A Therapy for Improving
Cognition in Schizophrenia

Brain Scan Analysis Reveals
Biological Subtypes of Depression

Brain & Behavior MAGAZINE

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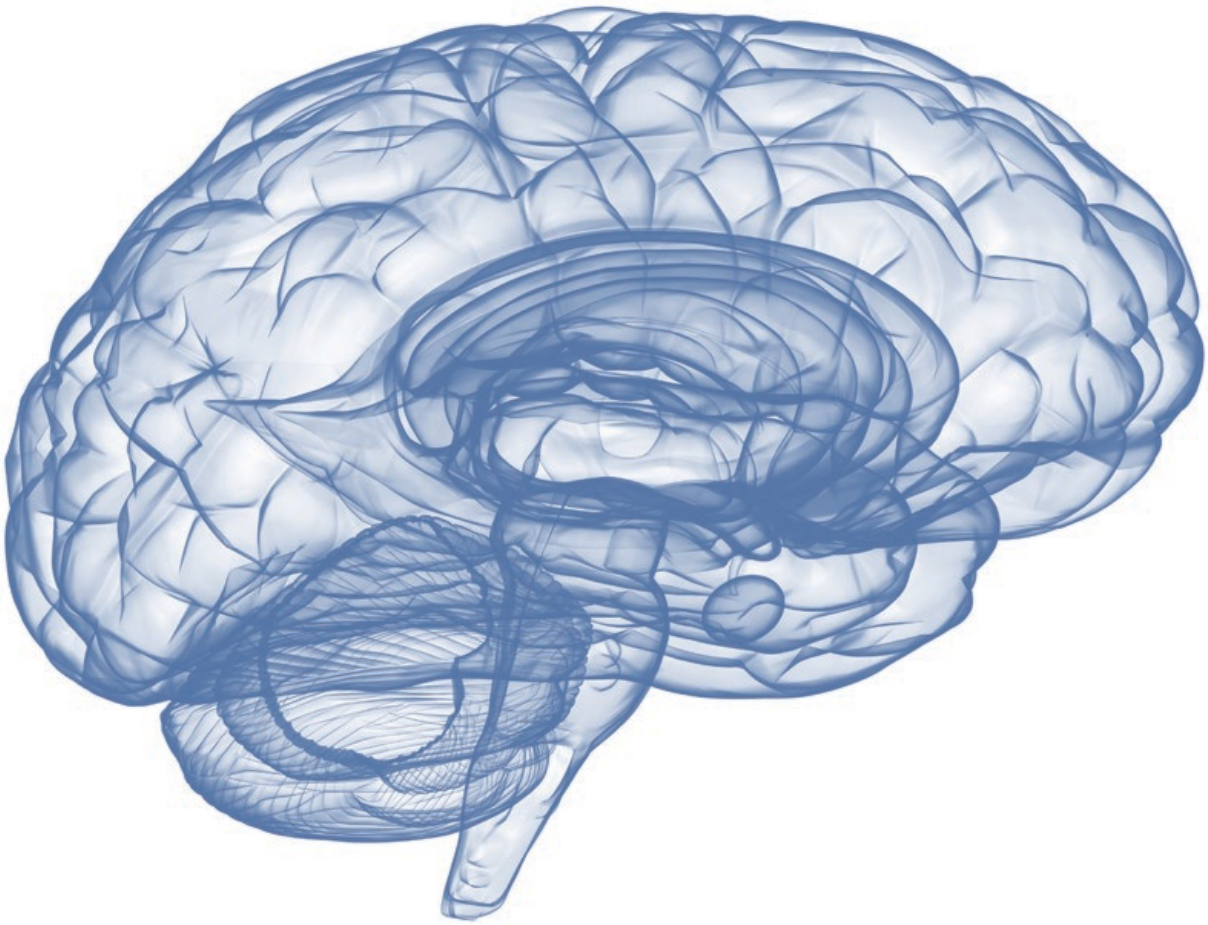

AMI KLIN M.D. PH.D.

Diagnosing and Treating Autism in the First Years of Life

PRESIDENT'S LETTER

This issue of Brain & Behavior Magazine features a number of articles that highlight the cutting-edge research of BBRF grantees and aims to show the implications for the future of prevention, better treatments and, potentially, cures for brain and behavior disorders.

Our *Science in Progress* story on page 4 profiles the work of BBRF grantee Dr. Connor Liston, who has used his BBRF grant support to make important discoveries about depression—specifically, identifying subtypes of the illness that can be measured objectively, based on analysis of data gathered from patients' functional MRI (fMRI) brain scans. The key takeaway is that by using big-data methods of analysis and applying them to biological criteria (in this case, as measured in the brain scans), major diagnostic categories like depression may be broken down into multiple subtypes, and that researchers may be able to figure out how people with specific subtypes will best benefit from available therapies.

This issue's *Pathways to the Future* (page 8) and *Parenting* (page 20) articles talk about a new approach to diagnosing and treating autism developed by Dr. Ami Klin, BBRF's 2018 Ruane Prizewinner for Outstanding Achievement in Child & Adolescent Psychiatric Research. Dr. Klin has pioneered a new technology—eye-tracking technology—that has given doctors important new insights about how and when autism spectrum disorders (ASD) emerge. Dr. Klin's work shows that the first signs of divergence from typical development can be discerned beginning at the age of only 2 months. This discovery has driven Dr. Klin's clinical work at the Marcus Autism Center in Atlanta, where he and his team provide training for parents that teaches them to engage their infants and toddlers daily, helping them to respond to cues in ways that make success in social development more likely.

A wonderful example of how BBRF grants have propelled innovative young scientists forward in their work can been seen in our *Research for Recovery* piece featuring Dr. Gregory Light, on page 14. Since his first BBRF award in 2003, Dr. Light's basic research has led to insights about the brain in people with schizophrenia that have shaped new treatment approaches. His major discovery was made in EEG (brain-wave) studies of patients, finding that patients who did least well on a test called "mismatch negativity"—where the patients have to correctly identify one "oddball" sound among many otherwise identical repeating sounds in a series—were also those with the greatest social impairment. From this finding Dr. Light and colleagues found that a brain-training computer program called targeted cognitive training (TCT) helped two-thirds of the patients in his study improve their performance. This research suggests a dimension of brain plasticity even in longtime schizophrenia patients that many experts doubted when Dr. Light began his research.

Our patient story is about Susan Burns, a registered nurse who was once an extrovert but fell into major depression after several setbacks in mid-life. After conventional SSRI antidepressants stopped working, she sought out the non-invasive brain stimulation therapy called TMS that was developed by BBRF Scientific Council Member Dr. Mark George. Read about her remarkable results on page 24.

In a Q&A with Nora Volkow, M.D., Director of the National Institute on Drug Abuse and a BBRF Scientific Council Member (*Mental Health & Society*, page 26), Dr. Volkow discusses the nation's opioid crisis, the rapid spread of teen vaping, and the use of vape devices to deliver THC, the psychoactive ingredient in marijuana, at very high levels of potency.

With your continued support we will carry on funding innovative and impactful research that will drive the field of mental health forward and bring about improved methods of prevention and ultimately cures for our loved ones.

Sincerely,

Jeffrey Borenstein, M.D.

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

CONTENTS

PUBLICATION CREDITS

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Patterns in Brain Network Activity Reveal Distinct Biological Subtypes of Depression

Conor Liston, M.D., Ph.D. aims for more precise diagnosis and individualized treatment

DR. CONOR LISTON, A 2013 BBRF Young Investigator, is modest in describing the progress recently made by his laboratory group at Weill Cornell Medical College—important research that is leading to a new way of classifying, and perhaps, treating depression. It's potentially pathbreaking research, but still very much "work in progress."

The research would not have been possible to do even a few years ago—a reflection of the rapid progress of his field, which many have called revolutionary.

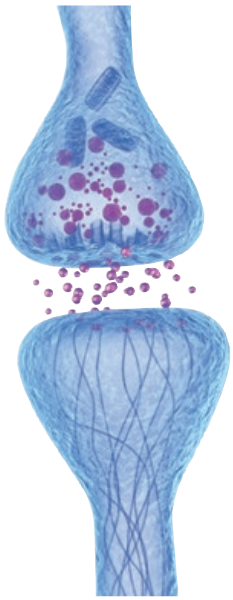
"One of the things that gets me excited about coming to work every day—and I think a lot of people in neuroscience feel the same way—is that our research is being transformed right now by amazing new technologies that are enabling us to ask questions in new ways that would have seemed like science fiction only a few years ago," Dr. Liston says.

For example, he says, "tools that provide read-outs of what groups of cells are doing at a particular moment, or during particular behaviors." Instead of being able to look at a few cells at a time, as in the past, new tools based on advanced imaging technologies "are enabling us to look at many thousands or potentially millions of cells in real time as they interact across different brain regions."

This capability is critical in Dr. Liston's research, which is trying to solve the puzzle of how behaviors are linked with actions occurring in the brain involving millions upon millions of neurons—actions which change over tiny intervals ranging from tenths to thousandths of a second.

"Let me give you an example," he says. "Every time you contemplate acting to pursue a reward, your brain performs an evaluation of the benefits, measuring the magnitude of the reward you expect to receive in terms of the amount of effort you expect to exert in order to obtain it."

"We think this brain function, which we call effort evaluation, is probably disrupted in depression and other brain disorders, possibly in different ways. People who are depressed will often complain about how they just don't feel any motivation to get out of bed in the morning, or pursue activities that may have once brought them pleasure."



Neurons communicate across tiny gaps called synapses. Changes in the strength of these connections underlies learning, memory, and behavior.

"We're trying to break down that experience, which we call anhedonia," he says, in terms of its biological components—"to understand how brain circuits are supporting different elements of those 'effort-evaluation' computations, and how they're affected by factors such as stress, or taking antidepressants."

In particular, Dr. Liston's lab is trying to understand how changes in the strength of connections between neurons—something called synaptic remodeling—affects the function of microcircuits (circuits that connect hundreds or thousands of neurons in a small area) and how these changes affect larger networks in the brain.

Another remarkable tool in the Liston Lab's toolbox is MRI, magnetic resonance imaging. Most people are familiar with it because of its widespread use in medicine, to figure out what's wrong after we limp home from a 5K run or find ourselves unable to swing a tennis racket. Adapted to neuroscience, MRI can reveal how various parts of the brain function—how a particular stimulus like looking at a picture of a person laughing or scowling causes neurons in different parts of the brain to fire. This is called functional MRI or fMRI, and it too is a key enabler of Dr. Liston's research.

