A Common Causal Circuit in Depression

Understanding Borderline Personalty Disorder

Brain&Behavior MAGAZINE

MAY 2022

Rethinking Eating Disorders

RESEARCH 19 35 years 87 FOR CURES

PRESIDENT'S LETTER

With this issue of *Brain & Behavior Magazine* we invite you to join BBRF in celebrating 35 years of scientific advancements for improved treatments, cures, and methods of prevention for mental illness.

Two of our articles discuss promising research on very important illnesses, both common in the general population and yet both infrequently discussed, in part due to stigma. These illnesses are eating disorders (EDs)—anorexia nervosa, bulimia nervosa and binge-eating disorder—and borderline personality disorder, the most prevalent of the 10 personality disorders (PDs) recognized in the *Diagnostic & Statistical Manual* (DSM) used to diagnose psychiatric illness.

Not only are eating disorders among the most prevalent psychiatric disorders; they are also among the most misunderstood. Our **PATHWAYS TO THE FUTURE** story focuses on recent research by BBRF Distinguished Investigator Dr. Cynthia Bulik of the University of North Carolina and the Karolinksa Institute which indicates that the most deadly of the EDs, anorexia, is also a disorder of the body's metabolic system. The same may be true of bulimia and binge-eating disorder, although genetic evidence is still being evaluated. The effort by Dr. Bulik and others to rethink eating disorders is already leading to new treatment ideas, which, along with helping to destigmatize the illness, potentially paves the way to better outcomes for patients.

In **ADVICE ON MENTAL HEALTH** we talk with BBRF grantee Dr. Anthony Ruocco of the University of Toronto, whose research focuses on borderline personality disorder. BPD affects over 3 million American adults, according to the National Institute of Mental Health, yet this and other personality disorders affecting millions more aren't well understood by most people. For this reason, we ask Dr. Ruocco to help clarify the symptoms of BPD, the most prevalent of the personality disorders.

We also ask him to inform us about what his imaging and behavioral research has revealed about BPD's possible biological underpinnings, and to offer some advice about treatments for this disorder.

This issue also features a **SCIENCE IN PROGRESS** story about innovative research funded in part by BBRF that is being conducted by Dr. Shan Siddiqi of Harvard Medical School. This research provides evidence of a "common causal circuit" in major depressive disorder. The circuit, which spans brain regions, is distressed in different ways in affected individuals, and, as the research shows, when it is modified using different types of brain stimulation, depression symptoms are often reduced in severity. This research finding could potentially help improve depression treatments, and, if replicated, suggests even broader possibilities—such as possibly working backward from brain lesions to find targets that can be modified by TMS, DBS, or other brain-stimulation techniques to treat symptoms of other psychiatric illnesses.

As always, this issue includes a summary of news on treatments for psychiatric conditions in our **THERAPY UPDATE** as well as important research advances that are moving the field forward in **RECENT RESEARCH DISCOVERIES**.

I thank you for being an important part of the BBRF community. Together, we will continue to fund innovative and impactful research that will pave the way forward for scientific advancements that are making a difference in the lives of those living with mental illness.

Sincerely,

Jeffrey Borenstein, M.D.

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

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A 'Common Causal Circuit' in Depression, With Possible Therapeutic Implications in and Beyond Depression

Shan Siddiqi, M.D.

IN BRIEF
It has been vexingly difficult to pin down depression's biological causes. Innovative research by a BBRF Young Investigator has now revealed a 'common causal circuit' spanning brain regions which is perturbed in affected individuals and which, when modified by brain stimulation, often provides relief. The finding could help improve depression treatments and suggests a new way of identifying causal circuits in other disorders.

If you want to cure an illness, you try to understand its underlying cause or causes, as a precondition for modifying, reducing, or eliminating them. That, in highly simplified terms, is one of the scientific rationales for much contemporary research on mental illness.

But determining causation is a difficult matter in many illnesses, especially those that are causally complex. Psychiatric illnesses such as schizophrenia, depression, and bipolar disorder are considered highly complex, the product of factors that can span an enormous range, from the unique specificities of an individual's genetics to those of his or her social (or even pre-birth) environment.

Shan Siddiqi, M.D., a neuropsychiatrist at Harvard Medical School who received a BBRF Young Investigator grant in 2019, was trained as a physician to take care of patients with mental illness. He continues to do so, although he devotes much of his time right now to research, and specifically, figuring out more about causation so that in the future he and others can provide more effective therapies.

In explaining the thrust of his research, and specifically a paper he and colleagues recently published in *Nature Human Behaviour*—one that may have important implications for improving current therapies—Dr. Siddiqi reflected on a longstanding problem regarding the question of causation in mental illness.

There's an expression well known among scientists that states: "correlation is not causation." By this, Dr. Siddiqi explains, researchers mean to say that "there is a big difference between things that are merely *correlated*"—things that occur together—and situations in which one can prove that *this* thing is the cause of this *other* thing.

"We have this problem when we study the brain," Dr. Siddiqi says. "What we have been doing for a long time is looking at correlates of symptoms. For example, we take a group of people who suffer from major depression and compare them in various ways with a group of people without depression. We hope to see what distinguishes the people who are depressed.

"That's quite useful sometimes, because some of the factors that correlate with depression—things we don't see in the non-depressed group—may turn out to be causal factors. At the same time, however, some of the correlates will prove not to be causal."

The issue is figuring out how to tell causal and non-causal factors apart. It's a grand-challenge problem addressed in the research Dr. Siddiqi and colleagues have performed with help from his 2019 BBRF grant.

Dr. Siddiqi says the project leading to his newly published paper had its origins in conversations he was having with a senior researcher at Harvard, Dr. Michael Fox. They had access to 14 highly detailed, independently collected sets of brain imaging data from 12 different institutions in the U.S. and other countries. The data documented 713 cases: individuals who had changes in depression in response to various forms of therapy or injury.

"Depression caused by brain damage affected the same circuitry that was modified by brain stimulation therapies that alleviate depression."

"Correlation is not causation": For example, boating mishaps and ice cream sales both rise sharply in summer, but this doesn't mean that these two facts are involved in one another's causation; they merely occur at the same time. If one had the objective of decreasing summertime boating accidents, it would be fruitless to focus on altering the volume of ice cream sales.

"There are so many variables in depression," Dr. Siddiqi notes. The question was: "How can we compare different people with the same symptoms—knowing that besides the depression symptoms that they share, there are many variables potentially making these individuals hard to compare." He refers to factors ranging from socioeconomic status to genetics to childhood exposures to other underlying medical or neurological conditions. A similar question about how to properly compare people applies to those who have the same diagnosis—in this case major depression—but report different combinations or severity of symptoms.

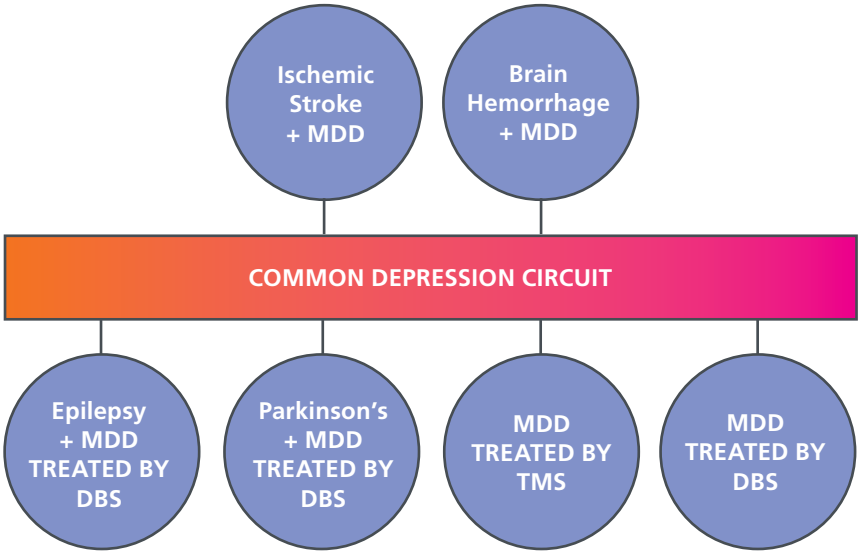
At one point, Dr. Fox said to Dr. Siddiqi: "What do you figure would happen if you were to combine every single dataset that we have—all 14? What would you get?"

Dr. Siddiqi's reply reflected what common sense would suggest: they would likely get nothing that would bear on the problem of causation, since the people covered in the 14 datasets were so fundamentally diverse. Some of the data was about people whose depression was a side effect of deep brain stimulation for Parkinson's disease; others had received DBS for epilepsy; still other data was about people who had major depression but no other significant co-occurring illnesses; other datasets focused on people whose major depression or Parkinson's disease was triggered after they had suffered a stroke or an accident that resulted in brain damage.

But both researchers were curious. Dr. Siddiqi ended up saying: "It probably won't work, but we should try it. If it fails, we can then figure out why and perhaps learn from that."

A COMMON CAUSAL CIRCUIT

The remarkable thing is that by combining the 14 datasets and



When 14 highly diverse datasets involving people with major depressive disorder (MDD) were combined, analysis revealed what Dr. Siddiqi and colleagues propose is a common causal circuit.

comparing them in very sophisticated and rigorous ways, Drs. Siddiqi, Fox and colleagues were able to identify what they believe is a "common causal circuit" involved in major depression, which was consistent across all of the diverse datasets that they scrutinized. Among the co-authors on their paper reporting the results were two members of the BBRF Scientific Council, **Mark S. George, M.D.**, and **Helen S. Mayberg, M.D.**, who are pioneers, respectively, of TMS (transcranial magnetic stimulation) and DBS (deep-brain stimulation), two therapies used to treat depression and other illnesses. Five other recipients of BBRF grants were members of the research team.

"We can now work backward from brain lesions to find targets that can be modified by TMS or DBS to alleviate a range of psychiatric illnesses."

"When I looked at the results," Dr. Siddiqi relates, "I said at first: 'This can't be right. Let me see if I can find a way to break it.'"—by which he meant, go back over the work to see if he could find a place or places where the team made an error or missed something. "I spent hours and hours—so many that I have to admit it got to the point of annoying my family. I literally stayed up all night, over days, trying to find ways to see where we went wrong."

But he couldn't. And this led to another remarkable moment. Dr. Siddiqi realized that "if we really did succeed in finding a common causal circuit in depression"—this will have to be replicated in follow-up work in his lab and others, which is now under way—"then we succeeded *in spite* of the heterogeneity, in spite of all the factors we know that make the people in the 14 datasets unalike." This, he says, makes the finding especially powerful.

