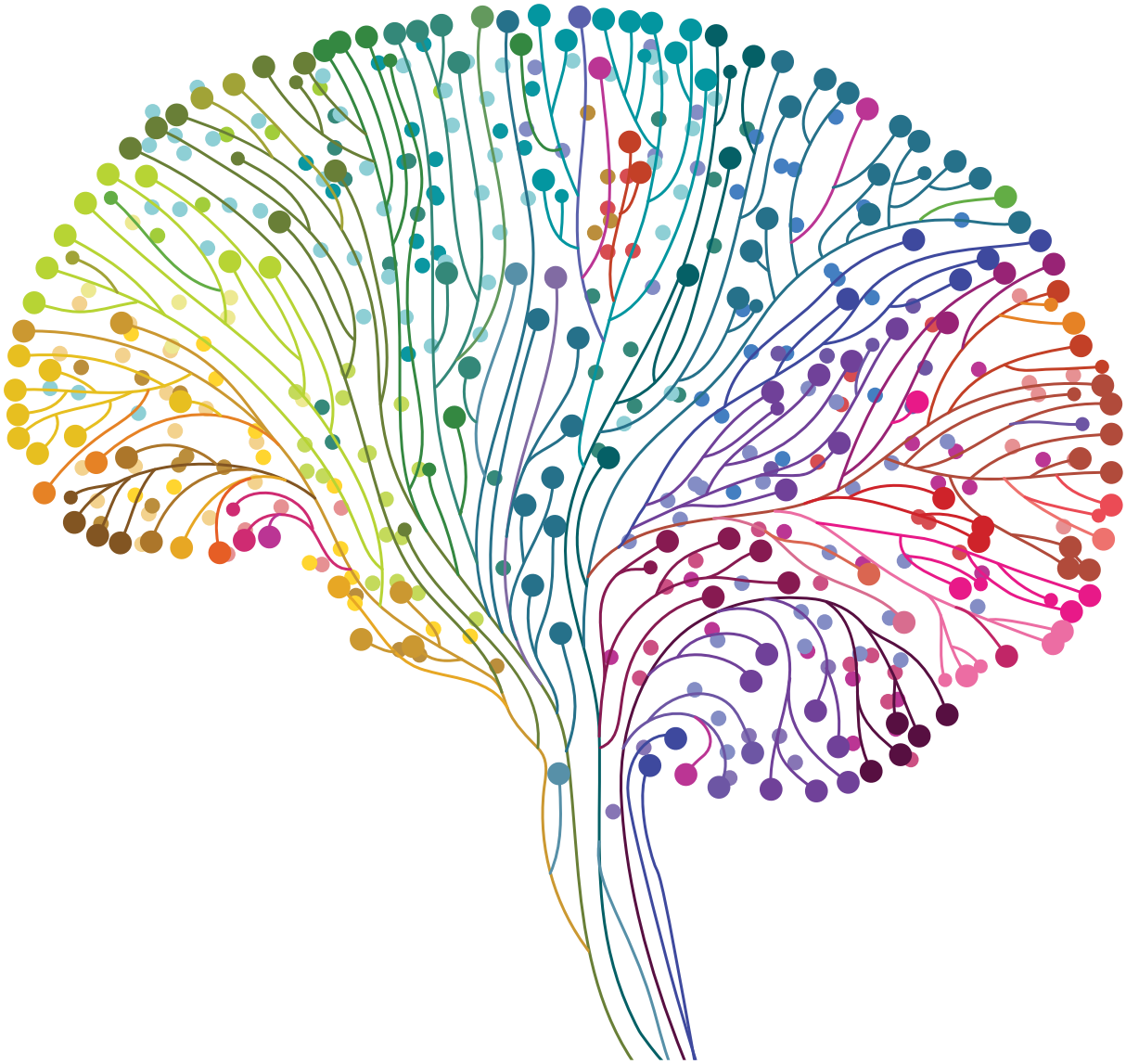
Parenting in a Time of Pandemic

Choline, COVID During Pregnancy, and Fetal Brain Health

Brain&Behavior

AUGUST 2020



A Tribute to the late Steve Lieber, BBRF's Chairman of the Board

PRESIDENT'S LETTER

This issue of *Brain & Behavior Magazine* is dedicated to Steve Lieber, BBRF's Chairman of the Board, who passed away on March 31, 2020. Steve was a deeply passionate and visionary philanthropist, and along with his late wife Connie, had a tremendous impact on psychiatric research and treatment.

For more than a quarter of a century, Steve and Connie served as extraordinary philanthropic supporters and leading public advocates of brain and behavior research. They provided unwavering support to unravel the mysteries of the brain, and to better understand and treat mental illness. Together, they mobilized every resource imaginable to fund cutting-edge research and educate the public, tirelessly working to grow the BBRF grant program to a total of $408 million today. Their generosity in supporting research on mental illness is a great model for all of us.

Our **TRIBUTE TO STEVE LIEBER** features, first, a dedication and remembrance by family members and BBRF Board members: Mary Rubin (daughter-in-law), Geoffrey Simon (nephew), Dr. Herbert Pardes (President of the BBRF Scientific Council), and myself. In the second tribute, "Remarkable in Every Way," Dr. Pardes remembers and celebrates Steve, as well as Connie, who led the organization for over 20 years. Dr. Pardes grew close to the Liebers over a long period that he traces to one day in 1986, when they approached him after a public meeting, saying "we'd like to do something for mental illness." In our third tribute, eight members of BBRF's distinguished Scientific Council, all renowned researchers, offer their tributes to Steve Lieber, remembering him as not only a major benefactor of research but also a brilliant, caring, and kind man who cared deeply about their work.

One of our **RECENT RESEARCH DISCOVERIES** relates to pregnant women with COVID-19 and the importance of higher choline levels to potentially protect the fetal brain.

Our **SCIENCE IN PROGRESS** story highlights the work of Dr. Nolan Williams, a mentee of Dr. Mark George, who pioneered the non-invasive brain stimulation technology called rTMS (repetitive transcranial magnetic stimulation). Dr. Williams, with his two BBRF Young Investigator grants (2016 and 2018) set out to improve upon rTMS, which is now an FDA-approved therapy for depression. Dr. Williams and colleagues devised SAINT, a new protocol for delivering non-invasive brain stimulation, and tested it in a small group of highly refractory patients with severe depression. Though preliminary, the trial was remarkably successful, enabling 19 of 21 patients to achieve remission within 5 days. If successful, this new protocol might serve as a rapid-acting antidepressant treatment for patients in crisis, including those at high risk of suicide.

In our **PATHWAYS TO THE FUTURE** feature Dr. Dennis Charney, an emeritus member of the BBRF Scientific Council and one of the world's leading authorities on resilience, discusses what decades of research have taught him about not only surviving severe stress and adversity, but taking advantage of such time to gain important life-skills that can actually make a person mentally stronger. The key takeaway from this piece is that these are skills that can be learned.

Our **ADVICE FOR PARENTS, FRIENDS & LOVED ONES** piece features Rachel Klein, Ph.D., a BBRF Scientific Council member and leading adolescent psychiatrist. Dr. Klein discusses challenges faced by parents of children in this time of a global pandemic. Dr. Klein's serious, yet encouraging advice points to how parents can make their children appreciate that they, too, play an important role in the family's response to unusual circumstances.

None of these advancements and discoveries would be possible without you, our donors. I am sincerely grateful for your support. Together we will continue to honor the Lieber legacy and fund the future of brain research and set the trajectory for new treatments, cures, and methods of prevention for our loved ones.

Sincerely,

Jeffrey Borenstein, M.D.

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

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IN REMEMBRANCE

STEPHEN A. LIEBER
August 30, 1925–March 31, 2020

Steve Lieber didn't set out to change the world…. but during a lifetime of passionate work, he and his wife Constance (1924–2016) did just that. What started as a quest for mental health therapy to aid a family member evolved into a lifetime commitment to advancing scientific research on the brain and mental health. Expanding rigorous scientific research to lessen human suffering caused by severe psychiatric disorders was his guiding star.

Steve and Constance were leading public advocates and philanthropic supporters of schizophrenia, depression and mental health research in the U.S. and around the globe. Their efforts launched thousands of careers in mental illness research. Their work included support for top-notch scientists from significant clinical and scientific institutions that gave rise to countless discoveries in the field of biological psychiatry and related patient services. The vast majority of major scientific investigators studying the brain and behavior have received Lieber philanthropic support at some point.

In the mid-1980's Steve and Constance met Dr. Herbert Pardes, the Chair of Psychiatry at Columbia (former director of the NIMH). Dr. Pardes introduced them to the National Alliance for Research on Schizophrenia and Depression (NARSAD), now Brain & Behavior Research Foundation (BBRF), which they joined in 1987. The result was a major step forward for the global attack on psychiatric disease. Under Steve and Constance's leadership the BBRF developed a uniquely warm, understanding and empathic approach to the patients, families and investigators of the broad mental health community.

BBRF is currently the world's most prominent private funder of mental health research grants. Constance served as President for 18 years, and Steve was Chairman for 12 years, until his death. Since 1987, BBRF has awarded more than $408 million to fund more than 5,900 grants to more than 4,800 international scientists of multiple and diverse disciplines.

In 2011, inspired by promising developments (in genetics, imaging, and other research categories) regarding how early brain development initiates trajectories that can lead to schizophrenia and related disorders in mental health, the Lieber family and the Maltz family created the Lieber Institute for Brain Development (LIBD) and the Maltz Research Laboratories at the Johns Hopkins Medical Campus in Baltimore, MD.

In 2014, Steve and Constance Lieber were honored by the American Psychiatric Association with a Special Presidential Commendation, stating "Constance and Steve have provided unwavering moral and material support to unravel the mysteries of the brain, and to better understand and treat mental illness."

At Columbia University, the Liebers founded two centers of excellence—the Lieber Recovery and Rehabilitation Clinic and the Lieber Center for Schizophrenia Research and Treatment.

Steve Lieber also endowed the neuroscience department at his alma mater, Williams College. His pervasive goal was to encourage outstanding young minds to pursue careers in neuroscience, and it worked. Neuroscience is currently the most popular undergraduate major at Williams College.

Steve Lieber's unwavering commitment to breakthroughs in mental health research was matched by his innovative and successful 70-year career in investment management. He had the kind of robust imagination that led to truly innovative strategies—in his business career and in his philanthropy—and the persistence and commitment to put these innovative strategies to work. He inspired a fierce, ongoing loyalty from his employees as well as from the hundreds of scientists who were granted his philanthropic support. At the time of his death, Steve was hard at work and actively engaged as CEO of Alpine Woods Capital Investors, as well as Chairman and Senior Portfolio Manager of Saxon Woods Advisors, LLC. In addition, he was General Partner of Alpine Woods Growth Values, L.P.

Steve Lieber's Wall Street career began in 1950. After attending Williams College and Harvard Graduate School, and newly married to Constance, Steve joined the Wall Street investment management firm Oppenheimer Vanden Broeck & Co. He was elevated to partner in 1953, and in 1956 became a co-founder of Vanden Broeck Lieber & Co. Thirteen years later in 1969 he started his own investment firm, Lieber & Co. In 1971 he formed the Evergreen Fund, one of the nation's first "no-load" mutual funds which invested predominantly in smaller entrepreneurial companies. According to Kiplinger's and Lipper rankings, the Evergreen Fund was the #2 best performing mutual fund in America from 1975–1980.

The Evergreen Fund was followed by a series of six additional mutual funds managed by Lieber & Co., or its affiliates, with assets of more than $3 billion in the early 1990s. In 1994, First Union Bank Corp. purchased Lieber & Co. (which was the parent firm of Evergreen Asset Management Corp., the investment adviser to the Evergreen Funds). For the following five years, Mr. Lieber continued as chairman, co-chief executive, and portfolio manager.

Upon leaving Evergreen Asset Management Corp. in 1999, Mr. Lieber formed Saxon Woods Advisors, LLC. In 2003, he joined his son Samuel's firm, Alpine Asset Management, to create Alpine Woods Capital Investors. Together Steve and Sam Lieber developed the successful Alpine Family of Mutual Funds, and Hedge Funds. The Alpine mutual funds were sold to Aberdeen Standard Investment Company in 2018. Last year, Steve Lieber added the Alpine Woods Masters Series to its existing hedge fund offerings. He was very enthusiastic about his talented team of investment portfolio managers and staff.

His devoted 67-year marriage with Constance serves as a stellar example of how two people can support and encourage each other to accomplish things of significant societal value. Many of their achievements came into being long after they were both past the "typical" age of retirement. During their marriage, Stephen brought his optimism, his creative imagination, and his adventurous spirit—all of which helped him become a financial titan. And, Constance was able to harness his whimsy—without constraining his creativity—by adding her own grit and analytical abilities. Their marriage was an ongoing love story as well as an enduring partnership.

During their lifetimes, Steve and Constance Lieber sought no fame or notice from the world. As a team they were the embodiment of generosity, brilliance, compassion, and the essence of selflessness. In their selfless way they put all their energy and effort into the goal of defeating the scourge of mental illness. In private, they were passionate about family and the people lose to them. They shared a love of art, architecture, nature, and science. Throughout his adult life and well into his 80s, Steve Lieber was an avid sailor, and a successful ocean racing competitor with his son Sam. He also loved swimming, rowing, and was a competitive windsurfer well into his senior years. Anyone knowing and viewing the Liebers' life together can understand why they are universally loved.

Steve Lieber is survived by his beloved daughter Janice. His son and business partner Samuel tragically passed away unexpectedly in 2019. Other survivors include his beloved grandson David and daughter-in-law Mary Rubin. ❖

"Remarkable in Every Way"

Dr. Herbert Pardes, President of BBRF's Scientific Council, Remembers and Celebrates Steve and Connie Lieber

Steve Lieber was a most special and unique man. He made everyone feel welcome and valued. He was a gentleman. He was warm. Almost to a fault, he spent little time promoting himself. He was an "ideas" person. He was brilliant and generous. There was a quality of sweetness about him that touched all who knew him.

Steve was inseparable from his late wife, Connie, who led BBRF for 20 years. He and Connie were a marvelous combination. They were not only smart, dedicated and gifted. Both were selfless.

