This issue of Brain & Behavior magazine contains feature stories about BBRF grantees who are working on scientific advances and breakthroughs related to early intervention and prevention.

Our SCIENCE IN PROGRESS story, “Understanding the Genetic Roots of Mental Illness,” is written in two parts and addresses what genetics and the sequencing of the human genome has told us, so far, about the connection between naturally occurring variations in our DNA and the risk of psychiatric illness.

What kinds of variations in the human genome substantially raise an individual’s risk of psychiatric illness? Genome experts have been getting better and better at answering this question. We know now that the genetic variations that put us at substantial risk for a complex illness such as schizophrenia are in many cases very subtle, and usually involve an individual having “many gene variants, each having a very small effect.”

In part one of our genetics story, we explore the relationship between genetic variation and risk for illnesses like schizophrenia, bipolar disorder, and autism. We also discuss the important recent finding that much of the risk for these illnesses comes from the part of the genome that doesn’t contain genes, but instead, the 98% of our genetic material that regulates our genes—tells them when to switch “on” and “off,” how long to stay “on,” and when to activate in which cells, in which parts of the body.

Part two discusses the pioneering work of a large consortium of researchers working on a project called PsychENCODE, which is trying to put together multiple layers of genome data to “connect the dots” between changes in genes and resulting brain and behavior disorders. Seventeen BBRF Scientific Council members, prizewinners, and grantees are among the founders of this pioneering effort.

Our PATHWAYS TO THE FUTURE piece features the diverse research interests of Dr. Deanna Barch. The four-time BBRF grantee and member of the Scientific Council discusses research which has shed new light on depression in preschool children. She tells us why the evidence clearly shows that some children aged 3 to 7 do indeed have depression, and she discusses a therapy she has helped test called PCIT-ED. Dr. Barch explains why this therapy for children so young seems to be effective—a reflection, perhaps, of the young brain’s remarkable plasticity.

A new feature in this issue, THE MULTIPLYING POWER OF BBRF GRANTS, explores how our grants have changed the scientific careers of many young scientists. BBRF Young Investigator Grants are often the catalyst that brilliant young scientists need to get their ideas off the ground. Our first installment in this series profiles Drs. Carolyn Rodriguez and Kay Tye, who both used their initial BBRF grants to generate data they needed to obtain career-sustaining support from the National Institutes of Health. BBRF Grants often have great impact on careers because of the multiplier effect. BBRF grantees usually go on to receive sustained grant support from other sources (both federal and private) that on average has equaled 10 times the original research grant amount.

Our ADVICE FOR PARENTS, LOVED ONES & FRIENDS story features a Q&A with Dr. Steven Hinshaw, a leading authority on ADHD, and the recent recipient of the BBRF Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research. Dr. Hinshaw is the author of numerous papers and books about ADHD, including The ADHD Explosion. In our interview we ask if the “explosion,” or the rapid rise in diagnosis of ADHD, continues. Dr. Hinshaw explains the full picture underlying the increase in diagnosis. He also urges us not to lose sight of the fact that ADHD is a real illness that can be successfully treated.

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

Sincerely,

Jeffrey Borenstein, M.D.

100% percent of every dollar donated for research is invested in our research grants. Our operating expenses and this magazine are covered by separate foundation grants.
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THE HUMAN GENOME’S THREE
billion pairs of DNA “letters” are
a code of instructions packed
tightly in the center of every cell, bearing
our genetic inheritance. The sequence
of those letters, which holds so much
potential to help us understand health
and illness, has been known to science
for less than 20 years.

Since the full human sequence was first
assembled, in the early 2000s, much
of the news about how our genes are
involved in psychiatric illnesses like
schizophrenia, bipolar disorder, and
autism has centered on the discovery
of variations in the DNA sequence—
variations that scientists have been able
to correlate with increased illness risk.

Now, a new phase of genome research
has begun, powered by major advances
in analysis pioneered by dozens of
experts involved in an National Institute
of Mental Health (NIMH)-funded
research consortium called PsychENCODE.
Among its founding members are 17
investigators who are members of BBRF’s
Scientific Council or have received BBRF
grant awards and prizes.

Their project, launched in 2015, has
moved an important step beyond
the identification of DNA variations
associated with elevated risk for specific
disorders. In PsychENCODE’s first set of
results—a set of 11 papers published in
the journals Science, Science Translational
Medicine, and Science Advances—the
focus is on figuring out how DNA
variations perturb the brain’s biology,
impairing its normal function. [see
accompanying article, page 8]

Obtaining a multi-dimensional picture
of how genetic variation affects
mechanisms in the brain, say members
of PsychENCODE, is essential if genome
discoveries are to be translated into a
basis for new treatments.

What is specifically new in
PsychENCODE’s mission is its focus on
understanding how genetic variations
affect the way the human genome is
regulated—the biological processes that
determine how, when, and where in the
brain genes are activated and silenced.
A CRUCIAL EARLY DISCOVERY

Figuring out how our genes are controlled has always been a part of genome science. But its special importance for understanding the mechanisms involved in psychiatric illness has taken a while to become a focal point of research. To understand why this new phase in research is important, we review in this article the deepest roots of the question, which can be traced to the years just after publication of the human genome. That was when researchers began to realize that they weren’t going to discover a single “gene for schizophrenia” or any other psychiatric illness, as some may have hoped.

Rather, researchers discovered that risk for psychiatric illnesses tends to be “highly polygenic.” This means that many combinations of DNA variations—cumulatively occurring in as many as 1,000 of our 21,000 genes—contribute to risk, when viewed at the level of the entire human population.

In light of this discovery, the question for an individual becomes: Which of these many variations, if any, do I carry in my own genome? And how, if at all, might the variations that I have in my genome affect my mental health and that of my children and grandchildren? Answers to these questions involve understanding what “risk” means in the genomic context.

EVERYONE CARRIES SOME DEGREE OF RISK FOR ILLNESS

Every one of us, on the basis of our unique gene sequence alone, carries some measurable risk of psychiatric illness, just as we do for cancer and other illnesses. And as with cancer and other illnesses, risk from our genes is typically caused by multiple factors which interact, both genetic and environmental. In this respect they are unlike disorders caused by problems in a single gene, like cystic fibrosis or sickle-cell disease. Importantly, people who have inherited DNA variations that confer risk do not necessarily develop an illness. In addition to environmental factors that interact with gene activity, other factors, biologically protective and conferring resilience, are thought to be involved in determining whether any individual remains healthy or develops an illness. These moderating factors are still poorly understood.

As for the genetic portion of total risk: Each illness has its own genome-based risk profile, which can now be “mapped” onto the full human genome sequence. So far, investigators have validated 147 genome locations where commonly occurring variations in the DNA sequence slightly raise an individual’s risk for schizophrenia. The search is still in progress; many more risk locations, or “loci,” in the genome are likely to be discovered.

Among the Founding Members of the PsychENCODE Project


YI = BBRF Young Investigator; II = BBRF Independent Investigator; DI = BBRF Distinguished Investigator
discovered as more genomes of both affected and unaffected people are sequenced and the sample size of studies grows. A significant but smaller number of commonly occurring genome risk variants have also been validated for bipolar disorder and autism spectrum disorder, as well as several other psychiatric disorders, and the search goes on in those diagnostic categories, too.

Some of the DNA variations that are associated with increased illness risk overlap across diagnostic boundaries—about 50% of those for schizophrenia have also been found to be risk factors in bipolar disorder, although not all of the shared variations have the same significance in the two disorders. Risk factors also overlap for schizophrenia and autism, leading to the hypothesis that some of the same underlying biological processes are disturbed in the two illnesses. This is a hopeful notion, since the discovery of a therapy in one disorder might therefore also help people with a different, but genetically related, diagnosis.

‘MANY GENES OF SMALL EFFECT’
Most of the common DNA variations raising risk for psychiatric illness affect short sequences of DNA, and sometimes only a single DNA letter. It wasn’t until 2007 that researchers discovered that every one of us carries small variations—dozens or hundreds—in our genome, relative to the human “reference” sequence (a representative sample based on multiple individuals of different races and ethnicities). This fact, which surprised scientists, provides a critical clue about how genome variations relate to health. Since all of us have DNA variations, and most of us are not ill, we can safely conclude that most small variations have no major impact on our wellbeing. The key question is: which variations matter? Part of the answer has to do with their location. Some places in the human genome are much more sensitive than others. Among the variations that have health

Schizophrenia Risk Locations. This is a representation of the full set of 24 human chromosomes (their “banded” appearance reflects their appearance under a microscope). Each of the small blue marks along the right side of each chromosome shows the location (“locus”) where a variation in DNA sequence or chromosome structure has been associated with elevated risk for schizophrenia. There are 108 commonly occurring “risk loci” in this 2014 rendering. More have since been discovered. One important question concerns the relation between each of these “risk” sites and brain function.
consequences are those that prevent genes from doing the job they have evolved to do. Sometimes, a single-letter DNA change can seriously impair the way a gene functions.