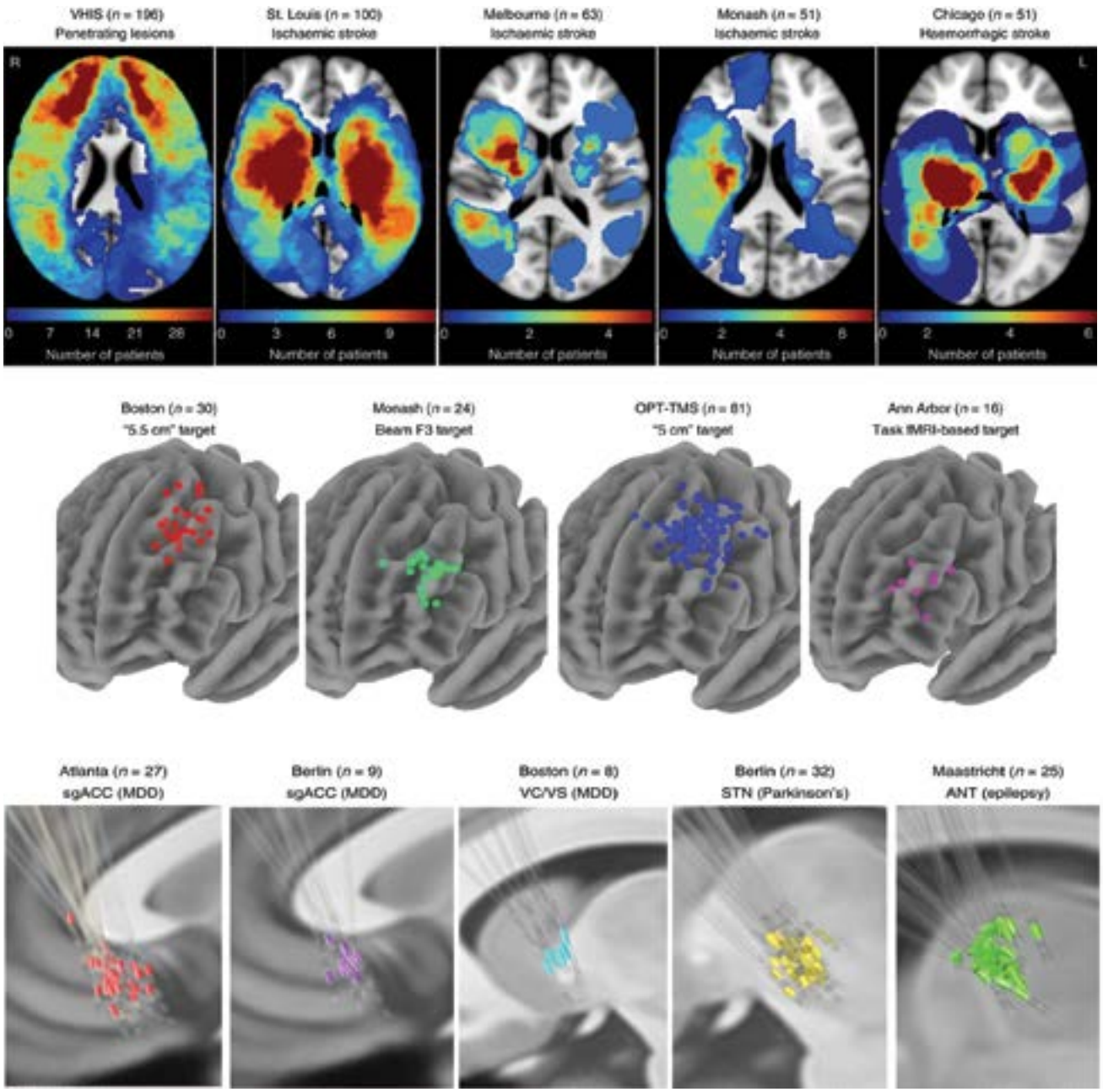
The team studied major depression severity and underlying brain circuit and network dynamics in the 14 datasets, mapping results against "connectome" information—consensus wiring diagrams showing how different parts of the brain are connected, in a typical person.

Five of the datasets comprised a total of 461 individuals who were assessed for major depression after suffering brain injuries; four datasets comprised 151 individuals with major depression who were treated with TMS, a form of non-invasive brain stimulation; and five datasets comprised 101 individuals diagnosed either with major depression, epilepsy, or Parkinson's disease, all of whom received DBS, which involves surgically implanting a kind of pacemaker in the brain to deliver therapeutic electrical stimulation.

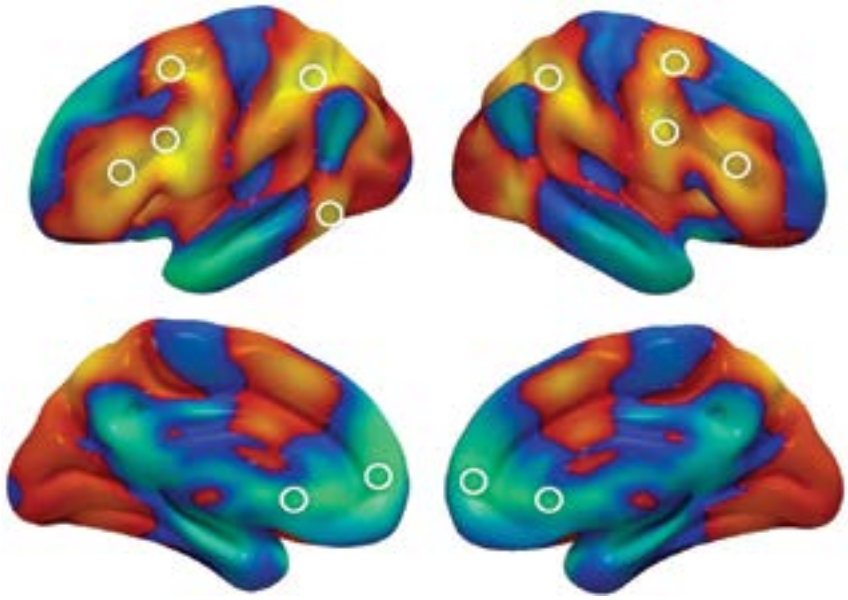
One thing that is interesting about the team's finding of a "common circuit" in depression is that it draws attention to circuitry that spans different regions. To use the example of the datasets that focused on people who had suffered brain injuries which led to their depression: these "lesions," as they are called by doctors, occurred in widely separated parts of the brain. There was no single spot in the brain at which, if tissue damage occurred, the patient would then develop major depression. The actual message was: at the many

lesion sites analyzed, injury at particular spots was found to impair the function of some portion of a common circuit or network spanning different brain regions.

A second important finding based on the 14 datasets has to do with people with major depression who had been successfully treated with either non-invasive TMS or invasive DBS brain stimulation therapies. Even though these treatments use different technologies, and even though they are not targeted in the same place in the brain in each patient, they were found to modify the function of a common circuit, the study indicated. Remarkably, this circuit was found to be



Basis for the "common depression circuit" finding: lesion locations and brain stimulation sites across the 14 independent datasets.
TOP: brain lesion locations in 461 patients with 3 diagnoses; CENTER: 151 TMS sites in patients with major depression;
BOTTOM: 101 DBS sites in patients with 3 diagnoses.



A combined 'depression circuit' was generated from all 14 datasets. Peaks in this circuit are depicted by white circles. Positive peaks (top row) included the dorsolateral prefrontal cortex, frontal eye fields, inferior frontal gyrus, intraparietal sulcus and extrastriate visual cortex. Negative peaks (bottom row) included the subgenual cingulate cortex and ventromedial prefrontal cortex. Theoretically, in treating depression, one might want to use brain stimulation methods to activate positive peak locations and inhibit negative peak locations.

"similar" to the common circuit found in the study subjects with brain lesions that caused depression. It was also "similar" to a circuit directly linked with causality in depressed patients with epilepsy and Parkinson's disease.

By "similar," the team means to suggest something stronger than a vague correlation. Their use of the term reflects an outcome, in Dr. Siddiqi's words, which is much stronger than would be expected to happen by chance. It's the result of complex mathematical analysis based on where the circuitry being measured in any given patient is arrayed within the three-dimensional space of the brain. A great deal of machine- and computer-guided measurement went into the determination that the "spatial correlation" of a causal circuit identified in people with brain lesions was similar in "robust" ways with the circuit impacted by brain stimulation therapies that alleviated depression in TMS and DBS patients.

For a century or more, physicians treating people who have suffered serious brain damage have documented a range of associated symptoms involving speech, vision, movement, and memory. In some instances, such lesions give rise to psychiatric symptoms, including those of major depression.

In their paper Drs. Siddiqi, Fox and colleagues do note that "our convergent [depression] circuit includes regions previously implicated in depression." These include the subgenual cingulate, ventromedial prefrontal cortex, and dorsolateral prefrontal cortex. But that is not the primary value of their findings, Dr. Siddiqi suggests.

WORKING BACKWARD FROM LESIONS TO TARGETS

In his view, the most important aspect of the team's work is that it may be feasible to work backward from brain lesions to find circuits and targets within them whose modification—for example, by TMS or DBS—might help to alleviate a range of psychiatric illnesses. "Our work provides concrete evidence that brain lesions map to treatment targets," Dr. Siddiqi has noted.

Among the datasets the team studied were those involving individuals with brain lesions that were causally linked not with depression but with the onset of motor symptoms of Parkinson's disease. A common circuit was found in these individuals. As with the common circuit identified in depression, this circuit in the Parkinson's patients with lesions was "similar" to the circuit that DBS brain stimulation modified to achieve reductions in Parkinson's symptoms.

IMPLICATIONS BEYOND DEPRESSION

"This is the strongest evidence to date showing that lesions causing symptoms can identify therapeutic targets for symptom relief," the team wrote. For this reason, they hope their findings will have "therapeutic implications well beyond depression and Parkinson's disease."

Using a circuit mapping method that they used to link lesions in major depression and Parkinson's disease with circuits that were modified in successful treatments for each illness, the team is now working on circuit maps for mania, hallucinations, movement disorders, as well as addiction, PTSD and OCD.

"On another track, we're also looking at targeting specific symptom clusters within a disorder," Dr. Siddiqi says. "In 2020 we published a preliminary paper on this question with regard to treating two clinically distinct manifestations of depression (called dysphoric vs. anxious/somatic depression)."

In their recent paper, Dr. Siddiqi and colleagues make an important point about their research approach which bears on the prospect of improving therapeutic targeting for people with different subtypes of an illness—in this case, depression.

"Our analysis may seem circular given that TMS and DBS targets for major depression were chosen because they were already known [due to therapeutic results] to be part of a 'depression circuit.'" However, they go on to explain, "the left prefrontal cortex appears as part of our depression circuit not because it has been targeted with TMS but because *different TMS targets* across the left prefrontal cortex produced *different effects* on depression."

Similarly, they noted, "different DBS sites produced different effects on depression symptoms, depending on their connectivity to the left prefrontal cortex. Also, different lesion locations were associated with different amounts of depression, depending on their connectivity to the same part of the cortex."

Among other things, this suggests that modifying the common circuit in depression (or in other illnesses if they are identified and verified) may end up having different degrees of impact upon patient symptoms, or may impact different symptoms, depending on where and how the circuit is modified.

These are among the many intriguing questions that Drs. Siddiqi, Fox and colleagues intend to address in their ongoing research—and they must perform this work, they say, before they will be ready to suggest specific modifications in current treatment targets for all or subsets of patients in depression or other disorders. ❖ **PETER TARR**

Rethinking Eating Disorders

IN BRIEF
Eating Disorders (EDs) are among the most prevalent psychiatric disorders yet also among the most misunderstood. Recent research by a BBRF Distinguished Investigator indicates that the most deadly of the EDs, anorexia, is also a disorder of the body's metabolic system. This is leading to new treatment ideas, which, along with decreasing stigma, opens the way to better outcomes for patients.

Dr. Cynthia Bulik's research reveals these psychiatric disorders also have a crucial metabolic dimension

2017 BBRF Distinguished Investigator **Cynthia Bulik, Ph.D.**, is one of the world's foremost experts on eating disorders (EDs)—anorexia nervosa, bulimia nervosa, and binge-eating disorder. A clinical psychologist and researcher, she has devoted her decades-long career to treating and studying all three EDs.

The Distinguished Professor of Eating Disorders at the University of North Carolina and founder of UNC's Center of Excellence for Eating Disorders, as well as Director of the Centre for Eating Disorders Innovation at Sweden's Karolinska Institute, Dr. Bulik arguably has done as much as any figure in the medical and research communities to sharpen our understanding of the origins and causes of eating disorders.

In addition to the 660 scientific papers and 60 chapters she has authored, she has devoted

considerable effort to communicating directly with the public as the author of seven books, containing specific advice for patients and families. In the process she has helped to raise awareness about what she and other experts suggest is a set of persistent and damaging myths about these life-threatening conditions.

Myths and misunderstandings about eating disorders, in fact, have been so pervasive, and have proved such an obstacle to understanding their underpinnings in medical and scientific terms, that Dr. Bulik prefers not to talk about them at any length. "Every time we mention them, it only tends to reinforce them," she says.

One in particular is probably familiar to most people: the popular notion of eating disorders, and especially anorexia, as affecting women and "caused" by powerful societal pressures for women to be thin.

Is there *no* truth in that popular conception of anorexia? Societal attitudes about femininity, thinness, and body image

"For patients, recovery from anorexia nervosa is fighting an uphill battle against their biology and patients need our support in doing so."

are by no means irrelevant, Dr. Bulik makes clear. But years of research in the clinic with patients, and in the laboratory, studying the genetics of eating disorders, leads her and others to stress the causal interplay of environmental factors and underlying biological factors that drive symptoms.

Indeed, Dr. Bulik's recent research has led her to suggest a full-scale "reframing" or re-conceptualization of eating disorders. Her most influential contribution has been to suggest that EDs not only have *psychiatric* roots but also roots in malfunction of the body's *metabolic* systems, which regulate how energy (sourced, ultimately, in food) is supplied to our organs.