The story of my friendship with Steve and Connie goes back to 1986. I was in my second year as head of the psychiatry department at Columbia University, a position I took after serving for about 6 years as director of the National Institute of Mental Health. We decided it would be a good idea to hold public conferences—all-day seminars—on mental illness, and invite the public to attend. We wanted non-professional people to better understand what was going on in the field. It was a way of working actively against stigma. Our biggest hope was that enlightenment would lessen stigma, lead more people to get treatment, and lower the pressure on families.

All of this sounded wonderful in theory, but then the day arrived when we were about to put on our first "mental health symposium," in Manhattan. It was a rainy Saturday morning. I worried about the size of the crowd we would draw. But 700 people showed up. It was a spectacular success, and marked the beginning of a series of symposia that continues to this day in BBRF's annual Fall mental health symposium. Those of us who gave talks that first day could feel the strong interest of those who came to hear us. Speakers and audiences seemed to understand that we were doing something important that day.

After the symposium ended, a couple came over to me and said simply: "We'd like to do something for mental illness." What an understatement that turned out to be. I was delighted—but the importance of that moment wasn't immediately apparent. What was on my mind that day was the fact that people all over the country who had reason to be interested in psychiatric illness were hiding it. They were scared of it, and they had many reasons why they didn't want to be associated with it. One rarely met people like Steve and Connie, who had a dedicated priority for psychiatric research. It turned out that these volunteers had a cherished daughter, Janice, with schizophrenia, and both wanted to get involved.

The Liebers intrigued me. I sensed they wanted to do something on a large scale, so I introduced them to the other members of the leadership of BBRF, which was then called NARSAD. They became members quickly. In our first year, when we decided to start giving grants, we had about $50,000. The worry was, if we spent that money, how would we know whether we could do the same thing next year? Not long after that, Steve and Connie started to make their impact on the organization. They strongly supported the idea of funding as many grants as we possibly could to worthy Young Investigators—the best young researchers not only in the U.S. but around the globe who could lead the field forward. The Liebers were always for spending more. In later years, if you told them, "Well, we have the funds to make 170 grants, but on the merits, there are 200 we'd like to fund," they would say: "Do it." Implicitly, the idea was they would cover it, and they did. Steve did that repeatedly. Any time we were short, Steve would say, "Don't worry about it, I'll pledge." He gave a pledge and he backed it up.

TRUSTING THE SCIENCE

In addition to the remarkable financial support the Liebers have given, there were countless other ways in which their approach to philanthropy and to life helped make BBRF an unusually effective organization.

One important thing was that Steve and Connie understood that scientific knowledge and competence in this organization resides in the Scientific Council (which I've had the honor of chairing from its beginning). The Liebers' way of acting upon this understanding was to defer to the judgment of the scientific experts when it came to selecting grants to fund. Committees of the Council, composed of world experts in particular fields, choose the best annual applications in grants. There are no politics, and everything is done on a volunteer basis. I do not participate in the choice of any of the grants or the research awards. The Foundation under the Liebers' leadership raised the money, and the Council has been able, year in and year out for over 30 years, to fund the best research, wherever it is, whoever is doing it. Steve and Connie not only "got" the idea of separating fund-raising from grant-giving, they championed it.

An important principle is that Steve and Connie, along with a number of other major donors, arranged to cover all the basic administrative costs of the Foundation. This enabled NARSAD,

Connie Lieber provided dynamic and insightful leadership to NARSAD and BBRF as its President from 1989 to 2007, and then as President Emeritus. Below: with Dr. Pardes.

and now BBRF, to say to the world: "If you give us a dollar, 100% of that dollar goes for research." That's a great message.

The Liebers also backed the idea of streamlining and simplicity. They supported the idea that the Scientific Council would not be burdened by complicated bylaws and rules and regulations. We were empowered to keep adding world-class expertise, in neuroscience, psychiatry, and related fields, to our Council as we went along. From a dozen or so members back in the '80s, the Council now has 181 members. It's depth, breadth, and broad intelligence is another thing that distinguishes BBRF under the leadership of the Liebers.

The Liebers' approach to grant-making was characterized by an enlightened open-mindedness. Early in the Foundation's history, we were approached by various potential benefactors, one of whom, I recall quite well, argued that he'd be a great leader of the organization because he knew exactly what research areas were the most important to fund. That kind of intervention is exactly what Steve and Connie did not do—and not just to please the scientists. They were always accepting of the breadth and diversity of the scientific work for which people were asking support. They didn't have any favorites. They were just looking for what and who worked and had promise. And no matter what the need was, they would be there, and would push for funding. Connie and Steve epitomized collaboration and non-intrusion. I never heard them complain about a single grant.

RECOGNIZING HIGH ACHIEVEMENT IN RESEARCH

In the late 1980s, Steve Lieber had the terrific insight that those involved in the field of psychiatric research were not

getting the kind of recognition in society that they deserved. He asked the Council, "Why isn't there anything like a Nobel Prize for this research?" That thought led in 1987 to the creation of BBRF's annual awards programs. We launched the Lieber Prize for Outstanding Schizophrenia Research, setting up a committee to administer it. Over time, the Lieber Prize has become one of the most coveted recognitions in the field. To date, two Lieber Prize winners have gone on to win Nobel Prizes.

Following on that idea, Connie and Steve drew other supporters to the BBRF, enabling the organization to develop additional awards to commend outstanding scientists working on disorders in children, depression and bipolar disease, and basic science, among others.

In 2014, the Liebers created the Pardes Humanitarian Prize in Mental Health to honor those scientists and humanitarians who comprehensively care, teach, investigate, work, and passionately advocate for improving the mental health of society and have had a powerful impact on reducing the pain inflicted by psychiatric illness. The Pardes Prize is presented annually at BBRF's International Awards dinner, and it is among the great honors of my life to have had this recognition named for me—something I did not seek but upon which Steve Lieber insisted.

These prizes are arguably the most successful and important awards for psychiatric research given anywhere. They carry great prestige. Just as Steve suggested they would. The awards bring well-deserved attention to researchers whose achievements too often go unrecognized. Just as with our grant programs, the awards we give continually help to advance the field, and at the same time bring great credit to the Foundation and its mission.

Creating the idea of an awards program was characteristic of Steve. He was always coming up with new ideas. He was always thinking, "We're still missing something." He was very creative. The awards and prizes help us understand why Steve and Connie were so respected by the scientific community. They had the absolute respect of the scientists, and of course vice-versa. The Liebers really knew what they were talking about. They got to know people personally. And their idea that whatever money we had was going to go to grants was as great for the scientists as it has been for the credibility and stature of the Foundation.

Dr. Pardes on Steve Lieber: "He was the essence of decency."

From left: Dr. Pardes. Dr. Eric Kandel, Steve Lieber, Dr. Jeff Borenstein.

The Liebers' generosity and vision extended to the forming of the Lieber Institute for Brain Development (LIBD) in 2011. The Lieber family and the wonderful and like-minded Maltz family made this possible. LIBD is chaired by Dr. Dan Weinberger, one of the world's leading schizophrenia researchers. LIBD is an international premier translational research institute devoted exclusively to understanding the developmental origins of serious mental illness. In less than 9 years it has become a leading research enterprise with more than 100 scientists and staff comprising a multidisciplinary intramural faculty that has already discovered promising new treatments for schizophrenia and autism.

A PORTFOLIO OF STUNNING SUCCESSES

Taken together, all that Steve and Connie touched makes for a remarkably impressive series of achievements. I don't know of anything like it in the world. And it is poignant to think that it all began when two people walked up to me after a meeting. I don't know if it can be called an accident, but it was certainly a moment of marvelously good fortune. These were people who wanted to help. There are lots of people with wealth, but there aren't many people with wealth who really know what to do with it, and how to make it work in a difficult field.

Thanks in large part to the vision and commitment of the Liebers, BBRF is one of the most admired charities there is. People in the field know it. Researchers are immensely honored and touched when they are asked to join the Scientific Council. I invite each one personally, and in all the years, only one person has ever turned us down. Those in the field consider receiving a BBRF grant a real honor and an important step toward career success. The prizes given by the Foundation are both coveted and respected.

BBRF began as a small group organized by private citizens. Today it is nothing short of a stunning success. Not long ago, someone came up to me and said, "Who brought this about?" I said, "You see that man over there? That man and his wife." I cannot say enough about Steve and Connie. Over decades, I have interacted with many, many different people, and many different awards. There are people with all kinds of personalities—but I have yet to meet two people like them. They were not ostentatious. They were not showy. Beginning with, "We'd like to do something," we can look today with pride upon a Foundation that has funded over $400 million in research and over 5,000 research grants all over the world. And it is a wonderful complement to the NIMH, a great institute, which is also a leader in the battle against mental illness.

A few years ago, Steve lost Connie. Last year, he lost his beloved son, Sam. Yet Steve persisted. He never seemed to miss a beat. Sam, who was so close to Steve, was cherished.

His passing was completely unexpected—a great shock. Steve and Connie both were extraordinary. I think back to a day when I went to see Connie when she was gravely ill and in the hospital. She was lying in bed; Steve was sitting nearby. I sat down. And I thought to myself, what does somebody who's so sick say to you? Well, she didn't complain about anything. She said to me, "You know, Herb, the doctors and nurses are wonderful here." Which was typical Steve and Connie. They only saw the good in people. They knew what was good.

The night before Steve passed away, in March, I called him up to see how he was doing; he'd not been feeling well. And he said, "I'm feeling a bit better." At about seven o'clock the next morning, I got a call, telling me that he'd passed away.

There have been a few times in my life when I felt overwhelmed by hurt and loss. This was one of them. I was devastated. It's a feeling that does not go away. As far as I was concerned, I wanted him to be there for another 100 years. This man was the essence of decency. He was such a gentle, warm, innovative, intelligent man. What a guy! I never heard a word of self-admiration. Just, "How's everybody else doing? What can we do now?" It was all generated by the drive that produced these great accomplishments.

I loved both of them, Connie and Steve. For me, losing Steve is like losing a brother. That's who Steve Lieber was, for me and for all who knew him. ❖

"It all began when this couple came up to me and said, simply, 'We'd like to do something for mental illness.' What an understatement!"

8 Leaders in Psychiatric Research Celebrate the Life and Impact of Steve Lieber, BBRF's Chairman of the Board

We asked several members of BBRF's Scientific Council to reflect upon Steve Lieber's remarkable personality, his contribution to philanthropy, and to the field of mental illness research.

William T. Carpenter, Jr., M.D.
University of Maryland School of Medicine
BBRF Scientific Council;
2019 Pardes Humanitarian Prize;
2000 Lieber Prize; 2008, 2001, 1996 BBRF Distinguished Investigator

Steve Lieber will certainly be missed. I first met him when he became involved with the precursor of BBRF, which we called NARSAD. It was around the third year of NARSAD's existence. Steve and his wife Connie had met Herb Pardes at a Columbia University meeting and struck up a friendship. This was in the 1980s.

From extraordinarily humble beginnings, and thanks to the relationship with the Liebers initiated by Herb, NARSAD began to gather momentum. This was when Connie came in. She was "no nonsense." The key was Connie's success in forming a Board that understood that decisions about what science to support was for the Scientific Council to decide; the Board members were responsible for finding, providing, and approving the funding. This was a critical shift from a Board that was challenged to raise funds but with strong views on what science is acceptable. This change was critical for success and launched NARSAD, now BBRF, on the path to becoming the most significant foundation supporting the acquisition of knowledge to enhance the understanding and care of persons with mental illness.

The Liebers gave strong support to the BBRF Young Investigator grant program. The reason was clear. At the beginning of BBRF there were far too few young scientists addressing schizophrenia and depression, the illnesses BBRF focused on at the time of its founding. Connie and Steve understood this need and pushed the funding. In a short period of time the Young Investigator award was the career launching program for today's skilled and successful mental illness scientific community. While Connie and Steve left the science to the scientists, they pushed hard for success in funding our initiatives. And each year, if we didn't have enough money for every high-quality grant, they would somehow assure sufficient funds were raised to protect the Young Investigator program. The program has been extremely successful—the critical first competitive funding success for today's leading investigators. It's had a great impact on the field.

My direct involvement with Steve would come with Scientific Council meetings or the annual gala and awards ceremony. My wife and I treasured these times. His modesty and humanitarian qualities were quietly, but always, present.

Connie and Steve were clear about what they wanted and how they wanted to go about it. And they were steadfast in that. Both were consistent in terms of the mission and how to plan the future. They knew how to make all this happen without drawing attention to themselves.

Robert R. Freedman, M.D.
University of Colorado School of Medicine
BBRF Scientific Council;
2015 Lieber Prize; 2006, 1999 Distinguished Investigator Grant

There's a story I will always remember. I think the year was 1989—the organization we then called NARSAD (now BBRF) had only been in existence for about 2 years. We had gotten a number of grants in our laboratory, Young Investigator grants that had been awarded to a number of our young people.

I was at an American Psychiatric Association meeting in Toronto, and I saw this couple approaching me, and I looked at the name tag and I saw that it was Connie and Steve Lieber. I'd never met them, and I went up to them and introduced myself. I said, "I want to thank you for everything you've done for our laboratory's young people." They immediately said, "Oh, Dr. Freedman. How is your work going on auditory gating? How is Dr. Hunter doing with her developmental studies? Is Dr. Ross still working on childhood-onset schizophrenia? Is Dr. Olincy helping you with the medication development?" They listed in detail each of the grants to our Young Investigators. They wanted to know how each of them was doing, developing in their careers as well as the status of their projects.

The wind was beginning to blow. The convention center was about a mile from the convention hotel. I thought, "This couple is not going to make it back up that hill to the hotel," so I hailed a cab and I put them in the back seat, and we drove up to the hotel. A small detail is that I paid the cab driver, and I've always been glad that in light of all that Steve and Connie have done for me and for all of my people, I was at least able to pay for a cab ride for Steve Lieber.

I wrote Steve and Connie afterward that I was so impressed. The funding meant a lot, but what really meant something to me was how involved personally they were in the meaning of the funding, of what it meant for the people who got it, and what it was designed to do. I had never encountered that in anyone else before. To be that interested in the research itself, not just saying, "Well, I've done something nice for schizophrenia, but I'm not sure what those people do." No, this was quite different. The two of them, each of them, knew exactly what was going on. They were trying to build scientists' careers with the grants. And that, I have always thought, was just amazing.