More typically, "gene-disrupting variations" involve larger structural flaws in the genome that are random and usually are present from birth, ranging from the deletion of a lengthy DNA sequence that contains one or more essential genes, to large-scale events like the breaking of a chromosome and the reattachment of the fragments to other chromosomes. While these large-scale events are rare, they account for a significant share of people diagnosed with psychiatric illness. Some researchers believe the figure may be 30% or more in autism, for instance.

What are the “key genes” whose disruption might have a causal role in a neurodevelopmental disorder like autism? They might include genes whose function is essential in order to build the brain during the fetal period; or genes whose activation is critical while newly born brain cells are wiring up to form circuits at the dawn of life. It’s relatively easy to imagine how rare, large-scale variations in DNA could impact one or more key genes. What’s not yet clear is how common, small variations can combine to have major impact.

THE “OTHER 98%”: DNA THAT REGULATES GENES

This helps explain why PsychENCODE has set out to comprehensively understand gene regulation in cells of the brain. The project proceeds from the observation that many of the common variants discovered—such as the 147 found so far in schizophrenia—tend to cluster in parts of the genome that are not occupied by genes, but rather, by areas of DNA that regulate genes.

“Regulatory areas,” it turns out, occupy most of the genome. In spatial terms, genes themselves only account for about 2% of the full human sequence. The “other 98%” is composed heavily of regulatory DNA, genetic code that regulates the activity of our genes.

What does regulatory DNA do? It influences the timing of when specific genes are active and inactive; it can control processes that block or provide access to the DNA that encodes proteins, and thus it can govern how much of various proteins...are made in which kinds of cells...at different moments of time...in different parts of the body.

To get a picture of gene activity in the human brain, PsychENCODE researchers have assembled a high-quality collection of postmortem brain specimens, representing "neurotypical" individuals as well as people who had been diagnosed with three psychiatric illnesses—schizophrenia, bipolar disorder, and autism.

Over 2,000 brains, harvested and frozen within hours of death, have been assembled from various meticulously curated collections and divided into samples that are shared in research labs spanning the nation. These brains provide snapshots of what is happening in actual tissue from 5 weeks of embryonic life, through the fetal period, and into the time after birth, with a heavy emphasis on infancy, childhood and adolescence, and ending in fully mature brains as old as 64 years post-birth.

As members of PsychENCODE point out in one of their 2018 papers, “Understanding the causes of neuropsychiatric disorders requires knowledge not just of endpoint differences between healthy and diseased brains but also the developmental and cellular contexts in which these differences arise.” Each postmortem brain is an endpoint for a single brain, but when layered genomic assessments have been made of the entire collection, a large set of snapshots can be pieced together to form a kind of movie, showing gene activity and gene regulation in the brain over the lifespan. What the initial studies have revealed is explained in the companion story on the next page. ✶ PETER TARR
Connecting the Dots, From Genes to Brain Biology to Disorders

How PsychENCODE research is relating “risk genes” to the brain biology underlying psychiatric illness

In the first group of 11 papers that PsychENCODE researchers have shared with the scientific community, they demonstrate that by layering different types of data, points of convergence emerge—offering insights about how gene activity in brain cells sheds light on mechanisms that may be involved in causing psychiatric disorders.

This connecting of dots begins to bridge the crucial gap between the discovery of “risk variations” in genome sequencing studies of people with schizophrenia, bipolar disorder, and autism, and the biological processes in the brain that these genetic variations are affecting. These are the kind of insights, it is hoped, that will provide a wealth of new targets for future therapies.

One of the three main papers by the Consortium, which is a good example of its broader approach, made use of 60 postmortem brains unaffected by disease. These brains were probed by many science teams to provide the most comprehensive analysis to date of how gene activity corresponds with the brain’s development. This is valuable in part because these pictures of genetic activity in the developing brain over time can be compared with data gathered from brains of people diagnosed with schizophrenia, autism and bipolar disorder.

The full human genome is compressed into chromosomes found in the tiny space of the nucleus in every cell. Epigenetic factors attach to DNA and change the way genes are activated—sometimes making them physically inaccessible and therefore “silent,” and other times making them accessible and therefore ready for activation. Epigenetic “tags” shown here include “methyl groups,” which attach to DNA, and “histone tails,” which attach to the histone proteins around which DNA is tightly spun for packing.
THREE LAYERS OF INFORMATION

The team used several kinds of data to make their analysis. One layer of data captured the activity of the full set of human genes, showing how different combinations of genes are important at different moments in life, and most dramatically at the beginning of life, as the brain is just coming into being. This picture of total gene expression is called the **transcriptome**, a term that refers to the total set of “transcripts” or messages in a cell, each of which is generated when a gene is activated.

The total read-out of gene activity in brain cells was compared at different times—in the early post-conception weeks, at different points in the fetal period, just after birth, and at various subsequent ages, in brains up to 40 years after birth. This comparison formed one layer of the data to be analyzed.

A second layer consisted of what researchers call an **epigenetic profile** of the brain, again, at different moments in development from the fetal period to adulthood. Epigenetic profiles are a record of how molecules—in this case, methyl groups (CH₃)—attach to DNA in the genome, impacting the way genes are expressed. Sometimes, a methyl group sits atop a sequence of DNA in such a way that it prevents a gene from being expressed. Other times, a methyl group attaching to DNA encourages the expression of a gene. Either way, these epigenetic “marks” change the way genes behave, and thus are important to know about in health and illness.

A third layer of data captured what scientists call **histone modifications**—alterations of proteins that package DNA in the cell nucleus. As with epigenetic marks, these modifications of our genes affect whether specific genes are active or inactive at particular moments in time.

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 Altogether, these three layers of data gave the PsychENCODE team a picture, in each of the brains they studied, of which genes were active, and the state of biological factors either promoting or preventing gene expression—in different kinds of brain cells, in different parts of the brain, and each in a brain that has been frozen in time at a particular developmental age.

**A MAJOR CHANGE IN GENE ACTIVITY, BEFORE BIRTH**

What did the layering of these data tell the scientists of PsychENCODE? For one thing, it enabled them to see how gene activity differs in different brain regions over time, in a way that directly reflects brain development.

Very early, in embryonic and early fetal development, gene expression varies greatly both within and across the 16 studied brain regions that are involved in higher-order cognition and behavior.

But this period of great variation is followed by a major transition late in the fetal period and continuing just after birth. In this interval, gene-activity differences diminish both in cells and between brain regions. This fact may be very important. This is the time in brain development when the dendrites along which synapses form begin to branch out. It’s also the time glial support cells and astrocytes, which are components of the neural immune system, begin to form.

Why is this important? The researchers note that the time just before this late-fetal transition “coincides with a key developmental period previously associated with the causation of autism spectrum disorder and schizophrenia.” If you want to understand these illnesses, they say, it is almost certainly important to understand how the brain develops and genes express themselves during this crucial period.

**RELATING THE ACTIVITY OF “RISK GENES” AND ILLNESSES**

The layers of data they collected enabled the PsychENCODE team to be more specific. They describe a group of genes that tend to be activated at the same time in neurons, and that are involved in related biological functions. During the major transition in the brain just before birth, the activity of this set of “co-expressing” genes—a grouping they call ME37—changes more than that of any other grouping of genes in the fetal brain.

The team then noticed that a number of the genes in the ME37 cluster have been identified as “risk genes” in autism, schizophrenia, intellectual disability, and in neurodevelopmental disorders generally. (see illustration, above)

This suggests how PsychENCODE is taking science beyond the mere identification of “risk genes.” All the layers of information in the study described here, when integrated, converged on the ME37 cluster in particular as being an area of risk for pathology and therefore one that is potentially rich in targets for future therapeutics.

A footnote: the team dedicated their first set of 11 papers “to Pamela Sklar, one of the chief architects and leaders of the PsychENCODE Consortium, whose ideas resonate throughout our studies.”

Dr. Sklar, an M.D., Ph.D., who was Chief of the Division of Psychiatric Genomics at the Icahn School of Medicine at Mount Sinai, died of cancer in 2017. Dr. Sklar was a member of BBRF’s Scientific Council, a 2016 winner of the BBRF’s Colvin Prize, and a 2006 BBRF Independent Investigator and 1998 and 1995 BBRF Young Investigator.

**BRINGING HIDDEN RELATIONSHIPS TO LIGHT:**

This “ball” is a computer-drawn representation of a “module” of related genes called ME37 in the fetal brain. Each hexagon represents a gene; its size correlates with its degree of connectedness to the others. The analysis brings together **TIME** (the activity in these genes is especially dynamic just before birth), **SPACE** (they are active in excitatory neurons in the cortex), and **FUNCTION** (these genes are very active when neurons are being born and synapses are forming to connect them). Finally, each of these related genes has separately been identified as a “risk gene” in more than one **DISORDER** (including schizophrenia, autism, and intellectual disability). This makes the case for linking damaging variations in ME37 genes with causation in these disorders.
PLAN YOUR FUTURE, SHAPE YOUR LEGACY

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

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

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

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

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

—Ken Harrison, Board Member

To learn more, please contact us at 646-681-4889 or plannedgiving@bbrfoundation.org
PATHWAYS TO THE FUTURE

A Strong Impulse to Help People Who Live with Mental Illness Propels a Diverse Career in Clinical Brain Research

Deanna Barch, Ph.D.