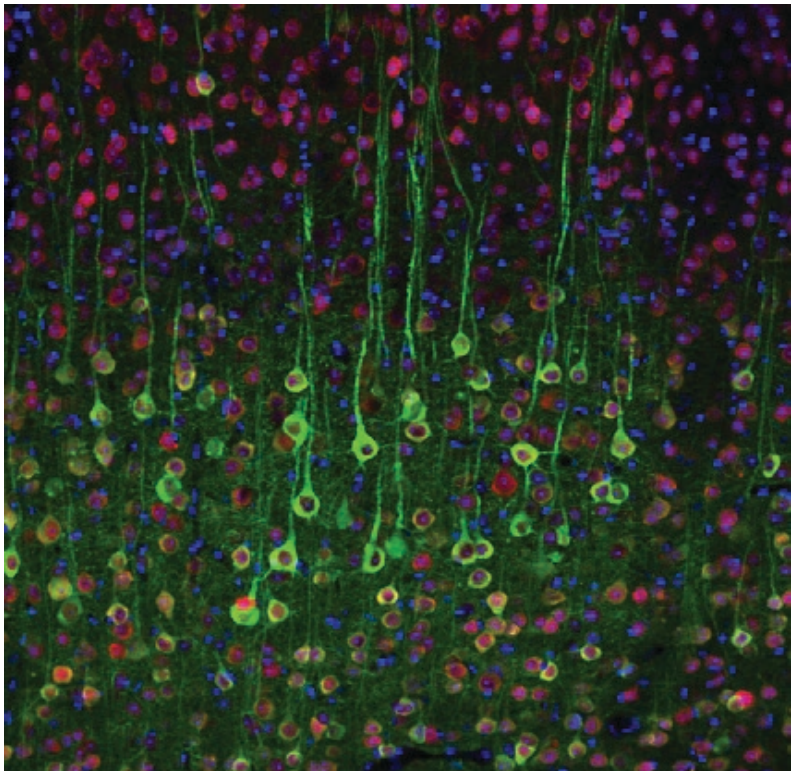
HUBS AND SPOKES

How can fMRI help us understand mental illness? Dr. Liston explains in terms that any air traveler can appreciate. "Our airports are organized in a hub-and-spoke system. There are a handful of airports like O'Hare or JFK or LAX that get tons of flights. The air network is organized so that to get from point A to point B, you probably have to fly through one or more hubs. We think the brain is organized in a similar way. Some brain regions act like hubs and other regions are connected to them."

The analogy becomes vivid when one considers how networks organized in this fashion become perturbed. "Let's say there's bad weather in Boston," Dr. Liston says. "The problem at that hub percolates out into the rest of the network. A delay in Boston will cause delays at New York and maybe even Denver, as well as in connections to other regions that each of them serves."

"This kind of dys-synchrony—where the hubs are not in synch—is similar to something that we think is happening in the brain in certain psychiatric disorders," says Dr. Liston. A dysfunction at a hub has consequences at other places in the network.

Conor Liston, M.D., Ph.D. (4th from right), and his team.



Behaviors are linked with actions occurring in the brain involving millions upon millions of neurons—actions which change over tiny intervals ranging from tenths to thousandths of a second.

Dr. Liston made news early in 2017 when a large team that he led published in *Nature Medicine* the results of a massive analysis of fMRI scans. From multiple medical facilities they collected brain scans from 1,188 individuals, a sample consisting of people diagnosed with depression and controls with no depression. They were able to train computers to discover in these scans distinct patterns of "dysfunctional connectivity" in brain networks. While others performed the scans, his team figured out how to solve the big-data problem that this large sample of brain scans provided—each with innumerable potential points to scrutinize in comparison with all the other scans in the sample.

The faulty connectivity patterns the team discovered could be divided into four groups—which they propose are subtypes of depression, also called "biotypes" by the team. One of the most notable things about these biotypes is the way they relate to the symptoms of the patients whose scans revealed them. Another is what the four biotypes may be able to tell researchers about how patients are likely to respond to treatment.

Dr. Liston explains that depression is not homogeneous. "There are many different ways to be depressed," he says. "*The Diagnostic and Statistical Manual*, or DSM, says that you can meet the criteria for depression if you have five or more of nine symptoms. This means that there are 256 unique combinations of symptoms that a patient can present with and still receive the diagnosis of depression."

Increasingly, says Dr. Liston, neuroscience is beginning to understand that how we currently conceptualize psychiatric disorders in broad diagnostic bundles like "depression" can actually be an obstacle to understanding the underlying biology that affects individual patients. This explains the rationale behind the study that led to the discovery of four depression biotypes.

SEEKING OBJECTIVE MEASURES

Dr. Liston says his team "flipped upside down" the usual procedure: rather than look for depression subtypes based on patients' symptoms and then asking whether there are known biological factors that correspond with those symptom-based subtypes, "we asked whether we could identify in a data-driven way any subtypes that were based strictly on biological measures. Objective measures—things you can measure in the patient's blood or in brain scans."

Each of the four connectivity patterns the team identified—the four proposed biotypes of depression—corresponded with different combinations of symptoms. "For example, one subtype was associated with high levels of anhedonia and low levels of anxiety. Another subtype was conversely associated with high levels of anxiety and low levels of anhedonia, and they broke down in other dimensions as well."

Dr. Liston says "the most exciting thing about the research" was the discovery that patients in the different subtypes tended to respond differently to a depression treatment called TMS, or transcranial magnetic stimulation. TMS is a non-invasive form of brain stimulation that patients receive in standardized treatments lasting 37 minutes, usually in treatment modules consisting of 4 to 6 weeks of sessions, given five times per week. "We knew from previous research that a patient's likelihood of responding to TMS was at least moderately related to how his or her brain networks were organized."

Because the *Nature Medicine* study was based on data from patients who had already been treated, the team could learn which of the patients received TMS

treatments and who among these had responded to it. The responders were overwhelmingly those who fit into just one of the four biotypes discerned in the study—if you were in that subset of patients, you were three times more likely to have been helped by TMS, the data showed.

The clinical symptoms of patients in this biotype could not, by themselves, predict the response to TMS; this valuable information only emerged when different combinations of symptoms were correlated with brain connectivity patterns.

"We aren't claiming that there are only four subtypes of depression," Dr. Liston stresses, "or that our way of defining them is the best way possible. On the contrary, we think there are likely many subtypes of depression that can be defined on the basis of objective biological data. We're certain that with steadily improving methods and larger data sets that we and others will be able to come up with even better ways of capturing the heterogeneity in depression and that this will reveal other subtypes and other kinds of correlations and biomarkers."

Dr. Liston's team is now engaged in studies designed to confirm the biotypes of depression already discovered, and separately, "whether the brain network dysfunctions that define them predict different combinations of symptoms that doctors see in the clinic, and whether biotypes can help direct patient care by correlating depression subtypes with treatments that are most likely to help specific patients." ❖ **PETER TARR**

DID YOU KNOW?

ANHEDONIA is the term used by doctors to note a symptom experienced by many people with clinical depression: a lack of interest in pursuing pleasurable activities, and/or an inability to experience pleasure.

SYNAPTIC REMODELING is a process that occurs at the synapses, or tiny gaps, that separate neighboring neurons. Neurons communicate across these gaps, and the brain's ability to strengthen or weaken these connections is a central feature of the brain's plasticity. Synaptic links are strengthened when we learn or remember; they are weakened when we forget or need to clear memory space for new information. Weaker cell-to-cell communication has also been linked with psychiatric disorders, including depression.

A New Way to Diagnose and Treat Autism

Ami Klin, Ph.D.

Director, Marcus Autism Center at Children's Healthcare of Atlanta
Georgia Research Alliance Eminent Scholar
Professor & Chief, Division of Autism & Related Disabilities, Department of Pediatrics
Emory University School of Medicine & Emory Center for Translational Social Neuroscience
2018 BBRF Ruane Prizewinner for Outstanding Achievement in Child & Adolescent Psychiatric Research

Dr. Klin, your research in the clinic suggests that there's going to be a new way to diagnose autism, and a whole new way of imagining the world of the child who has autism spectrum disorder (ASD) that seems more hopeful than what we're accustomed to. Tell us about how you've come to this view.

As a graduate student, I worked in a residential unit for adults with autism who had spent all of their lives in long-stay hospitals. They were profoundly disabled. My sense at the time was that autism was an unchangeable condition. We already knew that it was strongly genetic, and we wondered back then if a person's state in life was wholly determined on the basis of genes.

In the years to come, I began to work with babies. Why? Because the only way we could trace the early development of individuals with autism was if we were to follow the younger siblings of children already diagnosed with autism. We weren't sure of the recurrence rate in families, and in fact we greatly underestimated it. It became clear that about one in five of the younger siblings of children with autism also develop autism, and that an additional one in five developed something that either was a transient form of autism, or a sub-threshold form. We felt that we were looking at a broad spectrum, one that crossed thresholds of clinical diagnosis. We now know that this is true.

Once we began to follow babies from birth, it was possible to start tracing their developmental trajectories—those who developed normally as well as those who eventually developed autism. And what we and others in the field discovered is that there is much, much greater malleability in ASD than we once thought. We started looking into ways in which we could promote better outcomes by trying to intervene between birth and the age of 3 years. If we could increase their abilities by the age of 3, we would be changing their lifetime trajectory.

'We wanted to discover where we could intervene in the process, to normalize the trajectory in more children so they could have better outcomes.'

So the adults you observed early in your career had already been institutionalized for many years—and had passed that very early window of "plasticity." In retrospect, can you say that they had not been treated early enough?

Yes, that, plus the fact that in the years when those individuals were growing up, there were few or no services in the community for their rehabilitation.

But here you touch on a second thread in my story. There is now incontrovertible science suggesting that early detection and early intervention does optimize outcomes in children. Yet we have a huge public health challenge on our hands, because the median age of diagnosis of autism in this country is stubbornly stuck at around 4 and a half to 5 years of age. Diagnosis is particularly problematic in children who have less access to services—minorities, low-income families, and rural populations, in whom the diagnosis is usually made later on in life.

There is this need for us as a society to focus on early identification and diagnosis, and provision of early treatment and early prevention services.

Parents will be very interested to know about the distinction you make between genetic and environmental factors contributing to the way a child with autism develops.

Ami Klin, Ph.D.

What is inherited in autism is the *trait*, and the trait is reduced sociability. But there are many different routes to autism, not all of them strictly genetic. The important fact is that autism might not relate back to a single gene, or to even a combination of genes. Rather, it may be the result of deviations from normative socialization. By this I mean that liabilities that a baby is born with, whether for genetic or environmental reasons, could impact normal development, a result of which can be autism. We wanted to discover where we could intervene in the process, to normalize the trajectory in more children so they could have better outcomes.

Tell us about a technology you were instrumental in helping to develop, which makes early diagnosis possible. I'm referring to "eye-tracking" technology.

We began to develop eye-tracking technology around the year 2000. It is a quantitative way, using science and technology, to measure sociability—the way that children engage with the world around them. We learned how to quantify what happens when a child is looking at a caregiver, or a child is looking at some peers playing.