Anorexia nervosa (AN) is defined by restriction of food intake to the point that it causes a significant and dangerous decrease in body weight. Affecting both sexes, although more women than men, AN typically involves anxiety toward food, fear of weight gain, dissatisfaction with body size and shape, and a failure to recognize the seriousness of the low body weight. Untreated, it can lead to starvation and loss of life. It has the highest rate of mortality of any "DSM-5"-listed psychiatric disorder, with those affected over 6 times more likely to die than unaffected peers.

People with AN fall into two subtypes. One, called "restrictive," involves consistent restriction of food with or without excessive exercise. In the other subtype, called "binge-eating/purging," the affected individual ingests food, in some cases in large quantities, with a sense of loss of control, but then "compensates" (purging the food via vomiting, use of diuretics or laxatives).

In **bulimia nervosa (BN)**, there are recurring episodes of eating large amounts of food at one sitting with a sense of loss of control, usually coupled with efforts to purge. **Binge-eating disorder (BED)**, in contrast, involves similar binge-eating episodes that are not paired with purging. In BN and in BED—as well as in the binge eating/purging subtype of AN—the individual experiences a loss of control while eating (i.e., a feeling that one cannot stop/control how much one is eating), regardless of the amount of food consumed.

To help combat myths about EDs, Dr. Bulik and colleagues at the Academy for Eating Disorders published the **"9 Truths"** document, based on a talk given by Dr. Bulik in 2014:

9 Truths About Eating Disorders

TRUTH #1
Many people with eating disorders look healthy, yet may be extremely ill.

TRUTH #2
Families are not to blame, and can be the patients' and providers' best allies in treatment.

TRUTH #3
An eating disorder diagnosis is a health crisis that disrupts personal and family functioning.

TRUTH #4
Eating disorders are not choices, but serious biologically influenced illnesses.

TRUTH #5
Eating disorders affect people of all genders, ages, races, ethnicities, body shapes and weights, sexual orientations, and socioeconomic statuses.

TRUTH #6:
Eating disorders carry an increased risk for both suicide and medical complications.

TRUTH #7
Genes and environment play important roles in the development of eating disorders.

TRUTH #8
Genes alone do not predict who will develop eating disorders.

TRUTH #9
Full recovery from an eating disorder is possible. Early detection and intervention are important.

While the "9 Truths" document doesn't provide statistics, the National Institute of Mental Health, citing research conducted between 2001 and 2003, estimates that the lifetime prevalence of anorexia in women is a bit less than 1 in 100, and in men about 1 in 300. "Past-year" prevalence statistics from 2001–2003 were not available for anorexia, but were for bulimia, which affected 1 woman in 200 and 1 man in 1000. Binge-eating disorder was more common, affecting 1.6 per 100 women and 0.8 per 100 men annually between 2001 and 2003. Prevalence of EDs is much higher in young people, the NIMH statistics suggest. For the years 2001–04, estimated prevalence of EDs in adolescents was 2.7 per 100: 3.8 per 100 females and 1.5 per 100 males.

"Instruments we have to clinically assess eating disorders have been built around the way females 'present' them," Dr. Bulik explains. "One of the most famous questionnaires asks for responses to statements like, 'I'm satisfied with the size of my hips' or 'I like the size of my breasts.' "Men with anorexia will often say they are in pursuit of "leanness," or "low body fat" or "being ripped" rather than "thinness," Dr. Bulik notes. "It is likely that more women than men have EDs, but I think we're missing a lot of men just because of the way we diagnose."

Regarding the cultural value placed on thinness: Dr. Bulik acknowledges that this obsession so powerfully disseminated via advertising and now reinforced via shaming and bullying on social media, is certainly an important part of the story. For the sake of clarity, she notes that cultural attitudes

Eating disorders affect people of all genders, ages, races, ethnicities, body shapes and weights, sexual orientations, and socioeconomic statuses.

about thinness are an environmental factor in causation. Her research addresses eating disorders at the level of genes, cells, and regulatory systems of the body and how they interact with environmental factors.

As a scientist and physician, one specific question that motivates Dr. Bulik is to ask why, if the messaging about thinness in our culture is essentially ubiquitous, only some individuals develop an eating disorder. Research on the biological side of the question seeks to discover what it is about these individuals that distinguishes them or places them at high risk.

COUNTERINTUITIVE BEHAVIOR

There is a counterintuitive dimension in eating disorders, Dr. Bulik points out, which has led her to crucial insights. Why would any person deprive him or herself of food, to the point that they risk ruining their health and even dying?

"I think in the beginning," she says, "something has to be *reinforcing* about starvation in order for a person to persist in doing it. Because for the rest of us, who don't have this disorder, being hungry is not something we crave, not something we seek. It is not, in the language of psychiatry, 'reinforcing.'"

A remarkable fact was clear to Dr. Bulik as she treated patients with anorexia. She realized, "There is something about that first time or second time that they fasted and they realized: 'Oh, this feels *good*. I'm going to do this again.'" This elevated feeling, akin to a "high," is not only recollected by people diagnosed with anorexia; it can also be experienced by those with bulimia and binge-eating disorder, who sometimes restrict their food intake in between periods of binge eating. One contrast is that in the case of people with BN and BED, "their bodies don't seem able to maintain that [fasting] state, so they follow these periods with binges."

Are the three disorders connected? If so, in what way does environment interact with biology ? To help explain how, Dr. Bulik proposes that we consider a representative sample of young people of both sexes, all of whom are exposed not only to cultural messaging about weight, body shape, and fitness in advertising and social media, but who in this example receive a direct challenge from an authority figure to go on a diet, regardless of whether they are underweight, normal weight, or overweight.

"Imagine you have a classroom filled with 12-year-olds," Dr. Bulik posits. "Believe it or not, this actually happens: the teacher decides to go on a diet and invites the class to do the same. So they all decide to reduce their calorie intake by 40% on Monday and see how they feel later in the week."

"By Wednesday, *most* of the students will say, 'This is ridiculous. I want some pizza and ice cream. I'm moving on.' For *a couple*

New frontiers in research may translate in the coming years into much more effective and specific treatments for eating disorders.

of the kids, the 2 or 3 days of caloric restriction ends in a sensation of their body screaming out: they don't just want a slice or two of pizza and an ice cream cone; they eat a whole pizza and a half-gallon of ice cream. These are the children who are binge-prone. Then, there is *one young person, maybe two*, in the class who realize that being asked to go on that diet has been a watershed moment in their life. They say to themselves, 'Wow, this is awesome—and I'm good at this. I can do this and none of the others can. I also feel less anxious than I usually do.' These are the young people at risk for developing anorexia."

"This echoes something that so many of the parents we've worked with have told us. They say: 'It was as if from one day to the next our child was hijacked—as if they became a different person.' "

THE CONCEPT OF ENERGY BALANCE

What is really happening when a young person becomes conscious of deriving pleasure or satisfaction from extended caloric self-deprivation? Dr. Bulik explains it in terms of energy balance in the body. "People who maintain their weight can be thought of as being in energy balance; they are expending about the same amount of energy as they are consuming. People who are gaining weight are in positive energy balance, meaning they're eating more than they're expending. On the other hand, repeated fasting or consistent food restriction puts one in a position of *negative energy balance*—you're not consuming enough to match the body's energy needs and so your weight begins to decline."

Those whose initial experience of dieting is accompanied by a high

In a typical class of 100 adolescents, statistics suggest that several are likely at high risk for developing one of the three major eating disorders. Both genes and environmental factors are typically involved.

or feeling of satisfaction and then seek to repeat the behavior are at great risk of developing an eating disorder, according to Dr. Bulik. In the "restrictive" subtype of anorexia, the individual enters a potentially life-threatening state of negative energy balance. Those with anorexia who also binge and purge, as well as those who develop bulimia, experience energy imbalance in varying ways and degrees—depending on how much of their food intake they feel compelled to purge. People with binge eating disorder who in most (but not all) cases do not purge or otherwise "compensate" for excessive food intake can enter a state of positive energy balance and gain weight—although the term "positive" in this context is not to be confused with "desirable" since binge eating involves a dangerous loss of control over food intake.

A wide range of emotions are experienced by people with eating disorders. A few among these are potential anxiety associated with hypervigilance about body weight or shape; high or low feelings associated with periods of self-imposed deprivation of nourishment, whether or not followed by periods of loss of control over food intake; feelings of shame stemming from the societal stigma about eating disorders.

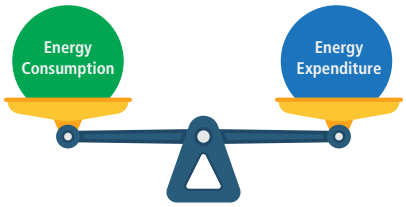
GENETIC LINKS WITH METABOLISM

The next question is how to understand why different individuals enter different energy-balance states. In 2018 and 2019, Dr. Bulik, heading a large international consortium, published influential papers reporting on what at the time was the largest genetic study of anorexia. This provided major new insights about anorexia and metabolism.

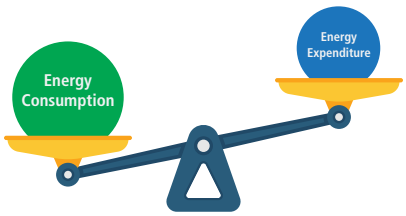
Results of the genome-wide association study (GWAS) identified eight areas in the human genome in which DNA variations are likely to contribute to risk for the illness. Unsurprisingly, it provided evidence that anorexia shares genetic factors with other psychiatric disorders including obsessive-compulsive disorder, anxiety, major depressive disorder, and schizophrenia.

But the GWAS data also contained a surprise. It revealed a significant correlation between the genetics of anorexia nervosa and metabolic traits. One key correlation was in body mass index, or BMI. As a result of restricting caloric intake and increasing energy expenditure, patients with anorexia nervosa typically have low BMIs. But studying the genomes of people with and without anorexia revealed that some of the same genes that increase someone's risk of developing anorexia nervosa also decrease their risk of having a high BMI. The same pattern was seen with Type 2 diabetes (T2D): genetic factors that place you at greater risk for developing anorexia put you at lower risk of having T2D. The processes in the body that normally regulate metabolism, including weight regulation and energy balance, may be malfunctioning in people with anorexia nervosa, underlying some of the weight and feeding symptoms that have previously been explained as purely psychological.

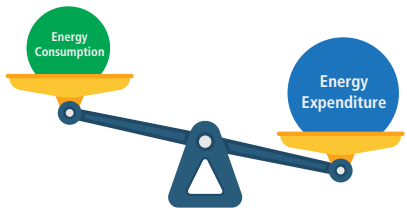
Not only do these results argue for treating anorexia as a *metabolic disorder* as well as a psychiatric one; they also have implications for the problem of severe stigma. Among the ways in which anorexia has been misunderstood, Dr. Bulik says, is that contrary to common belief, "patients often want to eat and desperately want to get well, but they find it enormously difficult to do so." The genetic data can help explain on



ENERGY BALANCE



POSITIVE ENERGY BALANCE



NEGATIVE ENERGY BALANCE

The concept of energy balance can help us understand eating disorders. While those who maintain their weight tend to take in roughly as much, in caloric terms, as their body consumes, those who deprive themselves of food enter a state of negative energy balance. In anorexia, remaining in this state for an extended period threatens one's very existence. In eating disorders that include episodes of binge eating, energy balance can actually move into positive territory, meaning more calories are being consumed than expended by the body, a situation in which weight can increase.

a metabolic level why, even after hospital-based weight restoration, patients with anorexia often rapidly lose weight again after discharge.

These findings, therefore, should help parents and loved ones understand that recovery is not simply a matter of "deciding" to eat more. As Dr. Bulik puts it: "For patients, recovery from anorexia nervosa is fighting an uphill battle against their biology and patients need our support in doing so."

The metabolic dimension of anorexia indicated by genome analysis has not yet been replicated in bulimia and binge-eating disorder. A consortium led by Dr. Bulik is working on a new, larger GWAS of anorexia nervosa and a GWAS of binge eating behavior. Results are due this summer. In the interim, she is leading a major international effort called the Eating Disorders Genetics Initiative (EDGI), which is conducting the largest study of genetic and environmental risk factors on all three major eating disorders.

