Brain & Behavior Research Foundation

Quarterly

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PRESENTING THE INDEPENDENT INVESTIGATORS

Parenting Advice on Enhancing Early Childhood Development

JAMES F. LECKMAN, M.D., PH.D.

Birth of New Nerve Cells in Adult Brains Suggests New Strategies to Treat Depression and Anxiety

RENÉ HEN, PH.D.

Hike for Mental Health is a Trek Toward Treatment

LEO WALKER

Constance E. Lieber

This issue of the *Quarterly* is dedicated to Constance Lieber who passed away on January 15, 2016.

Connie, who served as President of the Foundation from 1989 to 2007, felt that research was the best avenue to find meaningful and lasting solutions to alleviate the suffering caused by mental illness. Connie passionately believed in the need to seed the field of neuropsychiatric research with as many talented scientists as possible to make a substantive impact on the broad spectrum of mental health research, which she fervently understood holds our best hope for ending the immense suffering caused by mental illness.

Connie was a deeply caring and visionary philanthropist, who has had a tremendous impact on psychiatric research and treatment. Connie was our leader and guiding light, providing inspiration and motivation to all who ever had the honor and privilege of knowing and working with her.

She will be dearly missed by us all.

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PRESIDENT'S LETTER

Jeffrey Borenstein, M.D.

President & CEO
Brain & Behavior Research Foundation

One of the most fulfilling aspects of our work at the Brain & Behavior Research Foundation is seeing the basic research we fund evolve into preventative therapies or early interventions against mental illness. All of us who have seen the toll taken on patients and families by diseases such as schizophrenia, bipolar disorder, depression or any brain and behavior disorder want to see more possibilities for treating them in their earliest stages—along with the possibility of preventing them altogether.

This issue of the *Quarterly* features such a story (page 8) about the work of Robert Freedman, M.D., a member of our Scientific Council and 2015 recipient of the Lieber Prize for Outstanding Schizophrenia Research. Dr. Freedman and his colleagues were able to piece together a new understanding of early brain development that has led to a nine-year study of dietary supplementation in pregnant women that they believe may lessen the risk of schizophrenia developing in children. It's an exciting example of how the complex science we support with our Foundation grants can point the way to a specific attempt at disease prevention in a way that is all too rare for mental illness.

Researchers supported by the Foundation are working to find other ways to intervene early in mental illness. In our Parenting column this issue (page 4), James A. Leckman, M.D., Ph.D., shares his thoughts on the long-lasting benefits of early interventions that address parenting skills and bring together groups of parents and physicians to support early childhood mental health. And as Dr. Leckman also reminds us, the knowledge we use in building these nurturing interventions has been strengthened by decades of basic research on the developing brain.

The support that you and others lend to the Foundation allow our organization to play a role in some of the earliest stages of mental illness research, which we hope will translate into the advances and breakthroughs that have a positive impact on the lives of those we love.

Sincerely,

Jeffrey Borenstein, M.D.
President & CEO

FEATURE

Parenting
ADVICE ON ENHANCING EARLY CHILDHOOD DEVELOPMENT

James F. Leckman, M.D., Ph.D., is the Neison Harris Professor of Child Psychiatry, Psychiatry, Pediatrics and Psychology at Yale. He is well known for his research into Tourette Syndrome, Obsessive-Compulsive Disorder (OCD) and other related childhood onset neuropsychiatric disorders. For more than 20 years he served as the Director of Research for the Yale Child Study Center. Under his leadership, the Center emerged as one of the leading sites for child psychiatric research in the United States.

Most recently, in partnership with colleagues at UNICEF and the Mother-Child Education Foundation (AÇEV) based in Turkey, Dr. Leckman with several partners at Yale have begun to explore the question of whether enhancing child development can create a more peaceful world.

What led you to study the question of how to enhance early childhood development?

Early childhood development is such a crucially important issue. In the mid-1990s, after a lecture I gave, one of my colleagues at Yale suggested that we look at the subject of parenting. I was really curious to learn about the level of preoccupation (recurrent intrusive thoughts that resemble obsessions) that mothers and fathers (especially first-time mothers and fathers) experience as the birth of their child draws near. Then I looked at how that level of preoccupation changes in the weeks and months that follow the birth, and what changes in the structure and function of the mother's and father's brain as they become new parents. My research showed how early parenting behaviors and preoccupations resembled the symptoms of obsessive compulsive disorder. People don't really expect how transformative being a new parent will be.

I was also interested in how parents formed attachment to their children. In research I did with Ruth Feldman, Ph.D. (at Yale University) we found that the mother's level of the hormone oxytocin—which is released in social bonding situations—is correlated with the father's oxytocin levels. We also found that higher levels of oxytocin in the mother are associated with more responsive interactions with her new infant, while in fathers, higher levels of oxytocin are associated with stimulatory play, like throwing your child up in the air and catching them.

In October 2013 we held the Ernst Strungmann Forum, which brought together colleagues from around the world, who were experts either in attachment behavior in animals or implementation of parenting programs and early child development, to talk about the idea that if we raise our children better, are we going to create a more peaceful world?

Can you briefly state the case for why behavioral, mental health, and other health-related interventions are important to stress?

There are some wonderful analyses by the Nobel laureate James Heckman which show that if you intervene early in the developmental life of an individual you are much more likely to see higher cost-benefits—one of the biggest being savings on the costs associated with incarceration and with criminal behaviors.

If you intervene early, the person has a greater likelihood of finishing high school, of going to college, and is less likely to be involved in criminal behavior.

James F. Leckman, M.D., Ph.D.

Do parents who have mental health issues end up passing those or other issues to their kids either through genes or by social interaction? What advice can you offer these parents?

There is a greater risk either because of the symptoms or genetics. This is especially true for conditions like depression. Depressed mothers, for instance, have more difficulty taking care of their young children. This is an example of how symptoms of an existing condition can affect the outcome in a child. As for genetics, a lot of mental health conditions have a strong genetic component, but the genetic background to illness is highly complex, and determining an individual's risk is not straightforward by any means. In brief, the genetic portion of risk in various disorders is determined in part by different combinations of risk genes—versions of genes or sections of the genome that have mutations or other irregularities which may or may not affect an individual, and which may be active in one family or individual versus another.

The important thing I would say to a parent with mental health issues is to help yourself deal with those issues. Reach out to a mental health professional—find someone who is really invested in addressing the problem.

Adverse events early in life are detrimental to a child's development and associated with a broad range of negative outcomes, including major emotional and behavioral problems. Why do some children cope better than others and is it possible to foster resilience?

Adverse childhood experiences such as exposure to trauma or violence, even during the prenatal period when the brain is first developing, mold how the brain is organized, and have major impact on how our genes are expressed. Brain imaging studies show that traumatized children or children raised in poverty have different interconnections in their brain regions. If you've been exposed to violence, you're at an increased risk of being re-victimized.

To some extent it's a mystery why some people are more resilient than others. We are still struggling to have a deeper understanding of why people change. We really don't know all of the ingredients there are in terms of why some individuals go down one path versus another path. But I'm convinced that an important ingredient in fostering resilience is an understanding adult who in some ways sees in you something special, in some way idealizes you and sees you as someone who is able to make a positive contribution.

To what extent are we prisoners of our own family history?

I'm convinced that how you were raised and what the nature of your early experiences were, including in utero, shape your moral reasoning, compassion, equity and other character traits and set the stage for later life.