Chair and Professor of Psychological & Brain Sciences; Professor of Radiology; Gregory B. Couch Professor of Psychiatry
Washington University, St. Louis
BBRF Scientific Council Member 2013 Distinguished Investigator 2006 Independent Investigator 2000, 1995 Young Investigator

Deanna Barch, Ph.D., a much honored research scientist who now chairs the department of Psychological and Brain Sciences at Washington University in St. Louis, did not take long in life to discover her passion.

A member of the BBRF Scientific Council and the recipient of four grant awards from BBRF, Dr. Barch knew what career path she wanted to follow in her teen years.

In high school, she trained to serve as a peer-counselor so that she could work with fellow students who were having academic, social, or emotional challenges. She had been sensitized by problems encountered by her brother, who had dyslexia. By the time she went to college, at Northwestern University, she knew that she wanted to become a psychologist.

“I didn’t know anything about research, though, until I took abnormal psychology. My professor had a habit of asking students who did well in the class if they were interested in getting involved in her lab, to do research. She asked me; I said yes, and soon after I was hooked.”

After college, Dr. Barch took a gap year—not to travel the world, as many young people do, but with the idea of becoming a case manager for the chronically mentally ill in inner-city Chicago. Her motivation, once again, was to help people in need, and in a very concrete way—“to help them negotiate their lives with the goal of keeping people out of the hospital,” she remembers.

It was in this job in Chicago that the future Dr. Barch—the following year she would enroll at the University of Illinois, Champaign-Urbana, to pursue her doctorate—had an experience that proved pivotal. What really turned her head was “a young client who was pretty much my age who had recently developed schizophrenia. And it really struck me that here was this young gentleman who had just gotten a diagnosis that was disrupting all of his life plans—and here I was, just starting to act on my life plans.

“This poor person who was not responding well to medications could no longer go to school—this is what really convinced me to go to grad school, to get on a research track, and to work on risk factors and causes of mental illness.”
Today, Dr. Barch’s research seeks to determine the cognitive, emotional and neural bases of risk for the development of schizophrenia and depression, with an eye toward developing preventive measures. In particular she has used various kinds of brain imaging, including functional and structural MRI (magnetic resonance imaging), in search of the neural foundations of disturbances in cognitive control and emotional processing.

**INSIGHTS ABOUT MOTIVATION**

Some of her most interesting recent research has sought to understand what psychologists and psychiatrists call “motivational impairments.” These affect people with a wide variety of diagnoses, from depression and other mood disorders, to psychosis and schizophrenia.

In depression, patients are often observed to suffer from anhedonia. This means they find it difficult, or in some cases all but impossible, to experience pleasure. It is a characteristic symptom of the illness. People who don’t or can’t experience pleasure or joy are not motivated to seek it. This is a symptom, therefore, that seems to feed the depressed state. Overcoming anhedonia is an important goal of treatment for depression.

One crucial insight that Dr. Barch has recently had is being able to distinguish the problem of motivation, or lack of it, in depression, from something that looks a lot like it in schizophrenia (and indeed, is widely assumed to be the same issue.) Sophisticated research tools, including measurement of brain waves via EEG (electroencephalogram) and functional MRI have led Dr. Barch and her colleagues to hypothesize that in psychosis and schizophrenia, motivational issues “may not really be about a reduction in the ability to have moments of enjoyment or pleasure but perhaps more accurately reflect difficulty in planning or anticipating that various activities might be experienced as pleasurable,” she says.

In other words: while on the surface it may look as if someone with schizophrenia has motivational issues that resemble those of anhedonic depressed patients, in fact Dr. Barch’s research leads her to consider that in schizophrenia, the difficulty in getting motivated may be tied directly to the so-called negative symptoms of the illness—to a spectrum of cognitive impairments. That’s what she means when she points to an inability to anticipate a pleasurable experience. In schizophrenia or psychosis, unlike in depression, there is an ability to experience pleasure. The crux of the problem is in being able to seek it—being able to put oneself in a position to actually have the experience.

**DEPRESSION IN PRESCHOOLERS?**

Another strong research interest of Dr. Barch’s is related to the anhedonia issue in depression. Her master’s thesis in graduate school sought to develop a measure to assess anhedonia in young people. Over the last decade, often in collaborations with her Washington University colleague and fellow BBRF Scientific Council member Joan Luby, M.D., Dr. Barch has helped to shed important new light on the problem of depression in very young children, as young as the age of 3.

Can children be depressed at age 3? Part of the challenge in studying the subject has been longstanding skepticism about whether it is even possible for a child that young to be clinically depressed. “It’s getting to be less of a problem than it used to be,” Dr. Barch says. But the idea “that kids of this age are not cognitively or emotionally able to feel depressed has been clinical lore for a lot of years and it simply isn’t true. Kids are not always able to articulate what their internal emotional states are, but they certainly display behavioral evidence of poverty is one of the most powerful predictors of poor development outcomes in children. These brain scans by Dr. Barch and colleagues suggest one reason why. The areas shaded green had weakened connectivity in a group of 105 children, ages 7 to 12, raised in poverty. Such children are also likely to have symptoms of depression when they reach school age.
feeling depressed—not smiling, a lack of joy, expressing guilt, even, sometimes, expressing suicidal ideation.”

She begins her public talks on the subject by first acknowledging the doubts and then trying to dispel them with facts. “First I tell people about the epidemiological literature, which has documented the occurrence of depression as early as age three. Research shows that about 2 percent of very young children are depressed. This is consistent across the U.S. and other countries. We’ve seen it in Europe as well as in the states, and we’ve seen it in multiple samples. This is not a phenomenon, in other words, that a single research group is studying and no one else sees.”

A second persuasive line of evidence for depression in young children emerges from longitudinal studies, which follow children over their development, beginning in the earliest years of life. Children who are diagnosed with depression in the preschool years “are at a much increased risk of continuing to have problems with depression and mental health in general as they get older,” Dr. Barch says. This, despite the common response of skeptics that “they’ll grow out of it.” That can certainly happen, but “it doesn’t seem to be true for the majority of kids who have very early depression,” she adds.

A third line of evidence comes from brain activity and structure in affected preschool children. “We see some of the same differences that we see in school-age children, adolescents, and even adults with depression compared with those who are not depressed. This suggests to us that very early depression is on a continuum with depression that might arise later in life.”

Dr. Barch’s research has done much to establish this third line of evidence. The “differences” vis-à-vis children who are not depressed that she alludes to are of three kinds. One difference is that in preschoolers with depression, the brain structure called the hippocampus is reduced in size. The same reductions are seen in older people with depression, and this is important because the hippocampus plays a critical role in our response to stress.

The second difference arises from measurements of brain activity with EEG and looking at how the brain functions with MRI scanning. These show a very important reduction in the brain responses of very young depressed children to rewarding outcomes. In other words, areas that should be responding are less active in these children. This is also seen in older people with depression.

A third research finding concerns activity in the brain’s amygdala, “a brain region that responds to salient, important outcomes, including negative outcomes,” Dr. Barch explains. “We see that the severity of preschool depression corresponds with increased activity in the amygdala,” a phenomenon, again, that has been noted in older depression patients.

“TIPPING” CHILDREN BACK ONTO A HEALTHY PATH

Dr. Luby, with research help from Dr. Barch, has driven the development of a unique therapy for the youngest patients with depression. Called Parent-Child Interaction Therapy-Emotion Development (PCIT-ED), they have demonstrated its effectiveness in several studies in recent years. In a study published in 2018, they successfully tested a “module” added to the therapy
called “ED,” for “emotion development.” The therapy trains parents to learn to interact successfully with their young children, effectively teaching the parents to teach their children how to experience emotions successfully—“increasing their experiences of positive emotion and decreasing their experiences of negative emotion,” as Dr. Barch puts it. There are no other empirically proven treatments for young children with depression, the team points out.

In a study published last year in Biological Psychiatry, of 118 children aged 4 to 7 years considered to be at risk for early-onset depression, Drs. Barch, Luby and colleagues focused on children with mothers who suffered from depression—one of the known risk factors for early depression. They were able to measure a reduction in such children of what they call “event-related potential” (ERP), which translates into their ability to respond to pleasant stimuli. The children were divided into two groups, one of which received 18 weeks of PCIT-ED therapy and the other on a waitlist (they later received it).

At the end of the trial, children who received the therapy showed marked improvement in their neural responses to positive stimuli, compared with those who were on the wait list for the therapy. The team concluded that the ERP measure was able to predict in advance which children would respond to the PCIT-ED therapy. If replicated, this could be a very useful intervention.

Drs. Barch, Luby and team wrote that their findings “are particularly novel, given that they are in very young children.” They expressed their “speculative hope that [brain] plasticity is greater” in very young children, “and thus the impact [of the treatment] may be more enduring.”

Asked about this, Dr. Barch explained: “If you are 25 years old and have spent the last 15, 20 years experiencing depression on and off, that is likely to have an impact on a lot of important developmental experiences that you may either not have had or experienced in a different way. So when you treat someone for the first time at 25, you’re not only treating experiences that they’re having currently, but you have to deal also with the fact that they may have had years of atypical development because they’re experiencing depression or anxiety or something else. It’s very hard to roll that back and to help people relearn things that they couldn’t because they were experiencing depression.