METABOLIC 'BOOKENDS'?

The genetic link between BMI and anorexia that has been established has other potential implications. One pertains to a question that Dr. Bulik says she has been asked for years: "Is anorexia the opposite of obesity?"

It now appears to her that anorexia and obesity may be, to some extent, "metabolic bookends," conditions at opposite ends of a continuum. "On the high end of the weight spectrum, it's well known that it is fairly easy to get someone to lose weight, but that over time following weight loss, it's as if their bodies pull them back up to that higher weight. This happens even after bariatric surgery for many people. And of course, it's very common that we blame the patient—they've regained the weight because they lacked willpower or self-control.

"At the other end of the weight spectrum we see the exact same thing. You take someone with severe anorexia—it's fairly easy to get them to gain weight in the hospital. But so often after discharge, their bodies pull them right back down to that low weight again." Importantly, she says, "We really do our patients harm when we attribute blame for relapse on their choice or their willful behavior. That's the core import of the 'bookend' concept: we need to look metabolically and biologically why it is that when someone with anorexia or obesity loses or gains weight after seemingly effective treatment, they so often seem to relapse. In most cases, it is not a choice they are making. At least in part, the problem is the body's difficulty regulating energy balance or a natural inclination for the body to go off the rails and not keep energy balance within healthy parameters."

CRISIS IN TREATMENT

In two editorials published in 2021, one in *JAMA Psychiatry*, the other in the *American Journal of Psychiatry*, Dr. Bulik and a colleague called attention to "a crisis in care" for patients with anorexia. Mostly due to stigma, many patients are symptomatic for years before seeking treatment. No medications have specifically been developed to treat anorexia, and while some, like the SSRI antidepressant

Dr. Bulik stresses the importance of restoring regularity in the eating patterns of those recovering from eating disorders.

fluoxetine (Prozac), have been prescribed for some patients, they are not often effective, especially when given to patients already at low weight. Cognitive Behavioral Therapy is the most frequently successful treatment, but the overall relapse rate for adult anorexia patients is about 50%.

In recent years, a proliferation of privately run treatment programs for anorexia and other eating disorder patients has contributed to the closing of eating disorders programs in a number of academic medical centers, Dr. Bulik reports. Private-sector treatment tends to be available only for the affluent, as it is not often covered by insurance. And those who do enter such programs, like those in hospital-based programs, in Dr. Bulik's view, tend to be released too soon, after attaining 80% of "ideal body weight."

"This does not mean that recovery isn't possible," Dr. Bulik stresses. There is a window of 60 or more days after discharge from acute weight-restoration treatment during which risk of relapse is highest; it declines afterward. For this reason, Dr. Bulik advocates for "a fully integrated step-down model" of care for recovering anorexia patients in which renourishment is followed by participation in a residential treatment program or day program, and then intensive outpatient treatment followed by a less intense phase of such treatment. The key, in her view, is not to release patients from treatment after attaining "80% of ideal weight"—given what has been learned about the tendency of the body to return to a state of negative energy balance and relapse.

NEW FRONTIERS

New frontiers in research may translate in the coming years into much more effective and specific treatments for eating disorders. It is useful, Dr. Bulik says, to begin looking at the intestinal microbiome—the collection of microorganisms that each of us carries in our digestive system. "When you starve yourself," she says, by way of example, "you are also starving your bugs. This likely accounts for the lower diversity of microorganisms that we see in people with anorexia nervosa."

"One question we have is whether the remaining bugs that can tolerate a starvation environment actually contribute to perpetuating the illness. They may not react well when exposed to high-fat foods, for example. Also, there is constant communication between the gut and the brain, and we wonder about the extent to which an impoverished microbiome may seek to perpetuate itself by sending signals to the brain to, in essence, 'keep up the starvation.' "

Other recent research has indicated that the shape and function of the digestive system changes in people with eating disorders, and those changes may be a factor in explaining why it is so hard to renourish anorexia patients. The lining of the digestive system may lose some or much of its capacity to absorb nutrients. Various expedients have been proposed and are already being tested in preliminary research, using animal models: targeted probiotics, even fecal transplants (which can reintroduce new microorganisms to the microbiome).

A final point stressed by Dr. Bulik is "the importance across the three disorders, of regular eating." The aim, she says, is to try to restore regular eating: breakfast, lunch, dinner, timed snacks. "Because whether you have anorexia, bulimia or binge-eating disorder, if you are human, your body loves predictability. So restoring regularity is, in a sense, at the core of treatment across the three disorders." Among other ideas, Dr. Bulik and colleagues are experimenting with wearable technology like the Apple Watch to detect biometric signs of high risk for, say, binge-eating, accompanied by an alarm or text reminder to the patient.

Regarding the pace of much-needed change, Dr. Bulik comments: "Some people say we're paddling as fast as we can in research, but I challenge that. Our treatments haven't come very far in the past 20 years. It's not about how fast we paddle, it's about finding new ways of paddling to advance our understanding, improve outcomes, and eliminate mortality from these life-impairing illnesses." ❖ **PETER TARR**

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—Ken Harrison, Board Member

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Understanding Borderline Personality Disorder

Q&A with Anthony C. Ruocco, Ph.D., C. Psych.

University of Toronto
Professor, Interim Graduate Chair and Director of Clinical Training,
Department of Psychological Clinical Science

2014 BBRF Young Investigator
Families for Borderline Personality Disorder Research Investigator

Dr. Ruocco conducts research at the intersection of clinical psychology, neuropsychology, and cognitive-affective neuroscience. His focus is on externalizing psychopathology (disinhibited behaviors, personality disorder diagnoses and traits, substance use disorders), suicidal thinking and behaviors, and depression, with particular emphasis on executive functions, especially cognitive control.

Dr. Ruocco, personality disorders (PDs) are remarkably common in the population, perhaps affecting as many as 9% of adults, according to the National Institute of Mental Health. About 1.4% of U.S. adults (over 3 million) experience Borderline Personality Disorder in a typical year, the NIMH says, making it the most common PD. But you don't hear very much about BPD or other PDs. Is this due to stigma?

IN BRIEF
While affecting millions of American adults, personality disorders (PDs) are infrequently discussed. Our Q&A with a BBRF grantee on the most prevalent PD, borderline personality disorder (BPD), helps to clarify its symptoms, indicates what research has revealed about its biological underpinnings, and offers advice about treatment.

In the current DSM classification system, there are 10 distinct personality disorders [see box, below]. I study borderline personality disorder, in particular. Regarding BPD, I would say, yes, there is a stigma, but I would say we're starting to see change. We're starting to see more people talking about it. Although not as much, perhaps, as bipolar disorder, or autism, or depression, or schizophrenia.

One problem associated with the diagnosis is that many medical professionals don't know enough about personality disorders or how to treat them. You hear the story of the parent who goes to a local clinic and tells the doctor, "I think my child has borderline personality disorder." And the doctor replies, "Well, we don't actually treat people with that diagnosis at this clinic."

10 Personality Disorders
(as recognized in DSM-5)

Paranoid, Schizoid, Schizotypal, Antisocial, Borderline, Histrionic, Narcissistic, Avoidant, Dependent, Obsessive-Compulsive

Not because they don't want to, I assume, but because they don't know how?

Yes. The honest answer in such a case might be: "We don't have the expertise." Generally speaking, treatment for BPD [see p. 23] does need to be specialized to be effective. Because of this issue, many parents are being turned away and their children—often in their late teens and early 20s—are are not receiving the care they need. This can have real life and death consequences.

Let's start with some basics. What does it mean, exactly, to say someone has a personality disorder? It somehow sounds fundamentally different from saying a person has depression or schizophrenia.

In the way they have traditionally been defined, personality disorders can involve disturbances in up to four areas. One area is *identity*: how you perceive yourself, and yourself in relation to other people. A second area is disruption in *interpersonal functioning*—how you relate to other people. Those two areas are tightly related. A third area of potential disruption in the classical definition of PDs is in the area of *impulse control*. Finally, one can see disruptions in the *regulation of emotions*, or what we sometimes call affective stability.

There have been proposals in recent years to revise the way we clinically define PDs. The latest research suggests that while problems with impulse control and emotion regulation can be part of the clinical picture, it's likely that disturbances in one's identity and how one relates to others that forms the core of a personality disorder.

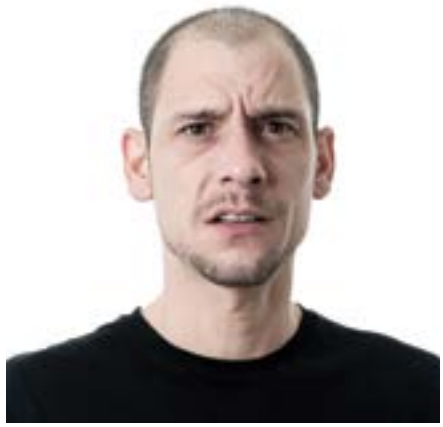
In this discussion, you and I will focus on one of the PDs, borderline personality disorder. I have to ask about the term "borderline." What does it mean?

Some people ask me, "Does it mean I'm at the borderline of having a personality disorder? Or does it mean something else?" In fact, when you are diagnosed with BPD it does mean you have a personality disorder. But the term "borderline" is a legacy of the original notion of the illness, from decades ago, when clinicians were unclear as to whether someone had psychosis, or whether they had some form of what was then called neurosis.

"Borderline" came into the picture because some people with BPD can appear "psychotic-like," and at the same time, have a severely unstable mood. When they're experiencing high levels of stress, they can experience difficulties with testing "reality." They might feel strongly that someone is out to get them, or they may have dissociative experiences in which they may feel they're floating above their body—or, that the world has slowed down; or, they have disruptions in their memory and time lapses they can't account for. At the same time, patients with BPD were described as having a very unstable mood, which could exacerbate their psychotic-like experiences. These are some of the reasons why the terms "borderline" was originally used and it has remained part of the terminology.

But to be clear: today, BPD is more strongly associated with the emotional components of the original conceptualization—it's largely thought of as a disorder centering on emotional dysregulation, and to some extent, impulsive behaviors.

The various behavioral phenomena seen in people with BPD can include anger, difficulty controlling emotions and impulses, chaotic and often severed personal and familial relationships, social avoidance and loneliness, instability in one's sense of self, and sometimes a feeling of emptiness.



On the other hand, that is not all that is involved, right?

Exactly. There are other types of symptoms. But the way many major theorists think about it these days is that emotion dysregulation might actually be the reason that people with BPD, for example, have problems having a stable sense of identity—because their emotions are so up and down, it's hard to have a sense of who you are. We also think they have difficulties with controlling their impulses because their emotions might be so intense that they do things that are out of character for them.

Why not, then, call it "impulse control disorder"? Perhaps that would carry less of a stigma?

You are not the first person to suggest something like this. Dr. Marsha Linehan, who is one of the main figures in the field of borderline personality disorder and developed dialectical behavior therapy (DBT) to treat it, proposed the term "emotion regulation disorder." That being said, BPD can be expressed in a range of additional ways. It's important to try to capture those, too.

If I hear you right, the aspect of the disorder that has to do with uncertainty about one's identity and/or a shifting perception of the self and one's relation to others, may be but isn't necessarily related to "emotion dysregulation"—and these other common aspects of BPD are important to keep in focus?

Yes. Another thing is that the disorder really differs from one person to another. One can be highly emotionally dysregulated and highly impulsive, but that doesn't necessarily capture whether the person has more of an identity or interpersonal problem. Often people with BPD have a really unstable sense of who they are. They're very fearful of people abandoning them. They have really chaotic interpersonal relationships. They may have anger difficulties. These are all aspects that can also be part of the picture.

Let us now turn to BPD as it is defined in the current 5th edition of the DSM. What kinds of traits are mentioned in DSM-5 and how many of them do you need to receive a diagnosis?