However, your early experiences don't mean that you don't have a choice. They are a significant but not a final determinant of who we become.

On balance, though: are you saying our development is more about nurture than nature?

There is a fascinating study looking at parenting behaviors in Norwegian rats. There were some mothers who licked and groomed their pups a great deal, and others who hardly licked and groomed at all. Turns out that if your mother had groomed you a lot, you were a high licker and groomer yourself when you became a new parent and vice versa.

Then the researchers took pups born to a high-licking mom and had them raised by a low-licking mom, and vice-versa. The offspring's parenting behavior was determined by how they were nurtured rather than what kind of mother they were born to. So the outcome had less to do with an individual's genetics and more to do with environmental exposure.

When we look at our genome, the actual protein coding regions, virtually identical to those of primates and rodents, account for a relatively small proportion of the entire genome. Our regulatory regions are what distinguish us from other species. They determine how or when certain genes are turned on or off. The big question is how flexible are these regions.

Many of the interventions you have advocated teach responsive parenting. Do moms and dads need to be taught how to parent?

We usually think that this is something that comes about naturally and that we don't need any special knowledge to be responsive parents. But attachment and responsiveness sometimes don't come easily. This can be especially problematic if you were raised in a family where unresponsiveness was the nature of the interaction you had with your parents, or if you received harsh treatment or punishment. The really sad thing is that a lot of trauma happens in the home.

Many of our interventions have focused on mothers, but the more we can engage fathers, the more likely there will be a positive long-term benefit.

What can parents do to have a better relationship with their children?

I would encourage people to have second thoughts about the way they were parented. If there are problems in their relationship with their children, then they should question whether it makes sense for them to learn more about positive parenting strategies. There are many programs out there to enhance parenting skills.

It's really the interaction between parent and child that matters the most when it comes to behavioral problems in children. Eli Leibowitz, Ph.D. at the Yale Child Study Center, for instance, has developed an intervention to help parents of children with obsessive compulsive disorder avoid what we call "family accommodation." Family accommodation refers to ways in which family members inadvertently take part in the performance of rituals, avoidance of anxiety-provoking situations, or modification of daily routines in response to their child's requests. The idea is, when a child approaches you and asks for reassurance, you should not respond to them with, "You are okay. I am okay. Don't worry." If you respond to those obsessive questions in the way the child is hoping and you do that as often as the child asks, you are providing reinforcement for them to continue to ask.

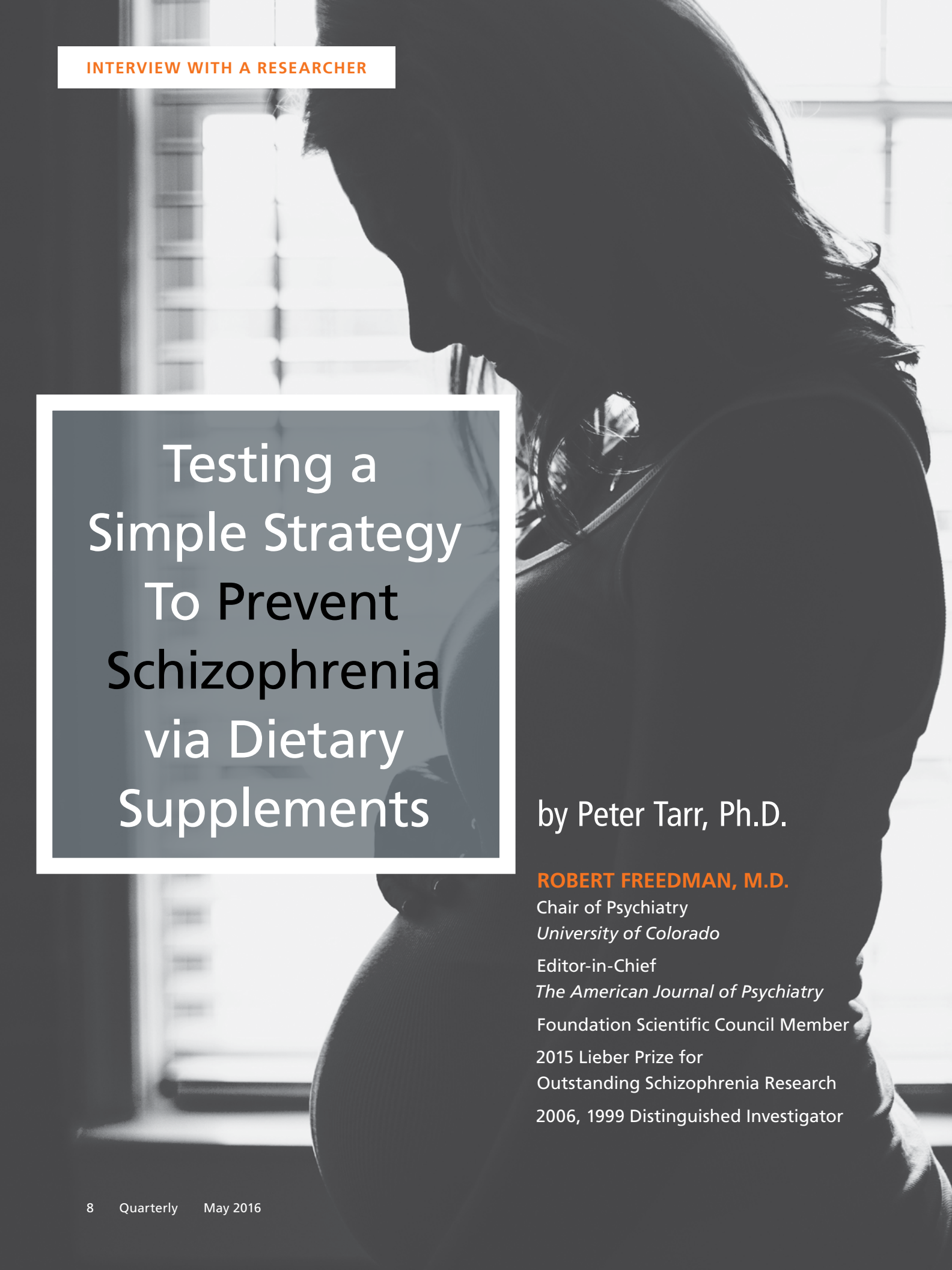
Significant improvement of OCD symptoms with treatment is associated with reductions in family accommodation. To achieve this Dr. Leibowitz suggests that parents wait for a time when your child is not acting fearful and you are not feeling frustrated by his avoidance. Sit down in a relaxed way and say, "We know how difficult it is for you to do [fill in]. We understand it makes you feel really anxious or afraid. We want you to know that this is perfectly natural and everyone feels afraid sometimes. But it is our job as your parents to help you get better at things that are hard for you. We are all going to be working on this for a while and it will probably take time, but we love you too much not to help you. Soon we'll talk about this again and we will have some ideas for things to do that will help with this. We are really very proud of you!"

Some of the interventions you have advocated are home-visitation based, but many are in group settings. What kind of advantages does the group offer?

One of the wonderful things about these programs—for example, those of the Mother-Child Education Foundation in Turkey—is that it's done in groups of moms and dads. The trainers in these group settings are obviously important, but so are the participants. If you respond to your child in a different way and the child changes, that can be enormously reinforcing to parents. When other parents in the group hear about these changes it's much easier for them to go out and try those changes themselves. Sometimes parents are also recruited as co-trainers.

