD patients, but results have been inconclusive, in part due to small patient sample sizes and brief trial test periods. To address this Dr. Leffa and colleagues conducted a randomized, placebo-controlled trial of tDCS in 64 adult patients diagnosed with moderate to severe ADHD.

tDCS involves application of a low-intensity current over the scalp intended to alter the excitability of cortical neurons and thereby increase brain plasticity. Conventional tDCS protocols involve daily treatments provided at medical centers or offices, thus requiring patients to make repeated visits over the several weeks of a typical treatment period.

In their trial, Dr. Leffa and colleagues employed a low-power tDCS device that can be used safely in the home without medical supervision. The device, featuring electrodes embedded at precise locations within a rubber skull cap, was designed to have a user-friendly interface.

Patients, most in their 30s and 40s and about evenly divided among men and women, were assigned to “active tDCS” or “placebo” groups and instructed on how to use the device. The placebo device, indistinguishable superficially, delivered the sensation of actual treatments but no actual stimulation. After receiving an initial tDCS (or placebo) session while assisted by staff, participants over the next 4 weeks were instructed to self-administer tDCS sessions at home lasting 30 minutes each day, seven days a week.

Importantly, participants were not taking stimulant medications for their ADHD (or agreed not to take them for 30 days before beginning the trial). A few were taking medicines for moderate depression or anxiety. After an initial evaluation, all were assessed after the 2nd week of the trial and after its conclusion in week 4.

Fifty-five participants finished the trial, and on average they completed nearly all (25 of 28) of the prescribed self-administered tDCS sessions. Analysis showed that those who received active tDCS had decreased symptoms of inattention as compared with those in the placebo group. The advantage of the active treatment was not seen until after the 2nd week of the trial, suggesting to the team that brief treatment courses may not deliver sufficient stimulation to have a noticeable therapeutic effect.

The active tDCS treatment was not associated with improvements in hyperactivity-impulsivity symptoms, which are also experienced by many people with ADHD. (About half of those who took part in the trial had such symptoms, in addition to inattention).

The home-based device used in the trial “opens a new window of opportunity,” the team suggested, “especially for patients who live in geographically remote areas or have disabilities which may hinder access to clinical centers.” ❖

The team included: **Joan Camprodon, M.D., Ph.D., MPH**, a 2010 BBRF Young Investigator; and **André Brunoni, M.D., Ph.D.**, a 2013 BBRF Young Investigator.



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—*Barbara Toll, Board Member & Research Partner*

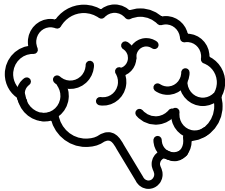
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GLOSSARY

HIPPOCAMPUS (p. 6) A crescent-shaped structure in the mammalian brain that is centrally involved in encoding memory.

ENGRAM (p. 7) The physical manifestation of memory—the constellation of neurons that happens to be activated while a memory is being recorded and stored, or recalled.

OPTOGENETICS (p. 7) A technology that enables researchers to control specific neurons in the brain. It involves making specific neurons sensitive to a particular wavelength of light. Threadlike fiberoptic wires are introduced into the brain of a research animal to deliver the beams of light to the desired neurons. When the light is delivered, the neurons are activated or silenced.

WINDOW OF RECONSOLIDATION (p. 10) A window in time that opens when a memory is recalled. During this time, which can last from minutes to hours in a person, the memory is highly malleable and may be updated with new information, or even rewritten, as experiments in mice suggest.

ODDBALL RESPONSE (p. 15) A phenomenon that neuroscientists measure when studying attention. It is the degree to which an individual's attention can be distracted, involuntarily, when they encounter a novel or unexpected stimulus. There is evidence that young children with anxiety are more distractible than neurotypical children.

HYPERVIGILANCE (p. 16) A tendency to fixate on challenges or threats—being on guard in a way that does not correspond with the objective level of challenge or threat. It is a symptom of anxiety disorders, as well as disorders like PTSD that arise following trauma.

POSITIVE and NEGATIVE SYMPTOMS of SCHIZOPHRENIA (pp. 28–30) The broad array of symptoms experienced by people with schizophrenia are often categorized as positive and negative. Positive symptoms are hallucinations, delusions, and unusual thoughts. Negative symptoms include blunted affect, difficulty speaking, low motivation, difficulty experiencing pleasure, and social withdrawal. Antipsychotic medications can be highly effective in alleviating positive symptoms, but they do not alleviate negative symptoms.

BRAIN ORGANOIDs (p. 40) Aggregations of brain cells grown in the lab from genetically re-programmed neural precursor cells. Such cells wire together to form circuits but have some limitations in the degree to which they can mimic human brain tissue. Dr. Sergiu Pasca implanted organoids based on human cells into the rodent brain, where they formed highly complex entities that functionally integrated with cells in the rodent brain.

EXPOSURE THERAPY (p. 42) Patients with impairing traumatic memories systematically confront their fears in a safe environment, the aim being to habituate to feared stimuli, thus retraining the brain to learn that the multi-sensory cues to fear that were learned during the trauma are now safe, and not signals that the feared event is happening again.

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747 Third Avenue, 33rd Floor
New York, NY 10017
646.681.4888 | 800.829.8289
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