Anybody who's going to receive a diagnosis needs to meet what we call the general diagnostic criteria for a personality disorder. That's in the DSM, and it includes having a disturbance in at least two of four domains, as I mentioned earlier: identity, interpersonal functioning, impulse control and emotion regulation. That's the starting point. For BPD specifically, you need to meet any combination of five of nine potential symptoms. Impulse control symptoms involve things like substance abuse, binge eating, reckless driving, etc. These in turn often go hand in hand with suicidal behavior. The latter can include self-harm without the intent to die and self- harm with the intent to die, which are often related to people's emotion regulation abilities and impulse control. People with BPD can be set off easily in terms of their emotions and have a difficult time getting back to their baseline emotion, because they tend to be so highly reactive. They find it difficult to control their emotions. Acute episodes like this can last several hours. Often what people talk about as being one of the most impairing aspects of BPD is feeling out of control of one's emotions and feeling like they're experiencing their emotions very intensely. In addition to this, patients sometimes express fears of abandonment. This is one of the other interpersonally relevant symptoms. Another symptom that's relevant to interpersonal functioning, as I said earlier, is chaotic, turbulent, up-and-down relationships, where people with BPD will view others in an "all or nothing" way.

This is splitting between "all good" and "all bad," and it can shift—the view of a person can go from positive, maybe unrealistically so, to unrealistically negative, and rather rapidly, right?

Exactly. It can be a really rapid shift, and we think this can contribute to chaotic relationships and having a really hard time maintaining relationships. This often comes out in a familial context as well. So many of the people that we've studied aren't in contact with family members because of this history of chaotic relationships.

Another trait often seen in BPD is outward displays of anger, where people are breaking things, or constantly experiencing feelings of anger, and really having a hard time regulating it and having that anger subside.

TREATING BPD

(Source: National Institute of Mental Health)

PSYCHOTHERAPY

Psychotherapy is the first-line treatment for people with borderline personality disorder. A therapist can provide one-on-one treatment between the therapist and patient, or treatment in a group setting. Therapist-led group sessions may help teach people with BPD how to interact with others and how to effectively express themselves. It is important that people in therapy get along with and trust their therapist. The very nature of BPD can make it difficult for people with the disorder to maintain a comfortable and trusting bond with their therapist. Two examples of psychotherapies used to treat BPD include:

- **Dialectical Behavior Therapy (DBT)**: This type of therapy was specifically developed for individuals with BPD. DBT uses concepts of mindfulness and acceptance—being aware of and attentive to the current situation and one's emotional state. DBT also teaches skills that can help, including controlling intense emotions, reducing self-destructive behaviors and improving relationships.
- **Cognitive Behavioral Therapy (CBT)**: This type of therapy can help people with BPD identify and change core beliefs and behaviors that underlie inaccurate perceptions of themselves and others, and problems interacting with others. CBT may help reduce a range of mood and anxiety symptoms and reduce the number of suicidal or self-harming behaviors.

MEDICATIONS

Because the benefits are unclear, medications are not typically used as the primary treatment for BPD. However, in some cases, a psychiatrist may recommend medications to treat specific symptoms such as: mood swings, depression, and other co-occurring mental disorders.

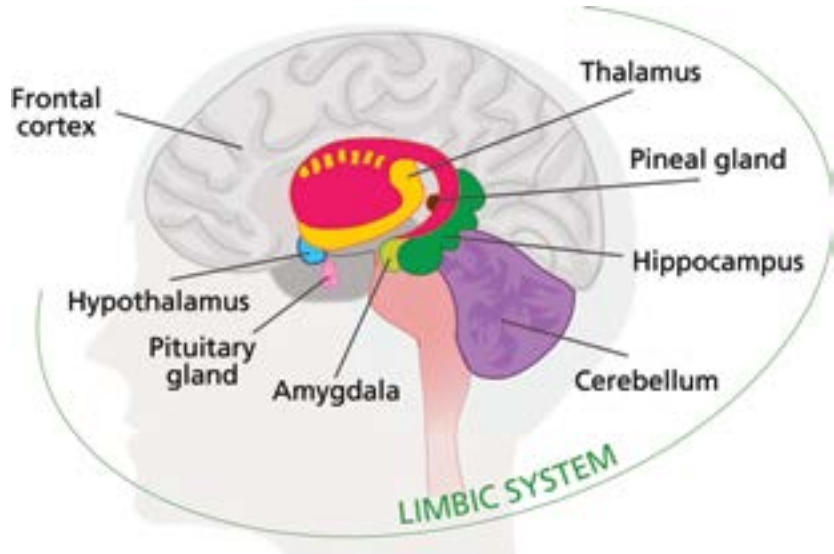
In contrast with the symptoms I've so far mentioned are two contrasting traits of the nine mentioned in the DSM. The first is a pervasive sense of emptiness. And, as I mentioned earlier, people with BPD may also have stress related to dissociative experiences, i.e., disturbances in one's sense of reality that occur under stress. Also, people with BPD could, when they're under stress, experience suspiciousness and paranoia around people they normally trust. So you can see it's a bit of a mixed bag, but at least five of these symptoms in combination is what leads to a BPD diagnosis.

And BPD is often comorbid or co-occurs with a number of other psychiatric diagnoses?

Yes, BPD is comorbid with a wide range of diagnoses. Most commonly, these include depression, especially chronic, long-standing depression. It can also be co-diagnosed with post-traumatic stress disorder (some have proposed that BPD might be a form of complex PTSD). BPD is also comorbid with substance-use disorders, whether it's alcohol or other substances. Occasionally BPD overlaps with bipolar disorder, but I think of this mainly in the area of mood instability. The two can sometimes be confused and it's important for patients to work with a psychologist or psychiatrist with expertise in BPD to understand whether one or both of these disorders might be diagnosed for a given person.

And what about ADHD?

Yes, we see high levels of comorbidity with ADHD, which is interesting to me because I study cognition, and a lot of people with BPD report difficulties with attention and memory. Interestingly, ADHD is also associated with impulsivity. So there's a lot of overlap in the symptoms of these disorders. The other piece that I think is really important to note is BPD's co-occurrence with social anxiety disorder. Social anxiety is often one of the more impairing aspects of BPD.



Research suggests that parts of the limbic system, which encompasses the brain's emotion centers, may be overactive in people with BPD relative to unaffected indivdiuals, while the frontal cortex, which regulates limbic areas, may be underactive.

Is there a common element of social avoidance in the two?

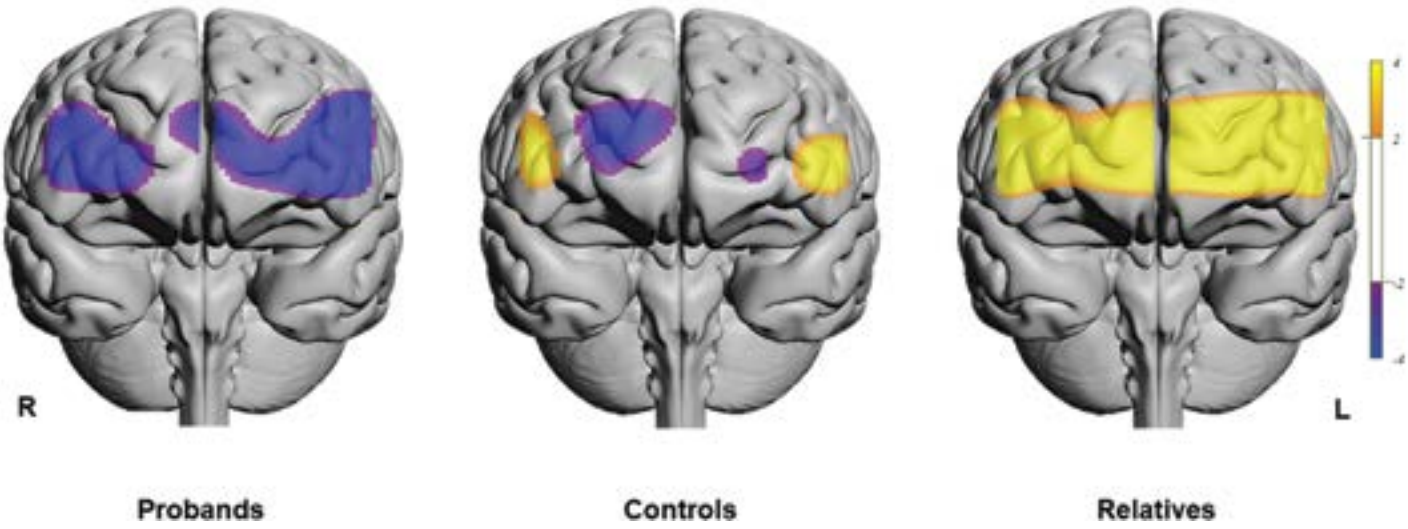
There can be. In BPD, as we've discussed there can be a fear of rejection. Because of interpersonal problems, and how easily a person with BPD can be emotionally triggered, some people tend to avoid social contacts and they can become isolated. Fear of rejection is such a painful experience, and avoidance may be an adaptive thing to do in the short-run. But this has consequences over the longer term for feeling connected to other people, feeling that you have a social support network, being able to rely on other people for support.

Is it true that more females than males have BPD? Or is that more of a myth than reality?

What I think can be a bit deceiving is that when you read research on BPD, often the people who are studied are women. I think the reason is that women tend to be more likely to seek treatment. And often, when people are doing research, they're recruiting from a clinic. And so we see treatment-seeking samples often being highly skewed toward women. However, if you study people at a population level, you start to see a greater balance in how many people of each gender are affected.

Dr. Ruocco, your field is clinical neuropsychology. Please explain the relation of your experience with patients with your work in research to discover what may be driving the symptoms of BPD.

My training was at the intersection of psychology, psychiatry, and to an extent neurology. Integrating them has been one theme of my career. As a clinician,



Brain scans have revealed patterns of prefrontal cortex activation in 3 groups: people with BPD ("probands"), unaffected controls, and 1st-degree biological relatives of the BPD participants. The scans were taken while each participant was engaged in a task testing impulse control. BPD patients (left) deactivated (blue-shaded) areas in the prefrontal cortex more prominently, whereas relatives (right) showed increased activation (yellow coloring) across the PFC. Controls (center) showed a combination of activation and deactivation patterns.

I've seen a lot of people with personality disorders, and have been involved, I would think, in diagnosing hundreds of them. What I love about what I do is trying to apply what we are learning about the biology of the brain to a disorder like BPD.

In the titles of a number of your papers on BPD there are references to the frontal and limbic regions of the brain. Tell us about the significance of those regions.

We often refer to regions deep within the brain, such as the amygdala—one of the brain areas central in processing fear and emotion—as parts of the limbic system. We tend to think about the limbic region as a somewhat more primitive part of the brain that is reacting to some type of an event—it is engaged in our response to stimuli.

In contrast, we have "higher," regulatory regions of the brain that come online, as the name implies, to regulate the emotion centers. The regulatory regions can be called frontal regulatory regions. The frontal, functionally more advanced regions of the brain evolved to presumably impose control over those more primitive systems.

In people with BPD, my research and the research of others has found greater activation [than typical] in the limbic regions, especially the amygdala. My research has also highlighted heightened activation in the insula—a brain structure that appears to be involved in how intensely somebody experiences emotion. These two limbic-related regions tend to be overactive in people with BPD.

The frontal regions of the brain that we believe are involved in regulating the limbic regions tend to be underactive in people with BPD. And so you start to see, perhaps, one component of the biological basis for BPD, an imbalance between the emotion-generating centers and an inadequacy of the control-related regions. This could help explain why we see emotion dysregulation in people with BPD.

The findings you sketch out in broad terms are based on imaging that your team has performed while people with BPD have performed tasks, right?

Probably the most common way that we study emotion in people with BPD is by presenting "emotional faces" to them—pictures of people—while imaging the brain in real time. Another method is to have people with BPD generate written scripts—to literally write down an account of a time when they were abandoned by somebody. They write that down, we have them read it, and record it, then play the tape to them when they're in the MRI scanner. We hope in this way to invoke responses that are specific to that person's history.

Then, in terms of better understanding of impulse control, one thing we do is present people with a very simple task, like pressing a button every time they see a letter of the alphabet that comes up on a computer screen, except for, let's say, an "S." That means if an S comes up on the screen, they must withhold their response. If we have somebody do that for, say, 15 minutes, we're building up their response tendency. When we infrequently present the S, they need to control that. We

"What I love about what I do is trying to apply what we are learning about the biology of the brain to a disorder like BPD."

study brain activation that occurs during those infrequent "Stop, don't press the button" moments.

And what have you discovered by doing this?