The participants form a support system. When I first met with the board of the Mother-Child Education Foundation (AÇEV) they wanted me to explain from a neuroscience perspective why it was that fathers who came from different social, cultural and religious backgrounds become friends with one another and decided to continue interacting with one another even after the curriculum ended. I reviewed with the AÇEV Board the direct interface between our affiliative and our stress response pathways in our bodies and brains and the power of group processes to break down social barriers and stereotypes of the "other."

Some good examples of early intervention programs include Circle of Security, a program designed to enhance attachment security that has various locations in the U.S., and in the world. Another program, Mom Power in Michigan, is a parenting group for mothers receiving Medicaid whose children are under age 6. Other programs for parents of children across the age range include Triple P the Power of Positive Parenting (originally developed in Australia) and Parenting Management Training (initially developed in Oregon). ■



Testing a Simple Strategy To Prevent Schizophrenia via Dietary Supplements

by Peter Tarr, Ph.D.

ROBERT FREEDMAN, M.D.
Chair of Psychiatry
University of Colorado
Editor-in-Chief
The American Journal of Psychiatry
Foundation Scientific Council Member
2015 Lieber Prize for
Outstanding Schizophrenia Research
2006, 1999 Distinguished Investigator

AT WHAT POINT do the fruits of basic research—the hard-won bits and pieces of knowledge about brain function that the Foundation's grants generate—result in the development of new treatments? There's an exciting example now emerging in the laboratory run by Robert Freedman, M.D.

Dr. Freedman, Chair of Psychiatry at the University of Colorado, editor in chief of *The American Journal of Psychiatry*, and a member of the Foundation's Scientific Council since 2001, has been on a long journey that began in medical school at Harvard in the late 1960s.

The winner of the 2015 Lieber Prize for Outstanding Schizophrenia Research and twice (2006, 1999) a Distinguished Investigator, Dr. Freedman has been on the trail of what neuroscientists call inhibition—specifically, its role in schizophrenia. Inhibition refers to the brain's ability to dial down the strength of signals being exchanged among excitatory nerve cells. In schizophrenia, evidence suggests that an insufficiency in inhibition leads to hyperactivity in key areas involved in cognition and emotional processing.

Much of what Dr. Freedman and his colleagues have learned over decades has been translated into a simple and safe preventive strategy to bolster inhibition in the fetal brain, and thereby lessen the risk and perhaps actually prevent some newborn children from developing schizophrenia—one of the great objectives in all medical research.

The strategy involves providing expecting mothers with supplements of choline, an essential nutrient that plays an outsized role in the fetal brain while it is developing in the womb. The fetal brain is hyperactive as it assembles itself. "It just fires up all of its nerve cells, no inhibition whatsoever," Dr. Freedman says. "Of the 20,000 genes we humans have, more are devoted to building the brain than anything else. And most of them are most active—about tenfold more—before birth compared with after."

Just before birth all this activity needs to quiet down, however. "The brain is settling down," Dr. Freedman explains. "This turns out to be the final step right before delivery, the last of five or six distinct steps which correspond with major changes in brain organization." In each step, he says, "you not only get more memory and more function—as you do each time you upgrade your computer—but you also install a new operating system. In the early brain, each operating system is installed by the one that came before it."

Robert Freedman, M.D.

Of the 20,000 genes we humans have, more are devoted to building the brain than anything else. And most of them are most active—about tenfold more—before birth compared with after.

Dr. Freedman's research focuses on one of the earliest operating systems, which unlike the others that follow it, "hangs around to do the very last installation." This final step in the pre-birth developmental program makes normal inhibition possible.

Evidence shows that in infants who go on to develop schizophrenia, the brain's inhibitory system does not establish itself as robustly as it should. The results are evident to those who treat and spend time with patients, including Dr. Freedman, still an active clinician.

"You may hear a patient say, 'I vaguely overheard someone talking and I concluded they were talking about me, and that they were saying bad things.' There is often a hypersensitivity to sound. When you investigate, the sound is really there, but misinterpreted. You or I would probably ignore it as noise, if we did hear it. We might say, 'This is a noisy apartment.' But we wouldn't say, 'And they're talking about me.'"

A hypersensitivity to sensory information, accompanied by difficulty discriminating the nature or emotional salience of the information, is characteristic in schizophrenia. It can be traced biologically, at least in part, to a deficiency in inhibition. There is too much excitation, not enough inhibition—as, indeed, Dr. Freedman and colleagues showed in a schizophrenia study of the brain's hippocampus, a vital center for emotional processing. Even in its "resting state," this part of the brain is hyperactive in people with schizophrenia, the study showed.

Several converging lines of evidence have pointed Dr. Freedman to a gene called *CHRNA7* (pronounced "CHUR-na 7"). Very active early in development, the gene quiets down just before birth to a low activity level that continues into adulthood. This is the gene, it turns out, that encodes receptors on nerve cells that become vital at the end of gestation, in the emergence of neural inhibition. The receptors are called alpha-7 nicotinic receptors, or α7 receptors.

CHRNA7 is the gene whose expression is most significantly decreased in the brains of people who have had schizophrenia (as measured in postmortem brain analysis). Genetic studies have also shown that a subset of schizophrenia patients have genomes in which the area on chromosome 15 containing *CHRNA7* is deleted, meaning they do not make enough α7 receptors.

In adults, α7 receptors are activated by a neurotransmitter called acetylcholine. In related research, Dr. Freedman and colleagues have been testing drugs that stimulate the α7 receptor in adults with schizophrenia—who, presumably, have had insufficient inhibitory activity from the time near birth when the system is first activated.

In the fetus, it is choline in the mother's amniotic fluid that activates these receptors. Choline is needed throughout pregnancy in considerable amounts for various purposes, not only to prepare the brain's inhibitory system but also to build the walls of cells throughout the body. Studies show that one expectant mother in five does not get enough choline in her diet. While meat and eggs are rich sources of the nutrient, which is also found in many other foods, poor diets do not supply nearly enough.

These facts led Dr. Freedman and colleagues to an experiment that has taken the last nine years to complete. They wanted to know whether giving expectant mothers extra choline in the second and third trimesters might help their children develop more robust inhibitory capacity. [The accompanying story explains how they conducted the experiment and showed that it works.]

"The larger story is that we've gone from learning ways in which the nervous system doesn't work in schizophrenia to actually doing something to prevent it from happening," says Dr. Freedman. "This is the first group of children that we can point to and say, yes, we can treat earlier and do it effectively."

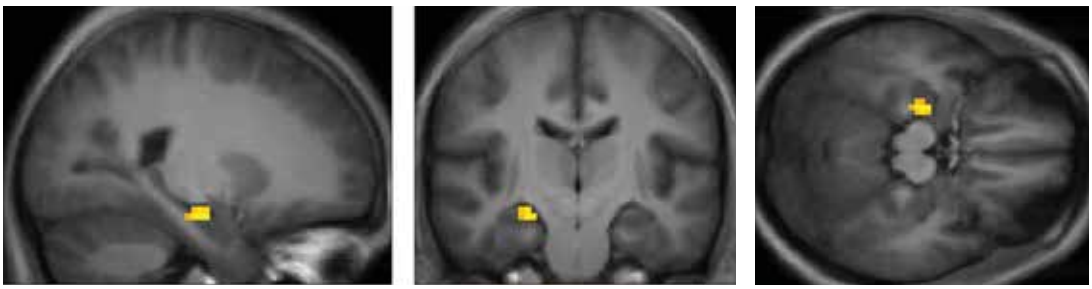
INTERVIEW WITH A RESEARCHER / SIDEBAR

Choline Supplementation in Mothers Has Yielded Positive Results in Children

"We know that babies born to moms who have schizophrenia, as well as babies from other moms who later go on to develop schizophrenia, already have recognizable differences from babies who don't carry that risk," says Dr. Robert Freedman. The problem, he notes, is that detecting these differences in the first years of life is not predictive of schizophrenia. All who develop the illness have biological differences from the beginning; but many infants with these differences don't go on to become ill.