John H. Krystal, M.D.
Yale University School of Medicine
BBRF Scientific Council;
2019 Colvin Prize; 2006, 2000 BBRF Distinguished Investigator;
1997 Independent Investigator

Steve Lieber is gone. His leadership, and that of Connie, was the backbone of NARSAD and BBRF. Under their stewardship, BBRF became the most important private foundation supporting mental health research. I have seen, first hand, the impact of BBRF Young Investigator Awards upon the careers of countless young scientists. Each one wondering how they would get their start. Each one using the opportunity of a Young Investigator Award to move them forward. Through it all, Steve and Connie remained curious about the science and uniquely supportive of the scientists, asking about our families and our careers. As I write this, I note that I refer to Steve and Connie as if they were still together to the end. I suppose that is how I think of them, as part of a very special partnership. Steve's passing marks the end of an era for BBRF and for psychiatric science. We are all deeply in his debt. I will miss him.

Helen S. Mayberg, M.D.
Icahn School of Medicine at Mount Sinai
BBRF Scientific Council; 2007 Falcone Prize;
2002 BBRF Distinguished Investigator;
1995 Independent Investigator; 1991 Young Investigator

Thinking of my interactions with Steve Lieber over the years, what strikes me is his warmth and seriousness, but also his ability to look at a problem and find the kernel that was really important. There was a deliberateness, a pragmatism accompanied by this deep, earnest sharing, and singular focus on the problem. There was a balance—between caring deeply, but also having radical candor about what's needed to accomplish the goal.

You have to have empathy, you have to want to solve the problem, but you also have to have the discipline, the resolve to solve the problem and to be creative about how to approach a problem that doesn't have an obvious solution. Steve never seemed frustrated by the fact that the problem was hard. It just made him more resolute. He was able to use his position to direct and advise and learn. It was always an iteration. It was always, "Help me to understand this so I can factor it into my own thinking."

He was never overly emotional, never hysterical about the urgency of the problem. His attitude was: "This is a hard problem. It will take resolute decision making and strategic planning to beat it. And I may not live to beat it, but I will give it everything I've got until I just can't do it anymore." And that's very admirable.

What makes a great leader is that circumstances can change and you have to be adaptive. You're trying to get from point A to point B; you set out a course and you have a map—and it turns out the map is wrong, or the map is old, or something's happened and you've got to adapt. Steve was just voracious in wanting to take in more information so that he could follow our progress. I think he definitely enjoyed learning about new things. And I think that he genuinely enjoyed seeing that my trajectory had critical anchor points in early grants I received from the Foundation, which meant that it played a fundamental role, from the very beginning, in my progress. I always felt like he was rooting for me, personally.

My very modest interactions with Steve have, over a lifetime, had a profound impact on me. And this helps me realize how tied we are to people. We influence each other. Over the years,

Dr. Mayberg admired Steve Lieber's "radical candor."

this has an indelible impact on who we are and how we evolve. So he's in here, in me, and I'm reminded that we have to think about this when people are gone—to think about how we may be different because of our interaction.

Thinking of the impact of Steve and Connie, I think it was the wisdom of their effort to enable a community—the community of researchers—to solve the very difficult problem of mental illness. It's the pragmatic realization that there isn't one solution. There's the appreciation that, as in money management, it pays to have a diversified portfolio. Steve and Connie created an environment that has enabled thousands of researchers to attack the problem from many different angles at once.

Steve Lieber speaking at Columbia University.

Herbert Y. Meltzer, M.D.
Northwestern University Feinberg School of Medicine
BBRF Scientific Council; 1992 Lieber Prize; 2007, 2000, 1994, 1988 BBRF Distinguished Investigator

Steve Lieber was enormously creative in his unending efforts, even to the day he died, to eliminate the scourge of mental illness. The Brain & Behavior Research Foundation, the Lieber Prize for Schizophrenia Research, other BBRF awards for accomplishments in psychiatric service and research, and the Lieber Institute are unparalleled legacies of his philanthropy and enlightened leadership.

Steve's devotion to this task was initially stimulated by his desire to help his daughter and led to a call to me in 1990, after the publication of the benefits of clozapine in treatment-resistant schizophrenia. He sought guidance on clozapine's use, and expressed support for my research on that drug and its successors, which he did for many years, culminating in an offer from Herb Pardes to be the first Lieber Professor at Columbia. I declined that offer for personal reasons, but we continued a warm relationship until the time of Steve's death, linked by our shared desire to improve outcome in mental illness.

Many throughout the world sought my advice on clozapine, to assuage their anxieties about its riskiness, but only Steve and his beloved wife Connie embraced the idea that if even more effective treatments than clozapine were to be developed, they would come only through profound knowledge of the working of the brain and the many ways in which it can malfunction. Thus, they joined me and others who founded NARSAD to develop it as a vehicle to attract and train the best minds to the field of neuroscience.

Steve was willing to devote enormous amounts of time and resources to build NARSAD, now BBRF, into the world's leading private resource for training and supporting researchers to devote their careers to the understanding and treatment of the brain and mental illness. On a personal note, I will treasure his graciousness and warmth, his interest in my current research on new treatments, like pimavanserin, the first non-dopamine based antipsychotic drug to be approved by the FDA, which his philanthropy enabled me to develop from clozapine. I deeply regret that I will not be able to share with him the new generation of drugs for schizophrenia I have discovered. They have the Lieber imprint on them as well, for sure.

Eric J. Nestler, M.D., Ph.D.
Icahn School of Medicine at Mount Sinai
BBRF Scientific Council; 2009 Falcone Prize; 2008 Goldman-Rakic Prize; 1996 BBRF Distinguished Investigator

NARSAD—now BBRF—began issuing its now well-established Young Investigator awards in 1987, the same year that I joined the faculty at Yale. I remember very well the dramatic impact that these awards, and NARSAD overall, had on psychiatry research

at the time. Now, over 30 years later, several generations of young researchers in psychiatry have benefited from BBRF's generosity in helping to launch their careers, with Independent and Distinguished Investigator awards programs contributing to sustaining those careers, including my own. Steve Lieber, and his wife Connie Lieber, thereby transformed the landscape of our field. They were tireless advocates for our fellow citizens who suffer from mental illness and for us researchers dedicated to better understanding and treating these disorders. Their kindness and generosity of spirit were boundless. While we miss Steve and Connie terribly, their timeless vision is embodied very well in the dominant role played by BBRF in advancing research into mental illness.

Daniel Weinberger, M.D.
Johns Hopkins University; Lieber Institute for Brain Development
BBRF Scientific Council; 1993 Lieber Prize; 2000, 1990 BBRF Distinguished Investigator

Steve Lieber was an inspirational patron of mental health research and his devotion to matters other than himself was limitless. He was for me, a personal friend, a colleague, and a mentor. The last 12 years of my professional life were closely intertwined with Steve in the shared pursuit of a new solution to an old problem: what are the causes of schizophrenia and how might we better treat it? The project we shared, to establish an innovative, world-class "bricks-and-mortar" institute, moved us in directions that we never imagined. None of what has been accomplished at the Lieber Institute for Brain Development in the past 9 years would have been possible without his exceptional intelligence, his insights, and his commitment. In our weekly telephone conferences, I looked forward to Steve's comments and to his invariably prescient advice. Our calls were rarely about budgets or operational details, though they occasionally included such subjects; they were always about science. Steve and Connie were interested in what was happening that was exciting, from where breakthroughs were coming, and where progress was in new drug development. Steve didn't just listen. He made substantive suggestions and gave feedback. As I have said repeatedly, Steve was a fountain of ideas, and most of them were put into action because they were good and right. I used to say to him that I viewed myself as the luckiest man in the world because I was given the historic opportunity to work with him (and Connie) on building a unique scientific institution and because I had their good faith and support. The faith that Steve and Connie put in me to lead this effort humbled me profoundly. Steve was a singular example of selflessness, commitment, humility, and unparalleled generosity.

I knew Steve and Connie for over 35 years. We shared an interest in how early brain development set the stage for early adult problems. Our personal interactions were numerous, at scientific meetings which they regularly attended until around 2010, at occasional lunches and dinners, at the BBRF gala at which they bestowed upon me the esteemed Lieber Prize, and at BBRF annual events as a member of the Scientific Council.

It's hard for me on Sundays without my reality checks with Steve. I miss informing him of the latest discovery, of the progress we are making in so many areas and of the fact that in less than a decade his institute has developed four new treatments for serious medical illnesses. The day I write this we received a major offer to out-license one of the signature drug products of the Institute, something I talked with Steve about literally every Sunday for the past six years. It is heartbreaking that I cannot share with him this exciting news that would have made him very pleased. I miss him deeply and my thoughts are of him and Connie, of Sam, and of the Lieber Family. I know that Steve would want us to continue on the path he laid out for us and walked with us. My commitment to realize the Lieber Family vision—that research will change the lives of people affected by serious mental disorders—has never been stronger.

Myrna Weissman, Ph.D.
Vagelos College of Physicians and Surgeons, Columbia University
BBRF Scientific Council; 1994 Selo Prize; 2005, 2000, 1991 BBRF Distinguished Investigator

Steve Lieber was an extraordinary man. He was very modest and very talented, very smart. This was the kind of man who, if there was a problem, didn't whine or complain. He said, "How are we going to solve it?" And that's how he handled BBRF, which was called NARSAD in the beginning.

Steve was a very modest man. He didn't look for attention. He and his wife, Connie, did what they did because they really believed in it—and they wanted to do a good job. They weren't looking to have parties where they could wear their best clothes or get their picture in the paper. They stayed in the background because everything was for the cause, and it was a cause they believed in so strongly, arising from their own family tragedy. Usually, when people are funding something, they want to get a lot of recognition for it. It's part

of who they are and how they're seen in the public. This was not Connie and this was not Steve.

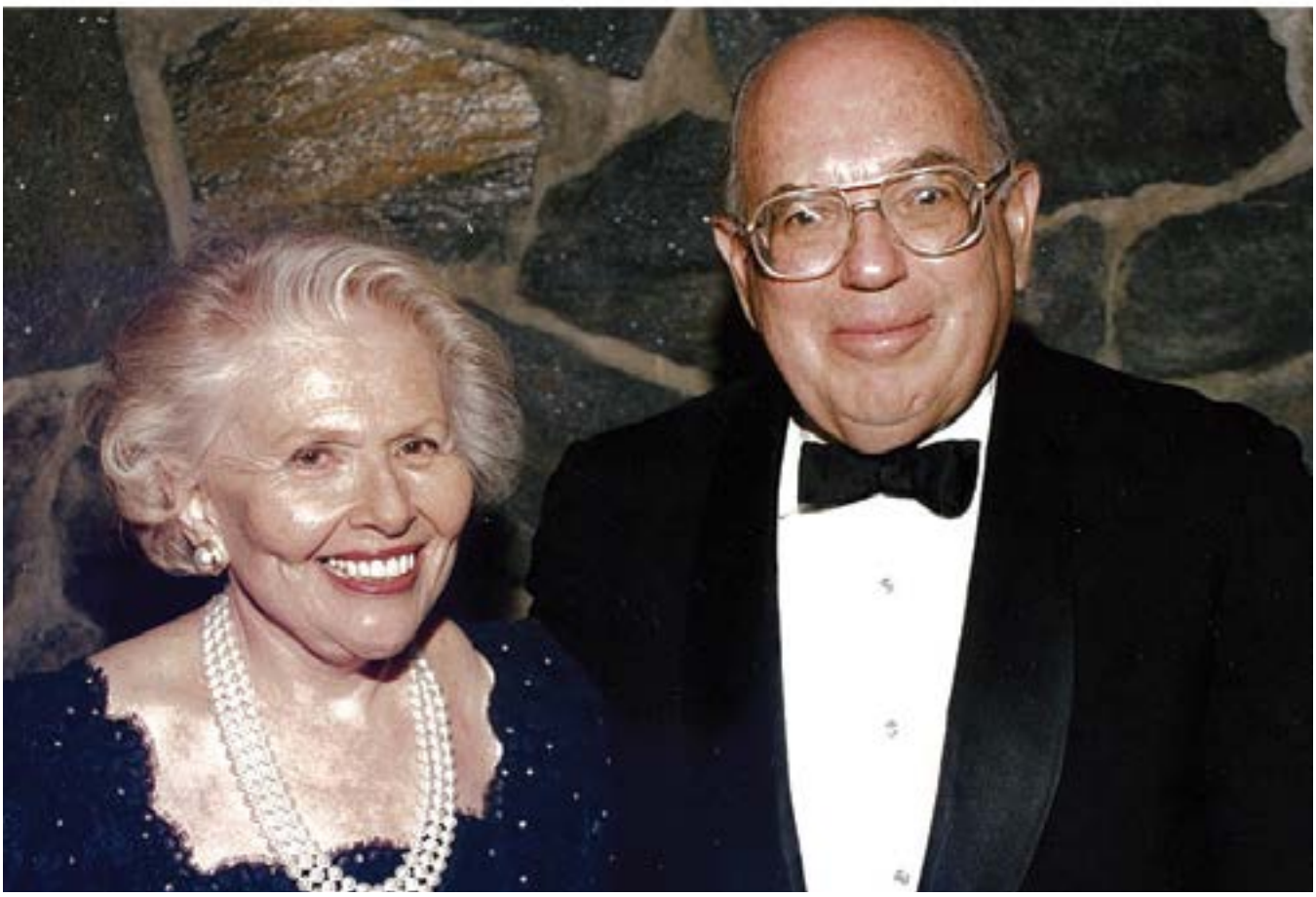
Steve was totally devoted to Connie in a wonderful way. When a couple is involved in a cause, it is typically the man who gets the attention, the credit. It's often assumed that "it was the man's idea." But I was part of many discussions where there would be an idea and Steve would make it quite clear that the idea was Connie's. "That's Connie. Talk to Connie about that." It was because the idea was hers and he didn't want to take it away from her. During the many years when Connie served as president of the organization, he would step aside, knowing he could rely on her because she was smart. She was capable and she was as committed as he was.