What we found in our recent family study of those with first-degree relatives with BPD was that people with BPD show less activation in the frontal regions of the brain that we think are important for bringing this inhibition to the fore. Interestingly, we expected that family members would show a similar type of a pattern. But instead we saw an overactivation in the frontal lobes of relatives. It was unexpected; the effect was quite robust. We think this may indicate that the close relatives of people with BPD might be compensating for a trait they share with their relatives with BPD. The difference being that they have a more capable regulatory system, so they can actually switch it on and maybe turn up the regulation, and it works for them.

But we went on to discover, also unexpectedly, that even if you compared relatives of people with BPD to controls who don't have a family history of mental illness or a relative with BPD...the relatives of people with BPD still showed even more activation of control regions than the average person. We don't really know what this means, but it could mean the relatives have some unique functioning within their brains that comes online when they need to control their behavior.

But regarding the BPD patients themselves. How do your discoveries so far about limbic and frontal regions inform the way we approach treatment?

I think there are two potential treatment implications. If these indeed are the regions that are activating differently in BPD, maybe intervening at the level of the brain will be therapeutic and help to control or reduce symptoms. There is emerging research to suggest that using a wide range of non-invasive brain stimulation techniques could potentially help, including Transcranial Magnetic Stimulation (TMS) and what I'm studying with help from my BBRF grant, Magnetic Seizure Therapy (MST), which is a newer form of brain stimulation treatment that's related to ECT. These types of treatments seem to be not only improving symptoms in some people with BPD but they might also be having an effect on the brain. At this point, it's too early to say precisely what effect. But there is some indication that the brain is changing, and that symptoms are changing. We need to know more.

MST is non-invasive, but does involve inducing a therapeutic seizure?

The patient is under general anesthesia, but MST is non-invasive in the sense that nothing is surgically implanted in the brain. In MST, magnetic field pulses are directed into the brain through a magnetic coil and produce a seizure. MST is applied in a more targeted way compared with ECT. One of the benefits of being more focal is that you see fewer side effects than with ECT, including cognitive side effects such as memory loss. The seizures are generated, of course, in a highly controlled environment and are thought to be changing the functioning of the frontal region where they are targeted. This research is done in collaboration with physicians who are experts in brain stimulation.

Two kinds of talk therapy, dialectical behavioral therapy (DBT) and cogntiive behavioral therapy (CBT), have been used to successfully treat some people with BPD. Women with BPD tend to seek treatment more often than men, which helps account for the possibly false impression that many more women than men have the disorder.

What are the impacts on symptoms?

Generally, studies using MST show improvements in depression and perhaps in suicidal ideation as well. In our research, it's being applied in a way similar to that in depression, but in people with BPD we're also interested in whether it can potentially be used to reduce suicidal thinking, which could ultimately reduce acute suicide risk.

We have read that BPD may be caused by "a collision of a person's genes and temperament with suboptimal or hostile environmental experience." Could you comment on that hypothesis?

I don't think BPD is necessarily all that different in this context from bipolar disorder or schizophrenia, to cite just two examples. It is likely that major psychiatric disorders such as these are influenced by both genetic and environmental factors. For BPD, there's a genetic component, a genetic predisposition. There is also an environmental component. Some people with BPD experience what is sometimes called an invalidating environment. You can also say, a stressful environment. A stressful, traumatic childhood, for instance. In many cases it could well be these things in combination, not necessarily in isolation.

At the same time, some people with BPD who I have talked to will say, "I didn't have a traumatic childhood, I didn't have an invalidating environment. But I still have BPD." So there are important differences, and not everybody looks the same. It's important to acknowledge that some people might have more of a genetic component and other people greater environmental stresses. It's plausible that those who have both are going to be at the greatest risk.

What is the typical long-term trajectory of BPD?

Generally, there tend to be ups and downs over time. But I think where the hope comes in is that when people enter treatment, within a few months, especially when we're talking about Dialectical Behavior Therapy, the more severely dysregulated behaviors, especially those that are more life-threatening, tend to come under control.

And then over time, you see an improvement in symptoms, and when they've been followed up, many patients experience what is called remission, or periods when they no longer have the full symptoms. "Recovery" is a different question, however. Is the patient actually engaging with people meaningfully again? Are they employed? Do they have meaningful social interactions? This is where my research is going. What are some of the reasons people may not achieve recovery? Might there be cognitive reasons? Are there other reasons?

Finally, if any of our readers want to know more about BPD, or are worried about the mental health of a loved one or dear friend, what would you advise?

I always recommend starting with the National Education Alliance for Borderline Personality Disorder (NEA-BPD) (https://www.borderlinepersonalitydisorder.org). It is an excellent place to connect people with BPD and families with helpful resources. The specifics about how to find help can vary depending on your geographical location and access to mental health services and specialists who treat people with BPD. The NEA-BPD website has some very useful questions for people to consider as they think through where to find treatment and what type and intensity of treatment might be needed depending on a person's specific situation. They also provide links to websites that can help you to narrow down your search. ❖ **INTERVIEW BY PETER TARR**

Create Your Legacy of Philanthropy with a Donor Advised Fund

Funding mental health research now is crucial to ensure the success of future scientific breakthroughs.

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Analysis Reveals Differences in Brains of Boys and Girls with Autism Spectrum Disorder

Researchers have reported distinct brain differences that enable them to distinguish between males and females with autism spectrum disorder (ASD).

The distinguishing brain features involve connectivity and the functional organization of several brain areas. These differences were identified in a large sample of affected boys and girls and were then replicated in a smaller, independent sample.

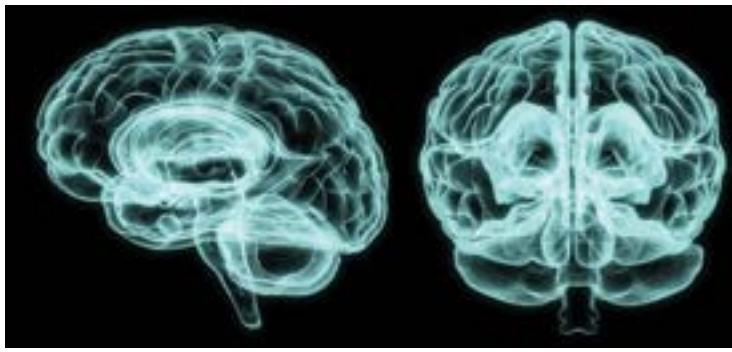
The researchers said the gender differences in ASD they identified appear to contribute to somewhat different clinical symptoms experienced by males and females. One of the distinguishing features, involving the brain's motor cortex, enabled the team to predict the severity in females of restrictive or repetitive behaviors, a specific and often-seen ASD-related symptom that usually is more severe in males with ASD.

Reporting in *The British Journal of Psychiatry*, the team was led by **Kaustubh Supekar, Ph.D.**, a 2014 BBRF Young Investigator. The senior author of the team's paper was **Vinod Menon, Ph.D.**, a 1998 BBRF Young Investigator. Both are based at Stanford University.

One reason the new findings are important is that ASD presents a variety of symptoms in different patients. Gender has long been thought to be among the more important contributing factors. Not only do symptoms tend to be somewhat different in males and females; about 4 times as many boys receive the diagnosis (1 in 42) than girls (1 in 189). Researchers want to know why, but answers have been difficult to determine.

The study by Drs. Supekar, Menon and colleagues was motivated in part by the fact that most autism studies have focused on males—perhaps in part because so many more boys than girls seem to be affected. But it is not clear if females are affected in ways, perhaps quite subtle, that may elude or be undetectable by some doctors, especially in the first years of life.

The new study was designed to focus on underlying biological patterns rather than overt or reported symptoms. It was based upon data from functional MRI imaging scans of the brains of 773 children with autism—637 boys and 136 girls. It was essential to statistically compensate for the numerical skew in the scans. To accomplish this, the team made an important advance in developing an artificial intelligence framework which relies upon a model called spatio-temporal deep neural network (stDNN) analysis.



This new technology was first applied to imaging data from 678 of the children. The analysis generated an algorithm which enabled the team to distinguish between boys and girls with 86% accuracy. The method was then verified on the 95 scans in the total sample that were intentionally not included in the initial analysis. In addition, stDNN was used to analyze 976 brain scans from typically developing boys and girls.

These were the results: among children with autism, girls had different patterns of functional connectivity than boys in several brain centers, including motor, language, and visuospatial attention systems.

The largest differences between the genders were in a group of motor areas, including the primary motor cortex. Furthermore, among the girls with autism, differences in motor areas were linked to the severity of their repetitive behaviors. Girls with autism usually have fewer repetitive behaviors than boys with autism, which may contribute to delays in their diagnosis, the team suggested.

The team's results suggested that girls with autism whose brain patterns were more similar to those in boys with autism tended to have the most pronounced repetitive behaviors. Another important finding was that while they were able consistently to distinguish between males and females with ASD based on stDNN analysis, that same model could not distinguish between typically developing males and females with no ASD diagnosis. This suggests the identified differences in autism in this study are indeed related to symptoms and symptom differences in boys and girls with ASD.

It is not yet possible to move from identifying factors which distinguish male and female ASD patients to knowing how each or in combination they affect the acquisition of motor, visuospatial, and social communications skills in specific individuals. That is a subject for future studies, as well as the question of how, and with what impact, the identified gender-distinguishing features overlap or do not overlap with other brain differences in people with ASD.

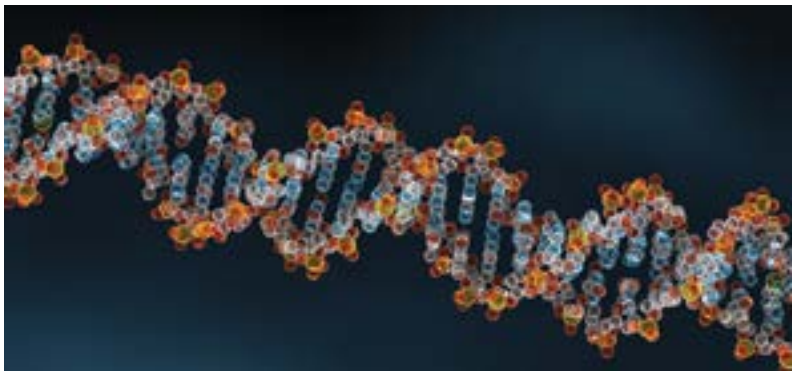
In an interview, Dr. Supekar expressed the hope that the findings of the present study might be used to guide future efforts to improve diagnosis and treatment for girls with ASD. Taken together, he said, "the use of artificial intelligence-based techniques" used in the analysis has promise in advancing "precision psychiatry" in autism. ❖

Genome Comparisons Reveal DNA Risk Variants for Depression Differ in People of East Asian vs. European Ancestry

An analysis of multiple genome-wide studies making associations between depression and "risk" locations in the human genome has provided a vivid demonstration that results can vary substantially depending on the ethnicity and even country of origin of those whose genomes are being studied.

Members of the major depression working group of the Psychiatric Genomics Consortium and an international team of researchers that included 10 recipients of BBRF grants and prizes and two BBRF Scientific Council members, **Kenneth S. Kendler, M.D.**, and **Murray B. Stein, M.D., MPH**, set out to compare results of genome-wide association studies ("GWAS") for depression based on DNA from persons of European ancestry vs. persons of East Asian ancestry. Their results appeared in *JAMA Psychiatry*.

GWAS studies to date have identified 102 specific DNA variants across the genome that correlate with depression risk. The great majority of participants in such studies have been of European descent. The broad question is: can the findings of GWAS studies be generalized across different ancestry groups and different regions of the world? Few studies have been devoted to testing these questions.



The research team performed a meta-analysis, or a study of multiple prior studies, of GWAS datasets on depression exclusively involving East Asian subjects. Meta-analysis adds significant power to the results of any study considered individually. The team drew upon genome data from 9 cohorts, all comparing the genomes of East Asian individuals with depression vs. East Asian controls with no depression diagnosis.

Altogether, 194,548 genomes formed the basis of the comparisons, which included 15,771 individuals with depression and 178,777 controls. While all were of East Asian descent, the sample included some people residing in East Asian nations, notably China and Taiwan, as well as some people with East Asian ancestors who now live in Western nations.