You're trying to measure how children are seeing the world, and your technology gives you an ability to do that by tracking what their eyes are looking at, where they're looking, how long their attention is sustained, and in general, the difference between children who are developing normally and are learning steadily to socialize, and children who diverge from that path. Your research reveals the significance of whether a child is looking at the eyes or the mouth of the caregiver, for instance.

When we study toddlers who have older siblings with autism, we have them look, for example, at a short film sequence of a couple of toddlers interacting. All of the children have this same stimulus in front of them, but brain connectivity—the neural tracts being formed as a result of those experiences—is radically different in the children who will go on to develop autism. They are looking at the same film, but what they are seeing is entirely different. What their brains are learning about is entirely different.

Eye-tracking data of very young typically developing children vs. children who go on to develop autism tell us amazing things that no parent could possibly detect. We found that children on the path to autism, beginning at a very early age, were missing about 500 moments of social learning in about 6 minutes of watching their peers playing. [This reflects where their eyes are focused while watching—the eyes and faces of those in the video, other objects in the room, etc.] If you do the math, if they are missing 500 momentary opportunities for social learning in 5 or 6 minutes, that translates into thousands of opportunities during one day, and into millions in the first 3 years of life.

Like all children, they are "creating" their own world, but they are diverging from the normative experience. As they are building their own brains, they are becoming autistic, as it were, every day of their young lives. If you're a clinician, you have to realize that that wonderful human being right in front of you is seeing the world entirely differently than you expect. That's why we needed a scientific and technological road into that child's mind and brain and it's why we developed the eye-tracking method.

When do the paths begin to diverge? One of your papers reveals that until a certain point, all newborns are processing the world in the same way.

Initially, in the first 2 months of life, all children are on the same track. All children are born with reflexes—social reflexes—signaling to caregivers that they are there. The caregivers accordingly will engage the babies, and it's out of this mutually reinforcing choreography that the "social brain" emerges.

We found out that between 4 and 12 weeks of age, babies are transitioning from these "reflex" behaviors to what we call "volitional" behavior. The initial reflex behaviors are guided by subcortical structures in the brain. But this normally transitions to reward-driven visual behaviors that are guided by the cortex. We can see this transitioning happening. We see the emergence of the interactional smile. We see the emergence of, basically, a human being that is reacting to the surrounding world.

‘Eye-tracking technology…is a quantitative way, using science and technology, to measure sociability—the way that children engage with the world around them.’

Because you were measuring a large group of children from birth—not knowing whether they would be typical or develop autism—were you able to see where the paths began to diverge?

Yes. In those babies who eventually, we found later, developed autism, those divergences began already by the age of 2 months. We learned this in 2013. They seem to be born with the typical visual and behavioral reflexes, but they don’t make that transition into volitional behavior. There is something that is not happening between 4 and 12 weeks of age that is not supporting that neurodevelopmental transition for children with autism.

Do you know what that is?

That’s the research focus of our Marcus Center here in Atlanta, which is a National Institutes of Health-designated Autism Center of Excellence, one of only five in the country. In our program we are looking at this from a social/visual engagement standpoint, because nothing shapes the brain of primates as much as sociality. The Marcus Center is the largest center of clinical care in the U.S. for children who have autism. Over 5,500 children are seen in the center every year, and another 5,000 are seen directly in the community. We are a diagnostic and a treatment center, with treatments ranging from skill acquisition early on in life, to severe behavior challenges, to feeding disorders, to maintenance in older children.

Having gained your insight about the diverging paths, what can you do to affect the outcome?

Our research suggested that if we could engineer the environment around these children in such a way that the environment would provide a kind of scaffold—one supporting the better engagement of affected children—we would be in a position of changing their developmental trajectory.

We are intervening in the child’s reduced level of engagement with others. The science that I described to you becomes the grounding for the kinds of treatments that we can offer children.

Tell us about the treatments.

Rather than having the child spend one hour a week with a developmental expert, we choose instead to treat the child through the engineering of social environments. The early divergence and our assumption that plasticity is greatest when these neural tracts are just being laid down, has led us to deploy a parent-mediated treatment approach. We take this approach because every single second throughout the week, the child is going to be diverging.

So, in a sense, we “treat” the parents. We train parents to use everyday experiences, what they do with their babies every day, through all of the routines, in order to engineer the social engagement that is crucial. We use a particular form of treatment called early

The Marcus Autism Center in Atlanta.

social interaction, and we send coaches to train parents in their homes, but we are also able to train parents who don't have access to us, so we can treat from far away.

When the environment becomes the daycare center, we train the daycare providers. When it becomes preschool, we train the preschool teachers. Really, what we need to do is to become architects of our own community. It makes no sense at all for us to create treatment for which there is going to be very limited access.

'There is much, much greater malleability in autism than we once thought. We started looking into ways in which we could promote better outcomes by trying to intervene between birth and the age of 3 years.'

A parent is interacting with the child, has a "bud" in the ear, there is a camera, and our interventionist is sitting in our center monitoring that engagement in the home, and coaching parents on how to take advantage of those moment-by-moment experiences that are learning opportunities for socialization.

It's literally one-on-one with the parents. It's very one-on-one, on the basis that babies spend most of their time with their caregivers. And so, by engineering that environment, we are able to use one hour a week to reach the level of intensity in that child's life in a way that can be scaled to work at the level of an entire community. That's what we're trying to do.

If I hear you right, you have to spend time with the parent and child together, but really aimed at getting the parent to be able to give the child that word-rich and support-rich environment, minute-to-minute, when you're not there.

Absolutely. Now, needless to say, we do the same thing as children grow older.

What about the diagnostic part? You said it is critical to make the diagnosis early.

Right now, there aren't enough resources to provide children with treatment. And yet, I go home every day with the thought that 66,000 children are born every year in the U.S. alone who are going to have autism. So, we are under tremendous pressure to take the NIMH motto seriously: We need to translate our science into solutions, and so that's what we are doing.

We are now completing a national clinical trial that uses eye-tracking technology in a diagnostic device that we hope will substantially increase access to diagnosis. With the device, which is mobile, we hope that in a 12-minute procedure a trained technician will be able to do what expert clinicians can do in a multi-hour diagnostic assessment.

That is one approach. At the Marcus Center we also have over 1,000 children who have been through a procedure that we built for children aged 16 to 30 months. We focused on this age group to capitalize on "well-baby" checkups that all children have at ages 18 and 24 months. Any child with actionable delays under the age of 3 should be provided with federally mandated services. We wanted to create a procedure that would make this actionable.

All the children we see who are at high familial risk for autism receive treatment. We are beginning the treatment at 6 months, but from 6 to 12 months, our treatment is entirely informational and is about training parents. We are training them to become more sensitive to child development milestones, and to principles of engaging their own child. At 12 months, children who we feel are now showing risks for autism are randomized into two groups. One provides treatment on the existing model: treatment is given by an expert clinician. The other group gets parent-mediated treatment. Then, there is another assessment at 2 years.

And for those who do develop ASD symptoms?

We can substantially and meaningfully improve their lives. These children are uniquely human. It is within our power, and it's both our responsibility and determination as a community to ensure that these children are afforded what they need in order to fulfill their potential and promise. ❖ **PETER TARR**

[Editor's note: Also see Dr. Klin's "Advice for Parents" on p.20]

PLAN YOUR FUTURE, SHAPE YOUR LEGACY

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

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

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

"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**

Advances in Cognitive Remediation: 'Helping Schizophrenia Patients Who Need It Most'

Gregory A. Light, Ph.D.

Professor, University of California, San Diego
VA San Diego Health System
2014 Sidney R. Baer, Jr. Prize for Outstanding Achievement in Schizophrenia Research (Maltz Prize)
2013 BBRF Independent Investigator Grant; 2006, 2003 BBRF Young Investigator Grant

PROGRESS IN RESEARCH USUALLY doesn't follow a straight-line path. But if you chart the advances in schizophrenia research made by Gregory A. Light, Ph.D. since he received his first BBRF grant—a Young Investigator Award in 2003—you can clearly see the line leading from his first working hypothesis at the start of his career to its recent successful application in the clinic.

Dr. Light studies how cognition may be improved in patients with schizophrenia by looking at brain activity patterns through electroencephalography (EEG). By delving deep into understanding how electrical waves measured by EEG are linked to cognition, Dr. Light's laboratory hopes to enhance recovery in patients with schizophrenia.

Schizophrenia is an illness marked by a variety of symptoms: hallucinations and delusions, apathy, limited emotional expressivity, and difficulty in daily functioning. Many patients also experience cognitive difficulties affecting memory, attention, and planning. Although hallucinations can be helped with antipsychotic medications, cognitive impairment is difficult to treat and make it challenging for many patients to interact with others, hold a job, and enjoy a high quality of life.

In the past year, Dr. Light and his team at the University of California, San Diego and the Mental Illness Research Education and Clinical Center at the VA San Diego Healthcare System, have made notable strides toward their goal of helping patients recover. In a paper appearing in *Schizophrenia Research* in July 2018, they reported the effectiveness of a method of

cognitive remediation called TCT (targeted cognitive training). The study involved 46 participants living with chronic, severe schizophrenia who were receiving state-mandated care in a locked facility 30 miles east of San Diego.

It was "a real-world test" of the methods Dr. Light has been working to develop since he received that early vote of support from BBRF—which was followed by another Young Investigator grant in 2006 and an Independent Investigator award in 2013. In 2014, Dr. Light was honored with the BBRF's Baer Prize for Innovative and Promising Schizophrenia Research.

"For too long, it has been thought that the neural systems in schizophrenia are fixed, that they can't be modified—and that the best one can hope for is to manage psychotic symptoms," he says. "But now we're learning that cognition itself is remediable and that recovery is a possibility."

'PEOPLE WHO NEED HELP THE MOST'

Although a great deal of pathbreaking schizophrenia research has focused on uncovering its roots in genetic variations, Dr. Light's experience as a student and young scientist led him in another direction. He was determined to find a way of helping "the people who need help the most, those who have established illness, who have been ill for years, who are chronically receiving antipsychotic medications, and are spending their days in locked long-term facilities or board-and-care facilities where too often they don't receive quality rehabilitative care."

As an undergraduate in the 1990s, Dr. Light was given the task of helping to assess patients in the 12-story Rochester Psychiatric Center, a facility that was "de-institutionalizing"—releasing its patients to the community. "A long tree-lined drive led to this building with locked double doors. I remember thinking, 'This is a pretty serious place,' figuring they must be delivering round-the-clock care and providing the best intensive services available."

That is not what he found. "Patients had been there for longer than two of my own lifetimes at that point, since the facility opened in the 1950s." They had been cared for in the custodial sense, but were not receiving systematic rehabilitation. Since there were no electronic medical records available, Dr. Light's early work at this facility was focused on interviewing patients to determine their diagnoses and making ratings of their symptoms. "I was surprised that people with schizophrenia who shared the same diagnosis seemed so different from one another. How could these different combinations of symptoms be the same illness? And why couldn't we do more to help these people beyond housing them for the majority of their lives?"