“On the other hand, if you can catch a young person early and perhaps intervene in a way that means it’s less likely they will continue to experience depression, then it seems to me they’re more likely to have normative developmental experiences that themselves may be promoting healthy brain development and behavior. I always think of this as tipping them back on to a healthier developmental trajectory. That’s why we’re hopeful, if this therapy does indeed have a long-lasting effect.”

Looking at trajectories of development over time is another of Dr. Barch’s research commitments. She is one of the founders and leaders of the NIH’s Adolescent Brain and Cognitive Development (ABCD) study, which has now enrolled over 11,000 youths aged 9–11 with the aim of studying them over the next decade. This relates to still other research projects she’s part of, which study how the brain develops during childhood and on how circumstances of adversity, such as poverty, stress, and access to healthcare, influence mental health outcomes. ✤ PETER TARR
A research career is all about a path.
And for me, the path really started with BBRF.”

So says Dr. Carolyn Rodriguez, now of Stanford University, whose undergraduate degree in computer science, Ph.D. in neuroscience and genetics, and M.D. degree—all earned at Harvard—put her on a trajectory to launch a career as a psychiatrist, neuroscientist, and clinical researcher.

Back in 2008, when she began putting together her application for a BBRF Young Investigator grant, Dr. Rodriguez was one of thousands of young people in the U.S. and around the world with an excellent academic background and great potential who nevertheless needed to secure financial support in order to set up a lab and get her first research project off the ground.

As she came to the end of the fellowship that followed her academic training, she recalls that “the BBRF grant was the very first grant in the psychiatry/mental illness field that I applied for. It was really where I got my start. I had come out of medical residency and I wanted to have a career in mental health research.”

Dr. Rodriguez succeeded on her first try in obtaining a highly sought-after BBRF grant—she was named a Young Investigator in 2009. “And having that money allowed me to do my very first study.” It focused on a drug that was thought to alter the activity of NMDA receptors, docking ports on nerve cells for the neurotransmitter glutamate. Glutamate is the main excitatory chemical messenger neurons use to communicate.

She wanted to test the idea that an excess of glutamate was responsible, at least in part, for some of the symptoms of obsessive-compulsive disorder (OCD). Minocycline was an antibiotic that had been reported to modulate glutamate’s effects in the brain. It seemed a good place to start: it was inexpensive, already FDA-approved for use in adults and children, and had minimal side effects.

The 2009 Young Investigator-supported study enabled Dr. Rodriguez to gather preliminary data that then persuaded the National Institutes of Health to extend her project with a K23 award, which, like the Young Investigator grant, seeks to sustain promising research careers in their early stages. “That K23 would not have been possible without having the pilot data directly generated from the BBRF Young Investigator grant,” Dr. Rodriguez says.
In the K23 extension of that work, she also studied ketamine, designed as a powerful anesthetic but discovered in the 1990s to have, at very low “sub-anesthetic” doses, a remarkably rapid anti-depressant effect in severely depressed people who did not respond to existing antidepressant treatments. (That discovery was made by Drs. Dennis Charney and John Krystal, both BBRF Scientific Council members and past grant recipients—work for which they were awarded the BBRF’s Colvin Prize in 2019. A chemical derivative of ketamine called esketamine was approved by the FDA in 2019 for refractory depression, making it the first rapid-acting antidepressant to reach the market.)

Research is all about surprises, and Dr. Rodriguez had a big one when she extended the work on that first BBRF grant. In her government-supported K23 grant, she was able “to do the first randomized study [in people] of ketamine in OCD, and we got fantastic results.”

ANOTHER BOOST
Carolyn Rodriguez benefitted from the multiplying power of BBRF grants not once, but twice. In 2014 she applied for and received a second BBRF Young Investigator award. “This grant enabled me to look at another molecule that modulates glutamate, called rapastinel. BBRF supplied the means that enabled us to do a small pilot study in OCD.”

As she noted in a letter to the American Journal of Psychiatry, in a sample of 7 OCD patients, she and her team “found rapastinel decreased symptoms of OCD, anxiety, and depression within hours, and was well tolerated. It did not produce the side effects seen with ketamine in OCD.” The helpful effects of the drug were not long-lasting—gone within a week in the 2016 pilot study—but were a hopeful step forward.

Being in position to do this small but consequential study on rapastinel was something Dr. Rodriguez attributes “directly” to BBRF support. Her second grant therefore, like the first, “provided a chance to generate exciting data that could then be funded on a larger scale by the NIH.” The point, she says, is that “the NIH isn’t going to give money for a project like ours that didn’t already have existing pilot data. That’s where BBRF grants bridge the gap.” In this and so many other cases, early-career BBRF grants have a “multiplier effect.” A start-up grant provides the basis for much larger, steady federal support which often endures for an entire career.

In 2017, Dr. Rodriguez received her first “career” grant from the NIH—a grant called an R01—which recognizes that an investigator has achieved results of sufficient interest and importance to justify long-term federal support. Indeed, that R01 grant is one of the main financial pillars sustaining the now bustling Rodriguez lab at Stanford.

“We are investigating the rapid therapeutic action of ketamine at the molecular, circuit, and network level in adults with OCD,” she says.

Dr. Rodriguez’s vision is to investigate the brain basis of intrusive thoughts and to use that knowledge to develop rapid-acting treatments for such disorders as OCD and PTSD. Her lab’s studies focus on targeted therapies in the glutamate and opioid pathways, extinction-based psychotherapy (used for example to

“The Scientific Council decided in its earliest days that its focus was going to be on Young Investigators. We thought it was essential to provide support for very bright people who were just beginning their careers. They have the unique problem of trying to accumulate a body of data to make the case for major, multiyear funding from the government. It takes time to formulate a hypothesis and perform experiments that generate the kind of data that’s needed.”

– Herbert Pardes, M.D
President, BBRF Scientific Council
control fear in PTSD), and non-invasive brain stimulation interventions.

Upon accepting her honorable mention for the Klerman Prize for Exceptional Clinical Research in 2017, Dr. Rodriguez shared these thoughts about BBRF: “I have seen first-hand how the Brain and Behavior Research Foundation has accelerated the pace of psychiatric research by fostering innovative research. The Young Investigator Award supported my launch as an independent investigator and fueled my discovery of glutamate-modulating compounds with rapid action in OCD. I am forever grateful for the generosity and kindness of donors for both supporting the Foundation and my passion for pioneering treatments that rapidly relieve the suffering of individuals with serious mental illnesses.”

In another confirmation of the excellence that BBRF saw in Dr. Rodriguez a decade ago, in July 2019, she was selected as a recipient of the Presidential Early Career Award for Scientists and Engineers. The award recognizes investigators who are pursuing bold and innovative projects at the early stages of their careers and is considered one of the highest honors in scientific research.

A SPARK THAT IGNITES

Much like Carolyn Rodriguez, Kay M. Tye performed spectacularly well in her academic training, which began auspiciously at the Massachusetts Institute of Technology, where she earned a bachelor’s degree in Brain and Cognitive Sciences. She went on to the University of California, San Francisco, where she earned a Ph.D. in Neuroscience in 2008. She was winning prizes, awards, and recognition all along the way. After completing her postdoctoral training in the Stanford lab of Karl Deisseroth, M.D., Ph.D.—a BBRF Scientific Council member whose team is credited with development of the now widely adopted technology called optogenetics (helped by 2005 and 2007 BBRF Young Investigator grants to Dr. Deisseroth)—Dr. Tye was in excellent position to launch a lab of her own.

Although during her postdoctoral years she had received support from the National Institute of Mental Health, Dr. Tye still faced the problem that all beginning researchers face, no matter how gifted. As she set up her lab at MIT and began to draw in promising postdocs of her own to help in her research, she can distinctly “remember my lab manager coming to me and saying, ‘So, the money flow—it’s all one-way right now,’

Kay M. Tye, Ph.D.
Professor, Systems Neurobiology Laboratory
Salk Institute for Biological Sciences
2013 BBRF Young Investigator
2016 Freedman Prizewinner
Scientific Council Member

meaning ‘out,’ of course—and he said, ‘Can you work on that?’ It was definitely stressful.”

She was brand new to the field as an independent entity; and she figured one way to get funded would be to focus narrowly on something not too risky—“to build up preliminary data” to support applications for large federal grants. But that wasn’t her style; from the start she wanted her lab to have an interdisciplinary focus and that meant supporting various related, but distinct lines of investigation at once.

That’s why she applied for and received, among other start-up grants, a BBRF Young Investigator award, in 2013. She would use optogenetics, the technology she learned in the Deisseroth lab, to manipulate specific neurons, and specific pathways of neurons in rodents, using colored beams of laser light to switch them on and off to study how the manipulation of these elements of basic brain infrastructure affected behavior in a line of rodents that modeled anxiety disorder. Behind this project was what Dr. Tye calls the “valence question—how do we determine if something is good or bad?”
She explains that everything we do is a product of motivation, which itself has various drivers, positive and negative. How these assessments underlying motivation are represented in the brain and then put to work by neural networks to guide behavior—“this is really the seed of everything my lab has done from the time of that first BBRF grant,” she says.