The results were dramatic: only 11% of genome locations associated with depression risk in past GWAS studies of people of European ancestry were also found to be risk locations in people of East Asian ancestry. The actual overlap in the two populations is probably greater, the teams said, and would likely increase somewhat with a larger sample of individuals of East Asian ancestry.

Still, the differences between individuals of European and East Asian ancestry were striking. Perhaps the most important difference between the two groups was that pertaining to high body mass index (BMI). In people of European ancestry, some of the gene variants linked to higher depression risk are also associated with higher BMI, and vice versa. In people of East Asian ancestry, the opposite was found: there was an association between variants for higher depression and lower BMI.

In addition to BMI, other correlations from depression studies with European ancestry participants that did not hold up in some East Asian samples were associations with type 2 diabetes and coronary artery disease.

Results of their study, the team said, "supports caution against generalizing findings about depression risk factors across populations, and highlight the need to increase the ancestral and geographic diversity of samples" for illnesses and disorders defined in a consistent way across populations.

"Extending this work to other population groups can yield new biological insights pertinent to specific populations and facilitate improved genetic risk prediction across ancestry groups," they added.

By combining GWAS studies of cohorts of East Asian and European descents, the team identified three novel associations that were not significant, statistically, in either European-based or East Asian-based cohorts considered alone. They also discovered a novel depression association on chromosome 7 in studies conducted with people of East Asian descent that was not detected in depression studies based on U.S. or UK datasets. ❖

In addition to Dr. Stein and Dr. Kendler, who in addition to being a BBRF Scientific Council member is a 2010 and 2000 BBRF Distinguished Investigator and 1995 BBRF Lieber Prize winner, the team included: **Margit Burmeister, Ph.D.**, 2008 BBRF Distinguished Investigator, 2004 and 2002 Independent Investigator and 1996 and 1993 Young Investigator; **Po-Hsiu Kuo, Ph.D.**, 2017 BBRF Independent Investigator and 2006 Young Investigator; **Stephan Ripke, M.D.**, 2015 BBRF Young Investigator; **Erin Dunn, MPH**, 2013 BBRF Young Investigator; **Andrew M. Mcintosh, M.D.**, 2010 BBRF Independent Investigator; **Eli A. Stahl, Ph.D.**, 2013 BBRF Young Investigator; **Roseann E. Peterson, M.D.**, 2019 BBRF Young Investigator; and **Niamn Mullins, Ph.D.**, 2020 BBRF Young Investigator.

Obesity Is a Risk Factor for Brain-Structure Changes in Schizophrenia & Bipolar Disorder, 2 Studies Show

Tomas Hajek, M.D., Ph.D., a 2015 BBRF Independent Investigator and 2007 Young Investigator at Dalhousie University in Halifax, Nova Scotia, has led two research studies exploring brain-structure changes in schizophrenia and bipolar disorder.

In *Schizophrenia Bulletin*, he and colleagues reported that obesity is a risk factor for accelerated aging of the brain, which they found to be correlated in some patients with more severe negative symptoms and lower functioning in the 1- to 2-year period following a first episode of psychosis (FEP). Separately, in *Molecular Psychiatry,* Dr. Hajek and a large international team reported that comorbid obesity may explain why certain brain-structure alterations are more pronounced in some individuals with bipolar disorder.

The psychosis study followed upon prior results Dr. Hajek and colleagues had obtained which demonstrated that obesity was associated with advanced brain age and reduced volume of the brain's cerebellum in individuals who had experienced a first psychotic episode. One objective in the new study was to establish whether obesity was contributing to observed brain changes in the FEP patients or perhaps had a role in causing them.

Dr. Hajek's focus on FEP reflects his belief that studying people early in the course of illness is particularly relevant for early intervention and for prevention of long-term negative outcomes.

One relatively new measure of the impact of psychosis and schizophrenia on the brain is to calculate the "biological age" of the brain in patients, and to compare that age with the individual's chronological age (i.e., time since birth).

In the *Schizophrenia Bulletin* study, structural magnetic resonance imaging scans (sMRI) were collected in 183 FEP patients during their initial hospitalization for psychosis as well as in 155 healthy controls. A second set of scans was made 1 to 2 years after the first. An additional sample of 504 healthy controls received sMRI scans, results of which were fed into a machine-learning computer program and used to train software designed to calculate the brain's effective biological age.

"We were most interested to find out whether any of the factors we assessed at the time of the initial scan would allow us to predict brain age when we performed the second scan, 1 to 2 years later," said Dr. Hajek.

The study revealed that participants with FEP had a higher initial biological brain age compared with controls—3.4 years older, on average. But these same patients and controls showed similar annual rates of brain aging during the average 1.6-year interval separating the first brain scan in the study from the second. This is good news for patients, the researchers say. At the same time, one factor measured at the time of the first scan did predict faster brain aging in the next 1 to 2 years in FEP participants: body mass index (BMI), a measure of obesity.

Brain aging between the scans grew more rapid at the rate of one month per year, on average, for each additional point on the BMI scale. In those FEP participants in whom brain aging was accelerated, negative symptoms also tended to worsen. (Negative symptoms in schizophrenia, which have a great impact on potential for recovery, include flattened emotions, reduced motivation, and a disinclination to socialize or seek pleasure.)

The findings reveal that obesity contributes to brain alterations in FEP, and that this relates to the severity of negative symptoms. This evidence, they advise, emphasizes the need to improve weight monitoring and management in FEP patients and to better integrate medical care and psychiatric care. The findings also suggest the future possibility that improved treatments for newly diagnosed psychosis patients might be developed based upon targeting factors in the brain which underly the obesity-brain age association.

A similar conclusion was reached in the study by Dr. Hajek and a different team, studying obesity and brain changes in patients with bipolar disorder. That study showed that higher BMI scores may account, at least in part, for one of the most often-noted brain changes seen in people with bipolar disorder: enlargement of the ventricles. The ventricles are four interconnected cavities in the brain in which vital cerebrospinal fluid is produced.

"The fact that a significant part of the association between bipolar disorder and ventricular volume was related to higher BMI," the team noted, "raises the possibility that targeting BMI could lower the extent of ventricular expansion in bipolar disorder patients."

Dr. Hajek said that jointly the two studies "suggest that obesity is relevant for the presence and progression of brain changes and related adverse mental health outcomes, and that future studies should explore the impact of weight-management on brain health and clinical outcomes in patients with major psychiatric disorders." ❖

In addition to Dr. Hajek, members of the team on the bipolar disorder paper included: **Paul Thompson, Ph.D.**, 2017 BBRF Distinguished Investigator; **Lakshmi Yatham, MBBS, FRCPC**, 2018 BBRF Colvin Prize winner, 2003 and 1999 Independent Investigator and 1996 Young Investigator; **Martin Alda, M.D.**, 2003, 1999 BBRF Independent Investigator; **Lisa Eyler, Ph.D.**, 2001 BBRF Young Investigator; **Janice Fullerton, Ph.D.**, 2007 BBRF Young Investigator; **Colm McDonald, M.D., Ph.D.**, 2009 BBRF Independent Investigator, 2002 Young Investigator; **Roel Ophoff, Ph.D.**, 2016 BBRF Distinguished Investigator, 2008 Independent Investigator, 2005 and 2002 Young Investigator; **Jonathan Savitz, Ph.D.**, 2015 and 2009 BBRF Young Investigator; **Dan J. Stein, Ph.D.**, FRCPC, 1991 BBRF Young Investigator; and **Eduard Vieta, M.D., Ph.D.**, 2012 BBRF Colvin Prize winner.

Therapy Update

Recent news on treatments for psychiatric conditions

OXYGEN THERAPY FOR MODERATE DEPRESSION SHOWED BENEFICIAL EFFECTS IN PILOT STUDY

Yuly Bersudsky, M.D., Ph.D.

In a pilot trial, researchers have reported that treating mild to moderately depressed individuals with oxygen-enriched air had "a significant beneficial effect" on some depression symptoms.

Fifty-one participants completed 4 weeks of the oxygen vs. placebo treatment. The trial was designed to test the idea that delivering oxygen at normal atmospheric pressure ("normobaric") in moderately higher concentration than ambient air might improve certain aspects of brain function and provide some measure of relief from depression symptoms.

The concept is not to be confused with "hyperbaric" oxygen therapy, or HBOT, which is used in medical facilities around the world to speed healing of carbon monoxide poisoning, gangrene, stubborn wounds, and infections in which tissues are starved for oxygen. Those who receive hyperbaric oxygen must enter a special chamber to breathe pure oxygen at air pressure levels 1.5 to 3 times higher than normal.

A team at Ben-Gurion University of the Negev in Israel co-led by 2007 BBRF Independent Investigator and 1996 Young Investigator **Yuly Bersudsky, M.D., Ph.D.**, and Abed N. Azab, Ph.D., had the idea of testing normobaric oxygen treatment in depression, after previously trying it in a pilot trial involving individuals with schizophrenia.

In their paper appearing in *Scientific Reports*, the team noted prior studies in which highly enriched or pure oxygen delivered at normal atmospheric pressure impacted a measure called oxygen partial pressure in brain tissue, leading to improved function of mitochondria, the ubiquitous energy factories that power our cells.

The researchers sought to determine whether treating depressed individuals with oxygen that is only moderately enriched, at standard atmospheric pressure, might similarly improve mitochondrial function or affect brain biology in other ways that might be therapeutic.

The 51 participants who completed the trial were randomized to receive either oxygen-enriched air (35% oxygen) or ambient air (21% oxygen), delivered through a nasal tube during the night, for 7-8 hours per night, over a 4-week period. Any medications the participants were already taking continued to be administered during the trial. Twenty-nine of the 51 received oxygen-enriched air treatment, while 22 received ambient air, which served as a placebo. The air was delivered via the same equipment, so that neither group knew whether they were in the treatment or control group. The study was double-blinded, meaning those administering the treatments also did not know the identity of participants receiving enriched oxygen therapy.

Sixty-nine percent of those in the enriched oxygen treatment group improved over the 4 weeks, compared with 23% in the control group. The severity of symptoms was measured in all participants using a number of different scales, two of which showed significant improvement while the others showed no improvement.

Benefits were experienced in depressive and anxiety symptoms and in "cognitive disturbance," including a decrease in suicidal thoughts, feelings of guilt, and insomnia, among other positive therapeutic effects. There was some suggestion that the therapy also improved coping ability. No significant side effects were seen in any of the study participants.

The team said that the notable differences between the treated and control groups was evident only after 4 continuous weeks of oxygen therapy. While their study was not designed to determine how or why oxygen therapy may have beneficially impacted brain function, they hypothesize that raising the pressure of the dissolved oxygen portion of blood plasma affects oxygen pressure at key enzymes, and perhaps in mitochondria, possibly causing beneficial effects.

The results were encouraging to the team, which said the concept, being "simple, non-invasive, and safe," merits further exploration in larger replication studies. These would ideally recruit more patients including some with severe depression symptoms, and might test enhanced oxygen over longer periods and with follow-ups to measure the efficacy and durability of the pilot study's results. ❖

ADDING LITHIUM MIGHT ENABLE KETAMINE'S ANTIDEPRESSANT ACTIVITY IN KETAMINE-RESISTANT PATIENTS, STUDY SUGGESTS

Susannah J. Tye, Ph.D.

Researchers have published results of experiments in rodents suggesting that lithium, a widely prescribed mood stabilizer, may have value as an adjunct to ketamine therapy in people who suffer from treatment-resistant depression (TRD).

The findings, published in *Translational Psychiatry*, are particularly interesting in view of disappointing results in a clinical trial published in 2019 that found no benefit from adding lithium to ketamine therapy in a group of patients with unipolar depression. In that study, importantly, all of the patients who participated showed an initial antidepressant response to a single ketamine treatment before being randomized into groups that received either ketamine plus lithium or ketamine plus placebo in three subsequent treatment sessions. The antidepressant response was not enhanced in those who received adjunctive lithium, an analysis indicated.

A team led by 2009 BBRF Young Investigator **Susannah J. Tye, Ph.D.**, of the Mayo Clinic Depression Center and the University of Queensland, Australia, decided to further explore the possibility of lithium's potential value as an adjunct to ketamine therapy. 2006 BBRF Independent Investigator **Mark A. Frye, M.D.**, also at the Mayo Clinic, was a member of the team. First author of their paper was J. Blair Price, Ph.D.