DID YOU KNOW?

EEG (ELECTROENCEPHALOGRAPHY) is a non-invasive way of measuring electrical activity in the brain. Different wave patterns reflect activity at different frequencies generated by the actions of brain cells and entire networks interacting across the brain.

MMN (MISMATCH NEGATIVITY) is a biomarker of cognitive function in the human brain. Measured by EEG, it is used to test a person's performance when faced with what is sometimes called an "oddball series." For example, an individual is presented with a series of tones, all of which are the same except one—the oddball. People with schizophrenia respond less to the "oddball" in the sequence of sounds. Dr. Light and colleagues discovered that patients with the lowest MMN scores had the greatest impairments in social functioning.

TCT (TARGETED COGNITIVE TRAINING) has been used by Dr. Light to teach schizophrenia patients to improve their response in the MMN test—a way of helping them gain social functioning skills that will facilitate their recovery.

Yet there was one symptom that he saw in almost all patients. "At some point over the course of the illness they all had experienced auditory hallucinations." This launched his interest in auditory neuroscience, and led him to seek out mentors who were starting to use advanced technology to dissect what was happening in the brain's auditory system.

When he moved to San Diego for his graduate and postdoctoral training, Dr. Light joined Drs. David Braff and Neal Swerdlow, who were using EEG and other neuroscience tools to find "core physiologic measures that might be linked to the underlying biology of schizophrenia." Both, among other honors, have been BBRF Distinguished Investigators, Dr. Braff in 2007 and Dr. Swerdlow in 2016.

They had a theory that the disabling deficits in cognitive function seen in people with schizophrenia are caused, at least in part, by problems receiving or analyzing signals that enter the brain through the senses. Perhaps the brain's auditory and frontal cortices, for instance, were not processing sounds properly.

Whatever the reasons for cognitive deficiencies, the results were evident to all who worked with patients: most were isolated from other people, often profoundly—a painful if infrequently discussed aspect of living with schizophrenia.

Targeted cognitive training is given via computer, 3 to 5 hours per week, over 4 weeks.

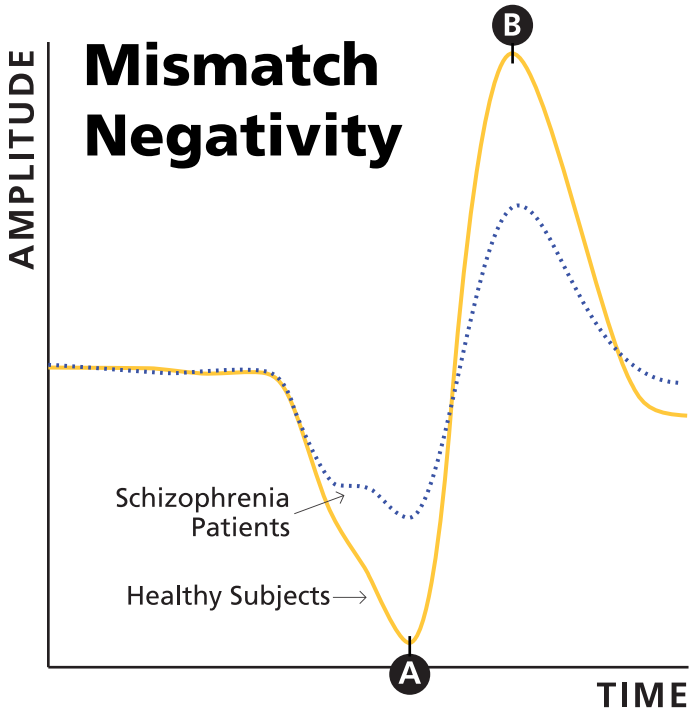
AUDITORY MARKERS

In early papers focused on the auditory neuroscience of schizophrenia, Dr. Light speculated that "maybe someday" work on auditory system dysfunction "would contribute to treatments or preventative strategies." Then he read a paper by Dr. Sophia Vinogradov, whose 2000 BBRF Independent Investigator grant had supported research on using computers to train schizophrenia patients to improve their results on cognitive tests.

"Sophia had applied an auditory-based cognitive training method to patients with schizophrenia and it seemed to work," says Dr. Light. "I thought, maybe we should try that." He had also been influenced by the work of a Finnish neuroscientist, Risto Näätänen, who had used EEG to explore cognition in healthy undergraduate volunteers. One measure Dr. Näätänen used, called mismatch negativity, or MMN, seemed to Dr. Light to be worth a test as a potential biomarker of response to cognitive training in schizophrenia patients.

Mismatch negativity is used to test a person's performance when faced with what is sometimes called an "oddball series." For example, they are presented with a series of tones, all of which are the same except one—the oddball. People with a normally functioning brain can automatically detect an auditory oddball—say, a single rising tone in a long series of descending ones, or a long sound in a series of short ones. Normally, the brain makes these discriminations routinely and unconsciously.

Dr. Light gives the example of his wife, sleeping alongside their newborn baby some years ago. "If there were any changes in the baby's rhythmic breathing, her brain would detect it and make a decision about whether that was an important change—automatically. Most of the time when this happened, she would never even awaken or would go right back to sleep. Our brains make these subtle auditory discriminations all the time as a basis for important decisions. It's a survival feature that is disturbed in schizophrenia."



This graph shows how the response of a person with schizophrenia (dotted line) to "oddball" tones at time-points A and B is much less than the response of a healthy control subject (yellow line). Patients whose responses are most muted tend to have the greatest difficulty interacting socially. TCT aims to improve their function.

With his first BBRF grant, Dr. Light discovered that schizophrenia patients had reduced MMN responses—the "oddball" tones were heard, but the brain responses to those tones were not well differentiated from responses to the other tones.

This research also produced a big surprise: those patients with the lowest scores in the MMN test had the greatest impairments in social functioning. This was a great "aha!" moment in Dr. Light's research—a discovery that led the federal government to extend robust career support grants to his lab beginning in 2007 and continuing through the present.

"Many now believe that MMN is a breakthrough biomarker for predicting and monitoring response to many treatments for neuropsychiatric disorders," says Dr. Light. "And it was my first BBRF Young Investigator Award that made possible identifying the robust correlation of mismatch negativity with daily psychosocial and cognitive functioning, which we first reported in 2005. Without hyperbole, I can say that I would not have the career I've had if it wasn't for BBRF—its attention to investigators who are just starting out or at transition points in their careers and in real need of support for innovative ideas."

Beyond the financial assistance he received, Dr. Light says part of the BBRF boost came in the form of validation, for there was plenty of resistance within the scientific community, early on, to his suggestion that MMN measurements could be used to predict how well people could function socially.

PREDICTING WHO WILL BENEFIT

His second Young Investigator award in 2007 and concurrent federal funding enabled Dr. Light to replicate his earlier results and to test the concept that MMN could predict which patients stood to benefit from cognitive training. He would test this concept in a variety of clinical settings.

In the most recent test, in the facility outside San Diego where he tested TCT in medicated patients with longstanding, chronic illness, not only did TCT provide a real, measurable benefit to two-thirds of these patients in the form of improved results on cognitive tests. The research also demonstrated that MMN measured after the very first hour of training accurately predicted which patients were going to benefit from the full 4-week program. This was confirmed once the training course was completed.

Dr. Light and colleagues still are not sure why some respond to TCT and others do not, but they speculate that MMN and possibly other measures of brain activity (one is called auditory steady-state response) are able to show which patients

have sufficient plasticity in their neural circuitry to benefit from this particular type of training—which, in essence, is a form of learning.

Plasticity refers to the ability of neurons to adjust the strength of their connections. Neuroscientists have long understood that such adjustments are part of the mechanical basis of memory and learning.

patient, since about one in three do not stand to benefit, at least from TCT. Some patients may not understand the tasks or cannot concentrate well enough to tolerate the exercises.

But patients who can benefit need to be motivated and guided through the training process as it plays out over a period of weeks. "It's not going to work well in isolation. It has

trial also showed a reduction in the severity of their auditory hallucinations and participated in significantly more of the other psycho-social groups and activities offered at their care facility. He speculates that this may be due to their being encouraged while receiving testing, or in noticing their own progress, which may have led them to be willing to try other activities.

'For too long, it has been thought that the neural systems in schizophrenia are fixed, but now we're learning that cognition is remediable and that recovery is a possibility.'

TCT, the training method recently used by Dr. Light, is itself not revolutionary, he says. His team used a commercially available "brain-training" software program that worked perfectly well. Other programs might also work well, he says. In TCT, auditory exercises are delivered to each patient for 3 to 5 hours weekly, via computer. The patient is asked to make progressively finer discriminations of sounds, beginning with comparatively easy discriminations and steadily moving to harder choices—but only after correct answers have been delivered. "If they get it right, it gets harder; if they make a mistake they go back to where they were challenged. They are constantly being pressed up against their ability level."

What makes TCT potentially valuable is how it or a similar training method is actually delivered in the clinic. It won't work, says Dr. Light, to give it to every

to be delivered by the right people to the people who are most likely to benefit," says Dr. Light. Ongoing encouragement is needed to maintain the intensity of the training. "It appears the training also needs to be delivered in conjunction with other rehabilitative services for an individual to maximally benefit. It is probably not sufficient to send out laptops to an isolated environment and hope that people will do the exercises on their own."

It's not yet known how long the benefits of cognitive training last, although one paper from Dr. Vinogradov's team showed that gains were still in place 18 months after training concluded. Dr. Light hopes to study the durability of gains in future research. For now, he is encouraged that the chronic, long-medicated patients who derived benefit from TCT in his most recently reported

This brings the subject of cognitive remediation back to a question long recognized among those who focus on the long-term care of people with schizophrenia. "The problem in scaling up TCT or similar training is much bigger than the intervention itself," says Dr. Light. "It is more a question of overall care. We need to deliver high-quality, high-intensity care to the patients who need it the most—and right now, we are not doing that for enough people with an established schizophrenia diagnosis."

Despite this, Dr. Light is very hopeful. In the years since his first BBRF grant, he has learned the value of an approach to helping people with schizophrenia that, in his words, "doesn't try to fix what's broken, but instead tries to take what is there and work with it. You work with what you have, and go for improvements. It's a recovery-oriented approach, and I think it can help a great number of patients, as we learn more, and our methods for delivering and predicting future response to treatments improve." ❖ **PETER TARR**

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Advice for Parents Concerned About Autism

A Q&A with Ami Klin, Ph.D.

Director, Marcus Autism Center at Children's Healthcare of Atlanta
Professor & Chief, Division of Autism & Related Disabilities, Department of Pediatrics, Emory University School of Medicine
2018 Ruane Prizewinner for Outstanding Achievement in Child & Adolescent Psychiatric Research

Dr. Klin, what advice would you give to parents concerned about autism in children under the age of 3? What is an intelligent course of action?