And once again, the “multiplier effect” was evident. On the strength of this and related research, Dr. Tye applied for and received her first R01 career award from the NIH in 2014, and has been enjoying great success ever since. In 2018 she received a second, simultaneous R01 career-sustaining grant, to explore neural circuit mechanisms underlying social contact and social isolation, both of which are of central importance in brain and behavior disorders ranging from schizophrenia and depression, to anxiety and autism. Like Dr. Rodriguez, Dr. Tye, in 2016, was awarded the Presidential Early Career Award for Scientists and Engineers. She has also received the NIH Director’s New Innovator Award and the NIH Director’s Pioneer Award.

Thinking back to the time of her BBRF Young Investigator grant, Dr. Tye, who recently accepted a new faculty position at the Salk Institute of Biological Studies, says that “it allowed me to take more chances, put a few more irons in the fire,” as she contemplated how to assemble the data the NIH would need to justify a career award.

“You’re essentially unknown. You don’t have the luxuries established principal investigators get to enjoy. It’s almost like you’re saying: what makes a car go? Well, it’s the spark plug, the point of ignition. Yes, a car needs gas. But I like the metaphor of the spark plug. If I hadn’t gotten that early award and a few other start-up grants, it would have been like pushing the car uphill. I would never have been able to get the momentum. So I think it’s really important to give promising young investigators a chance to get the ignition going, to get the motor running. At that point, then it’s up to us to keep the tank full of gas—and that’s what the government enables us to do if all goes well.”

In 2016 Dr. Tye was recognized again by BBRF, receiving its Freedman Prize for Exceptional Basic Research. The prize cited work that traced back to the project supported by her 2013 Young Investigator grant. The vision it supported, which continues in Dr. Tye’s lab today, is exciting: to understand mechanisms underlying behavior well enough to design manipulations of neural circuits. These would “induce plasticity to potentially cure—not just treat—a disorder like anxiety,” Dr. Tye says. That translational goal, moving from research to new understanding to clinical applications that benefit patients, is what the entire game is about for her and her team.

“**It’s really important to give promising young investigators a chance to get the ignition going, to get the motor running. At that point, then it’s up to us to keep the tank full of gas.**”

– Kay M. Tye

In 2016 Dr. Tye was asked by Dr. Pardes and members of the BBRF Scientific Council, to join them on the Council. Dr. Tye proudly accepted, and therefore now finds herself in position to repay a debt. Council members volunteer their time to select 200 new Young Investigators each year, a task in which Dr. Tye now participates. Not so long after getting some “spark” for her own research program from a BBRF award, she now has the pleasure of helping to decide who will benefit from this consequential gift for years that stretch far into the future. ✰ PETER TARR
Q&A with Stephen P. Hinshaw, Ph.D

Professor of Psychiatry and Vice-Chair for Child and Adolescent Psychology
University of California, San Francisco
Professor of Psychology
University of California, Berkeley
2019 BBRF Ruane Prize for Outstanding Achievement in Child & Adolescent Psychiatric Research

Can you describe ADHD and the emotional and behavioral problems associated with it?

ADHD is called Attention Deficit Hyperactivity Disorder but in reality, it’s not about the inability to pay attention, per se. In fact, some people with ADHD are hyper-focused—they can’t get off the video game they’re playing, or their preferred activity, for many hours. Instead, ADHD is actually a disorder involving an inability to regulate one’s attention as situational demands shift.

If you have an underlying genetic vulnerability to be either impulsive or not highly focused, the challenges of sitting still in school and learning to read (things that the human brain did not evolve to do) renders about 1 in 20 kids (about 5%) vulnerable to serious impairment. We have good evidence that ADHD predicts academic failure, difficulties in social relationships, high risk for accidental injury, elevated risk for self-harm and suicidal behavior, and neuropsychological deficits in executive functions, all of which make life difficult in a productive society.

How does ADHD present itself?

The two classic symptom dimensions of ADHD are inattention (disorganization, lack of focus) and hyperactivity-impulsivity (impulsive actions often paired with fidgeting and running around). A child who comes to clinical attention with deficits in focus and organization but not much in the way of hyperactive behavior would get diagnosed with the “inattentive presentation” of ADHD. Conversely, a kid who is impulsive and interrupts all the time but seems to be relatively well-focused would get diagnosed with the “hyperactive-impulsive” presentation. This happens most often in preschoolers.

But the most common presentation that comes to clinical attention pertains to a child presenting with both inattention and hyperactivity-impulsivity. Such youth are not able to follow the teacher’s directions, can’t get homework organized or done, and can’t sit still very well.
Do we know if ADHD is caused by purely biological factors?
Let me put it this way: Is ADHD real? Yes, decidedly so, despite the myths and the propaganda that it’s just lax parenting or lazy kids or bad classrooms. ADHD has an underlying psychobiological reality. The symptoms are highly heritable, meaning that genes play the major role in dictating your risk. However, home environments—inconsistent discipline, shouting matches, and the power struggles, as well as chaotic classrooms—can certainly maintain and intensify the symptoms.

ADHD can be tricky to diagnose. What is the right way of diagnosing this condition?

Many kids are diagnosed on the basis of 10 or 15 minutes in a pediatrician’s office without evidence-based rating scales from parents and teachers, without a thorough developmental history, and needed diagnostic testing.

In the past few months, the American Academy of Pediatrics (AAP) and the Society for Developmental and Behavioral Pediatrics (SDBP) issued new guidelines for assessment and treatment of ADHD. These involve the use of parent and teacher ratings of the child on standardized and normed scales to get a sense of what percentile of disorganization, inattentiveness, and impulsivity the child shows. There’s a recommendation, as well, that the provider, or an assistant, visit the classroom to assess the level of disorganization in the teaching environment. In short, it takes time and effort to gather and appraise the relevant information.

You’re saying that some kids might look hyperactive in instances where the teacher is not exerting proper control of the classroom and in those cases it really has less to do with the kids than the teacher.

Exactly. Even more, a child can seem to have ADHD because of maltreatment or abuse, or certain seizure disorders, or seriously deprived early home environments. Again, without a thorough developmental history (for example, were there speech delays? maltreatment? lack of structure?) and without standardized ratings from parents and teachers, ADHD can be mistaken for a host of other conditions and factors.

In some cases, there could be evidence for both trauma and ADHD, but you can’t figure that out by just “examining” the child and family for a few minutes in a pediatrician’s office. It’s going to take at least a couple of hours of detective work to uncover if the symptoms are consistent with ADHD. A doctor should always ask: Is there another condition or an unstructured classroom environment that explains the symptoms better?

In 2014, you published a much-discussed book called The ADHD Explosion in which you discussed the skyrocketing rates of ADHD in the U.S. What triggered this explosion in diagnoses? Has the surge in diagnoses peaked?

The answer is that we don’t know for sure if the explosion has peaked, but new national survey data are emerging in the years since the book came out. Apart from the U.S. and Israel, all nations around the world with compulsory education have similar rates of ADHD diagnosis—around 7% of the school-age population. The rates are much higher here and in Israel, where it’s over 11%.

Now, does that mean that there’s truly more ADHD in these two nations? It’s hard to know because we don’t yet have biomarkers—a blood test or a brain scan that definitively shows its presence. What we have is “diagnosed prevalence.” This could accurately reflect the actual prevalence, but may be subject to bias because of the way things get diagnosed.

I think of ADHD as a disorder that would probably be diagnosed more frequently in a culture with high expectations for achievement and performance. The reason? Because of its documented and real detrimental effects on school achievement and adult employment.

Not only are rates of ADHD diagnosis rising across the U.S., but major state-by-state variation exists. My colleagues at Berkeley and I set about to investigate the association between state-by-state rates of ADHD and laws in those states that link school funding to test scores. In the 21 states that passed so-called “consequential accountability legislation” in public schools after 2003, we found a 59% increase in ADHD diagnoses of kids at or near the poverty level, compared to states that had passed those
laws passed previously—or compared to kids in private schools in those states, not subject to “consequential accountability.” 2003 was the year that the No Child Left Behind Act went into effect, influencing practices in the states lacking previous consequential accountability laws, creating real urgency to yield the best possible results.

In short, if a state feels pressure to improve its test scores, there’s going to be a sudden increase in ADHD diagnoses given to the poorest kids. This is because test scores tend to be lower in high-poverty public schools and an ADHD diagnosis for some of the low-achieving students can justify their removal from a school’s test-score statistics, falsely raising the district’s average scores. Especially when ADHD can be diagnosed in a brief, non-evidence-based evaluation, there’s evidence that such gaming of the system helped to fuel rising rates of ADHD diagnosis.

Let’s return to the situation that parents face: How do you find the right pediatrician and get the most out of your visit?

Often ADHD emerges in elementary school when the child begins to fall behind. Parents should talk to other parents about their own experiences, and ask for recommendations for pediatricians or other professionals who know the score. In this way they can figure out which doctor really understands the condition and which doctors may tend to diagnose every other kid who walks in the office. To find support, parents should look to self-help and advocacy groups. There’s a national self-help advocacy group called Children and Adults with ADD (CHADD). There are local groups, too, that should have a good sense of which professionals in your community can provide an evidence-based assessment.