Steve listened to people. He didn't just kow-tow to people in power or authority. He listened to people who had something to say. He did not suffer fools. He chose well. He knew who to trust. He chose what he thought was of high quality and he was very supportive. He was looking to have the job done and to get the best people on the team. He didn't care if everybody else got the credit. He knew a lot. He read a lot and that's how he was able to choose talent and let them go with it.

At the start of my career, I received funding from (what was then) NARSAD to get pilot data. Steve and Connie supported innovative research, risky research, and they agreed with the Scientific Council, which made sure that they didn't drive you crazy with 300 pages of grant writing. If you look broadly at the people who've had BBRF grants over the decades, they are extraordinary and they were chosen by a committee who had two or three pages about their dreams and the names of their mentors. Asking for that salient information but not a voluminous file on each applicant was part of what made the organization successful. It was something that Steve and Connie Lieber supported. They understood how to determine quality and let the experts on the Council do their job.

Another thing they did that was very important: they saw to it that all the money the public gave would go for research. The administrative extras and events were funded by them. If they were going to have a benefit or a party or a meeting, the Liebers paid for it. But if you gave $50 to support research, you could be certain that it went to that research.

In losing Connie Lieber some years back, and now Steve, we have suffered a tremendous loss. ❖



Remarkable Results in a Preliminary Clinical Test of a Rapid-Acting Antidepressant Treatment

SAINT, a protocol for non-invasive brain stimulation, spurred remissions over 5 days in the most treatment-resistant patients

Imagine a new treatment for people with major depression who have not responded to existing treatments—one that acts rapidly and helps a much larger fraction of such patients than any current treatment.

The new treatment has the following characteristics. It is optimized for each patient who receives it. It takes a total of 5 days to receive the full treatment dose. Antidepressant effects are felt by most patients between days 2 and 3. By the end of the 5th day, when the treatment course is completed, 90% of patients are in remission—they are no longer clinically depressed. Those who had reported suicidal thoughts prior to treatment no longer report having such thoughts. The treatment appears to have no serious or lasting side effects. One month after being treated, 70% of patients continue to experience an antidepressant "response"—defined as a reduction in initial symptoms of at least 50%.

This is not a fantasy. It's a summary of the results of a small, preliminary clinical test of a protocol called the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) for treatment-resistant depression. SAINT is a new approach to delivering non-invasive brain stimulation—via a magnetic coil placed just above the scalp and focused on a precise spot in the brain. The results, based on an "open-label" clinical trial involving 21 patients with refractory depression, were reported in the *American Journal of Psychiatry* in April.

Leading the research team that developed SAINT is Nolan R. Williams, M.D., Assistant Professor of Psychiatry and Behavioral Sciences at the Stanford University Medical Center. Dr. Williams developed the protocol with the help of his two BBRF Young Investigator grants, received in 2016 and 2018. In 2019, Dr. Williams was the recipient of BBRF's Klerman Prize for Exceptional Clinical Research.

Dr. Williams trained with Mark S. George, M.D., a BBRF Scientific Council member, two-time grantee and 2008 Falcone Prize winner at the Medical University of South Carolina who in the 1990s pioneered the non-invasive brain stimulation method called rTMS (repetitive transcranial magnetic stimulation). In 2008, rTMS was approved by the FDA for treatment-resistant depression, and is now used more broadly in depression, as well as in obsessive-compulsive disorder.

The SAINT protocol developed by Dr. Williams and Stanford colleagues, including Alan Schatzberg, M.D., a senior team member who is also a member of the BBRF Scientific Council, is a refinement of a variant form of rTMS called intermittent theta-burst stimulation, or iTBS. iTBS has been validated in a number of clinical trials, including one led by 2010 BBRF Young Investigator Daniel M. Blumberger, M.D., of the University of Toronto. In iTBS, the patient receives the same "dose" of brain stimulation as in FDA-approved rTMS, but receives it in much shorter treatment sessions, lasting 3 minutes per session as compared with 37 minutes in conventional rTMS. iTBS is now FDA-approved for treating patients with refractory major depression.

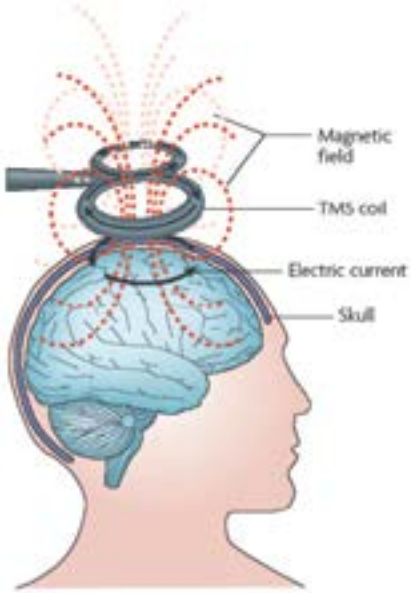
THREE IMPORTANT 'TWEAKS'

Dr. Williams set out to improve upon iTBS—which has been shown to be just as effective as rTMS, enabling about one-third of patients with treatment-resistant depression to achieve remission. Dr. Williams wanted to test the hypothesis that iTBS could be much more effective if three "tweaks" were made.

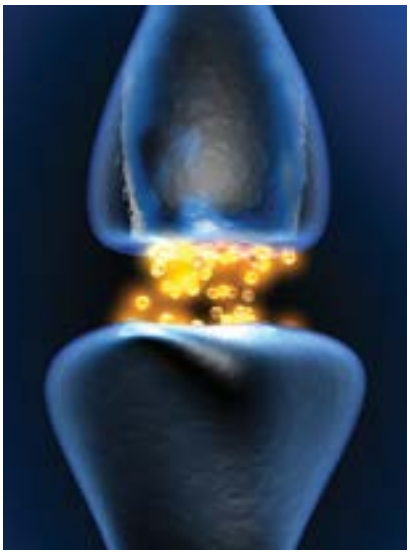
These tweaks are actually major changes in the protocol, involving giving a refractory patient five times as much total stimulation over a 5-day period than iTBS or rTMS delivers over the FDA-approved treatment course of 6 weeks. Dr. Williams also wanted to see if he could optimize the targeting of the iTBS stimulation in SAINT in each patient, individually, to boost its effectiveness.

Nolan R. Williams, M.D.

While increasing the stimulation dose five-fold and decreasing the treatment course from a month and half to only 5 days may seem radical, there were both practical and scientific reasons for developing SAINT and receiving institutional approval to test it on patients. The first reason has to do with the intended beneficiaries: Dr. Williams, as a neurologist and psychiatrist, is deeply concerned with the dire situation faced by the "most-difficult-to-treat patients," he says. These are individuals whose major depression not only renders them non-functional, unable to hold jobs



In non-invasive brain stimulation, pulses generated by a magnetic coil pass through the skull and into cells of the brain beneath, changing their activity. Depending on the target and frequency of the pulses, activity can be increased or decreased. In rTMS, iTBS and SAINT, the immediate target is the brain's dorsolateral prefrontal cortex.



Changes in neural connectivity induced by SAINT may contribute to the strengthening of synapses, the tiny gaps across which brain cells communicate. This in turn may help reduce depression symptoms.

or conduct conventional lives when in the throes of a depressive episode, but who also have a significantly elevated risk of suicide.

Their condition, therefore, is life-threatening in many cases, he notes. Dr. Williams refers to people who have tried and not been helped by multiple courses of conventional antidepressant medicines of various types, but who also have not been helped by rTMS or conventional iTBS, and who in some cases have even not been helped by electroconvulsive therapy (ECT), a procedure performed under anesthesia that involves inducing a brief seizure and which is sometimes accompanied by short-term memory loss. An alternative for such patients is ketamine, a powerful anesthetic delivered at very low dose that doesn't induce anesthesia. It has proven very effective in many instances and acts within hours, although a single treatment works only for about a week. An FDA-approved derivative of ketamine called esketamine is now available, but like ketamine, its therapeutic impact is short-term following discontinuation. More research is being conducted to further enhance its effectiveness.

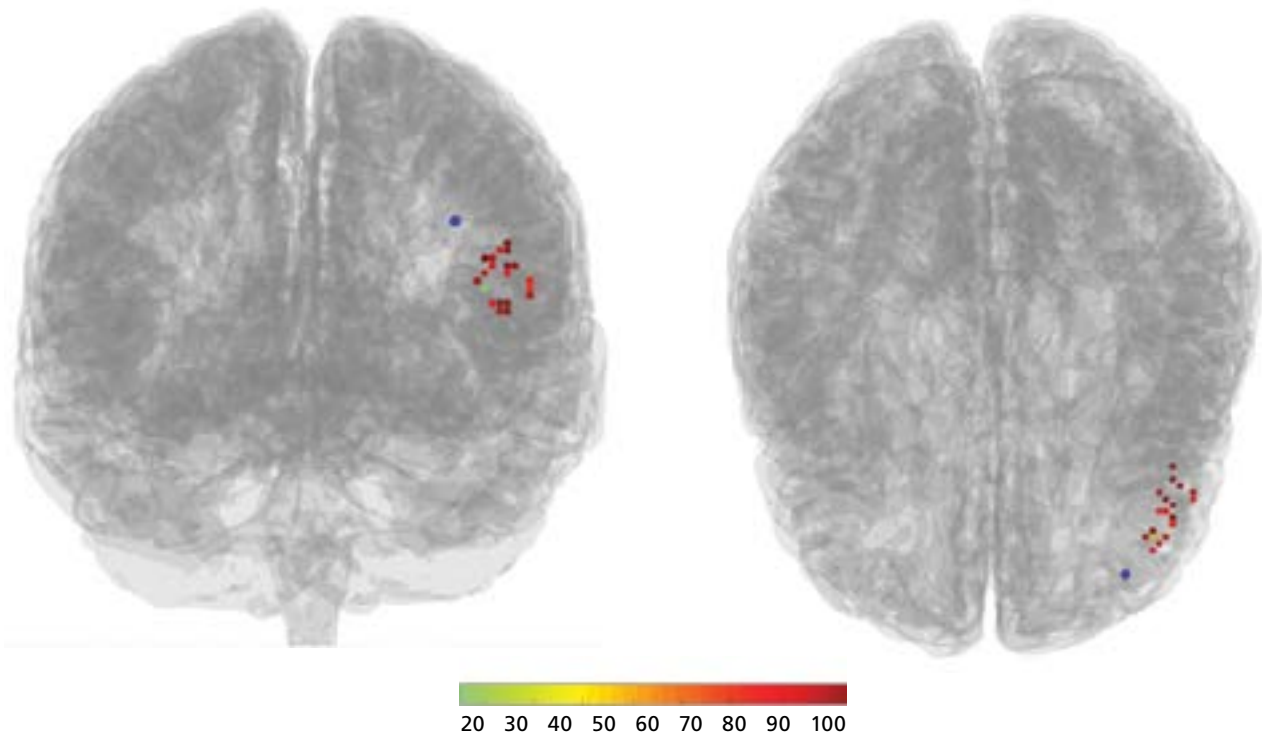
The still unaddressed needs of such patients were therefore an important motivation for SAINT's development. But there were specific scientific reasons to pursue it as well. Dr. Williams and colleagues built upon a decade of research studies that have provided a sense of why conventional rTMS and iTBS appear to help many patients feel better.

In summarizing his take-away from this body of research, Dr. Williams explains the aim of SAINT treatments in terms of three targets in the brain, which for convenience he calls A, B and C. He wants to focus stimulation on A to cause an effect upon B, which in turn induces a change in C.

"A" is an area of the cerebral cortex positioned in the skull just above the left eye. It's called the dorsolateral prefrontal cortex, or DLPFC, and it has been the target of rTMS treatments since the pioneering days of Dr. George. Dr. Williams says he wanted SAINT to target a specific portion of the DLPFC—one defined by its function. He wanted his iTBS pulses to focus on that spot in the DLPFC which induces the maximum possible effect upon a second spot. This spot, which he calls "B" for convenience, is the subgenual anterior cingulate cortex, or sgACC. Why is "B" important? Because the change in "B" caused by focusing iTBS pulses upon "A" causes an impact upon a *third* entity in the brain, "C"—the Default Mode Network (DMN).

The DMN is not a spot in the brain but rather a circuit that links a number of brain areas. The aim, says Dr. Williams, is to impact the connection between the sgACC and the default mode network. In depression, researchers have discovered that the sgACC is "hyperconnected" to the DMN. By sending pulses into the DLPFC, one can indirectly diminish this hyperactivity—which is thought to be at least one cause of what doctors call "dysphoria" in depression, the symptoms of depressed mood, a state of unease or dissatisfaction.

Dr. Williams explains that one can seek to direct rTMS or iTBS pulses either at



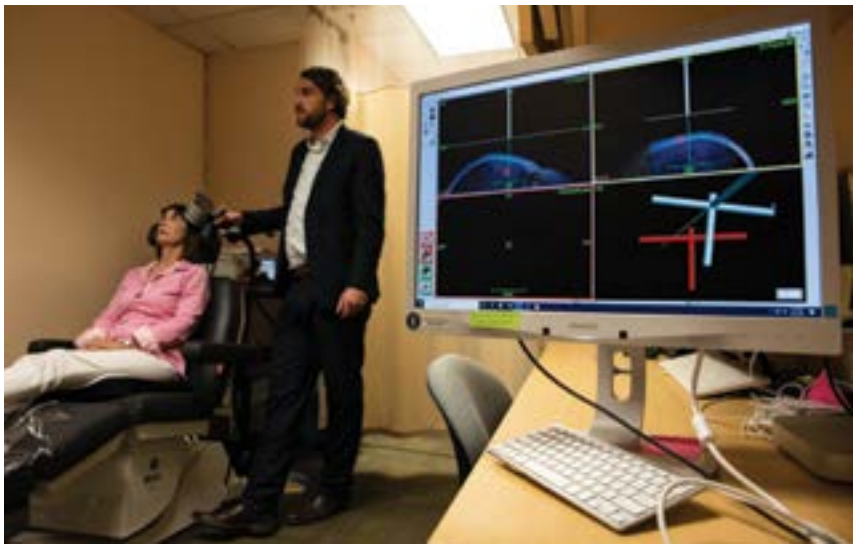
Treatments in the SAINT protocol are individualized. Brain scans made prior to treatment enabled the team to find the optimal spot in the brain of each patient for targeting of non-invasive magnetic stimulation pulses. Here, two views of the brain showing the typical spot targeted in non-SAINT treatments (blue dot) compared with the locations of the focal points actually used, based on the imaging scans. The average distiance from the "standard" site was 25 millimeters. The colors of the dots correspond with the amount of response each patient had to 5 days of treatment; all but two achieved remission.

a spot on the skull, or a spot in the brain beneath. There is a subtle distinction. One wants to hit the precise spot in the DLPFC that has the greatest functional effect on the sgACC, but one must allow that each person is slightly different. The question then becomes: how does one hit this spot in the brain precisely when its position, relative to the outer skull, varies a bit from person to person?