According to a report from the Centers for Disease Control and Prevention (CDC), the time between a parent's first concerns and the time that they gain access to an expert clinician takes, on average, 3.5 years. So, my first piece of advice for parents is to trust themselves. If you have a concern, start by talking to your primary care physician. Your primary care physician is the gatekeeper for your child's health. Engage.

Now, primary care doctors are often concerned about worrying the parents. Doctors are often concerned about access to treatment and whether the treatment is beneficial. So, parents should know that primary care physicians often adopt a wait-and-see approach, which basically means a delay in the diagnosis. However, parents need to advocate for their child. In cases where the parents are concerned but the primary care doctor suggests waiting, I would recommend they take their child to a clinician who is an expert in the development of speech, language, and communication, and has some awareness of autism.

So, you encourage parents not to ignore their own concerns.

Trust your instincts and pursue them until you are reassured otherwise. Do not accept old notions like, "Boys [begin to] speak late" or "This is just a temporary phase" that your child is going through. Or, "Let's wait another year; let's wait and see." All of those things may alleviate the parents' anxiety, but they also delay action. I'd rather have a parent becoming more anxious early on, and then being reassured by the child's positive development, than somehow being falsely reassured only to then see their child, years later, developing ASD symptoms.

What are some of the very first signs and symptoms of autism?

By far, parents will tell you the most common sign is delays in speech and language. In fact, however, the most robust signs of autism have to do with nonverbal communication. The little gestures that babies make in response to others are the most robust predictors of autism because they can indicate a breakdown in communication. FirstWordsProject.com, for example, has a list of 16 nonverbal gestures that babies should be showing by the age of 16 months. Other signs have to do with playing the games that we all play with babies. For example, Peek-a-boo. Is the baby engaged by you? Is the baby engaged with objects? Is the baby seeking more interaction with objects than with people? Other clues can come from things that we do with babies that are reciprocal, for example, vocalizing back and forth. Is the baby responsive to the adult's interaction?

‘The most robust signs of autism have to do with nonverbal communication. The little gestures that babies make in response to others are the most robust predictors of autism because they can indicate a breakdown in communication.’

Is there some kind of screening test that parents can take?

When a child is at least 12 months old, a parent can complete a screen online that is going to deliver that result directly to the baby's primary care physician. Let me mention again the fabulous website, FirstWordsProject.com, which has a built-in screener that parents can complete online. And if the screening is positive, the parent can actually enroll in the program that is going to connect them directly to their physician and services.

What are some other resources that parents can use?

There are ready-made packages that parents can access, whether it is the Autism Speaks 100-day package, or whether it is FirstWordsProject.com. Through these they can learn everything that they ever wanted to know online, so that they are empowered to seek services for their own children. The most important thing that parents can do is to learn and be aware of and gain access to the many resources that can help them navigate what is going to be a labyrinth of services.

Are you saying that not only does FirstWordsProject.com help parents identify the potential for autism but also helps connect them to resources?

We use the resources of both FirstWordsProject.com and AutismNavigator.com to create an electronic communication system that brings together the family, the primary care physician, and the early intervention provider, all within one communication system, so that communications don't break down, and parents can go more easily from one point of care to the next point of care. These websites also provide training modules tailored to parents, primary care physicians, and early intervention providers. The modules are customized because we need the early intervention providers to be cognizant in delivering treatment. We need the primary care physicians to recognize the early signs of autism, and we need the parents to navigate the system.

Please explain how genes and environment interact when it comes to autism.

There are hundreds and hundreds of protein-encoding genes that have so far been associated with autism. So, let’s start from a science standpoint, and assume that children are born with genetic liabilities. Whether or not those genetic liabilities translate into disabilities is something that I believe very much is within our power to influence, through our actions. It's our responsibility. There is a reason why it takes so much time for babies to mature, and the reason is that so much of early brain

development requires experiences. The way the brain develops is not fully "programmed" or predetermined. It involves interaction of the individual with their surroundings, "the environment."

One thing that you make a point of suggesting is that we—parents, caregivers, teachers, family physicians—can absolutely affect outcomes in many instances. This is not something that one often hears about autism.

Autism in this day and age is no longer a doomsday diagnosis. It is within our power, and it's both our responsibility and determination as a community to ensure that children are afforded what they need in order to fulfill their promise. It's a partnership. It's a partnership that, both in the past, in the present, and in the future, is always going to be guided by parents, because parents are always concerned about their children's wellbeing.

What would you say to parents who are going through this difficult time?

I borrow the title of a book by my close friend [Dr.] Barry Prizant when I say that our children with autism are "uniquely human." According to CDC prevalence rates, 36% of 8-year-olds with autism have intellectual disability. The rest do not. That does not mean that they don't have challenges. But what it does mean is that we can substantially and meaningfully improve their lives and ensure that they make a very meaningful contribution to society.

Temple Grandin, who is famous for talking about autism in her life, says the world needs all kinds of minds. She actually attributed her own success to her autism and the fact that she thought so differently than people who have a so-called "typical" brain.

Firstwords.org: check out the website to learn more about how to evaluate your baby.

Well, we run a very competitive fellowship here in neuroscience at the Marcus Autism Center. This year we had 98 candidates, of whom we selected two. One of them comes from Carnegie-Mellon University, speaks four languages and can program computers in seven. She is going to be working with us on a large computational project on gene expression. And she is a woman with autism. ❖ **FATIMA BHOJANI**

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Combining Transcranial Magnetic Stimulation with Psychotherapy for Treating Depression
Tuesday, August 13, 2019 2:00pm–3:00pm EST
Sarah Lisanby, M.D.
National Institute of Mental Health

Choline: a New Prenatal Supplement to Improve a Child's Mental Health
Tuesday, September 10, 2019 2:00pm–3:00pm EST
M. Camille Hoffman, M.D., MSc
University of Colorado School of Medicine

Deep Brain Stimulation for Treatment Resistant Depression: A Progress Report
Tuesday, October 15, 2019 2:00pm–3:00pm EST
Helen Mayberg, M.D.
Icahn School of Medicine at Mount Sinai

Integrating Virtual Reality into Psychotherapy for Anxious Youth
Tuesday, November 12, 2019 2:00pm–3:00pm EST
Michelle Pelcovitz, Ph.D.
Weill Cornell Medicine | NewYork-Presbyterian

Changing the Way the World Thinks About Eating Disorders
Tuesday, December 10, 2019 2:00pm–3:00pm EST
Cynthia M. Bulik, Ph.D., FAED
University of North Carolina at Chapel Hill

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‘Like a Shiny New Penny’

How Non-Invasive TMS Brain Stimulation Helped a Nurse Overcome the Dulling Impact of Major Depression

SUSAN BURNS WAS A WOMAN WITH few options. Her medicines—selective serotonin reuptake inhibitors (SSRIs), a commonly used class of antidepressants—had caused her sodium levels to drop precipitously. After spending an entire year, in her words, “walking a tight rope” trying to find an alternative treatment approach, she finally settled on a cocktail of three antidepressant medications. They helped, but they did not lift her depression.

Susan had once been an extrovert, with thriving friendships and close family ties. But, despite her three medications, she now had gotten to a point where she didn’t really care about going anywhere or doing much of anything. She was fearful of going out at night by herself or driving. She couldn’t even pick up the phone and talk to someone and regressed to only texting. Tasks she had once enjoyed, like shopping and hunting for little treasures, became a struggle. In the midst of her anhedonia—the medical name for the inability to experience pleasure—she couldn’t even play with her adorable little puppy.

On and off in her life Susan had had bouts of depression, going as far back as her teenage years. Her twenties and thirties had gone well, but in her mid-forties Susan had a major depressive episode following the end of her first marriage. Around the same time, her dad died, followed by the deaths of a best friend and her beloved brother-in-law. She went on antidepressant medication (Paxil) for the first time. A few years later, in 2006, Susan met her now-husband, and built herself a house. Feeling good, she stopped taking Paxil. However, her depression returned a few months later. She began to feel like a failure at her very stressful nursing job. Paxil no longer worked in alleviating her depression. Neither did any other new medication that she tried.

Her psychiatrist mentioned electroconvulsive therapy (ECT), a procedure conducted under anesthesia, in which a seizure is induced electrically in the brain. For Susan, as for many patients in her position, ECT seemed a last resort. She wasn’t ready to try it.

An R.N. for four decades, Susan was no stranger to the world of medicine. She began reading up on transcranial magnetic stimulation (TMS), another treatment option brought up by her psychiatrist. TMS, unlike ECT, is non-invasive. It involves the application of magnetic pulses to the scalp above the left eye, which corresponds with an area of the brain involved in depression. TMS does not induce a seizure, and has only minor side effects such as treatable headaches. For Susan, this seemed to be the best next-step treatment option.

Susan’s research led her to the Medical University of South Carolina (MUSC) in Charleston. It was at

that institution two decades earlier that Mark S. George, M.D., now a distinguished professor and member of the BBRF's Scientific Council, pioneered methods that led in 2008 to F.D.A. approval of TMS for treatment-resistant depression—depression that fails to respond to at least two prior courses of standard treatment. Dr. George performed his early work with the help of BBRF Young Investigator awards.

Susan's TMS treatment was typical: intensive, with a daily session Monday through Friday for six weeks, followed by a tapering-off period involving an additional six treatments.

At her first appointment, the TMS physician put a skull cap on Susan to measure and mark exactly where to apply the magnetic pulses. At every subsequent session, Susan wore the marked cap as she reclined in what seemed to her like a dentist chair, ears protected by ear plugs. The machine whirred to life, with the magnet (placed over the brain's left occipital lobe) turning on for 4 seconds, then off for 10 seconds. This on-off sequence was repeated for 37 minutes, the standard therapeutic dose established in large clinical trials prior to FDA approval of TMS. The repeated on-off pattern of pulses explains the formal name of the treatment: Repetitive Transcranial Magnetic Stimulation, sometimes abbreviated rTMS.

Susan describes her first few sessions as eliciting an odd feeling in her left eyebrow, almost like a little spark traveling down to the tip of her nose. The oddness of that feeling dissipated after a few sessions as Susan got used to it. Within a week of her first session, which was performed this past January, Susan began to feel better. The joy she had lost began trickling back.

Susan recently finished her course of TMS treatment, and she gratefully reports that it has completely transformed her life.

"I feel like the joy has returned in my life. I feel like I'm back where I was years ago," she says.

She can once again enjoy going out and seeing friends and family, especially her grandchildren. Her husband, who has been her cheerleader throughout, feels that the woman he married has returned.

Susan's depression has lifted for now. About one-third of treatment-resistant patients who try TMS similarly have a remission; about half of all who try it have what doctors define as a clinical response, which means they have a significant decrease in depression symptoms. Like other "responders," it's possible that Susan may not need further treatment, or that she may need a short course of TMS from time to time to maintain her remission.