By the time of the first definitive diagnostic symptoms—typically, a first "psychotic break," in the late teens or early 20s—it is already too late to prevent schizophrenia from occurring. Hence, Dr. Freedman decided to focus on reversing or blunting the first step in the multi-step process toward disease onset. "We thought that if we could bolster the brain's inhibitory system even before a child is born, then perhaps we could lessen the risk that the other biological steps toward the illness would occur. We might even prevent the illness in some cases."

His team demonstrated, first in rodents and then in people, that supplying choline in high doses to expectant mothers would suffice to activate the inhibitory system in the developing fetus. They noted that this supplementation would bring the choline level up to levels others had measured in the amniotic fluid of healthy mothers. The team also drew heavily on medicine's past success with another kind of prenatal supplementation—that of folic acid, another vital nutrient that expectant moms must have lest their infants



An experimental drug that targets the A-7 nicotinic receptor reduces hyperactivity in the brain's right hippocampus (yellow), a prime site of emotional processing and affected in schizophrenia.

suffer from neural tube defects and a variety of associated birth defects. Folic acid fortification, ideally begun before conception and continued throughout the perinatal period, especially in women with poor diets, is accepted practice in the U.S. and worldwide.

Dr. Freedman, with critical help from Camille Hoffman, M.D., an assistant professor of maternal-fetal medicine, and Randal Ross, M.D., a professor of child psychiatry, both at the University of Colorado School of Medicine, took a parallel approach with choline. Led by Dr. Hoffman, who was awarded the Foundation's Sidney R. Baer Jr. Prize in 2015, the team recruited 100 healthy women from the Denver area. In a double-blind trial they tested whether giving choline supplements during pregnancy to increase the nutrient's level in the amniotic fluid would enhance the development of inhibition in the fetal brain's cerebral cortex. The supplements (twice normal dietary levels) were given by pill, twice a day throughout the second and third trimesters, and then to mother and newborn through the third postnatal month.

Happily, there were no adverse effects in maternal health, delivery, birth or infant development. But did the supplements make any difference? Dr. Freedman's team gave the newborns a crucial test after five weeks. Each child was exposed to two identical sounds—a succession of clicks. The team measured the activity of the brain during this test. A baby or adult with normal inhibition responds much less robustly to the second sound, which is filtered out as comparatively insignificant. A sharp response to the second sound is what scientists call a "surrogate marker" of a deficiency in inhibition.

This marker, called the P50 response, indicated normal inhibition in 76 percent of the infants whose mothers had been given choline supplements. In babies whose mothers received placebo instead of extra choline, only 43 percent had normal inhibition. That figure would likely have been lower if every mother in the trial, regardless of her treatment, had not received special instructions from visiting nurses to eat a diet rich in choline. (The aim was to compare choline supplementation with normal, not subpar, choline intake by the expecting mother.)

The study showed, too, that choline supplements even benefitted the infants of mothers who carried genetic risk factors for schizophrenia, including variants of *CHRNA7*. But in mothers carrying these risk factors who received placebo, even the benefit of dietary advice (as opposed to supplementation by pill) during pregnancy did not prevent their children from showing diminished P50 inhibition after birth. In 2015, Dr. Freedman's team reported follow-up results when infants in the original trial reached 40 months of age—the time when behavioral patterns become settled and incipient problems are discernable.

"Children who will go on to develop schizophrenia already have recognizable motor problems in the first year of life," Dr. Freedman says, "which are not in themselves diagnostic. But by early childhood they also show clear signs of attention difficulties and social withdrawal, effects that we can trace at least partly to deficits in inhibition."

At 40 months, the team was excited to observe that children of mothers who had received choline supplements had fewer attention problems and less social withdrawal compared with children in the placebo group. It is of course impossible to know the "final" outcome of this experiment until the children reach their 20s. Right now, says Dr. Freedman, "what we know is that the babies exposed to supplemental choline as four year-olds are healthier children than if we had not intervened."

The team will continue to test whether the specific form of choline used in the trial—called phosphatidylcholine—is indeed the best supplement to give. The optimum dose also remains under study. ■

Have A Question?

Send questions for Robert Freedman, M.D. to **asktheresearcher@bbrfoundation.org.**

Select questions and answers will be in the next issue of the *Quarterly*.

ASK THE RESEARCHER

Huda Akil, Ph.D.

Co-Director and Research Professor
The Molecular & Behavioral Neuroscience Institute
University of Michigan

Foundation Scientific Council Member

My daughter is a risk taker and very social, but my son seems shy and more tentative about trying new things. Based on your research, should I be more worried about him developing depression?

Thank you for the opportunity to clarify this point. The majority of children who are shy do not become depressed, so a tendency to be shy does not foretell a mood disorder. Similarly, the majority of risk takers do not become drug addicts. The research, both in animals and humans, looks at the connection from the other direction—it says if someone is severely depressed or anxious, then they are more likely to have an inhibited temperament. But many factors need to come together before a person has a depressive episode—there is often a genetic predisposition coupled with several fairly significant life stresses, especially during childhood and in adolescence, before a depressive episode is triggered.

A very important idea, and one we are funded to study, is that it is possible to build resilience specifically in individuals who are predisposed to anxiety and mood disorders. Remarkably, we are learning that while severe stress can be a trigger for depression, smaller stresses, in limited doses, can actually build resilience—in other words, vulnerable individuals toughen up. It's like building a muscle gradually by working it but not pushing it to the point of damage. To translate this into everyday life, it suggests that you can make your son more resilient and help him build confidence by finding activities or occasions where he can take little risks, deal with the outcome, and then take slightly bigger risks. A combination of support and optimism on your part about his ability to stretch his limits is a strong basis for building that resilience. And these experiences, as they teach him about himself, actually change the brain, through modifying brain cells and brain circuits, and through other mechanisms. Just as a negative environment can render children more vulnerable, a positive environment with enough challenge but not undue pressure can strengthen them, give them confidence and provide them with valuable tools for meeting life's demands in the future.

Your description of a "depressed brain" was very interesting. Has anyone ever looked at the brains of people after they've been treated for depression for several years—does treatment change the way the brain looks?

This is an excellent question and one that we have thought about and begun to investigate. In fact, the Brain Bank of the Pritzker Consortium under the directorship of William Bunney, M.D. (at UC Irvine and also a member of the Foundation's Scientific Council) collects careful data on medication history. And the answer is: Yes, treatment reverses *some* of the damage caused by the illness, but not all the way back to normal. It is important to note that the brains we are studying are those of people who have died while carrying a diagnosis of depression. So, by definition, the antidepressants were not fully effective in helping them clinically, and we can see that they were not effective in reversing the biological impact of the illness on the brain. If we had access to brains of individuals who had a history of depression that was well-controlled by antidepressants, we might see either a more complete reversal of the damage induced by depression, or some compensation where other genes and brain circuits are induced to counteract the consequences of the illness. From animal studies, we actually believe that this would be the case. But this process takes time, which is why even when people feel better after receiving some fast-acting treatments, repeated treatment is needed for sustained recovery—brain remodeling is not instantaneous.