Some HMOs have big practices where pediatricians team up with psychologists. They also have school psychologists who help with the assessment. You want to make sure to observe child behavior in the natural environments in which it occurs—at home, in school, and within the kid’s peer group.

Parents can also obtain parent and teacher ratings of the child well ahead of the pediatrician visit, so that the doctor can review these scores. It would be a great idea to get impressions from last year’s teacher as well. And I would caution parents to be very suspicious if the doctor doesn’t spend 30 to 60 minutes asking about developmental history from birth till today.

How early do the signs of ADHD start to appear?

Many toddlers look a lot like kids with ADHD because that’s their natural developmental sequence. It takes the brain a long while to start to develop and exert self-control over a child’s behavior. The AAP and SDBP suggest strongly that a valid diagnosis can be made between ages 4 and 6, with a lot of diligence. Still, one must be careful not to mistake an exuberant, normal-range preschooler for a kid who’s actually got underlying ADHD. The future will bring reliable early-detection devices. But right
now, the preschool years provide an opportunity for early intervention. We know that children with ADHD in the preschool years can die of accidental injury more often than other children, and too many are already set on a course that might predict academic failure unless you start to intervene early.

**What does intervention look like?**

For ADHD, until you’re in your late teen or adult years, the main consumers of behavioral therapy are parents and teachers. Through parent management training and classroom interventions that include behavioral supports, parents and teachers can break down skills into small steps. For instance, parents can use a reward system with their children because so many youth with ADHD don’t develop intrinsic motivation as fast as other kids. So instead of yelling, “I told you a thousand times you’re going to sit still for dinner for 20 minutes,” parents can start the clock at 5 minutes and use extra dessert as positive reinforcement. And then gradually increase the time. If done well, and if coordinated with schools, such behaviorally based interventions can promote real gains.

By late adolescence and adulthood, cognitive-behavior therapy (CBT) is effective, including time management, anger control, organizational skills, and relationship management.

**And what about medications?**

ADHD-related medications include (a) stimulants such as Adderall and Ritalin and (b) other kinds of medicine that focus on what we call the noradrenergic pathways of the brain. These are effective in managing symptoms for most individuals with ADHD. However, it takes clinical skill and close observation to decide which medications (and at which dosages) are optimal for a given patient.

For preschoolers, behavioral interventions are considered first-line treatments; for grade-schoolers, both medications and behavioral interventions are treatments of choice. A number of studies reveal that the most effective treatment regime for most individuals with ADHD is “multimodal,” involving a combination of behavioral and medication interventions, carefully monitored.

**You are renowned for your multi-year ADHD studies of girls. What have you learned?**

When I was in graduate school a long time ago, the field used to believe that girls don’t get ADHD. So, 25 years ago, my team began the Berkeley Girls with ADHD Longitudinal Study (BGALS). We designed therapeutic summer camps to observe how girls with and without ADHD interact with one another in the playground and the classroom. We have followed our sample regularly.

We have found that girls with ADHD are just as academically impaired as boys. They have the same kinds of executive function deficits. And they actually encounter more peer rejection because other girls are very sensitive to intrusive, impulsive behaviors.

During our 5-, 10-, and 16-year follow-ups, we have found that girls with ADHD, in addition to maintaining these core problems, also have different sets of long-term outcomes. More than boys, they’re more likely in their late teens and twenties to engage in self-harm, including both non-suicidal self-injury and actual suicide attempts.

We also found that girls with ADHD who had also been physically or sexually abused or neglected had 50% higher rates of suicide attempts than those girls with ADHD who had not experienced maltreatment. It’s a classic example of genetic risk being compounded by early adverse experiences.

**Is the treatment course in girls any different?**

There’s no data to suggest that girls respond any differently than boys to medications or behavioral interventions. There’s still a lack of recognition of ADHD in girls because the doctor may say, “Well, she wasn’t running around the waiting room.” Or the teacher might report that she’s not climbing up on desks like her male peers with ADHD. Girls are more likely than boys to have the purely “inattentive” form of ADHD and they’re more likely to be hyper-verbal rather than hyperactive physically. So, clinicians must recognize some of the gender-specific manifestations of ADHD.

**You said in one of your papers that few girls with ADHD show “positive adjustment” later in life. What does this mean?**

With our Berkeley sample we didn’t find much evidence for the kind of magical thinking that if you just wait long enough,
kids with ADHD somehow grow out of it. Yes, when you’re 18 compared to 8, you may not be running around a classroom but academic problems may well magnify, as do organizational problems, relationship problems, and problems on the job.

We found one out of five of our girls with ADHD were doing well in most domains of life by their adolescent years, and we’re trying to explore what predicts such resilience or “positive adjustment,” on into adulthood. But sadly, we find that most are struggling academically and socially. Sixteen years after the summer camps, girls (now women in their 20s) with ADHD show a 45% risk of unplanned pregnancy compared to a 10% risk for the comparison group Both inattention and impulsivity contribute to that high risk for unplanned pregnancy, which demonstrates that there are consequences beyond immediate symptoms of the disorder.

You make clear that ADHD continues to have consequences as you go forward in life. So would you agree that a key takeaway is for parents to intervene as early as possible?

Yes, please be concerned as a parent, so long as you’re not over-concerned with fidgeting or temporary lack of focus. Every child is inattentive sometimes, right? But if you’re getting feedback in preschool and grade school, from teachers, coaches, and peers, please look into it. On average, if these behaviors are above the developmental norm and they’re causing real problems in life, they’re not likely to go away on their own without some serious intervention. I think that’s the core message here.

HOW ADHD IS DEFINED AND DIAGNOSED

Symptoms
Typically, ADHD symptoms arise in early childhood. According to the DSM-5, several symptoms must be present—and impairing—before the age of 12 to validate a diagnosis. Many parents report excessive motor activity during the toddler years, but ADHD symptoms can be hard to distinguish from the impulsivity, inattentiveness, and active behavior that is typical for kids under the age of 4. In making the diagnosis, children should have six or more symptoms of the disorder within either domain of symptoms; individuals 17 and older should have at least five of the symptoms. The DSM-5 lists three presentations of ADHD—Predominantly Inattentive, Hyperactive-Impulsive and Combined. The symptoms for each are adapted and summarized below.

ADHD predominantly inattentive presentation
- Fails to give close attention to details or makes careless mistakes
- Has difficulty sustaining attention
- Does not appear to listen
- Struggles to follow through with instructions
- Has difficulty with organization
- Avoids or dislikes tasks requiring sustained mental effort
- Loses things
- Is easily distracted
- Is forgetful in daily activities

ADHD predominantly hyperactive-impulsive presentation
- Fidgets with hands or feet or squirms in chair
- Has difficulty remaining seated
- Runs about or climbs excessively (in children); extreme restlessness (in adults)
- Difficulty engaging in activities quietly
- Acts as if driven by a motor; adults will often feel inside as if they are driven by a motor
- Talks excessively
- Blurs out answers before questions have been completed
- Difficulty waiting or taking turns
- Interrupts or intrudes upon others

ADHD combined presentation
- The individual meets the criteria for both inattention and hyperactive-impulsive ADHD presentations.

These symptoms can change over time and as situational demands change, so individuals may fit different presentations as they get older.

Source: Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD)
Uniting Donors with Scientists

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

—Barbara Toll, Board Member & Research Partner

To learn more, please contact us at 646-681-4889 or researchpartner@bbrfoundation.org. Visit bbrfoundation.org/research-partners.
PROGRESS IS REPORTED IN RESEARCH ON BRAIN WAVE PATTERNS TO PREDICT AUTISM OUTCOMES

The brain mechanisms involved in the causation of autism spectrum disorder (ASD) are still poorly understood. Yet certain biological phenomena that may serve as biomarkers of these mechanisms have come to researchers’ attention. One of these is a relationship between differences in brain waves—oscillations created by the activity of neurons—and ASD pathology emerging in the first 3 years of life.

These brain wave differences—seen in comparisons of infants who go on to develop autism compared with those who do not—are measured via EEG (electroencephalography). They are now thought to be among “the core features of ASD pathophysiology,” write the investigators in a paper published in *Nature Communications.*

The research team’s senior member was 2017 Ruane Prizewinner Charles A. Nelson, Ph.D., and included 2016 BBRF Young Investigator April R. Levin, M.D., both of Harvard Medical School and Boston Children’s Hospital.

EEG can be measured, even in very young children, by placing sensors on the scalp. In the new Harvard study, a small cap bearing a dense array of sensors was used, which made their placement a simple matter. EEG readings of the underlying brain activity were conducted in 2 to 5 minutes’ time in each child.

The team was most interested in discovering how early in life it is possible to identify brain wave patterns that distinguish children who go on to develop ASD symptoms by age 3 from children who do not develop ASD. It turned out that such a signal became measurable in the frontal part of the brain during the first postnatal year.

The researchers recruited a cohort of 102 infants at high risk—children with one or more older siblings diagnosed with ASD. Such high-risk children are estimated to have a 1 in 5 chance of developing ASD, a rate about 10 times higher than that in the general population. EEG patterns of these children (of whom 31 ended up developing ASD) were compared with one another and with those of 69 children with low familial ASD risk.