Susan continues to take her standard antidepressant medications, even though she acknowledges that it was the addition of the TMS therapy that actually made the depression start to dissipate. Experts continue to investigate how antidepressant medications and TMS work together. It is possible, although unproven, that they may be working synergistically.

What makes TMS so exciting for patients like Susan is that unlike ECT, it has almost no side effects. Some patients get a temporary headache, and there is a rare risk of seizures. Susan experienced nothing but a temporary feeling of fullness in her head.

On her journey to wellness, Susan discovered something else: she no longer wanted to hide her depression. While once, she had never wanted anyone to know about her illness, she says she is now very open about what she is going through.

Susan recalls a conversation with a young doctor when she was at one of her darkest points. She told him that she felt like a dull penny that had been in circulation for many years. There are pennies that are shiny and look brand new. And then there was Susan. She told him that she always wanted to be the shiny penny. That was her goal.

"I'm almost that shiny penny again, with a few little rough spots on it. But that's where I am," says the 65-year-old. "That dull stuff is wearing off and this shiny person is coming out again." ❖ **FATIMA BHOJANI**

Looking at Addiction and Suicide Through the Lens of Brain Science

Q&A with Nora Volkow, M.D.

Director, National Institute on Drug Abuse, NIH
Member, BBRF Scientific Council

The New York Times reported on March 7th that drugs, alcohol, and suicide together claimed more than 150,000 American lives in 2017. The grim statistic, attributed to two public health nonprofit groups, was based on mortality data compiled by the U.S. Centers for Disease Control. Suicides accounted for over 47,000 of these deaths. Five hundred deaths per week were attributed to overdoses of synthetic opioid drugs such as fentanyl. We called upon Nora Volkow, M.D., the Director of the National Institute on Drug Abuse (NIDA), to help us make sense of these numbers. Dr. Volkow, a pioneer in brain imaging with "PET" technology (Positron Emission Tomography), is one of the world's leading experts on the biological basis of addiction and a longtime member of BBRF's Scientific Council.

Dr. Volkow, the numbers seem to keep going up. This must be disturbing to you.

Yes, and it leads us to ask what is driving the unexpected mortality associated with opioid drugs. Opioid-associated fatalities are still going up even though opioid prescriptions have started to decline. Many of the deaths from overdoses are likely to be suicides, but there's no easy way of distinguishing them from those caused by unintended overdoses. Overall, it's estimated that between 20% and 30% of opioid fatalities are intentional. Thus, the contribution of suicide to overdose fatalities is not negligible and their prevention will require additional interventions.

The question is complex. Is someone committing suicide because they are depressed? And when they are depressed, have they taken drugs as a means to escape their depression? Or is it someone who is taking opioid drugs without being depressed—but becomes depressed because of chronic opioid use? There are many possibilities of why a person abusing opioids could be at greater suicide risk and it is notable that so many people with an opiate-use disorder (OUD) also have a co-morbid mood disorder.

Can you explain the connection between mood disorders and OUD? I mean, in terms of the biology of addiction.

The association of OUD and mood disorders is not surprising, because the mu-opioid receptors [in the brain], which are the target of drugs like morphine or heroin or Oxycontin, among their other functions modulate the serotonin system, which plays a

major role in regulating mood. Many antidepressant medicines act on the serotonin system, too. So, recognizing that opioid drugs will affect the serotonin system in the brain leads you to predict that they are likely to affect mood.

But we must also ask: why is this problem with opioid addiction happening in the United States, and to whom, exactly, and why right now? A lot of people have written about it. We need to look at how it all started. Two sociologists at Princeton, Angus Deaton and Anne Case, have looked into the demographics of people who have borne the brunt of drug- and alcohol-associated mortality.

You're referring to their important paper, which was published in the *Proceedings of the National Academy of Sciences* in 2015. It focuses on "rising morbidity and mortality in midlife among white, non-Hispanic Americans."

Exactly. They point out a midlife "reversal" in mortality statistics—numbers that were dramatically improving throughout most of the 20th century that are now showing a reversal. Who is affected? Many are lower-middle-class white Americans, people in their 40s, 50s and 60s. Deaton and Case ask: What are the factors that are driving it? They propose that it is the loss of jobs and the lack of new opportunities, driven in part by limited education, that explains the rising mortality in lower-middle-class white Americans. Addiction to drugs and alcohol (along with suicides) are illnesses of the body that can be thought of as "diseases of despair."

The analysis of Deaton and Case is very enlightening, because it suggests what we might do to address the problem. They distinguish those people who have a very high risk of actually dying by overdose. Among white lower-middle-class people, it's those who do not go beyond high school. Which, of course, then limits their opportunities for work and constrains them in other important ways. This forces us to think about the socio-economic and cultural factors that underlie the rising mortality from the so called "diseases of despair."

Whether you call it "addiction with overdoses," or you call it "suicidality," or you call it "alcoholism" (which is also a substance-use disorder), you have to consider those aspects of our social system that help people overcome stressors so that they can be strengthened, versus factors that weaken the social structure, and limit possibilities and alternatives for individuals.

In light of what you say, I suppose it would be unrealistic to expect a quick drop-off in the mortality—because this is a very deep problem with structural causes that far transcend even medicine.

Correct. It definitely transcends medicine. But interestingly, the data reminds us of something that prior research has told us: that one of the best predictors of your health is your level of education. We do not normally see education as part of public health. But they are closely interlinked. That's why I like the analysis of Deaton and Case, because they highlight an element that you can target for prevention in the future. If you want to create resilience in your citizens, to protect them against these conditions, you have to ensure that they are properly educated. That will give them multiple alternatives for how they are going to develop talents, and earn a living, and build their life.

It has been said that doctors have been responding to their role in the opioid crisis. In the last couple of years, their prescription practices have become more conservative.

Addressing the wide availability of opioid prescription drugs is fundamental in addressing the opioid crisis. But it's not sufficient. You also have to provide proper treatment for people suffering from pain. Because if you don't address their needs for pain treatment, they are at great risk of seeking out opioid drugs in the black market, exposing them to very potent and dangerous products.

We also need to address the fact that as a nation, we still over-prescribe opioid drugs. Last year, 170 million opioid prescriptions were given in the United States. While that is less than the peak in 2011 of around 275 million, it is much higher than the rates in other countries. This number of prescriptions is hard to justify when one considers that opioid medications should be reserved for the most severe pain.

We have to recognize that opioid analgesics, when used properly, can be life-saving. In this sense they are not like other addictive substances with no medical utility. Getting rid of opioids would do a tremendous disservice to health, because they are extraordinarily useful for management of severe pain and for anesthesia. A person with severe pain who does not respond to other medications may require the use of opioids. And if you make it much harder or impossible for them to get opioid analgesics while not providing any viable therapeutics, some patients will go to the black market to seek relief for their pain condition.

In view of this, what is your recommendation?

We need to educate physicians on the proper utilization of opioids, and we need to structurally change reimbursement practices for the management of pain. Because right now, it's much cheaper to prescribe an opioid than to provide multi-pronged approaches for treatment and management of chronic pain. And many insurance plans won't pay for it.

Also, we need to focus on prevention, including aggressive campaigns to educate people about the dangers of opioids. In visiting some of the areas most affected by the opioid crisis, I've been surprised by the fact that many people do not know how dangerous the synthetic opioid fentanyl is. I ask myself, how can this be? We need to do an education campaign so that people recognize why these drugs can be so harmful. We also need to provide, as part of the prevention, activities and support systems that will give resilience to those who are vulnerable, so that they don't end up taking a drug as a means of escaping their realities.

If you look at the demographics, those who are at greater risk of using synthetic opioids or heroin are young people in the transition from adolescence to young adulthood. That's also a group with some of the highest rates of overdoses. It's also the age group in which we're seeing some of the largest increases in overdose mortality over prior years—very significant increases. So, we need to develop prevention efforts that target the transition into young adulthood.

I wonder if we can also talk about vaping. It seems that due to the rapid increase in teen vaping, nicotine addiction may actually begin earlier and become even more entrenched than it ever was in the past, when smoking cigarettes was the main "delivery device" for nicotine.

We've made major advances in prevention efforts for reducing smoking among young people. It's actually quite dramatic, and a beautiful example that prevention works when you put your mind to it.

The concern now is that we're starting to see very rapid and very significant increases in vaping among teenagers. NIDA has been recording it for the past three years. In the first year, many of these kids were claiming that they were using the vaping devices just for the flavors. But in the second year, we had more kids claiming that they were using it for nicotine than for flavors.

Nicotine is an addictive drug. They're going to become addicted to nicotine by vaping, which is a reason for concern. We may lose ground on all of the advances that we have made in the prevention of cigarette smoking. It is worrisome, and we need to take it very seriously.

Vaping devices also make it possible to ingest very high concentrations of THC, the active ingredient in marijuana, right?

Correct. In our most recent survey, which we released this past December, 10% of those who were vaping said they were vaping THC, which is the ingredient that produces the "high" in marijuana. With vaping, you can concentrate it and get a very high content of THC. This highly potent version is linked with adverse effects, including the risk of acute psychosis. In those who are vulnerable, this can lead to chronic psychosis.

Can anything be done about this on the part of the device makers? Or is this another problem that must be tackled via better education?

DID YOU KNOW?

FENTANYL is an artificial opioid—one not native to the human body—that is sometimes used under strict medical supervision as an anesthetic or pain reliever. Fentanyl-like drugs, sold illicitly, can be hundreds of times more powerful than heroin. Sometimes sold as mislabeled pain relievers or as heroin, the drug has been behind thousands of suicides in recent years—deaths which are often confused for heroin overdoses.

THC (TETRAHYDRO-CANNABINOL) is the "psychoactive" component in marijuana (cannabis). It interacts with receptors in the brain that process endocannabinoids, chemicals in the body that are involved in a variety of processes from appetite to pain to memory, in addition to mediating the pharmacological effects of cannabis.

We should create policies to regulate these products. These include regulating vaping devices and the cartridges that are used in them. We also need to create policies that interfere with the selling of these devices to minors, just like we have done for cigarettes and alcohol.

Dr. Volkow, for years you have been eloquent on the subject of addiction being a brain disease. Yet some people continue to resist that idea. What would you say to skeptics who claim that addiction, in the end, is a failure of personal self-control?

We all see reality through our own experiences. And when someone has not been addicted themselves, they see that they are able to control and regulate their actions. Even while sometimes they may not be successful, most of the time they are able to regulate their emotions and desires.

It may help to do a thought experiment to help illustrate the significance of losing the capacity to self-regulate. You normally don't think twice about picking up a glass of water. But if you have a stroke in the motor area of your cortex, you will not be able to do it. And why not? Because the area of the brain that sends the signal to the muscles in your arms is not working. It cannot send the signal.