Ideally, as we understand more and more about the causes of various types of depression, we can target treatments more strategically to reverse or, better yet, prevent the changes we see in chronic depression. In fact, preventing or rapidly reversing these brain changes should greatly accelerate clinical recovery and prevent recurrence.

I was surprised to see that you mentioned "better eating" as something that can help people with depression re-engage their brain. What kinds of foods should a person with depression eat—or avoid?

Broadly speaking, it is important to recall that brain health, be it emotional or cognitive, is intimately connected to overall health. And this is bi-directional—if someone has heart disease, they are more prone to depression, and if someone is depressed they become more prone to heart disease. There is also increasing evidence about the relationship between so-called "metabolic syndrome" and depression. Metabolic syndrome refers to a cluster of changes that increase the risk for heart disease and diabetes, and this includes high blood pressure and obesity. Even very young people who are obese can increase their risk of brain changes and the likelihood of mood disorders. While we might think that this is only relevant in cases of severe obesity or clinically diagnosed cardiovascular disease, we now know that this is a continuum. Finally, in the last few years, we have begun to learn about the connection between our microbiome [the collection of microbes that live inside us] and our brain function. There is still much to learn in that area, but again it emphasizes the close connection between the state of our bodies and the state of our brain.

So, I am not recommending specific foods to combat depression. Rather, the general recommendation is to eat a healthy, nutritious, balanced diet, to be active and sleep well. To be as physically fit as possible. Our brain can tell the difference.

In your work with the Pritzker Neuropsychiatric Research Consortium, have you uncovered any new genes that you think might be related to mental illnesses besides major depression?

Yes, the Pritzker Consortium is interested in three severe psychiatric disorders—major depression, bipolar disorder and schizophrenia. We hope to discover the genes involved in these illnesses by studying the genetic variations that are associated with these illnesses and by studying the brains of individuals with these disorders to discover genes and proteins that are altered either because of the original genetics or because of environmental and developmental factors that have converged to change the brain.

The first class of studies relying on genetics is more fruitful in bipolar illness and schizophrenia as these disorders are more clearly heritable. Although, it is also clear that genetics is by no stretch the only determinant, and even identical twins can diverge on whether or not they develop these illnesses. We have learned that many different genes are likely to contribute to these disorders, and genes that are at play in one family may not overlap with genes in another family to produce a similar syndrome. This complexity requires that we gather information from a huge number of individuals who are affected, and the Pritzker Consortium participates in a broader Psychiatric Genomics Consortium where information is pooled and analyzed from tens of thousands of individuals to discover genes that can cause vulnerability to these illnesses.

The other approach of studying postmortem brains relies on the Pritzker Brain Bank. We have samples from individuals who had been diagnosed with bipolar disorder and schizophrenia as well as major depression and people without a mental illness. We have somewhat fewer samples for the first two, since the disorders are rarer than depression. But our studies are teaching us a great deal about the signature of these illnesses on the brain, their similarities as well as their differences. For example, genes related to the circadian clock are altered in bipolar illness, and many genes related to neurotransmitters and to immune function are altered in schizophrenia.

The challenge is to combine the information on genetics and on brain function to define key players that might represent new types of targets for treatment. ■

2016
INDEPENDENT INVESTIGATOR GRANTS

326 Applications
40 Grants Awarded
$3.9M Funded

ROBERT M. POST, M.D.

Professor of Psychiatry
George Washington University School of Medicine

Bipolar Collaborative Network

Chair of the Independent Investigator Grant Selection Committee and Foundation Scientific Council Member

"The Independent Investigator Grants provide outstanding basic and clinical scientists with unique opportunities to conduct important, novel, and clinically relevant studies. These studies are not being funded through the traditional NIMH mechanisms because of a shortage of money, and in some cases risk aversion. I believe that many of these grants will help open new vistas in treating major psychiatric illnesses and understanding them better. The Foundation has been heroic in raising the funds for so many extraordinary grants each year, so it is gratifying for me and an honor to help distribute these funds in the best way possible."

—DR. ROBERT POST

Forty mid-career neuroscience researchers from 30 institutions in 16 countries have been chosen to receive a total of $3.9 million in funding from the Brain & Behavior Research Foundation. These grants fund research on brain and behavior disorders in the following three areas:

Basic Research

to understand what happens in the brain to cause mental illness

New Technologies

to advance or create new ways of studying and understanding the brain

Next-Generation Therapies

to reduce symptoms of mental illness and ultimately cure and prevent brain and behavior disorders

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The Foundation's NARSAD Independent Investigator Grants provide each scientist with $50,000 per year for up to two years to support their work during the critical period between the start of their research and the receipt of sustained funding.

Every year, applications are reviewed by members of our Scientific Council, led by Dr. Robert Post. The Council is composed of 164 leading experts across disciplines in brain and behavior research who volunteer their time to select the most promising research ideas to fund. We are very grateful to them and to all of our donors whose contributions make the awarding of these grants possible.

This year's 40 Independent Investigator grantees represent an exciting group of basic and clinical proposals which should make major contributions to the better understanding and treatment of serious psychiatric illness. 326 grants were reviewed by 60 members of the Scientific Council.

We are delighted to support these researchers' work and are pleased to introduce them to you in the pages that follow.

BASIC RESEARCH

Anxiety Disorders

JOHANNES GRÄFF, PH.D.
EPFL-École Polytechnique Fédérale de Lausanne, Switzerland

"This grant will allow us to significantly advance our research projects, while it also recognizes the importance of the questions we are addressing therein—an important step on my path as an independent group leader."

Dr. Gräff seeks to improve treatment for anxiety disorders by uncovering how memories are updated in the brain. Dr. Gräff hopes to lead the first published study to investigate which connections in the brain make it possible for old, fearful memories to be revised with new information. Looking at mice, his team will track the activity of brain cells in the hippocampus, a crucial brain region for memory formation.

ANDREW TAPPER, PH.D.
University of Massachusetts

"This funding will allow my lab to help characterize circuits within the brain that may be critical for regulating anxiety under normal and pathological conditions."

Dr. Tapper will study connections throughout the brain that contribute to anxiety disorders. Dr. Tapper's team will focus on a group of brain cells that contributes to the brain's reward system by releasing the neurotransmitter dopamine. They hope to produce evidence that this dopamine release helps to regulate the experience of anxiety. Confirming this prediction would point to this specific neuron group as a possible target for anxiety treatment. The results will also shed light on the underlying pathology of this common disorder.

Bipolar Disorder

ANA CRISTINA ANDREAZZA, PH.D.
Centre for Addiction and Mental Health, University of Toronto, Canada

"Receiving the 2016 NARSAD Independent Investigator grant is a real honor and a strong encouragement to strive for continued research excellence and a renewed commitment to identify the role of mitochondrial dysfunction in bipolar disorder…"

Dr. Andreazza will explore genetic abnormalities that lead to bipolar disorder. Her team will look specifically at genetic defects that interfere with the activity of mitochondria, which produce energy for cells. Sometimes these defects produce a disease specific to mitochondria, and other times they appear to contribute to bipolar disorder. Dr. Andreazza will use stem cell reprogramming technology to compare the cells from bipolar disorder patients who have these defects with cells from their relatives who instead have mitochondrial disease.