EEGs were performed in the study group every few months beginning 3 months after birth and ending in an assessment at 36 months, by which time ASD symptoms are usually manifest and a diagnosis, where appropriate, is possible.

The team discovered that EEG differences in the children who did go on to receive an ASD diagnosis at age 3 were not only detectable but were clearest during the first year of life.

The “signal” was seen in two kinds of brain waves in particular, called delta and gamma waves. These names refer to the frequencies at which different groups of neurons oscillate in the brain. Gamma waves reflect activity of the fastest-oscillating neurons (between 30 and 50 cycles per second) and delta waves the slowest (a few cycles per second).

It is good news, Dr. Levin says, that readings during the first
year were most predictive of future ASD outcome. It is widely thought that the earlier such children are identified, the better their chances of receiving care that might minimize the impact of the disorder.

At the same time, however, Dr. Levin stressed that there is an important ethical question in play. Even if a biomarker predicting a later autism diagnosis is ultimately developed for clinical use, "you don’t want to be diagnosing a disorder early if you’re not sure that treatments you have at hand are really going to be effective.”

For this reason, she says, “it’s really important to recognize that we’re not yet at a point where we can make clinical recommendations based on the findings in our paper.” Apart from the question of treatments, the EEG signal needs to be replicated experimentally and optimized, so that it is as specific to future ASD diagnosis and sensitive enough to minimize the chances of generating false positives and false negatives.

The team continues its work toward these goals, with the hope that future results may result in a tool that might be used routinely to screen every newborn, and certainly those at high family risk, for autism liability.

EARLY-LIFE ABNORMALITY IN AUDITORY CORTEX IS LINKED WITH VULNERABILITY TO HALLUCINATIONS IN SCHIZOPHRENIA

A team of researchers has reported new evidence about the cause of auditory hallucinations, suggesting that in schizophrenia, and perhaps other illnesses, it may be traceable to an abnormality in the functional organization of part of the brain’s auditory cortex.

If confirmed in subsequent research, this would suggest that vulnerability to hallucinations may be detectable very early in life, long before psychiatric symptoms become apparent.

The research team was led by Sophia Frangou, M.D., Ph.D., of the Icahn School of Medicine at Mount Sinai, recipient of BBRF’s 2019 Colvin Prize for Outstanding Achievement in Mood Disorders Research and a 2008 BBRF Independent Investigator and 2002 Young Investigator.

Her team used functional MRI imaging driven by a high-powered magnet to compare the auditory cortex of 16 patients with schizophrenia with those of 22 unaffected controls. The high-resolution scans were obtained while each individual passively listened to a series of sounds ranging widely across audible frequencies, first from low to high (88–8000 Hz) and then in reverse order.

Each of the patients in the study had a history of frequent (in many cases, daily) auditory hallucinations, which, at the time of the testing, were in remission thanks to antipsychotic medications. Knowing they were in remission enabled the team to compare their auditory cortex responses in a non-hallucinatory state to those of people who never experience hallucinations. About 80% of people with schizophrenia experience auditory hallucinations, which are not only distressing to patients but increase the risk of suicidal and aggressive behavior, the team notes.

Experts have debated for years about whether hallucinations are caused by “bottom-up” or “top-down” factors in the brain—i.e., factors affecting the perceptual apparatus itself or problems in high-order interpretation of sensory signals in the brain. Results obtained by Dr. Frangou and colleagues suggest the earliest deficit involves bottom-up processes.

Specifically, their scans revealed that schizophrenia patients with a history of regular hallucinations had abnormalities in primary sensory processing—in what scientists call the tonotopic organization of the auditory cortex. Tonotopy refers to the ordered representation of sound frequencies. Tonotopic maps of patients, as compared with controls, revealed that patients had greater activation in response to most sound frequencies. The team also noted a kind of “scrambling” in the way patients’ auditory cortices mapped the range of sounds presented during the fMRI scanning.

Importantly, the tonotopic organization of the auditory cortex is established during prenatal and early postnatal life. It follows a genetic blueprint, the researchers explained. Thus, if the team’s findings are replicated, they will indicate that abnormalities in the organization of the auditory system actually begins prior to the development of both hearing and speech—and, on average, 15-20 years before the onset of psychotic symptoms in people with first-episode episode psychosis, which often marks the onset of schizophrenia.

This means that the tonotopic organization or other abnormalities in the organization of the auditory cortex are
potential early-life biomarkers for vulnerability to hallucinations as well as schizophrenia, the team said.

The team’s results, which appeared in the journal Nature’s sister publication npj Schizophrenia, are informative about the symptom of auditory hallucinations particularly within the context of schizophrenia. It is unclear if similar problems are present in other disorders, including bipolar disorder and depression, in which hallucinations sometimes develop. The team next hopes to replicate and expand these results and to quantify tonotopic disruption in the auditory cortex during hallucinatory experiences.

The research team also included Iris Sommer, M.D., Ph.D., a 2007 BBRF Independent Investigator and 2005 Young Investigator; and Priti Balchandani, Ph.D., a 2015 BBRF Young Investigator.

RESEARCHERS IDENTIFY SENSORY NEURONS IN THE GUT THAT SIGNAL THE BRAIN TO STOP EATING

New research has revealed specific types of neurons that control eating behavior. This basic research about how the body and brain work together has important implications for obesity and metabolic disorders, and possibly also for eating disorders such as bulimia and anorexia nervosa.

A team at the University of California, San Francisco led by Zachary A. Knight, Ph.D., used genetic methods to classify and distinguish various types of neurons that are bundled together in the vagus nerve. One of the most important nerve conduits in the body, the vagus nerve connects the brain with the stomach and intestines.

“Given how central eating is in our lives, it’s remarkable that we still don’t understand how our bodies know to stop being hungry when we eat food,” says Dr. Knight, whose 2013 BBRF Young Investigator award supported some of his initial explorations of regulatory systems linking the brain and other parts of the body.

Lining the human gut is an extensive array of nerve endings, which are broadly known to play an important role in controlling how much we eat. The prevailing belief has been that hormone-sensitive nerve endings in the gut keep track of nutrients we ingest and initiate signaling when we have eaten enough. But until the new study, no one has been able to discern the specific populations of different neuronal types that convey these “satiety” (fullness) signals from the gut to the brain.

Genetic tools enabled Dr. Knight’s team to map the molecular and anatomical identities of sensory cells in the vagus nerve that have endings in the stomach and intestines. Once different cell types were discernable by markers distinctive to them, it became possible for the researchers to use a technology called optogenetics to manipulate them, individually or in groups. (Optogenetics, which uses beams of colored light to turn neurons on and off, was developed by a team led by BBRF Scientific Council member and 2005 and 2007 BBRF Young Investigator Karl Deisseroth, M.D., Ph.D., of Stanford University).

In freely behaving mice, Dr. Knight’s team experimentally manipulated various subtypes of vagus nerve neurons that have nerve endings in the gut. To their surprise, manipulation of several neuronal subtypes that sense hormones in the intestine—previously hypothesized to control appetite by keeping tabs on nutrient intake—had no impact on the animals’ feeding. Rather, it turned out to be a type of cellular receptor in the intestines, called stretch receptors, which proved a potent target for changing the animals’ appetite. Even more powerfully than similar stretch receptors in the stomach, those in the intestines, when activated via optogenetics, made the mice stop eating.

Their ability to halt eating independently of other signals makes them an intriguing target for future research on treating metabolic disorders and possibly eating disorders.

Eating disorders are thought to involve, at least in part, problems with signaling between the brain and gut. Bulemia is characterized by binge-eating, followed by purging, while anorexia nervosa involves inaccurate perception of one’s weight, food restriction, and perhaps also underlying metabolic dysregulation, as suggested in research published last year.

“We don’t yet know if our research has any connection to eating disorders like bulimia,” Dr. Knight says. “We think that these intestinal receptors [‘stretch receptors’] become activated when people overeat. Given that bulimia is associated with binge eating, dysregulation of these receptors could contribute to these conditions.” Research on the newly discovered regulatory mechanism is just getting under way, he stressed.
DEPRESSED PATIENTS GETTING CBT MAY HAVE ADDED BENEFIT FROM tDCS BRAIN STIMULATION

In recent years, researchers have been trying to find ways of making an effective treatment for depression even more effective. Cognitive behavioral therapy (CBT), a form of talk therapy, has a response rate of about 60%. That means 6 patients in 10, on average, will have at least a 50% reduction in depression symptoms, although not all of those will have a complete remission.

Researchers in the UK led by 2013 BBRF Independent Investigator Jonathan P. Roiser, Ph.D., of University College London, have recently reported results of a clinical trial in which they tested whether adding another form of treatment to CBT would raise the response rate. Specifically, they combined CBT with a type of non-invasive brain stimulation called transcranial direct current stimulation (tDCS).

tDCS has been tested as a stand-alone treatment for depression, although results have been inconsistent across various trials. It has also been tested as a treatment for Parkinson’s and Alzheimer’s diseases (as a cognitive enhancer), as well as schizophrenia and stroke. Like rTMS, a different form of non-invasive brain stimulation that can be used to treat depression, tDCS has been well-tolerated by patients; but unlike rTMS, its consistency in helping patients has not yet been established.