The researchers noted that lithium is commonly prescribed as an adjunct to conventional treatments for treatment-resistant depression and "shares overlapping mechanisms of action with ketamine." Dr. Tye and colleagues also noted that lithium has been observed in rodent models of TRD to enhance the duration of ketamine's antidepressant effects.

One theory of ketamine's mechanism of action centers on its ability to increase the number and activity of AMPA receptors—cellular receptors for excitatory neurotransmitters—as well as "upregulate" the activity of the protein BDNF, a growth factor with various roles in the brain that are linked with neural and synaptic growth and antidepressant activity. The molecular pathways impacted by AMPA receptor activity and BDNF stimulation are also activated by lithium, the team noted, as well as other growth factors including insulin.

The theory the team tested in their in a rat model of TRD was that adjunctive lithium might generate an antidepressant response in animals that are not responsive to ketamine administration alone.

To create resistance to antidepressants in rats, the team administered a hormone called ACTH for 14 days, which helps boost the rodent equivalent of the stress hormone cortisol. Treatment-resistant rats were then divided into four groups of 12 each: one group was treated with ketamine, one with lithium, one received both ketamine and lithium, and the last received a placebo. Two kinds of behavioral tests were given to the rats once the treatments had been administered—standard tests which are widely used in rodent studies to gauge antidepressant activity.

Lithium treatment alone produced no antidepressant activity in the ketamine-resistant animals. But those receiving lithium in addition to ketamine "displayed robust antidepressant responses," the researchers noted. "Of particular interest," they added, was the observation that animals receiving both drugs "expressed elevated biochemical markers" including plasma insulin levels accompanied by an increase in insulin signaling, which in past studies have been linked with antidepressant activity.

The ability of lithium plus ketamine to generate antidepressant responses in animals that were non-responders to ketamine alone is thought by the team to

reflect lithium's impact on the molecular pathways responsible for increasing the plasticity of neurons, specifically, by boosting insulin levels and insulin signaling.

It is possible, the researchers said, that "lithium augmentation of ketamine may only be necessary and beneficial when there is an inherent deficit in critical modulators of [ketamine] response, such as insulin signaling."

The team said their approach has the potential to "reshape our understanding" not just of lithium augmentation of ketamine therapy, but more broadly of treatment-resistant depression. "Failed drug efficacy may have more to do with misalignment of drug target with [an individual's specific] physiology," they wrote.

The mere addition of lithium or the amount added to ketamine treatment may not be the most critical factor in future clinical applications, they said. Rather, future clinical trials might focus on testing how treatment response might be enhanced by "promoting molecular signaling cascades and bioenergetic pathways essential for enabling [any] antidepressant responsivity. Clinical studies using this precision medicine approach are needed." ❖

EVIDENCE THAT COGNITIVE BEHAVIORAL THERAPY CAN HELP PEOPLE WITH INSOMNIA WHO ALSO ARE DEPRESSED OR ANXIOUS

Lauren D. Asarnow, Ph.D.

In a review of available randomized, controlled studies, a research team has found evidence of the importance of treating insomnia symptoms in people who also suffer from either depression, anxiety, or PTSD.

It is estimated that 35% to 50% of adults suffer from insomnia symptoms and 10% to 20% of all adults have insomnia disorder. The latter is defined by a dissatisfaction with sleep quality or quantity due either to difficulty falling or remaining asleep, and resulting in clinically significant distress or impaired functioning.

Insomnia symptoms and psychiatric disorders often occur together. People with insomnia, for example, are estimated to be five times more likely to have anxiety or depression than people who don't have insomnia. Sleep disruptions, notably including nightmares, are also common in those who suffer from PTSD.

The first-line treatment for adult insomnia is a specialized form of cognitive behavioral therapy, called CBT-I. It is often recommended before drug therapy, and it is the most widely used non-drug treatment for sleep problems.

According to researchers at the University of California, San Francisco, led by 2019 BBRF Young Investigator **Lauren D. Asarnow, Ph.D.**, "a large body of research" has already demonstrated the effectiveness of CBT-I in treating chronic insomnia in adults without psychiatric co-morbidities. But in view of the high rates of comorbidity, the team set out to examine the evidence for CBT-I's effectiveness in treating those with insomnia symptoms and either major depressive disorder (MDD), generalized anxiety disorder (GAD), or PTSD. The team's paper reporting results appeared in *Current Psychiatry Reports*.

CBT-I, the team notes, draws directly from basic science on sleep and circadian rhythms, combining multiple treatment elements including sleep education; controlling environmental and biological stimuli that affect sleep; restricting sleep to certain times of the 24-hour cycle; and cognitive psychotherapy.

Sleep problems are closely associated with major depression, affecting up to 90% of those with the diagnosis. The team notes that among those with and without MDD, sleep disturbance, especially problems falling asleep, are "one of the more important predictors of a future depressive episode." At the same time, depression symptoms have been found to raise the risk of future insomnia. The comorbidity is associated with poorer outcomes for both conditions, the team notes. Also, insomnia may be an independent risk factor for suicide, suicidal thoughts and behaviors, as well as non-suicidal self-injury, among both adults and young people.

The team assessed the best available prior clinical trials addressing MDD and insomnia comorbidity. The criterion applied to past studies was their statistical power, a reflection of study size and design. The team noted that based on these studies, augmenting depression treatment with CBT-I does

not appear to significantly improve depression outcomes compared with a control or placebo augmentation.

However, they say, comorbid participants of such trials who did experience an improvement in insomnia symptoms were more likely to have better depression outcomes. They propose that improvement in insomnia symptoms "is likely a critical component of depression symptom reduction." The team also noted interest in the possibility that CBT-I might be tested as a preventive measure for individuals with sub-clinical depression.

With respect to comorbid depression and insomnia, the team concluded that CBT-I was "promising," and that when compared with standard CBT for depression or treatment with antidepressant medications, CBT-I "may be comparably effective for depressive symptoms and superior for insomnia symptoms." But when paired with antidepressant medications, CBT-I "may not have a significant additive effect" on outcomes. More research is called for, they said.

With regard to anxiety, evidence does suggest that anxiety disorders are a risk factor for later insomnia, but not necessarily the other way around. "A potential mechanism underlying the anxiety-insomnia association is the role of worry—namely, inappropriate worry about sleep" which may lead to arousal, which tends to perpetuate insomnia, the team noted. Given the linkage, it makes sense, they say, to treat insomnia in patients with anxiety disorders—but no adequately powered trial has yet tested CBT-I in comorbid patients.

As for PTSD and insomnia: the team noted that multiple studies have shown that disturbed sleep "often precedes and predicts subsequent PTSD," and that current PTSD treatments "may not effectively target sleep-related symptoms." Yet there have only been a handful of clinical trials of CBT-I for patients with comorbid PTSD and insomnia. These studies, which "show some promise" in the team's view, have mostly involved adult military veterans and so their results are hard to apply to other populations.

The team also looked for evidence of potential "moderators" of CBT-I outcomes in cases of comorbid depression or anxiety—factors which may alter the effectiveness of CBT-I in such patients. There were hints in past data that "evening preference" (circadian rhythm in an individual that favors activity in the evening vs. earlier in the day) may be one such factor. Another possible moderating factor is the severity of depression or anxiety symptoms before treatments begin. As with other observations in the paper, the team said additional research is needed to further assess potential moderating factors. ❖

BBRF Grants are Making a Difference

Research supported by BBRF grants is playing a vital role on some of the most important fronts in the fight against mental illness

The First Rapid-Acting Antidepressants

In 2019, the FDA approved esketamine, the first-ever rapid-acting antidepressant for patients with treatment-resistant depression, and brexanolone, which can lift postpartum depression within 48 hours. 90 BBRF grants over 20 years helped build the foundation for these long-sought advances.

Non-Invasive Brain Stimulation to Treat Depression, OCD, PTSD

BBRF grants seeded research which led to FDA approval in 2008 of rTMS (repetitive transcranial magnetic stimulation) for treatment-resistant major depression. BBRF grantees are now testing more powerful and faster-acting brain-stimulation technologies with a wide range of potential applications.

Computer-Guided Cognitive Remediation for Enhanced Recovery in Schizophrenia

Recovery may be possible for more people with schizophrenia and other disorders in which cognitive function is impaired, including bipolar disorder and depression. Recently, BBRF-funded scientists clinically validated computer-guided methods of enhancing verbal and auditory learning capacity, processing speed, working memory, and recall ability in chronic schizophrenia patients.

Lowering the Child's Mental Illness Risk via Maternal Choline Supplements

BBRF grantees have pioneered choline supplementation in the diet of pregnant women to reduce the risk of mental illness in children. Today, the American Medical Association recommends including choline in prenatal vitamin supplements.

Harnessing Stem Cell Technology to Study Autism, Schizophrenia

BBRF grantees have pioneered the use of stem-cell technologies to create functioning brain "organoids"—living test-beds that can be used to assess new drug candidates as well as reveal how genetic variations cause pathologies in the fetal brain as it develops. This research is especially pertinent in autism, schizophrenia and other disorders with developmental roots.

Computer-Guided Early Diagnosis of Mental Illness

BBRF-funded investigators are training machines that, in turn, train themselves—ultimately, to a level of precision not possible in humans—to recognize potentially diagnostic patterns of clinical data or biological markers in schizophrenia, first-episode psychosis, major depression, and bipolar disorder.

BRAIN & BEHAVIOR RESEARCH FOUNDATION
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GLOSSARY

BRAIN LESION (p. 7) A term that refers to various forms of damage to brain tissue, whether caused by an accident or illness. For over a century, doctors have known that some brain lesions generate psychiatric symptoms. Now, precise mapping of lesion locations in such instances, when analyzed in concert with brain scan and other data from depressed individuals, has helped researchers to posit a "common circuit" that is perturbed in many cases of depression. Researchers now hope that it may be possible to apply this example of lesion/circuit connection in other psychiatric disorders.

METABOLIC SYSTEM (pp. 10-17) The body's metabolic system regulates how energy—sourced ultimately in food—is supplied to our organs. Genetic studies of people with anorexia nervosa have revealed a metabolic dimension to the illness, which was previously regarded exclusively in psychiatric terms. A gene-based biological tendency to have a low BMI (body mass index—see below) may help drive the illness in some individuals.

BMI (pp. 15, 31, 32) The acronym for Body-Mass Index, defined as body mass (weight) divided by the square of body height. BMI is commonly used to broadly categorize a person as underweight, normal weight, overweight, or obese.

DSM-5 (pp. 11, 20) The 5th (and current) edition of the *Diagnostic and Statistical Manual*, used by clinicians to diagnose individuals with psychiatric disorders. Often a DSM-5 diagnosis is a precondition for insurance coverage.

COMPENSATING BEHAVIOR (pp. 11, 15) In the context of eating disorders, the term refers to actions and behaviors intended to reduce or prevent weight gain after eating. Such behaviors include self-induced vomiting, the use of laxatives or diuretics, and excessive exercise.

GWAS (pp. 15, 30) Genome-wide association studies, a type of genetic study which seeks to discover commonly occurring DNA variations that confer risk for disease. In complex illnesses such as schizophrenia, autism, and depression, large sample sizes help to make discoveries of genome "risk areas" more accurate.

STEP-DOWN TREATMENT (p. 17) A gradual model of care for recovering anorexia patients in which renourishment is followed by participation in a residential treatment program or day program, and then intensive outpatient treatment followed by a less intense phase of such treatment. The key is not to release patients from renourishment treatment after attaining "80% of ideal weight," given what has been learned about the tendency of the body to return to a state of negative energy balance and relapse.

NORMOBARIC (p. 33) Normal atmospheric pressure. A newly tested treatment for mild to moderate depression delivers oxygen, in moderately higher concentration than ambient air, at normobaric pressure.

CBT-I (p. 35) A specialized form of cognitive behavioral therapy that is first-line treatment for adult insomnia. CBT-I is often recommended before drug therapy, and is the most widely used non-drug treatment for sleep problems.

Image credits: pp. 7, 8: *Nature Human Behaviour*/Fox and Siddiqi labs, Brigham and Women's Hospital and Harvard Medical School; p. 23: *Progress in Neuropsychopharmacology & Biological Psychiatry*/Ruocco lab, University of Toronto

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