MANPREET KAUR SINGH, M.D.
Stanford University

"This is one of the few awards specific to mental health that continues to maintain a high bar for the accomplishment of clinical, basic, and translational neuroscience. With this award, we will be even more poised to answer fundamental questions in our field related to who benefits from treatment and who is vulnerable to side effects."

Dr. Singh will explore the potential negative side effects of antidepressant medication given to youth at high risk for psychiatric disorders. In youths with emotional dysregulation, side effects have been noted including irritability, agitation, and elevated mood. For some youth, these adverse events lead to the development of lifelong psychiatric disorders such as bipolar disorder. Looking at youth with family histories of bipolar disorder, Dr. Singh will investigate how antidepressant use, combined with typical psychotherapy, alters brain activity and triggers negative side effects.

JUN-FENG WANG, M.D., PH.D.
University of Manitoba, Canada

"We are hopeful that this work will be a positive step toward identifying new drugs targeting components of oxidative stress and neuroinflammation and result in new and more effective therapies for bipolar disorder with fewer side effects."

Dr. Wang hopes to identify mechanisms in the brain that lead to bipolar disorder in order to improve treatments for the illness. Dr. Wang's team will look at brain cells that may be degraded by stress and inflammation to determine whether these cells show impaired activity in bipolar disorder. They will also test whether any such impaired activity fails to respond to the gold standard treatment for bipolar disorder, lithium, and whether interfering with this system in mice produces depression- and bipolar-like symptoms.

Depression

CHRISTINE DELORENZO, PH.D.
Stony Brook University School of Medicine

"Our goal is to use brain imaging to uncover a pretreatment marker of antidepressant effectiveness. The identification of such a marker would improve treatment selection for depressed individuals, potentially eliminating failed treatment trials. The NARSAD Independent Investigator Grant will…enhance our work aimed at improving the lives of people with depression and their families, as well as integrate us into a larger community of researchers dedicated to similar causes."

Dr. DeLorenzo hopes to improve treatment for depression by identifying what makes antidepressants effective. Most antidepressant medication targets levels of the brain chemical serotonin. Dr. DeLorenzo believes the effectiveness of this medication depends on the balance between two other chemicals: glutamate, which promotes communication throughout the brain, and GABA, which inhibits communication. Her team will study whether that balance changes after eight weeks on typical antidepressants that alter serotonin levels.

KIRSTEN A. DONALD, M.D.
University of Cape Town, South Africa

"This award will allow us to investigate the early neurobiology of very young children exposed to prenatal maternal depression. We hope to be able to identify the most vulnerable brain regions to exposure…in order to understand mechanisms as well as help provide a focus for intervention strategies."

Dr. Donald will investigate how depression can be "passed on" from parent to child, given that children of depressed mothers are especially likely to develop the disorder. A mother's depression may affect the child through passed-on genes, other changes to the child's physiology, and environmental factors stemming from the mother's symptoms. Dr. Donald's team will use imaging to study the brains of toddlers whose mothers have depression, and compare that information to images of their brain activity during pregnancy.

TIMOTHY YORK, PH.D.
University of British Columbia, Canada

Dr. York will investigate the biological mechanisms underlying postpartum depression. His project seeks to identify chemical changes in gene expression that may contribute to development of the disorder. His team will look for patterns in these chemical changes that can predict whether mothers will develop depression before or after giving birth. They will also test whether improvements in depression symptoms correspond with reversal of these chemical changes to gene expression.

Mood Disorders

ARIE KAFFMAN, M.D., PH.D.
Yale University

"In a midst of a lengthy funding crisis at the NIH, the NARSAD Independent Investigator grant provided my lab with a remarkable opportunity to look deeper into the mechanisms by which toxic stress early in life alters the innate immune system in the developing brain and how these changes modify connectivity and complex behaviors in mice."

Dr. Kaffman will study how early life stress impairs function in the hippocampus, a brain region important for memory formation. In mice, Dr. Kaffman's team will eliminate a protein that regulates gene expression needed to reduce the profusion of neuronal connections in the brain during childhood. This is important for healthy brain development. Dr. Kaffman hypothesizes that deleting this protein will have the same impact on hippocampal development as early life stress.

Multiple Disorders

LINDA BOOIJ, PH.D.
Concordia University, Canada

"In addition to obtaining a better understanding of the impact of early adversity on the human brain, our neuroimaging study will yield crucial information for designing (early) interventions to treat and prevent the long-term detrimental consequences of childhood adversity."

Dr. Booij hopes for the first time to measure levels of a protein in the brain, HDAC, that may contribute to a range of psychiatric disorders. The protein affects the way genetic material is packaged in cells, influencing gene activity. Dr. Booji's team will study how levels of this protein vary in relation to childhood trauma, which is known to impact gene expression. The project will also investigate the connection between the target protein and the size of brain regions linked to emotion regulation.

JOSEPH D. DOUGHERTY, PH.D.
Washington University School of Medicine

"It is a long-standing mystery why males are more at risk for some psychiatric disorders (autism, ADHD) and females are more at risk for others (depressive and anxiety disorder). This NARSAD award is giving our team the ability to pursue a new lead—a surprising sex difference in a deep brain structure whose neurotransmitter is a known target for therapeutic drugs."

Dr. Dougherty will study the basis of sex differences across common psychiatric disorders. While depression and anxiety are more prevalent among women, both autism and attention deficit hyperactivity disorder occur more among men. Dr. Dougherty's team will search for possible differences in brain cell activity, and possibly structure, that give rise to these sex differences. In particular, they will look for genetic differences between men and women in a specific brain region, the locus coeruleus, which is a key treatment target for many psychiatric conditions.

KYUNG-AN HAN, PH.D.
University of Texas at El Paso

"The Foundation's support and recognition of our project is a huge energizer for us—we are fully charged and going forward!"

Dr. Han will help define the cellular mechanisms driving dysfunctional response inhibition, a deficit common to many psychiatric disorders. Response inhibition refers to the ability to suppress impulses or the thought of actions that will not help the current situation. Studying a fly population, Dr. Han's team will manipulate genetic, environmental, and social factors that affect response inhibition to identify the brain structures and chemicals involved in this crucial behavior. They will focus especially on dopamine, the chemical that controls the brain's reward system, and the pathways in the brain that change response inhibition in response to social context.

COLLEEN ANN MCCLUNG, PH.D.
University of Pittsburgh

"The funding of this Independent Investigator award will allow our lab to perform pioneering studies which investigate changes in circadian rhythms in the human brain that associate with bipolar disorder, schizophrenia and major depression. This is a new and exciting area of research for our laboratory and I'm thrilled to once again work with this terrific Foundation on these studies."

Dr. McClung aims to help improve treatment for bipolar disorder, major depression, and schizophrenia by examining disruptions to sleep patterns, which can destabilize mood. Dr. McClung's team will study coordinated patterns of brain activity tied to the stages of consciousness and sleep—in particular, how these stages look irregular in major depression, bipolar disorder, and schizophrenia. The researchers will also test how strongly these disruptions are linked to outcomes such as suicide and psychosis. These findings will shed light on the underlying pathology of sleep irregularities in psychiatric disorders, laying the groundwork for new treatments.