In the newly reported trial, which appeared in the journal *Neuropsychopharmacology*, Dr. Roiser, with first author Camilla Nord, Ph.D., and colleagues, recruited 39 unmedicated people diagnosed with major depressive disorder, all of whom received CBT therapy, and 20 of whom also received active low-dose tDCS treatments (19 patients received a “placebo” version that feels like tDCS but does not generate a current that penetrates the skull). Active tDCS or the placebo version were given to patients in eight weekly sessions, which lasted 20 minutes each. Immediately following each session, patients received their regular weekly hour of CBT therapy. The timing was intentional: knowing that brain areas stimulated by tDCS remain excited for about 90 minutes after each session, the researchers hoped that patients receiving active stimulation would derive enhanced benefit from CBT therapy if their treatments occurred during this interval.

The trial generated an intriguing result. While about 20% more patients responded or had a remission following CBT plus active tDCS (as compared with CBT plus the placebo version), this result did not reach statistical significance. Since the study population was small this will warrant retesting with a larger group, the team said. But one result of the study was clear: the discovery of a biomarker that may be useful in predicting which depressed patients are likely to have a response to tDCS.

The biomarker is a signal of activity in the brain’s dorsolateral prefrontal cortex, as measured prior to the initiation of tDCS and CBT treatment. This “baseline” level of activation, which was measured in each participant in the trial, was “strongly and specifically associated” with clinical response to tDCS, the team reported. With an accuracy of 86%, high levels of activation in the left prefrontal cortex at baseline retrospectively identified which patients had a significant benefit from tDCS, compared with the placebo treatment. This marker, the team said, could potentially be used in advance of actual treatment, to provide an indication of who would be most likely to respond to it.

The team concluded, “We discovered a biomarker that explains variability in tDCS response.” At other levels of stimulation intensity—the trial used it at low intensity—tDCS might show the same relationship to the biomarker, or a different one, another subject for future study, they said. “Ultimately, these data could guide patient selection in larger clinical trials, and, if confirmed, inform clinical use of tDCS in depression.”
HIGHER MATERNAL CHOLINE LEVELS IN PREGNANCY HAD PROTECTIVE ROLE IN INFANT BRAIN DEVELOPMENT

Researchers have obtained further evidence that during pregnancy, the presence of adequate levels of choline, an essential nutrient, in the mother’s system has a protective role in the development of the fetal brain and on behavior in children following birth. This finding has potential implications for future mental illness prevention efforts.

The new evidence, published in the *Journal of Pediatrics*, bolsters the case for choline supplementation during pregnancy, a measure now advised by the American Medical Association but which is not yet common practice in this country or worldwide.

A team led by Robert Freedman, M.D., and M. Camille Hoffman, M.D., both of the University of Colorado Denver School of Medicine, enrolled 201 pregnant women in a study, 82 of whom (41%) developed an infection by the 16th week of gestation. Prior research has established that the mother’s immune response to infection affects the placenta and compromises its support of the fetus, although in ways that are not yet fully understood.

The question in this study was: did levels of choline in the plasma of mothers with second-trimester infections affect brain development and early postnatal indicators of brain function in their newborns? The working hypothesis was that infected women with higher levels of choline in the plasma—the blood component which supplies choline to the fetus via the placenta—would have babies that performed better in two key areas of brain function compared with babies of infected mothers whose choline levels were lower during pregnancy.

That is exactly what the data revealed, after 136 of the participating moms stayed in the trial and brought their babies in for key tests at 1 and 3 months after birth and submitted a detailed questionnaire about their newborns’ behavior at 3 months of age.

The test given to the newborns in the months after birth is a well-established measure of the response to repetitive sounds. It is used by neuroscientists to test a property of the brain called cerebral inhibition. Dr. Freedman, a member of the BBRF Scientific Council, winner of the 2015 Lieber Prize and 2006 and 1999 BBRF Distinguished Investigator, has used the test over the last two decades in pioneering studies helping to explain implications of a major transition in the fetal brain that occurs just before birth.

This transition, which marks the emergence of the maturing brain’s capacity to modulate, or dial down, the activity of excitatory neural communication, is an essential step if the newborn brain is not to be overexcited or hyperactive. Hyperactivity is one of the aspects of brain dysfunction that may contribute to a number of mental illnesses, including schizophrenia and attention-deficit disorder.

The brain’s emerging inhibitory capacity, Dr. Freedman and colleagues have discovered, is partly dependent upon the action of choline during the fetal period. In addition to its role in enabling brain cells to build cell walls, choline is the substance that engages receptors which are abundant in the placenta and fetal brain. They are called alpha-7 nicotinic cholinergic receptors.

A deficiency of choline, Drs. Freedman, Hoffman and colleagues have proposed, prevents or impairs the maturation of neurocircuits, including inhibitory circuits, possibly contributing to pathology seen in schizophrenia and other disorders.

As they have pointed out, levels of maternal choline dip naturally during the second trimester of pregnancy, making it a particular period of vulnerability for the fetus. Since many pregnant women have choline deficiencies, it is especially important, the researchers suggest, for pregnant women to take dietary supplements.

In two past studies, Drs. Freedman and Hoffman have demonstrated a correlation between maternal choline supplementation and improved outcomes in newborns on the test that measures the brain’s inhibitory function.

Dr. Hoffman is a winner of the BBRF’s 2015 Baer Prize. Team members also included Amanda Law, Ph.D., a member of the BBRF Scientific Council, winner of the 2011 Baer Prize, 2009 BBRF Distinguished Investigator and 2006 Young Investigator; and Sharon Hunter, Ph.D., a 2003 BBRF Young Investigator.
DNA ‘LETTERS’ (p. 4) The human genome consists of approximately three billion paired combinations of four organic molecules called nucleotides—or DNA “letters”—that are arrayed in a long twisting molecule called the double helix. The miracle of all life traces, then, to a string of information encoded by only four chemical entities: Adenine, which always “pairs” with Thymine, and Guanine, which always pairs with Cytosine. To sequence a human genome means to “spell out” these letters in the order in which they occur in our chromosomes. The information in our genome and that of all other living things provides instructions for cells to manufacture proteins, and to regulate when, where, and how much they produce. Variations in the sequence, which are sometimes called risk variants, can interfere with this process, sometimes leading to pathology, but other times in ways that do not have overtly harmful effects.

POLYGENIC (p. 5) Sequencing of the human genome laid bare the fact that many serious illnesses, to the extent that genetics is a factor in their causation, are usually not caused by a single gene mutation, but rather, by combinations of genetic variants—with different combinations in different individuals determining their relative level of risk for illness. Compare “gene-disrupting mutations,” below.

HUMAN REFERENCE GENOME (p. 6) A consensus version of the human genome, based on the sequencing of individuals of diverse races, ethnicities, and geographic origins. Variations can be thought of as departures from the reference genome—although most variations are trivial in their impact. No two human genomes are identical, save for those of identical twins. But health outcomes in such twins typically diverge, indicating there are other powerful factors, such as environment, that interact with genes and the DNA that regulates genes, to produce health outcomes.

GENE-DISRUPTING MUTATIONS (p. 7) Genome sequencing has revealed that while individual risk for complex illnesses like schizophrenia is to a large degree related to the particular genetic variations that one is born with, such illnesses can also be caused by rare variations, sometimes occurring spontaneously in a person, that have a catastrophic impact on essential biological mechanisms. For instance, rare structural variations that cause the deletion or multiplication of DNA in our chromosomes or the fragmenting of chromosomes can disable vital mechanisms, by disrupting or deleting genes whose proper function is essential for brain development during the fetal period, or brain function later in life. Some gene-disrupting mutations can render a fetus non-viable; others are survivable but may underlie serious illnesses, including some brain and behavior illnesses.

EVENT-RELATED POTENTIAL (p. 15) A measure of brain function in research by Deanna Barch and colleagues that appears to correlate with a child’s ability to respond to pleasant stimuli. ERP is reduced in children who are anhedonic—have difficulty experiencing joy, one of the symptoms of depression. Improvements in ERP were correlated in one recent study with lessening of depression symptoms after a therapy called Parent-Child Interaction Therapy—Emotion Development (PCIT-ED).

NORADRENERGIC PATHWAYS (p. 23) Pathways through which the chemical neurotransmitter norepinephrine (also called noradrenaline) acts. It increases arousal and alertness, promotes vigilance, enhances memory, and focuses attention; it can also increase restlessness and anxiety.

DELTA AND GAMMA WAVES (p.26) Detected by electroencephalography (EEG), these are, respectively, brain waves of the fastest and slowest frequencies. They reflect oscillations of neurons, and in preliminary research, were analyzed in the first year of life to identify infants at high risk for developing autism by age 3.

CEREBRAL INHIBITION (p. 30) A critical transition in brain development just before birth provides the brain with the means to inhibit excitatory signals. Failure to properly develop this capacity may be linked with hyperactivity in the brain in individuals who develop certain disorders, perhaps including schizophrenia and ADHD. Adequate levels of the nutrient choline in the perinatal period may help to prevent adverse outcomes.
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