For this reason, SAINT begins with each patient getting an MRI brain scan. Specifically, a functional scan of the brain in its resting state, when the individual is not focused on any particular mental task. This enabled Dr. Williams' team to increase the specificity of the iTBS pulses "to the person's actual functional anatomy"—the spot in that person's DLPFC that would induce the maximum effect on the sgACC that would in turn impact the functional connection between the sgACC and the DMN (reducing hyperconnectivity). It is thought that these changes in connectivity contribute to the strengthening of synapses, the connections between neurons, which may correlate with diminishing depression symptoms.

As for the other key innovations in SAINT: it was Dr. Williams' hypothesis that the patients most resistant to treatment would do better if the intervals between iTBS session were radically decreased and the total number of sessions were substantially increased. This is accomplished by reducing the interval between sessions, termed the "intersession interval," from 24 hours to 50 minutes. Ten sessions are given per day. This timing is based on research that has given rise to what is called "spaced learning theory." The reduction in the intervals between iTBS sessions allows for a substantial increase in total dose per day, Dr. Williams explains, and in the reduction of the number of days of stimulation to just 5 days. In short, the idea behind SAINT is that patients who weren't being helped by conventional rTMS or iTBS were not receiving enough stimulation quick enough in the FDA-approved protocols to reduce their depression.

Drs. Williams, Schatzberg and others had already gotten a preliminary reading that this approach might work: in another open-label study published in *Brain* in 2018, they showed that 5 of 6 highly refractory patients receiving 10 conventional iTBS treatments per day, each separated by 50 minutes, over a 5-day period, achieved remission.



Dr. Williams is shown (top) adjusting the precise focus of magnetic stimulation pulses to be used in treatments, guided by results of this patient's functional brain imaging scan made prior to the beginning of treatments. Lower image shows that the iTBS coil is placed just above the scalp on the left side above the eye, an area corresponding with the dorsolateral prefrontal cortex, which lies beneath.

This was the basis for the test in 21 patients just reported, which generated results that were quite similar, with 19 of the 21 (90.4%) achieving remission by the end of the 5th day.

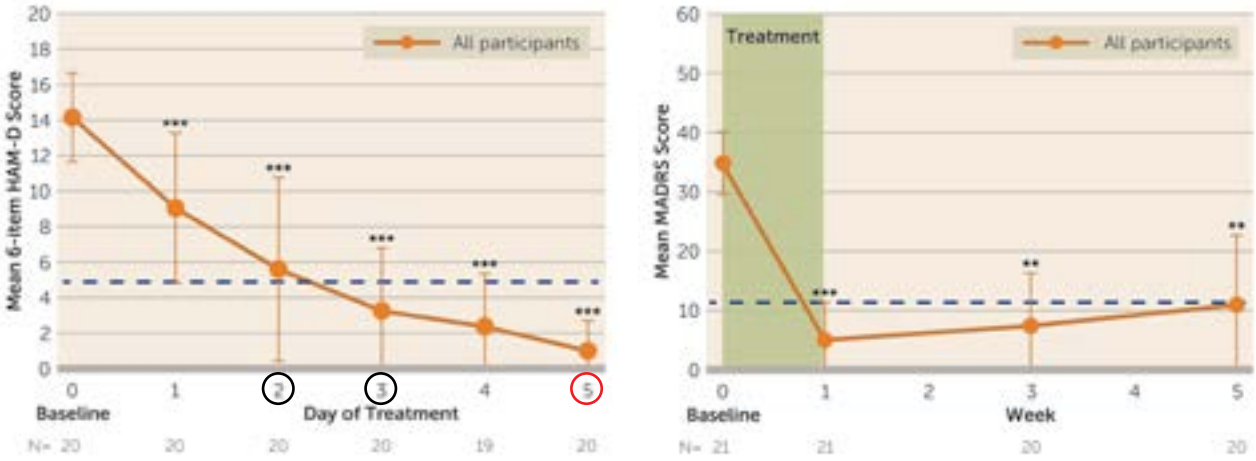
WHY CAUTION IS ADVISED

While highly gratified by the newly reported results, including the remarkable 90% remission rate, Dr. Williams urges that they be viewed as preliminary. The same SAINT protocol, he stresses, must be tested in larger patient populations and in trials that involve two things that the preliminary trials did not: patient randomization and placebo-control.

Each of the 21 patients who took part in the just-reported trial knew that they were going to receive the experimental treatment protocol, as did the doctors who administered the treatments. Thus, there was no blinded control group against which to compare the results of an "active treatment" group. This is the gold standard for such trials, since knowledge that one is receiving an experimental treatment tends to spur what researchers call the placebo effect: a natural desire of patients (and sometimes doctors, too) to believe the treatment is working.

Even so, a 90% remission rate over just 5 days in a clinical test of an antidepressant treatment in a group of patients who have "failed" one or multiple prior antidepressant courses is extraordinary—and hence, the great hope that the preliminary SAINT results hold up when put to the gold-standard test.

Safety is an important factor. Conventional rTMS and iTBS have very strong safety profiles; neither is associated with anything more than temporary headaches or a tingling sensation while the treatments are being administered. This has proven the case so far in patients who have received SAINT treatments. As an extra measure of caution, the team gave some participants in the SAINT trails a full battery of cognitive tests before and after receiving treatment. "In addition to not seeing any cognitive deficits from treatments, we actually saw improvements in certain cognitive domains," Dr. Williams says.



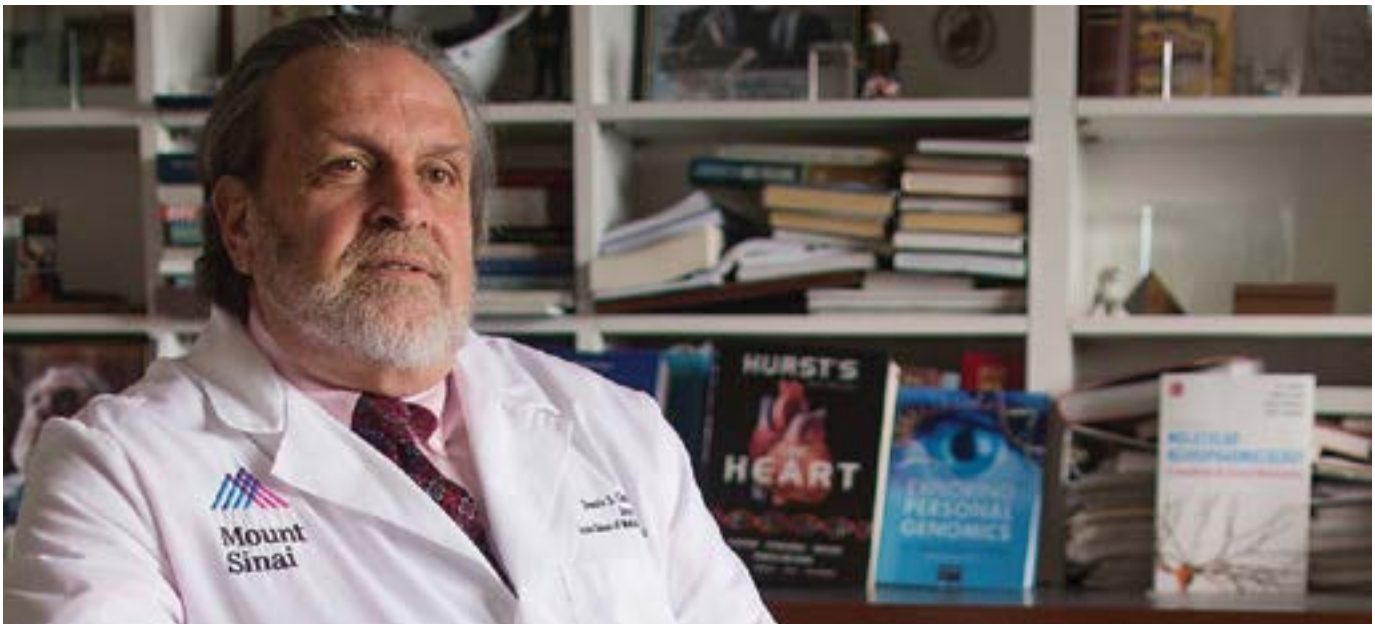
These graphs display the effectiveness of the SAINT protocol in 21 patients. LEFT graph: At the far left, prior to treatment, the 21 participants are shown to have had depression symptoms ranging between 12 and 17 on a scale (vertical axis) for measuring depression symptoms. Between days 2 and 3 of treatments (black circles, horizontal axis) most patients dropped below the threshold (dotted line) measuring "response to treatment" (symptom reduction of 50% or greater). By the end of the 5th day (red circle), symptoms were neglibile in nearly all patients—they had achieved remission. RIGHT graph: Patients' response to the 5 days of treatment were found to hold up well over time. A month after the completion of treatments (week 5), most patients continued to register a clinical "response," i.e., symptom reduction of over 50% (a level marked by the dotted line).

The observed durability of the antidepressant effect in the preliminary SAINT trials is also encouraging to Dr. Williams. While not all refractory depression patients have access to ketamine or eskemtaine, those who are helped by these agents usually don't hold their remissions for more than a few weeks, which means they need repeated doses.

The 70% continued repose rate at one month post-treatment in the preliminary SAINT trial will be significant if replicated in subsequent studies.

The impact would be especially felt, Dr. Williams says, in inpatient situations. "ECT is available in only about 10% of U.S. psychiatric hospitals, and ketamine availability on inpatient units is spotty," he says. For patients at suicide risk, he adds, conventional rTMS is impractical because it takes too long to deliver; the average length of stay in hospital for such patients is only about 12 days for those who don't get ECT, he points out. "We've got something that works in 5 days. We've tested it on inpatients, and we're preparing a paper on how SAINT works in these acutely suicidal patients."

If results are positive, it is possible, Dr. Williams says, that SAINT could "rapidly transform the landscape of inpatient psychiatry for suicidal depression." Beyond that application, there will likely be others, for less acute depression cases and for other indications. There is a place in the brain to focus iTBS pulses to address anxiety, for example, and that might be one subject of future clinical trials. ❖ **PETER TARR**



RESILIENCE

A World Expert Discusses What Research and Personal Experience Have Taught Him

Dennis S. Charney, M.D.

Dean, *Icahn School of Medicine at Mount Sinai*
President for Academic Affairs, *Mount Sinai Health System*
Professor of Psychiatry, Neuroscience and Pharmacological Sciences, *Mount Sinai School of Medicine*

BBRF Scientific Council Member Emeritus
2019 BBRF Colvin Prizewinner for Outstanding Achievement in Mood Disorders Research

We all face adversity at different times in our life, and some of us, unfortunately, may experience serious trauma. How do we develop resilience in order to better deal with these situations? Recently, I had the opportunity to discuss this important subject with Dr. Dennis Charney. Dr. Charney is a world expert in the neurobiology and treatment of mood and anxiety disorders, making fundamental contributions to the understanding of the causes of human anxiety, fear, depression, and resilience, and the discovery of new treatments for mood and anxiety disorders. This Q&A is adapted from episode 12 of the 6th season of my "Healthy Minds" series on PBS, which is available online.
– **Jeffrey Borenstein, M.D.**

Dr. Charney, what is resilience?

There are a couple of definitions of resilience. One is if you've been traumatized in some way and you develop post-traumatic stress disorder (PTSD), or depression, or other problems, but you recover—that's resilience. Another definition is that you've been traumatized or experienced a lot of stress in your life but you don't develop issues related to depression, or post-traumatic stress disorder, or things like that. Those are two definitions that are used commonly.

You've studied resilience. Tell us about the research you've done and what you found out about it.

This has been a team effort. My close colleague, Dr. Steve Southwick, has been working with me for 30 years in studying resilience. We started out studying the causes of depression and PTSD to understand those conditions and develop new treatments. We felt that if we could understand resilience—why some people are able to rise above difficulties in their life—that it might help us understand the conditions that I just mentioned and develop the new treatments. We decided to study resilient people, and along the way, we got to meet incredible people that we admired, who had changed their own lives.

What's the secret sauce? What did you find out about these people who are so resilient?

Let me give you some examples of the people we studied. POWs from Vietnam, Navy Seals, members of the Special Operations team in the U.S. Army, victims of natural disasters like earthquake in Pakistan, individuals that had to face poverty, or physical and sexual abuse, even people who were born with congenital physical abnormalities and rose above them. We started with a blank slate. We wanted to learn from those people. How did they do it? How do they experience growth based on their trauma? And common factors ultimately came to light in our research.

Tell us about some of those factors that you discovered.

Ultimately, we came up with roughly 10 factors, and we concluded one major thing, and that is: while everybody is born with a certain level of resilience, you can make yourself more resilient. Genes are not destiny. You can, essentially, train to become a more resilient person.

There are steps people can take to become more resilient in the face of adversity.

Absolutely. Here are some of the factors. One is optimism, positive attitude. Now, that might seem obvious. Some people seem to be born with the glass half-full, but others are not. You can work at helping people be more optimistic, and it's not what you might call "Pollyanna" optimism. That is optimism that is not justified. You need to develop other skills to be optimistic in the face of serious stress or trauma in your life. But, ultimately, having the ability to be optimistic and know that you could overcome what you're facing is critical.

So, being realistic about the circumstances—not Pollyanna, but realistic; but also being able to be optimistic given whatever the circumstances are.