GLEB P. SHUMYATSKY, PH.D.
Rutgers University

"Winning the award was critical for our efforts to move forward with some exciting and outside-the-box projects for which we need financial support."

Dr. Shumyatsky will investigate gene activity crucial for long-term memory, which degrades in a range of neurological illnesses including Alzheimer's disease, autism, and mood disorders. Dr. Shumyatsky will study a particular protein that helps facilitate gene expression, active during learning and other activities relevant to memory. His team will test how the intensity of memory training and strength of activity in the brain's memory center, the hippocampus, relate to the activity of the target protein. They hope this work will further elucidate the mechanisms of long-term memory and identify a new means of enhancing memory, through this particular gene expression.

RUDOLF UHER, M.D., PH.D.
Dalhousie University, Canada

"This award also means a lot to me personally. It feels like joining a family of great people who are working together to alleviate the impact of brain disease on individuals, families and society."

Dr. Uher will study specific connections in the brain that may provide paths to treating many forms of psychiatric illness by expanding on the predictive factors of family history and early symptoms. Dr. Uher's team will test whether emotional training in youth improves connections between the brain's emotion and memory centers, and whether training to reduce psychotic symptoms improves connections between the sensory processing and executive control centers. This work may point toward new measures that help prevent schizophrenia, bipolar disorder, and other serious adolescent brain disorders.

LARRY S. ZWEIFEL, PH.D.
University of Washington

"This grant will afford us the opportunity to study genes implicated in mental illness… to assess the common and distinct impact of these genes on activity pattern regulation and behavioral control."

Dr. Zweifel will explore genetic mutations previously linked to mental illness that change activity in the brain's reward system, implicated in disorders from addiction to depression. These mutations regulate the activity of brain cells that produce the reward-regulating chemical dopamine. Dr. Zweifel's team seeks to better understand how these genes regulate activity in the brain's reward areas and influence behavior. Their findings will lay the groundwork for intervening within the dopamine system to treat psychiatric disorders.

OCD

STEPHANIE DULAWA, PH.D.
University of California-San Diego

"Winning the 2016 NARSAD Independent Investigator award is an incredible privilege that will allow my lab to pursue an important new finding regarding the neurobiology of obsessive compulsive disorder."

Dr. Dulawa hopes to shed light on the genetic basis of obsessive compulsive disorder (OCD). Dr. Dulawa will study *BTBD3*, a gene thought to be a contributing factor; it regulates the forging of connections in the brain based on experience. Using a mouse model, Dr. Dulawa's team will test whether certain activity levels of the target gene are needed to produce all the treatment effects of standard antidepressants, and at which points in development this gene's role has notable impact.

PTSD

KELLY PATRICIA COSGROVE, PH.D.
Yale University

"I will be able to conduct an innovative study into the biological mechanisms of PTSD using a new radiotracer that we have recently developed to image the glucocorticoid system in the living brain. Hopefully, what we learn will open up new avenues for treatment."

Dr. Cosgrove will examine differences in brain chemistry between individuals with and without Post-traumatic Stress Disorder using a combination of brain imaging techniques: positron emission tomography (PET), which measures molecules of interest in the living brain; and functional magnetic resonance imaging (fMRI) which measures brain activation in response to a task. They will focus on levels of an enzyme called 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1), an enzyme in the stress pathway that modulates the amount of stress hormones present in the brain, as well as activation of the amygdala relative to subjects' recollection of a traumatic event in their life.

Schizophrenia

STEWART ALAN ANDERSON, M.D.

Children's Hospital of Philadelphia, University of Pennsylvania

"This award will be invaluable to taking my research in new directions…to screen for novel agents that may treat or even prevent the development of psychosis in vulnerable people."

Dr. Anderson will study the possible role of mitochondria, the "power plants" of human cells, in schizophrenia. He will study a genetic irregularity that increases the risk of schizophrenia and its link to the activity of mitochondria. He will use advanced technology to reprogram stem cells from skin samples of healthy individuals (controls), and from patients with a genetic variation on chromosome 22 previously linked with the illness. He will force the stem cells to rapidly mature into active neurons and compare measures of bioenergetic health in neurons from the patients compared to controls. He hopes these studies will open up a new way of thinking about the neuropathology, prevention, and treatment of schizophrenia.

KRISTEN JENNIFER BRENNAND, PH.D.

Icahn School of Medicine at Mount Sinai

"The NARSAD Independent Investigator Grant provides my laboratory the flexibility to take risks in our research and pursue projects that might otherwise never get off the ground. This support will allow us to characterize the effect of precise genetic mutations in both human neurons and astrocytes…"

Dr. Brennand will explore a possible new route to treating schizophrenia, focusing on a gene mutation associated with the illness. Dr. Brennand will use a technology called hiPSC to reprogram stem cells from four individuals with mutations in the *NRXN1* risk gene. Her team will characterize aberrant *NRXN1* expression in neurons and astrocytes derived from patients with deletions in the gene and then restore *NRXN1* expression to normal levels, to better understand the mechanisms that produce schizophrenia.

MATHIEU WOLFF, PH.D.

Universite Bordeaux II, France

"This, more than anything, encourages my research to grow stronger toward understanding the functional principles at play within the brain architecture. Basic science is mandatory to fuel preclinical research and provide new therapeutic strategies to alleviate or cure mental diseases."

Dr. Wolff will investigate brain areas possibly involved in generating cognitive symptoms of schizophrenia, which are not sufficiently relieved by current treatment options. Dr. Wolff will focus on the brain's medial prefrontal cortex and hippocampus. The team will interfere with cells that connect to those regions and then test for any resulting changes in the activity of both brain regions. They will also test for any resulting cognitive impairment and try to reverse the disruption to the target group of cells. Their findings will help determine the role, and potential therapeutic value, of these cells in schizophrenia.

Next Generation Therapies

Addiction

RACHEL ALISON ADCOCK, M.D., PH.D.

Duke University

Dr. Adcock will investigate a possible treatment for nicotine dependence, an addiction especially common among those with schizophrenia and other chronic mental disorders. Addiction causes the brain's reward system to respond more strongly to drugs, but less strongly to typically pleasurable non-drug stimuli. Dr. Adcock's research will attempt to teach patients to respond more positively to non-drug stimuli by altering their levels of dopamine, a chemical in the brain that regulates our response to rewards. She hopes this work will lead to the development of personalized interventions for addiction and other disorders involving the dopamine system, including depression.

Autism

PETER GREGORY ENTICOTT, PH.D.
Deakin University, Australia

"This award allows us to advance our work toward establishing a first medical treatment for core symptoms of autism spectrum disorder. Most importantly, this research has the potential to promote real improvements in quality of life for people with ASD and their families."

Dr. Enticott is seeking a biological treatment for autism that targets its core symptoms. Using transcranial magnetic stimulation (TMS), he will target the disrupted communication between brain cells that is a hallmark of autism. He will then compare efficacy of TMS when applied to two different brain regions, to determine which areas hold promise for new interventions. Dr. Enticott's team will focus on adolescents and young adults with autism, a crucial population whose autism symptoms can interfere with the transition to adulthood.