Similarly, in an addicted person, the area of the brain that regulates the desire to have the drug isn't working properly. It's not sending the signal. Nobody would question this when someone has a stroke. We would say: well, that person's brain can no longer send the proper signal. But people have difficulty in bringing that logic into a situation like drug-seeking which concerns an inner, cognitive control process as opposed to one that concerns the movement of a limb.

'We should regulate vaping devices and cartridges. We also need to create policies that interfere with the selling of these devices to minors.'

For people who have never lost control, it becomes very difficult to conceptualize. And that's why, to me, it's very important to imagine what it might be like. Say you haven't eaten anything for five days. You are starving. And someone places food in front of you that is likely to be contaminated with salmonella. You know you shouldn't eat it. But the ability to stop that extreme hunger from taking over is very hard, and with further food deprivation it might be almost impossible. Your brain is processing it as a state of emergency. You feel that if you don't eat now, you'll die. The threat of your getting sick in the future becomes almost theoretical. This kind of situation of overvaluing the "now" at the expense of the "later" is at the heart of addiction.

This relates to the science you and others have done on this subject, concerning the way our brains are wired for motivation and reward. You have said that these mechanisms, so central to our survival as a species, get hijacked in addiction.

Yes. In the brain of a person who is addicted, an artificial sense of deprivation is generated, akin to the sense of hunger that leads the starving person to eat the contaminated food. The hunger for the drug is equivalent in its power to motivate the behavior of an addicted person. For in addiction, the survival circuits that motivate your actions have been hijacked.

In addiction, you've generated an artificial sense of being in a state of deprivation that is just like one feels in a desperate survival situation. You feel that unless you address it, it could cost you your life.

How ironic.

But this may help a skeptic understand that addiction is, indeed, an illness in which the brain is not functioning properly. This illness can be overcome, but it is not a trivial matter of simply wanting to assert self-control. Addiction is a chronic illness that must be treated in a continuous model of care that includes the social support systems necessary. ❖ **PETER TARR**

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Barbara Toll, Research Partner

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

—Barbara Toll, Foundation Board Member

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‘Breaking the Silence About Mental Illness’ with *Tipper Gore*

May 1, 2019

PHOTO CREDIT - CHAD DAVID KRAUS PHOTOGRAPHY

CLOCKWISE FROM TOP LEFT:
Dr. Jeffrey Borenstein and Tipper Gore in conversation; Carol Atkinson, Carole Mallement, Tipper Gore, and Suzanne Golden; Beth Elliott, Carole Mallement, Dr. Jeffrey Borenstein, Sheila Scharfman (the women are the Co-Chairs of the Luncheon Committee); VIP and Committee Group Shot; Carole Mallement, Ellen Levine, Dr. Myrna Weissman, and Dr. James Frauenthal

TIPPER GORE, ADVOCATE, artist, philanthropist and former Second Lady of the United States, was the speaker at the Brain & Behavior Research Foundation Luncheon, "Breaking the Silence About Mental Illness," on May 1, which kicked off BBRF's celebration of Mental Health Awareness Month.

The event, co-chaired by Carole Mallement and Virginia Silver, who are BBRF Board Members, along with Beth Elliot and Sheila Scharfman, was attended by more than 300 people.

Mental illness affects the lives of one in five people. BBRF presents an annual spring luncheon to support psychiatric research and address the need for public engagement to solve issues around stigma that keep people from seeking help and accepting treatment.

"Tipper Gore is a powerful voice in eliminating the stigma that is all too often still associated with mental illness. We were honored she was our speaker as we continue to expand the conversation about the importance of banishing stigma and supporting psychiatric research helping people with mental illness lead full and productive lives," said Dr. Jeffrey Borenstein, the President & CEO of BBRF, who hosted the event.

Tipper Gore's commitment to mental health was first evidenced when she brought mental illness to the forefront of politics and public policy by hosting the nation's first White House conference on mental health in 1999. At this year's luncheon she discussed her public advocacy work for mental health, including the pressing need for public engagement to solve the issues around the stigma that still keeps people from getting the care they need.

"If you have somebody who's on the street and they've got a broken leg, do you just walk by? No. But if somebody has a mental illness, which is just another part of the body, do you ignore that? People tend to not know what to do, or ignore it, or think it's going to go away. We need to treat it the same," Gore noted, when talking about the state of mental health today.

The BBRF Luncheon series is designed to pay tribute to the brave people who are willing to speak candidly and personally about mental illness and use their experiences as an inspiration to galvanize all of the necessary resources needed to speak out, remove stigma, and break the silence about mental illness.

"Our luncheon shows how everyone is touched by these conditions," said Dr. Borenstein, who noted that 100% of every dollar the Foundation raises for research—all from private donations—goes to support BBRF research grants. ❖

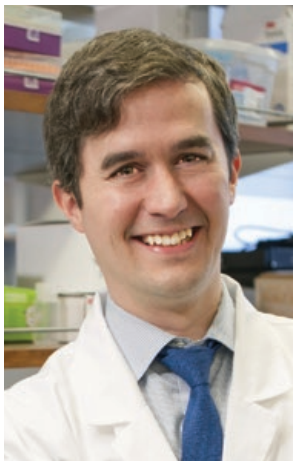
FROM TOP LEFT:

Judy Daniels, Lilian Sicular, Beth Elliott and, Lillian Clagett (Luncheon Committee Members); Stephen Lieber (BBRF Chairman of the Board) and Tipper Gore; Barbara Arenz, Carole Mallement, Tipper Gore, Judy Wertheim, and Geraldine Stanko; Dr. Jeffrey Borenstein, Ellen Levine, Tipper Gore, and Dr. Herbert Pardes; Ellen Levine and Dr. Jeffrey Borenstein

Recent Research Discoveries

Important Advances by Foundation Grantees That Are Moving the Field Forward

KETAMINE RESTORED NEURAL CONNECTION POINTS LOST IN STRESS & DEPRESSION



Conor Liston, M.D., Ph.D.

Researchers led by 2013 BBRF Young Investigator Conor Liston, M.D., Ph.D., have reported a surprising finding about the way ketamine acts on the brain. Approved many years ago as an anesthetic, ketamine has been used experimentally in recent years as a rapidly acting antidepressant. Severely depressed patients have reported a dramatic lifting of symptoms within hours. Esketamine, a ketamine "cousin," was approved by the FDA in March for use in patients whose depression has not responded to two or more conventional treatments (see p.37).

Ketamine's mechanism of action is not well understood. To learn more, Dr. Liston and colleagues at the Weill Cornell School of Medicine in New York took advantage of the fact that ketamine works rapidly to reduce depression-like symptoms in rodents as well as people. By administering the drug to rodents, they hoped to solve the puzzle of the drug's action via sophisticated brain imaging techniques.

As they reported in the journal *Science*, the researchers noticed that an infusion of ketamine promotes the growth of tiny knob-like structures called dendritic spines. These provide connection points at synapses, tiny gaps across which neighboring neurons exchange information.

In depression, dendritic spines of neurons in the prefrontal cortex tend to disappear. This is associated with reduced connectivity between neurons. Dr. Liston and colleagues intentionally caused spine loss in rodents by exposing them to physical stress and to stress hormone. Some of the same spines that disappeared were observed to reappear following ketamine treatment; some new spines were also seen. Ketamine also restored activity among small groups of cortical neurons, forming microcircuits known to be involved in antidepressant behavior.

Surprisingly, the resurgence of spines did not occur until after ketamine's behavioral impacts had already taken hold in the rodents. The initial antidepressant effect was therefore not attributable to the reappearance of lost spines. But further experiments demonstrated that unless new and restored spines were present, ketamine's initial antidepressant effect could not be sustained.

The discovery suggests that therapies might be devised, such as pharmaceuticals or neural stimulation methods, which would aim to preserve or even enhance the "rescue" of lost synapses, in order to sustain the benefits of ketamine and perhaps other rapid-acting antidepressants that are in development.

SOME PATHOLOGIES IN AUTISM ARE TRACED TO STEM CELLS IN THE DEVELOPING BRAIN

Simon T. Schafer, Ph.D.

Evidence continues to mount that some of the biological abnormalities that underlie autism spectrum disorder (ASD) begin well before birth, as the brain's cerebral cortex is developing. It's still not known, however, when and where in the emerging brain these irregularities first manifest.

These questions are addressed in *Nature Neuroscience* by a team led by 2018 BBRF Young Investigator Simon T. Schafer, Ph.D. and 2013 BBRF Distinguished Investigator and Scientific Council member Fred H. Gage, Ph.D., both of the Salk Institute for Biological Studies. They show that some autism-related abnormalities in neural cells are traceable to a time when they were still stem cells—that is, a time before they matured into neurons.

All of the mature brain's neurons and support cells begin their existence as neural stem cells (NSCs). These cells cannot be "sampled" from living people, including those diagnosed with autism. But in recent years, a technology has emerged that enables scientists to take skin cells from people—patients included—and reprogram them to re-develop, in a culture dish, as cells of different types. This enables scientists to watch neurons develop from NSC precursors—and to do so with cells sampled from patients, bearing all of the genetic variations they carry, some of which may be implicated in ASD pathology.

The new research found abnormalities in ASD patients' reprogrammed cells that occur very early, in the stem-cell phase. NSCs derived from patients were genetically "primed" to activate specific sets of genes in abnormal ways that caused emerging neurons to mature more rapidly than normal, among other differences.

"Our analysis suggests that some ASD-associated changes are likely the consequence of pathological events triggered during NSC stages early in development," the team said. "Although our work only examined cells in cultures, it may help us understand how early changes in gene expression could lead to altered brain development in individuals with ASD," said Dr. Gage, the study's senior author and president of the Salk Institute.

LONG-TERM STUDY REVEALS HOW BIPOLAR DISORDER EMERGES IN HIGH-RISK YOUTH

A multi-decade study focusing on children of parents diagnosed with bipolar disorder quantifies the risk—24.5%—that they themselves will develop bipolar illness, and suggests a "progressive sequence" in which the illness typically unfolds between the ages of 12 and 30. The "trajectory" proposed in the study is expected to help doctors to diagnose bipolar disorder in young people, which is challenging because symptoms often overlap with those of other disorders.

Anne Duffy, M.D. F.R.C.P.C.

One of the new study's findings—that childhood sleep and anxiety disorders are important predictors of emerging bipolar disorder—is an example of how long-term follow-up of high-risk populations can help diagnose and treat future patients.

The study was led by Anne Duffy, M.D. F.R.C.P.C., of Queen's University at Kingston, Ontario, and Paul Grof, M.D., Ph.D., of the Mood Disorders Centre of Ottawa. Dr. Duffy is a 2005 and 2003 BBRF Independent Investigator and a 2000 Young Investigator; Dr. Grof is a 2002 BBRF Falcone Prizewinner (now Colvin Prize).