And the skills that you have developed to be able to handle those obstacles in your life. A good term is what you just said, *realistic optimism*. And in fact, among the most courageous of the POWs was Jim Stockdale. He ultimately won the Medal of Honor based on heroism as a POW. A term has been coined called the Stockdale Paradox related to optimism. And that means, on the one hand, you do have to face the brutal facts that you're dealing with. On the other hand, you have to feel that you will prevail.

American soldiers being taken prisoner in North Vietnam. Dr. Charney learned from POWs the importance of being realistically optimistic and seeking support.

That is the kind of optimism that really characterized resilience.

Another element that is really important is role models, to learn from people who've gone through what you're going through. You can find role models in your personal life. They can be a parent or a sibling. It might be somebody who's gone through the same thing who you've become friendly with. They provide you a roadmap on how to overcome what you're facing. Role models are extremely important, and in many respects, that's where things start in becoming resilient.

So, having someone that you can look to—the path that they took in response to their adversity.

Yes.

And it inspires you that, well, maybe I could do that too.

Very important. We found that over and over again. A couple of other things. Having a moral compass, a set of beliefs that very few things can shatter. For some people, that's religion in the traditional sense, having a strong faith, going to church or synagogue, getting support from that faith, but also the people you meet along the way. But in other people, it wasn't traditional faith but it was a set of beliefs about who you are, what you stand for, and that you get the feeling that "I might be traumatized, but that doesn't change who I am as a person. I'm still that same person." That's very important: moral compass.

Another very important factor is a support system—people who really care about you who are there during the toughest times, to provide light at the end of the tunnel. You can't go through it alone. You need a safety net. I'll give you one example from the POWs. We interviewed maybe 40 or so of the POWs from Vietnam who were held in prison in Hanoi for 5, 6, 7, even 8 years, and many of them were in solitary confinement. That was the most stressful part of being a POW. They developed a "tap" code in which they could communicate to each other through the wall about what was happening to them. And the way the tap code worked is: there were five rows of five letters. If you tapped once, that was row one, A, B, C, D, E. And then, if you tap three times after that, that'd be the third letter in that row.

They used a tap code because they weren't even allowed to talk. They tapped through the wall, and many times communicated very intimate things about what they were feeling, about their lives, about their families. And they told us over and over again that without that tap code, they wouldn't have survived. The analogy for all of us is everybody needs a tap code and everybody needs that support.

Tell us some of the other key steps towards resilience.

Another step is to reappraise what happened to you, and put it in the context of your life so you can derive meaning from it. For example, if, unfortunately, you're the victim of a rape. That's not about you. That's not who you are, but it happened to you. You don't want it to change your life going forward. You want to be able to have relationships and have a joyful life. You've got to put that rape into context. You don't want it to change your life, but it did happen. You can't undo it. It happened to you. You want to become stronger from that experience. You reappraise it in the context of your life and say, "I'm going to move forward from that. I'm going to find role models who have gone through the same thing that I did. I'm going to have my own moral compass so it's not going to change who I feel I am as a person. I'm going to get my support system to help me move forward." That's another important element of becoming a resilient person.

So, really, it's taking a perspective on the situation, being realistic as to what happened, but also a perspective of the broader picture of one's life.

Yes. And you also have to face your fears. There are things that may have happened to you that made you very fearful. You

have to actively face your fears, actively cope. For example, when we got to know the Navy Seals, we thought, "Oh, the Navy Seals, they don't experience fear. They're fearless." But, when we got to know them, they said, "Oh yeah, we experience fear. In fact, fear is a guide. Fear can help you overcome failure." So, you have to face your fears, but you do it in a way that's step-by-step. As an example of what the Navy Seals do, sometimes they have to go into a foreign country, jump out of an airplane at 20,000 feet in the middle of the night. That's not easy. You don't do that as step one. You train to get to the point that you can jump out of an airplane in the middle of the night. You're gradually facing your fears until you feel optimistic and competent that you'll be able to move forward.

In addition to the research that you've done on resilience, you yourself have had to face an adversity, and test your own, and further develop your own resilience. I'd like you to tell us about that.

As our team had been studying resilience for decades, I was always wondering whether I was a resilient person. I'm Vietnam-era, but I did not go to Vietnam. I was in college, so I got a deferment, then I went to medical school and I got a deferment, and by the time I got out of medical school, the war was over.

While I faced certain obstacles in my life, I'd never been challenged like the people who I was learning from, in developing a prescription to become a more resilient person. That is, until August 29, 2016. I was coming out of a local delicatessen in Westchester, New York, and I was the victim of a violent crime. From about 20 or 30 feet, I was hit with a shotgun blast in my right shoulder and chest area. The individual who shot me was a disgruntled former Mount Sinai faculty member who we had determined had been the culprit of scientific misconduct. As a result of that, I decided, as the Dean, to terminate him. After that, 6 years later, he ultimately tracked me down in Westchester where I live, coming out of a local deli. I was hit seriously with this shotgun blast, was taken to an ICU (intensive care unit)—in fact at Mount Sinai, and stayed in the ICU as part of my recovery.

"While everybody is born with a certain level of resilience, you can train to become a more resilient person."

Luckily, the pellets—and I still have the 15 pellets in my shoulder area—did not hit a vital organ or vessel, or else I would have been killed. But there was a recovery

process, and my recovery was public because it was in the newspaper. Lots of articles, I'm the Dean, I'm recovering at Mount Sinai…The press picked it up.

During my recovery I was with so many people who I knew and had close relationships with. One of the first reactions I had in my mind was, "Okay, I'm going to find out if I'm resilient because I've got to face this recovery." I also thought, "Well, all the things that I learned, let's see if they're actually true."

"I'm a fan of Bruce Springsteen and there's a song he wrote called 'Tougher Than the Rest.' The lyrics don't quite get what I was going through, but I'm in the ICU and I kept saying to myself, 'I'm going to be tougher than the rest in how I recover.' And believe it or not, just repeating that to myself was very helpful."

I experienced that recovery process. One thing I should mention is that once it happened you find out the truth of that quote, "ordinary people can be really heroic." One story that always gets to me is: I get in an ambulance, I'm taken to the local hospital first and a police officer who was off duty comes to my room in the hospital, sits outside the room. And my son, who was also a doctor, when I'm ultimately being transferred to Mount Sinai, sees the police officer standing outside my room, and he said, "Well, thank you. Who are you?" It turns out it's Police Officer Davenport who was off duty. He said to my son, "I just wish I was there to take the bullet." I didn't know Police Officer Davenport. I do now. He's just a heroic police officer who wanted to do his job.

Then you had to face the recovery process.

Yes. And, ultimately, I did find that a lot of the factors that we are discussing played a major role in my own recovery.

Were you able to step back and say, "Am I having the right perspective on this? Am I being optimistic but realistic?" What did you do with regard to all of these different steps towards resilience?

I do tend to be an optimistic person and so I was optimistic that I would recover. I did feel I had the wherewithal or the psychological toolbox to recover, but I did use certain tools in helping me recover.

One will sound a little bit odd. I'm a fan of Bruce Springsteen and there's a song he wrote called "Tougher Than the Rest." The lyrics don't quite get what I was going through, but I'm in the ICU and I kept saying to myself, "I'm going to be tougher than the rest in how I recover." And believe it or not, just repeating that to myself was very helpful.

I had enormous support. I'm very close to my family, five children, been married for 50 years and had very close friends, so that really helped. The environment at Mount Sinai was extremely supportive. Ultimately, the students, as I recovered, formed an award called the Dean Charney Award for Resilience, which I tell the students is the best award I've ever gotten, and now they give it out every year.

For me, setting goals was extremely important. For example, when I was in the ICU, in about two weeks the White Coat Ceremony was scheduled. That's a ceremony for the incoming medical students, to welcome them to medical school and they get a white coat. Their parents come, it's a very emotional event.

It's sort of the start of becoming a doctor.

It's starting become a doctor, and I always give a speech. I said to my doctors, "You better get me in shape so I can give that White Coat Ceremony speech." Two and a half weeks after I was shot, I gave that speech. And then I set other goals for myself along the way. The bottom line is I did validate, personally, a lot of the factors that I think help you become more resilient.

Thank you for sharing that. And it certainly shows that, for you, it worked and, obviously, for many, many other people it works as well. If somebody's reading right now and they've had a traumatic event, what do you say to them?

I say you can recover. Have confidence. Utilize some of the things that we're talking about. I will also say to them, believe it or not, you can come out of this stronger. I have done that with other individuals who have been traumatized. In fact, a number of years ago there was a shooting in one of the other hospitals in New York City, at Bronx-Lebanon. A disgruntled employee went in and shot a lot of people. A number of those who were shot were transferred to Mount Sinai, including some young doctors. One of those doctors was having issues around recovery, particularly from a psychological point of view. So, they asked me would I go and see him. I told him, "I know what you're going through. I may be the Dean, but I'm your brother."

What do you see down the road? Where do you think it's going to go in terms of further understanding about building resilience?

One area that I'm particularly committed to relates to children. Frankly, and your audience may be surprised at this, it's not a good idea to raise your children in a stress-free environment—because they won't be prepared. I have permission to talk about my own kids, in this regard.

Kids can learn resilience by being taken outside their comfort zone, Dr. Charney says.

I have five children. Now they're adults, and when I started studying resilience, they were younger, they were teenagers, and they noticed that I was a little tougher on them. Now, I didn't traumatize them, but I would work to put them a little bit out of their comfort zone so that they would develop skills on how to handle stress.

We would take trips to different parts of the country, national parks, go on hikes, and so forth, trips that I would say were semi-dangerous. There was one instance in the family where one of my daughters was around 13, and we were on a mountain. Bad weather came in, there was some wildlife around that was a little scary. In front of all my other kids, she said from her heart and soul that she despised me. Okay. But over time, she became a very confident woman. Now, what does she do now, as a mother, and a professional? She goes to Yellowstone National Park—in winter.

You can help your children become more confident and able to handle stress that, inevitably, everybody faces in their life. I think it has implications. Resilience research has implications for how you raise your children.

A message to any parent reading is: you certainly don't want your child to, God forbid, be traumatized, but a little bit of stress, and giving them some guidance to deal with it, is a healthy thing because, ultimately, we all face stress at some point.

We all face it. Maybe stress is not the right word, but to put them in situations that are challenging, that are out of their comfort zone, so that they ultimately gain skills that are going to help them later in life. I think that's a very important area we can do more research on, and make part of teaching people how to be good parents. ❖

Parenting Young Children in a Time of Pandemic

Q&A with Rachel Klein, Ph.D.

Fascitelli Family Professor Emerita of Child and Adolescent Psychiatry,
Department of Child and Adolescent Psychiatry
NYU Grossman School of Medicine

BBRF Scientific Council Member
2004 BBRF Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research
1995 BBRF Distinguished Investigator

Dr. Klein, there is uncertainty about the degree to which society will return to "normal" in the coming months. With this in mind, we note that the lockdown brought on by the spread of COVID-19 has caused psychological stresses that have been felt by both parents and children. What advice do you have for parents who are working from home while also managing kids who are learning remotely or can no longer go to daycare? This problem is all the more urgent, I would think, when the living space is limited, as it is, for instance, in urban apartments.

It's reasonable for parents to be wondering how they can maintain their professional lives or work activities while the children are with them, at home. There is also the question of how to deal with particular problems associated with living together as a family under lockdown conditions.

I would say, first, that it depends on what else is going on in the home. Who else is there? And what are the living circumstances? If it's a small apartment with limited space, it is very different than if you live in a house where there's a back yard and other people around, with access to outdoor space.

Let's assume the children and their parents are together, they can't be separated, and that the children are young, in daycare or elementary school but not currently attending because of the coronavirus.

I think it is very important for parents in this situation to communicate with children and to do so early, in very simple terms. Why are we doing this? Why are we home? Why does mom or dad have to work? These things have to be articulated very clearly to the child, and not all at once. Of course, how and whether one does this depends on the children's ages. In general, young children do not

It may help to communicate directly and honestly with a young child, encouraging them to propose how they can help the family.

require special considerations. Typically, they are happy as long as they are with their family.

Messages have to be repeated. How often to repeat also depends upon the child and how well he or she absorbs and identifies with the information. But it has to be understood well by the child "why we are doing this." Otherwise, it's confusing, and resentment develops on both sides.

As part of this process, parents should also ask questions of the child. "If this is what we need to do, how do you think we can get there?" "We are trying to be safe. How do you suggest we do that?" It's important to let the child think and talk, not just lecture them. Often parents forget that. At the same time, parents tread a fine line because we do not want to alarm the child. Therefore, there should not be an emphasis on "being safe."

Would it be a good idea to assign chores or tasks to children to occupy them and give them a sense of purpose?

Yes, but again, it's how you do it. Unfortunately, some parents give arbitrary commands and often don't communicate enough with their kids. I'm not saying you have to explain everything, but you want to foster a spirit of collaboration rather than just say, "You have to do this." It's very tempting to behave that way, but if you want to be effective, it's better to say "We need to do this…" and ask the child for their suggestions. Since this is a prolonged situation and not a one-off thing, it's especially important to develop a dialogue with your child.

What would that dialogue sound like?

"We're all going to be together in this house for a long time. We don't know for how long, and we have to do A,B,C,D. How do you think we should manage it among us?" "We have Dad, we have you, we have your brother, your sister. What do you think each of us should try to do?"

Of course, as I noted above, this conversation depends on the age of the child. If the child cannot come up with an answer, you should make suggestions; the child is more likely to respond to suggestions. But you want to give the child the *illusion of control*. It empowers children to make them think that they contributed to the solution. And this can happen at almost any age. I'm not just talking about chores necessarily, but about simple household issues. It is obvious that children cannot be in control, but this doesn't mean that there aren't different means of giving

commands. It can facilitate compliance and limit conflict if parents are able to instill a sense of participation in the child, by giving him/her the illusion of control.

So what you are saying is that there is a sense of involvement; the child feels as if he or she has some say in deciding how to proceed.

Exactly, yes. They participated, they contributed to what happened. They're not just being told what to do.

"It's a little ironic. Children who are anxious are typically anxious about unreasonable events like monsters under the bed and rarely worry about something that an adult might think one should worry about, for instance, living though a pandemic."

What happens if the child comes back with: "I'm bored, I'm bored," and they're testing your patience because they have run out of things to do.