In the *American Journal of Psychiatry*, they and colleagues reported patterns based on 116 "high-risk" families—those with at least one parent diagnosed with bipolar disorder—and 55 control families. Altogether, 279 high-risk offspring and 87 control offspring were followed over the course of their youth and into adulthood. The high-risk offspring were split into two subgroups: those whose parents either did or did not respond to the medication lithium.

Depressive episodes predominated during the early course of bipolar disorder, especially among children of lithium responders. Childhood sleep and anxiety disorders were linked with 1.6 to 1.8 times normal risk that a high-risk child would develop a mood disorder. While three-fourths of high-risk children don't develop bipolar disorder, a majority do develop a mood disorder of some kind during their lifetime.

The overall model of emerging bipolar disorder gleaned from the study was a progressive sequence: from childhood symptoms not specific to bipolar disorder (such as sleep and anxiety symptoms) to minor mood disorders and then to adolescent major depressive disorder, followed finally by full-blown bipolar disorder in the transition to adulthood. Progression to a bipolar diagnosis was typically heralded by an episode of mania or hypomania and/or a first episode of psychosis following a single episode or recurrent major depression. The results, say the researchers, "underscore the importance of taking into account both the family history and developmental trajectory of emerging psychopathology to improve earlier diagnostic precision in young people manifesting clinically significant symptoms and syndromes." ❖

Therapy Update

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

FDA APPROVES TWO RAPIDLY ACTING ANTIDEPRESSANT DRUGS

In March 2019, the U.S. Food and Drug Administration approved two medications for the treatment of depression, both of which act rapidly to reduce symptoms. The first was esketamine, a chemical cousin of the experimental drug ketamine, for patients with treatment-resistant depression. Two weeks later, approval was granted for brexanolone, the first-ever medicine specifically designed for women who suffer from postpartum depression.

Esketamine, delivered via nasal spray and sold under the trade name Spravato, is indicated for use in conjunction with a conventional oral antidepressant in patients who have tried other antidepressant medicines but have not benefited from them.

Like ketamine, which has been used for years as an anesthetic, esketamine has been shown in multiple clinical trials to dramatically reduce the symptoms of intractable depression in many patients often within minutes or hours of administration. Its effects typically last 1 to 2 weeks, but can be continued in "maintenance" dosing following initial treatment.

Esketamine is the first pharmaceutical since Prozac in the late 1980s to have a new mechanism of action to treat depression. Although there are many members of the Prozac "class" of drugs—called SSRIs (selective serotonin reuptake inhibitors)—all of them are thought to exert their effect via the serotonin neurotransmitter system. Esketamine's mechanism of action is still being studied, but it is thought to act by affecting the function of the brain's glutamate neurotransmitter system.

The overriding concern about esketamine has been side effects. Closely related ketamine has been misused as a party drug, sometimes called "Special K." One of its adverse effects is called dissociation, a sensation of detachment sometimes described as an "out-of-body" experience. Another important concern centers on its addictive potential. These factors and other side effects including dizziness, sedation, and increased blood pressure, were carefully monitored across clinical trials for esketamine. The drug's developers say that dissociation, when experienced, was usually seen during the hour or so immediately following the drug's administration, while patients were still under the observation of clinical personnel, and were resolved the same day. The manufacturer also says that addictive behavior was not a serious issue in the trials.

BBRF grants totaling $6.5 million helped lead to the development of this first rapidly acting antidepressdant. Among the pioneers were BBRF Scientific Council member Husseini Manji, M.D., now of Janssen Pharmaceutical/J&J after many years as Chief of the Laboratory of Molecular Pathophysiology & Experimental Therapeutics at the National Institute of Mental Health. Dr. Manji is a 1999 Falcone Prizewinner (now Colvin Prize) for Outstanding Achievement in Affective Disorders Research and a 1998 BBRF Independent Investigator. Among the many other BBRF-affiliated researchers who have made major contributions to the search for rapid-acting antidepressants include John H. Krystal, M.D., of Yale University, a BBRF Scientific Council member and a 2006 and 2000 Distinguished Investigator and a 1997 Independent Investigator; BBRF Scientific Council member emeritus Dennis S. Charney, M.D., of Icahn School of Medicine at Mount Sinai; and Carlos A. Zarate, Jr., M.D., of the National Institutes of Health, a 2011 Bipolar Mood Disorders Award Prizewinner (Colvin Prize), 2005 Independent Investigator and 1996 Young Investigator.

Brexanolone, while unrelated to ketamine, acts much more rapidly than conventional antidepressants, usually within two and a half days. It is given via continuous intravenous infusion to women diagnosed with moderate or severe illness, over a 60-hour period in a hospital or other medical care facility by qualified medical personnel.

It is being marketed under the name Zulresso. Its benefits are thought to be related to its modulation of receptors of the inhibitory neurotransmitter, GABA.

Postpartum depression can begin in the weeks prior to childbirth, or in the days, weeks, and months following it. It is the most common complication of childbirth, affecting approximately 10% to 15% of women who give birth in the United States. It can have profound effects on the ability of new mothers to care properly for their newborns, and has been associated with increased risk of longer-term behavioral and psychiatric disorders as the children of affected mothers mature.

Although brexanolone can be administered to women already taking standard antidepressants, a majority of the 246 women who took part in the pivotal phase 3 clinical trials were not taking antidepressant medicines when they received their single, continuous brexanolone injection. The research team conducting the studies, led by Samantha Meltzer-Brody, M.D., M.P.H., of the University of North Carolina at Chapel Hill School of Medicine, concluded that "this indicates that brexanolone injection is a primary, rather than an adjunctive therapy in postpartum depression."

The researchers said the drug "was associated with rapid onset of action (within 60 hours) and durable responses that were sustained for up to 30 days after infusion. Of the patients who had a response at 60 hours, 94% did not relapse at day 30." The drug's most common side effects were headache, dizziness, and sleepiness. Although "typically mild," according to the researchers, these effects, especially dizziness, compelled the FDA to specify that the drug be given under continuous medical supervision, with a stayover of two additional days in a medical facility to insure that side effects abated.

Several BBRF grantees were on the teams that tested brexanolone: Cynthia Neill Epperson, M.D., a 2005 BBRF Independent Investigator and 1997 and 1995 Young Investigator; Steven M. Paul, M.D., a BBRF Scientific Council member; and Handan Gunduz-Bruce, M.D., a 2007, 2005 and 2003 BBRF Young Investigator.

ADDING GUANFACINE BOOSTED BENEFITS OF COGNITIVE REMEDIATION IN SCHIZOPHRENIA SPECTRUM DISORDER

Adding the drug guanfacine to a proven therapy program to treat cognitive deficits led to even better results for individuals with schizotypal personality disorder, said researchers who reported results of a small clinical trial the *American Journal of Psychiatry*.

The double-blind, placebo-controlled trial, led by 2013 BBRF Young Investigator Margaret M. McClure, Ph.D., of the Icahn School of Medicine at Mount Sinai, involved 28 patients, all diagnosed with schizotypal personality disorder (SPD), a schizophrenia spectrum disorder. Those with this diagnosis are usually socially isolated and suffer from perceptual distortions. Like schizophrenia patients, patients with SPD also frequently have cognitive impairments in such areas as verbal and spatial memory, attention, abstract reasoning, verbal fluency and verbal and spatial working memory—the short-term memory needed to perform tasks immediately at hand.

For this reason, people with cognitive impairments of this kind often have trouble functioning, not only socially but also in jobs. Impaired cognition is the best predictor of functional outcome for such patients, Dr. McClure and her colleagues point out.

All 28 of the trial participants received computer-delivered cognitive remediation therapy plus social skills training for 8 weeks. Fifteen of the 28 also received guanfacine, an FDA-approved drug sometimes prescribed for ADHD and hypertension; 13 patients received a placebo. Guanfacine stimulates a receptor on brain cells that increases activity in part of the brain's frontal cortex that is critical in attentional functioning and working memory performance.

"Our most important result was that cognitive remediation and social skills training had greater beneficial impact in those patients who were treated with guanfacine," the team noted. In particular, "there was significantly greater improvement in their reasoning, problem-solving, and functional skills." Additionally, the team noted improvements in social cognition in many of the guanfacine-treated participants.

In addition to boosting the impact of cognitive remediation therapy, the researchers suggested that adding guanfacine might help some people who don't respond to cognitive remediation alone. More research will be needed to demonstrate this. ❖

GLOSSARY

DENDRITIC SPINES: Tiny knob-like structures that provide connection points at synapses, gaps across which neighboring neurons exchange information. In depression, dendritic spines of neurons in the prefrontal cortex tend to disappear. This is associated with reduced connectivity between neurons. Researchers are now testing the theory that antidepressant treatments can restore "lost" spines.

NEURAL STEM CELLS (NSCs): Cells in the brain begin their life as neural stem cells, which, when activated by various signals, develop into a variety of specialized cell types. A technology called iPSC (induced pluripotent stem cell) enables researchers to reprogram mature skin cells, sampled from a living person. Reprogramming takes these cells back to their stem-cell origins, and enables observation of the process by which they become mature cells. Thus the technology is invaluable for exploring what goes wrong in the maturation of cells that harbor disease-linked genetic mutations.

POSTPARTUM DEPRESSION: The most common complication of childbirth, affecting approximately 10% to 15% of women who give birth in the United States. Postpartum depression can begin in the weeks prior to childbirth, or in the days, weeks, and months following it. In addition to its link with elevated suicide risk, it can have profound effects on the ability of new mothers to care properly for their newborns, and has been associated with increased risk of longer-term behavioral and psychiatric disorders as the children of affected mothers mature.

PROTEIN-ENCODING GENES: The 21,000 genes of the human genome, packaged within the nucleus of every cell in a long molecule shaped like a double helix, are essentially blueprints. When a cell needs a specific protein or proteins to accomplish a task, it activates the corresponding gene or set of genes. The DNA sequence of each gene to be "expressed" is read by an enzyme that copies the information into another molecule, called RNA, which in turn, serves as a template for manufacture of the encoded protein in cellular factories called ribosomes.

SCHIZOTYPAL PERSONALITY DISORDER (SPD): A schizophrenia spectrum disorder. Those with this diagnosis are usually socially isolated and suffer from perceptual distortions. Like schizophrenia patients, patients with SPD also frequently have cognitive impairments in such areas as verbal and spatial memory, attention, abstract reasoning, verbal fluency and verbal and spatial working memory—the short-term memory needed to perform tasks immediately at hand.

TMS (TRANSCRANIAL MAGNETIC STIMULATION): A form of non-invasive brain stimulation approved by the FDA in 2008 for treatment-resistant depression. Delivered in treatment units usually lasting 4 to 6 weeks, TMS is now used more broadly for depression as well as for other conditions, including obsessive-compulsive disorder and epilepsy.

TREATMENT-RESISTANT DEPRESSION: Depression that has not responded to two or more courses of conventional antidepressant therapies.

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