You have to find things that the child may enjoy. Each child is different, but we are very fortunate in this generation to have iPads and almost endless video entertainment. You can have some leeway in allowing entertainment that you might not under other circumstances. You have to be creative and find things that the kid likes and allow them to do it even if it's not exactly what you would prefer. You have to be flexible.

You're saying that this might not be the best time to obsess about screen time.

Exactly. This also brings to mind something else that is important: plan exercise with the kids. You are promoting a state of better health by stressing regular exercise. This can be done very easily at home and parents should schedule time for it. It won't just happen if you wait for everyone to feel the inspiration to be physically active.

Let's say the kids who live in private homes want to have their friends come by the house—to wave and talk at a distance in the front yard, say. But the parent worries: "Now I have to monitor them, how close they are, and can't do anything until the visit ends." It's not so easy for a small child to understand why they have to stay distant from people.

I don't think it's realistic to expect a young child to understand distancing and to practice it. But by now COVID has been around for a while. And, if you know that a child has been confined for weeks, I don't see anything that suggests the kids should not get together, provided that they come from one home directly to the other. That is, if you can reasonably make the assumption at that time that no one in your household or that of the visitors is infected.

On the subject of friends, how would you judge the importance of the child not being able to interact with friends? How much of a hardship is this likely to be?

Small children are much more parent-oriented than, say, teenagers. As long as within the family they feel safe, they may miss their friends but it doesn't have the same salience for them. The family is much more critical to them. Very young children are happy as long as they are with the family. In elementary school their friends become much more important but they're not the most important, if the family is a reasonably happy one. Typically, young kids won't get dismally miserable unless the parental relationship is really problematic and they're suffering.

Let's talk about anxiety for a bit. With the coronavirus you have something that is objectively terrifying. Wouldn't it be normal for children to feel and express fear? What does the parent do when this happens?

It's a little ironic. Children who are anxious are typically anxious about unreasonable events like monsters under the bed and rarely worry about something that an adult might think one should worry about, for instance, living though a pandemic.

The pandemic is something "rational" and it's a little bit beyond them intellectually, especially young children. Is this what you are saying?

Yes, and if the family expresses fear and it's palpable in the home, the child is very likely to pick that up. But on their own, young children do not get very anxious about realistic dangers.

For parents who are caretakers—let's say a woman who works in a nursing home or a hospital—I could easily imagine such a person coming home from work and obsessing about it with her husband. In other words, there might be quite a bit of this kind of discussion in certain households, given the jobs parents do.

At the same time many people try to escape and may avoid talking about it completely. However, if you're the kind of person who relives the work day or goes over it in detail, worries included, when you come home, then you may indeed be communicating to your children—whether you mean to do so or not—that you're in this bind and you are very worried about it. This is not a good situation.

What would you say to a parent in that situation?

Try to not bring home your stress. If you do, don't express it where the child can see, hear or feel it. It doesn't mean you have to be completely fake. You can acknowledge that you're doing something difficult. I'm talking more about a feeling and a mood in the home. If the parent works with patients who have COVID-19, then they are in a very difficult and possibly tragic situation.

Exercise is an excellent outlet, all the more for a child who has been confined indoors.

But it doesn't help the small child to be aware of it.

You don't want to be untruthful or false with your children, who will pick up on that. But perhaps, in a situation where there is real danger at work, Daddy could say that Mommy is a hero because she works with people who need help?

Yes, you have to essentially slant it in the positive. You could say that she's helping people. I also think that parents have to accept that they're going to lose it once in a while. The expectation that you're going to be upbeat and do the right thing all the time is wishful thinking.

For this reason, you have to anticipate that it's going to get unbearably hard and plan to take breaks. The idea is to know your limits well enough to acknowledge them, and try to take steps to avoid losing your temper.

Knowing your limits, if you have opportunities to get outside, then do so. If you can go into another room, do so deliberately, even when you feel okay. You know your own tolerance. If it's every two hours, that's it. If it's every four hours, that's fine. But it's important to know that you have limits.

Should we be worried about any long-term impact on children from the stress of this pandemic?

Children are highly resilient. Should your child develop anxiety, or other difficulties, during this stressful crisis, it does not indicate that there will be long-term negative consequences for the child. If anything, dealing with stressful situations facilitates appropriate, constructive, means of problem solving later on. ❖

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—Ken Harrison, Board Member

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In Pregnant Women with COVID-19, Higher Choline Levels May Protect Fetal Brain Development

Women who develop a COVID-19 infection during the early months of pregnancy have more to worry about than their own health. They must also worry about whether or how their infection will affect the fetus as it develops in the womb.

COVID-19 is usually not transmitted directly to the fetus. When faced with an infection, the mother's body mounts an immune response. It is this response which poses a potential health risk to the fetus.

Newly published research sheds light on how COVID-19, like other respiratory infections, is likely to affect fetal brain development and what can be done to minimize harmful impacts. The focus is on a crucial developmental window occurring around the beginning of the second trimester of pregnancy.

This is the period in which the emerging brain begins to build neural circuitry that can inhibit excitatory signals in neural networks. When robust neural inhibition fails to emerge prior to birth, the child will be at significantly increased risk for behavioral problems and for developing illnesses including autism, attention-deficit disorder and schizophrenia.

Preventing such outcomes has been a high priority in research at the University of Colorado School of Medicine led by BBRF Scientific Council member **Robert Freedman, M.D.** A two-time BBRF Distinguished Investigator and 2015 winner of the BBRF Lieber Prize, Dr. Freedman has demonstrated how levels of the essential nutrient choline in the mother's serum (the portion of the blood that does not include clotting factors) correlate with the fetus' ability to develop proper neural inhibition.

Since many pregnant women have diets that are deficient in choline, Dr. Freedman and colleagues have strongly recommended dietary supplementation with choline or phosphatidylcholine, sometimes called lecithin.

That advice is renewed in the context of COVID-19 infection during pregnancy, in a paper appearing in the *Journal of Psychiatric Research*, authored by Dr. Freedman with colleagues including **M. Camille Hoffman, M.D.**, 2015 BBRF Baer Prize winner; **Amanda Law, Ph.D.**, BBRF Scientific Council member, 2011 Baer Prize winner, and 2006 Young Investigator; and **Sharon Hunter, M.D.**, a 2003 BBRF Young Investigator.

The team drew upon data collected in their prior studies of women who developed infections (bacterial and viral) during the first 16 weeks of pregnancy—the point at which the fetus is most vulnerable to maternal inflammation.

The team compared 36 pregnant women who had developed moderate to severe respiratory infections by week 16 with 53 mothers who reported no infections. Choline levels were determined at week 16 in both groups, and at other time points. When infants reached 3 months of age, their mothers completed an extensive questionnaire seeking to gauge, among other things, the infants' duration of attention, their ability to enjoy quiet play, their cuddliness and engagement with parents and caretakers, and their soothability.

The team made two major findings, both suggesting the importance of women getting adequate amounts of choline during pregnancy. The first was about children of mothers who had respiratory infections during the first 16 weeks

M. Camille Hoffman, M.D., MSc

Robert R. Freedman, M.D.

of pregnancy. At 16 weeks, when mothers had choline levels at or above the minimum level advised by the FDA—the equivalent of 550 mg per day—their children 3 months after birth were better able to pay attention and to form a bond, compared with children of mothers whose choline levels were below the FDA daily minimum at 16 weeks.

The second finding was that children of infected mothers with adequate choline levels fared just as well as children of mothers who had no infection during pregnancy.

"Higher choline levels obtained through diet or supplements," the team concluded, "may protect fetal development and support early behavioral development even if the mother contracts a viral infection in early gestation when the brain is first being formed." Importantly, choline levels are most important early in pregnancy—levels beginning at 22 weeks were not observed to affect infant outcomes.

Although the FDA's current suggested minimum dietary requirement for choline is 550 mg daily, Dr. Freedman and colleagues advocate for higher levels, noting that supplements containing 900 mg of choline "have been safely used during pregnancy from 15 weeks gestation until delivery, with subsequent positive effects on the child's attention and social behavior through 3 and a half years of age."

Distinguishing Depression in Bipolar Disorder from Major Depression

Mary L. Phillips M.D.

Holly A. Swartz, M.D.

Diagnosing bipolar disorder can be difficult. While it is not hard to distinguish between its two characteristic phases—mania and depression—it is challenging to tell whether someone who reports low mood is suffering from depressive disorder or is in the depressive phase of bipolar disorder. A bipolar diagnosis is only confirmed, clinically, once a depressed patient has experienced at least one episode of mania.

Manic symptoms (elevated mood, racing thoughts, ill-considered risk-taking, a decreased need for sleep) are distinctly unlike those experienced during the depressive phase of bipolar disorder or by people suffering from major depressive disorder. The problem is that symptoms of the *depressive* phase of bipolar disorder are clinically similar to those of depression.

This diagnostic problem has motived researchers to search for measurable biological markers—aspects of brain activity, for example—that might differ in patients with major depressive disorder and patients in the depressive phase of bipolar disorder, perhaps facilitating more accurate diagnosis. Preliminary success has now been reported in such an effort, led by **Mary L. Phillips, M.D.**, a member of the BBRF Scientific Council, winner of the 2017 BBRF Colvin Prize for Outstanding Achievement in Mood Disorders Research, and a 2005 BBRF Independent Investigator.

Dr. Phillips and colleagues at the University of Pittsburgh and the Western Psychiatric Institute and Clinic, including **Holly A. Swartz, M.D.**, a 2006 BBRF Young Investigator, followed clues from prior studies that pointed to potential differences in the way the brain prepares for and performs working-memory tasks in patients with major depressive disorder vs. those in the depressive phase of bipolar disorder.

Working memory is a system the brain uses to maintain, manipulate, and update information pertaining to tasks immediately at hand. Damage to neural networks that are engaged during working memory result in impairments in learning, reasoning, and decision-making that are observed in some people with mood disorders, including depression.

For their research, Dr. Phillips' team recruited 18 people with bipolar disorder who were in the depressive phase of the illness; 23 with major depressive disorder who were also depressed; and 23 heathy controls. All of the participants received whole-brain scans with functional magnetic resonance imaging (fMRI), in two segments: one in which they were *anticipating* a task requiring working memory, and another in which they were actually *performing* the task. Each participant was scanned for both "easy" and "difficult" working memory tasks, and under conditions in which they were exposed to a range of emotional stimuli, from positive to neutral to negative.

These many permutations of working-memory tasks reflect the fact that people form expectations of what they need to do before performing a task, an assessment which can depend on whether the task is expected to be emotionally unchallenging or problematic.

Results of the analysis of the brain scans confirmed the hypothesis that patterns of brain activation during anticipation of a working-memory task vary according to whether the task is easy or difficult. Further, results suggested that anticipation and performance of working-memory tasks "can help distinguish depressed individuals with bipolar disorder from those with major depressive disorder."

Specifically, patterns of activation in the lateral and medial portions of the brain's prefrontal cortex during anticipation of easy vs. difficult tasks "may be an important biological marker for bipolar disorder vs. major depressive disorder classification," the team wrote in a paper appearing in *Neuropsychopharmacology*.

In trying to explain the measurable differences in neural activation they observed, the researchers theorized that "individuals with bipolar disorder may 'block' anticipation of negative stimuli to avoid negative emotions prior to performing a task." They suggested such "blocking out" could be "a defensive mechanism that depressed individuals with bipolar disorder use to remain functional."

In a Surprising Clinical Trial, Ketamine's Antidepressant Effects Were Extended in Time

When a team that included eight BBRF grantees, prize winners and Scientific Council members put to the test an idea they had about how the drug ketamine functions in the brain to rapidly produce antidepressant effects, they didn't get the result they expected—but they did learn something that could be of great importance.

John H. Krystal, M.D. and **Gerard Sanacora, M.D., Ph.D.**, both BBRF Scientific Council members and recipients of multiple BBRF grants, were senior members of a team at Yale University that, with first author **Chadi G. Abdallah, M.D.**, a 2014 and 2012 BBRF Young Investigator, and others, proposed to extend a finding from animal tests to human subjects. Their surprising results appeared in *Neuropsychopharmacology*.

In rodents that modeled depression, it had been previously shown that a drug called rapamycin (generic name sirolimus), when administered prior to an infusion of ketamine, prevented ketamine from alleviating depressive-like symptoms in the animals. This was interesting for several reasons, among them that rapamycin is known to block a protein complex called mTORC1, which separate research has suggested is an important mediator of ketamine's action in the brain.

The team wanted to see whether in people with major depression, as in rodents, administering rapamycin before giving a dose of ketamine would diminish or block ketamine's remarkable antidepressant effects. The Yale researchers conducted a randomized placebo-controlled trial.

Chadi Abdallah, M.D.

A group of 23 patients with active, treatment-resistant depression was randomized, with one subgroup receiving rapamycin followed 2 hours later by a ketamine infusion, the other subgroup receiving placebo followed by ketamine. After two weeks, the groups "crossed over," switching roles, one getting placebo plus ketamine, the other rapamycin plus ketamine. Doctors and patients were blinded throughout the trial, so no one knew who was getting placebo or rapamycin at any point.

The results of the rodent experiments were not confirmed in people: patients who received 6 mg of oral rapamycin received just as great a benefit from ketamine after 24 hours as those who received placebo. Rapamycin blocks mTORC1, but does not prevent ketamine from exerting rapid antidepressant effects.

A second surprise delighted the research team. When patients took rapamycin prior to receiving ketamine, 41% still showed a clinical antidepressant response after two weeks, with 29% in full remission. This compared with 13% response and 7% remission when placebo was given prior to ketamine instead of rapamycin. In other words, rapamycin pretreatment apparently extended ketamine's antidepressant effectiveness, for at least some patients.

"While preliminary, the unanticipated finding of prolonged response is highly important," the researchers wrote, "considering the urgent need for treatment approaches to prolong the antidepressant effects of ketamine and other rapid-acting antidepressants." In most patients, when ketamine is given alone, its effects are robust for several days and fade after about a week.

Rapamycin is a potent suppressor of inflammation. Inflammation has often been suspected of involvement in the biology of depression. The team speculates that the anti-inflammatory effects of rapamycin may protect new or restored synaptic connections between neurons in the cortex that are forged after an infusion of ketamine.

"Our ultimate goal is and should be to find a cure for clinical depression and related illnesses," Dr. Abdallah commented. "These unexpected rapamycin findings may have got us a step closer toward realizing this goal. As a field, we next need to figure out how to maintain the restored synaptic and functional connections following ketamine treatment, and how to prevent the relapse of depressive symptoms."

The research team also included: the late **Ronald S. Duman, Ph.D.**, 2005 BBRF Distinguished Investigator, 2002 Falcone Prize winner, 1997 Independent Investigator and 1989 Young Investigator; **Deepak Cyril D'Souza, M.D.**, 2013 BBRF Independent Investigator; **Kyung-Heup Ahn, M.D.**, 2009 BBRF Young Investigator; **Mohini Ranganathan, M.D.**, 2007 BBRF Young Investigator; and **Lynette Averill, Ph.D.**, 2015 BBRF Young Investigator. In addition to serving on the BBRF Scientific Council, Dr. Krystal is a 2006 and 2000 BBRF Distinguished Investigator and 1997 Independent Investigator; Dr. Sanacora, also a BBRF Scientific Council member, is a 2014 BBRF Distinguished Investigator, 2007 Independent Investigator, and 2001 and 1999 Young Investigator.

Therapy Update

Recent News on Treatments for Psychiatric Conditions

TRIAL MEASURES IMPACT OF COMBINING COGNITIVE TRAINING WITH DRUG TREATMENT IN AGE-RELATED COGNITIVE DECLINE

Christopher R. Bowie, Ph.D.

Progress has been reported in the effort to help those over age 65 who are suffering from cognitive decline. Such decline is experienced by most older adults at some point, although the degree and type of impairment varies greatly among individuals.

A research team led by Eric Lenze, M.D., of Washington University, and **Christopher Bowie, Ph.D.**, a 2013 BBRF Independent Investigator and 2007 and 2003 Young Investigator, at Queen's University, Ontario, set out to discover if computer-delivered cognitive training would help patients more if accompanied by an FDA-approved antidepressant medicine that is thought to boost cognition. That drug is called vortioxetine. Results of the trial appeared in the *American Journal of Psychiatry*.

One hundred people over age 65 who were diagnosed with age-related cognitive decline were randomized in the clinical trial. All participants received 26 weeks of computer-guided cognitive training, as well as a 2-week training period that preceded the start of the trial. Once the 26-week trial began, half the participants took 10 mg of vortioxetine daily, while the other half took a placebo pill.

Vortioxetine is a serotonin reuptake inhibitor, with effects that other widely prescribed drugs in the class such as Prozac or Lexapro do not have. Specifically, it is thought to interact differently with two variant types of neuronal receptors for serotonin, called the serotonin-3 and serotonin-7 receptors, possibly increasing neurotransmission in the dopamine, cholinergic, and histamine neurotransmitter systems.

The researchers measured cognitive functioning using a battery of cognitive tests for all study participants, at "baseline," when the trial began, and at 4, 12, and 26 weeks during the intervention phase. The primary test used measured participants' ability to handle tasks related to skills in solving problems, thinking and acting quickly, and adapting to new situations.

The cognitive training program that all study participants received over 26 weeks was a software program called Scientific Brain Training Pro. Participants were instructed to use the program five times each week for 30 minutes a day.

Results of the trial were modestly positive. The combination of the cognitive training software plus daily vortioxetine showed a clear statistical advantage overall and at the 12-week time point in the trial—but not at any of the other time points, including the end-point at 26 weeks.

Still, the team considers this result "important, because this is the first study, to our knowledge, to demonstrate that a putative pro-cognitive drug could be combined with cognitive training in age-related cognitive decline" to provide greater improvement than cognitive training alone. Studies with more participants would add power to the results, the team said, and perhaps reveal whether the advantage of combined treatment is durable.

Further study might also address the question of whether any advantage of combined treatment was additive—the result of cognitive training and drug treatment each adding an increment of benefit; or interactive, with, for example, the drug "driving beneficial [brain] plasticity such that cognitive training is more efficient." The researchers also want to know how the combination approach fares in patients whose cognitive decline is observed to progress over time, especially whether combined treatment slows such advance.

ADDING AMBIEN TO AN SSRI ANTIDEPRESSANT COULD HELP SOME DEPRESSED PATIENTS WITH SEVERE INSOMNIA

Andrew D. Krystal, M.D.

New research suggests that in some cases, patients with major depressive disorder whose symptoms include both insomnia and suicidal ideation (thinking about suicide) may benefit by regularly taking a prescription sleep medication, such as Ambien, when they begin treatment with an SSRI antidepressant such as Prozac or Zoloft.

A research team led by William McCall, M.D., of the Medical College of Georgia, Ruth Benca, M.D., Ph.D., and **Andrew D. Krystal, M.D.**, a 1997 and 1993 BBRF Young Investigator, set out to test whether targeting insomnia symptoms in such patients might reduce their risk of suicide.

Among the rationales for this approach is evidence indicating that changes in insomnia symptoms precede suicidal ideation in patients with major depressive disorder. Furthermore, patients with insomnia and survivors of suicide attempts—compared with those who have not made a suicide attempt—perform less well on tests measuring the ability to solve interpersonal problems. "Impaired problem solving associated with insomnia could play a role in suicide," the researchers wrote.

To test this theory, they enrolled 103 medication-free individuals with major depressive disorder, insomnia, and suicidal ideation in a double-blinded randomized clinical test. The average patient was about 40 years old; 62% were female. All received an SSRI antidepressant in the 8-week trial; half also received time-released Ambien (Zolpidem-CR), while half received a placebo in lieu of active sleep medicine.

None of the patients attempted suicide during the trial. At its conclusion, the researchers, reporting in the *American Journal of Psychiatry*, concluded that the addition of Ambien to an SSRI was superior to placebo plus an SSRI in reducing insomnia symptoms. The advantage of adding Ambien was most evident in those patients whose insomnia was severe when the trial began.

The results were less clear regarding whether adding Ambien to an SSRI helped to reduce suicidal ideation. "The clinical significance of the advantage seen for suicidal ideation was modest, even in the severe insomnia group," the team reported. One clinical measure of suicidal ideation did show a benefit while another measure did not.

Taking all the evidence into consideration, the team—which also included **Steven Szabo, M.D., Ph.D.**, a 2012 and 2003 BBRF Young Investigator—concluded that "while the results do not support the routine prescription of sleep medicine for mitigating suicidal ideation in all depressed patients with insomnia, they do suggest that co-prescription of a sleep medicine during initiation of an antidepressant may be beneficial in suicidal outpatients, especially those with severe insomnia."

IN 2 TRIALS, KETAMINE PLUS BEHAVIORAL THERAPIES HELPED PEOPLE WITH COCAINE AND ALCOHOL DEPENDENCIES TO ABSTAIN

Frances R. Levin, M.D.

Although new knowledge about the brain's reward circuitry has provided insight into the biology of addiction, this has not yet resulted in new treatments. In animal models of addiction, it has been possible to therapeutically modify reward circuits using techniques that alter gene expression or switch individual neurons or groups of them "on" and "off." But such experiments involve genetic engineering and surgical interventions in the brain, and are not directly translatable in human subjects.

Looking for novel approaches, researchers at Columbia University and the New York State Psychiatric Institute have taken another path. In separate randomized clinical trials reported in the *American Journal of Psychiatry*, they have combined an existing form of therapy that has so far proven only modestly beneficial in addiction with an experimental therapy that has been neither validated nor approved for use in addiction.

The existing therapy involves behavioral modification. The experimental therapy is a drug—a single, low-dose infusion of the anesthetic ketamine. It has repeatedly shown its power to act rapidly (within hours) as an antidepressant in individuals who haven't responded to other forms of depression therapy. A chemical derivative of ketamine called esketamine received FDA approval last year for use in treatment-resistant major depression.

In the two trials they designed, the Columbia team, led by Elias Dakwar, M.D., and Edward Nunes, M.D., which also included BBRF 2000 Independent Investigator **Frances R. Levin, M.D.**, employed ketamine—at a sub-anesthetic dose, given a single time—in patients with cocaine and alcohol addictions who were also receiving behavioral therapies. **Sanjay Mathew, M.D.**, a 2009 BBRF Independent Investigator and 2006 and 2001 Young Investigator, was also on the research team in the cocaine trial.

In the cocaine trial, ketamine was combined with mindfulness-based behavioral training; in the alcohol trial, it was paired with motivational enhancement therapy. In both trials, while all participants received behavioral therapy, only some received ketamine; participants who served as controls instead received what researchers call an "active" placebo: the drug midazolam (Versed), a tranquillizing agent that can be used as a sedative, anesthetic, or sleep aid.

In both trials, patients who received ketamine and behavioral therapy fared markedly better than did those who received the placebo plus therapy.

Specifically, in the cocaine trial: 55 cocaine-dependent individuals received an intravenous ketamine infusion or placebo during a 5-day hospital stay, during which they also began a 5-week course of mindfulness-based relapse prevention therapy. Overall, 48% of those in the ketamine group maintained abstinence over the final 2 weeks of the trial, compared with only 11% in the group that received placebo. Also, the ketamine group was 53% less likely to relapse and had cravings scores that were 58% lower than those who received placebo.

In the alcohol trial: 40 alcohol-dependent individuals (averaging 5 drinks per day) received either ketamine or placebo during the 2nd week of a 5-week outpatient regimen of motivational enhancement therapy. Ketamine as compared with placebo "significantly increased the likelihood of abstinence, delayed the time to relapse, and reduced the likelihood of heavy drinking days," the researchers reported.

The results tended to support the hypothesis that ketamine affects the glutamate neurotransmitter system, possibly by modulating cellular docking ports for glutamate called NMDA receptors. It is also thought to have "downstream" effects on synapse formation in the prefrontal cortex. The team hoped that these mechanisms may also help overcome resistances known to impede the progress of people who are treated with behavioral therapies: craving, low motivation to quit or abstain, and difficulty controlling behavioral reactions.

In the cocaine trial, "mindfulness training" sought to teach participants "an attitude of deliberate, present-centered awareness, coupled with a suspension of behavioral reactivity, cognitive associations, judgments, and distortions." Noting the positive results relative to controls in the cocaine trial, the team proposed that ketamine may indeed affect brain biology in ways that make the behavioral therapy component more effective than when given alone.

The researchers reached a similar conclusion in the trial with alcohol-dependent participants. It appeared that, compared with placebo or no complementary therapy, "ketamine provided protection against a lapse [in abstinence] evolving into continued use—relapse—or into a dropout from treatment."

Given the general lack of progress in addiction treatments, the team in each trial expressed the hope that their results would be replicated in much larger trials—perhaps, in the process, validating a broad new potential use for ketamine and ketamine-like molecules in combination treatment for addiction and substance abuse. ❖

GLOSSARY

NON-INVASIVE BRAIN STIMULATION (pp. 18–23): In non-invasive brain stimulation, a doctor places a magnetic coil just above the surface of the patient's scalp. Repetitive, spaced pulses emanating from the coil pass through the skull, generating a small electrical current that changes the activity of brain cells in regions beneath the skull. Depending on the target and frequency of the pulses, activity in the targeted brain area can be increased or decreased. Three types of non-invasive stimulation for treatment of major depression are mentioned in this issue. **rTMS**, (repetitive transcranial magnetic stimulation), was first approved for treatment of refractory depression in 2008; sessions lasting 37 minutes are delivered once weekly over a period of 6 weeks. **iTBS** (intermittent theta-burst stimulation), approved in 2019, delivers the same amount of total stimulation, but in 5 sessions per week lasting only 3 minutes each, over a period of 4 to 6 weeks. The experimental **SAINT** protocol discussed in this issue delivers the equivalent of 6 weeks of rTMS or iTBS treatments in a single day, in ten 3-minute sessions separated by 50-minute intervals, and repeats this procedure for 5 consecutive days.

TREATMENT-RESISTANT DEPRESSION (pp. 18, 33): Also called "refractory depression," the term refers to major depressive disorder that has not responded to conventional forms of therapy. Especially when accompanied by symptoms of suicidal ideation, treatment-resistant depression can be a life-threatening condition. Various options are sometimes attempted in such patients: ECT, or electroconvulsive therapy, is a procedure in which a therapeutic seizure is induced in an anesthetized patient. Although often effective, ECT has been associated with short-term memory loss in some individuals. Deep-brain stimulation, an experimental surgical procedure, involves implantation of electrodes in a portion of the brain; their pulses have alleviated depression symptoms in select patients over extended periods of time. Non-surgical options now also include the administration of esketamine, an FDA-approved derivative of the anesthetic ketamine, delivered in a sub-anesthetic dose. THE SAINT protocol for delivering non-invasive brain stimulation, discussed on pages 18–23 of this issue, has also been tested with promising results in highly refractory patients.

OPEN-LABEL TRIAL (p. 19): A clinical trial in which both doctors and patients know that all trial participants are receiving the treatment being studied. Such trials can provide an early indication of the potential benefit of a given treatment, but must be followed by the "gold-standard" type of clinical test, which involves the random assignment of participants into groups that will receive the investigational treatment and those that will not. In such trials, the group(s) not receiving the treatment under study will receive a placebo—but neither participants nor doctors know which patients are in either group until after the completion of the trial. This minimizes the impact of subjective judgment in both patient reports and researcher interpretations.

DEFAULT-MODE NETWORK (p. 20): The DMN is a circuit that connects a number of brain areas. Its activity has been described by some as reflecting a kind of "baseline" brain activity when an individual is not actively performing a conscious mental task; the DMN's activity is "anti-correlated" with that of attentional circuitry in the brain, for example. By targeting a part of the brain called the dorsolateral prefrontal cortex (DLPFC), non-invasive brain stimulation in the SAINT protocol is designed to alter activity in a region called the sgACC (subgenual anterior cingulate cortex), whose connectivity with the DMN is thought to be overly strong in depression. The procedure may exert therapeutic effects by reducing or normalizing that "hyperconnectivity."

CHOLINE (p.34): An essential nutrient with many functions in the body. During pregnancy, abnormally low choline levels in the mother may perturb fetal brain development, raising the post-birth risk to the child of autism, schizophrenia and possibly other conditions. Hence, choline supplementation may be advised, particularly beginning in the second trimester.

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