Bipolar Disorder

BENEDIKT LORENZ AMANN, M.D., PH.D.
FIDMAG Research Foundation (Fundació per a la Investigació i la Docència Maria Angustias Giménez), Spain

"There is clear evidence that traumatic events initiate and worsen severe mental disorders but clinical trials are scarce. This NARSAD award will help to overcome this gap and give us the opportunity to test whether a specific EMDR bipolar protocol can reduce affective relapses…"

Dr. Amann aims to improve treatment for people with bipolar disorder who have experienced traumatic events, which often worsen their experience of the disease. His work will test the effectiveness of a possible treatment, called Eye Movement Desensitization Reprocessing, that starts by directing patients' eye movements in particular patterns. Bipolar patients will either undergo EMDR or more traditional therapy. Dr. Amann predicts that EMDR will be more effective at reducing troubling emotional events in the short-and long-term, making it a strong treatment option for traumatized bipolar patients.

PETER L. FRANZEN, PH.D.
University of Pittsburgh

Dr. Franzen will investigate the potential of dialectical behavior therapy (DBT), a psychosocial treatment, in reducing suicides among adolescents with bipolar disorder. Dr. Franzen's team will focus on DBT's therapeutic value in reducing sleep disturbances, both a risk factor and symptom of bipolar disorder. They will compare the effects of DBT, which targets emotion regulation processes, by looking at brain imaging and measures of sleep quality in adolescents both with and without bipolar disorder.

KEMING GAO, M.D., PH.D.
Case Western Reserve University

"This award allows me to study the changes of more than 45 molecules in mononuclear blood cells in patients with bipolar disorder…to potentially find biomarkers for predicting lithium treatment response."

Dr. Gao will try to explain why only some individuals respond to the gold standard treatment for bipolar disorder, lithium. Dr. Gao will use highly sensitive tests to track how gene expression within white blood cells differs between people with bipolar disorder whose symptoms improve with lithium, and people whose do not. If his team is able to pinpoint these differences, researchers may in the future be able to use this blood test to predict whether patients will respond well to lithium and tailor their treatment accordingly.

Depression

OLIVIER BERTON, PH.D.
Icahn School of Medicine at Mount Sinai

"The funding will allow me to make progress on an exciting research line that has been difficult to support through the conventional routes."

Dr. Berton will test the potential for combining drug therapy with deep brain stimulation for cases of depression that do not respond to psychotherapy and antidepressants. Deep brain stimulation has already shown promise but the relief it provides is not always consistent. Dr. Berton will try to make these effects stronger and more stable by giving patients a drug that alters genetic activity in neurons that are usually changed by deep brain stimulation itself.

PAUL HOLTZHEIMER, M.D.
Dartmouth-Hitchcock Medical Center

Dr. Holtzheimer will try to distinguish between two kinds of treatment-resistant depression to better tailor treatments to symptoms. He will look at a population whose depression has not improved in response to typical treatments. Dr. Holtzheimer predicts refractory depression is rooted in one of two distinct brain areas, requiring two distinct kinds of treatment. His team will test this idea by applying transcranial magnetic stimulation (TMS), an alternative treatment, to the two different brain areas in people with depression and then measuring how it affects their symptoms and behavior.

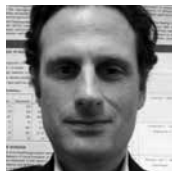
MARIA LINDSKOG, PH.D.
Karolinska Institute, Sweden

"During my first years as principal investigator I have made discoveries that I now want to follow up—however, the opportunities for funding at this stage are much fewer compared to the start-up money you can apply for in the beginning of your career. Thus the NARSAD Independent Investigator grant is very important…"

Dr. Lindskog will build on a new wave of depression treatment focusing on the antidepressant effects of an anesthetic drug, ketamine. Ketamine may produce antidepressant effects by altering the brain's levels of the chemical glutamate. This work will investigate how inflammatory chemical signals that the body produces in response to stress affect glutamate levels throughout the brain. Dr. Lindskog predicts that a particular inflammatory signal acts on support cells in the brain that regulate glutamate levels. Testing this prediction will help determine whether this particular signaling can be targeted, in the body's immune response system, to improve depression treatments.

PETER NAGELE, M.D.
Washington University, St. Louis

Dr. Nagele seeks to identify the ideal dose of a potential new medication to treat intractable depression. He will test the efficacy of "laughing gas," the anesthetic often used in dental treatment, which produces antidepressant effects by altering levels of the brain chemical N-methyl-D-aspartate, or NMDA. The team will give people with treatment-resistant depression different doses of laughing gas. They can then compare the success of each dose in relieving depression symptoms while producing the fewest side effects, which might include psychosis, the feeling of disconnect from reality, and euphoria.



ROLAND ZAHN, M.D., PH.D.
Institute of Psychiatry/King's College London, United Kingdom

"Unlike other funding agencies, NARSAD appears to be truly committed to innovation for patients even if that means taking the risk that novel ideas may not always succeed. The grant will allow me to probe whether a novel approach to functional MRI-based neurofeedback for depression is promising."

Dr. Zahn will explore a potential new treatment for treatment-resistant depression. Dr. Zahn will test the efficacy of "neurofeedback" in patients who haven't responded to treatment. This technique involves patients viewing their own brain activity as viewed through functional magnetic resonance imaging, and then using this activity as a guidepost for behaving differently to reduce their symptoms. The project will compare this technique against a psychological, thought-based training technique, to isolate any unique improvements from the neurofeedback not caused by purely psychological effects. If successful, these tests will support neurofeedback as a promising new treatment, especially for currently intractable depression.

PTSD

ISABELLE ROSSO, PH.D.
Harvard University

"I am all the more galvanized to conduct this study of riluzole therapy targeting hippocampus phenotypes in PTSD."

Dr. Rosso will test riluzole, a new potential treatment for post-traumatic stress disorder (PTSD), which does not always respond to current treatments. Riluzole reduces activity of the brain chemical glutamate, which facilitates much of the symptoms by reducing abnormally high glutamate levels and increasing low levels of a chemical biomarker of brain cell health, called NAA. The trial is based on the theory that high levels of glutamate injure brain cells, perhaps helping to account for the well-documented shrinkage of the brain's hippocampus in patients with PTSD.

Schizophrenia

BRIAN JAMES MILLER, M.D., PH.D., M.P.H.
Georgia Regents University

"I am excited for the opportunity to pursue adjunctive immunotherapy as a potential new treatment for patients with schizophrenia… It is my desire that our research inspires hope in patients and their families, towards reduction of symptoms and improvements in quality of life."

Dr. Miller will explore a possible new treatment for schizophrenia that may help relieve cognitive symptoms of the illness. Dr. Miller's work will test the efficacy of a drug that breaks down immune system chemicals that the body produces in response to stress, and which have been linked to cognitive impairments in schizophrenia. The team will administer the drug once a month to schizophrenia patients, who will continue on their antipsychotic medications.

RAFAEL PENADES, PH.D.
University of Barcelona (Universitat de Barcelona), Spain

"Receiving the NARSAD Independent Grant is giving our team an extraordinary impulse in order to consolidate the line of research in which we have been working hard the last years. Nowadays, it is not at all easy to find a way to get the means for conducting innovative clinical research on the field of mental illnesses. I personally feel this grant is an extraordinary opportunity…"

Dr. Penades will investigate how a treatment method called cognitive remediation helps reduce cognitive impairments in schizophrenia. Dr. Penades' team will test whether cognitive remediation achieves its therapeutic effects by changing a brain chemical in a way that has been previously associated with psychotherapy. They will study those changes, as well as whether related changes in gene expression affect the success of cognitive remediation in treating schizophrenia.

MARTA RAPADO-CASTRO, PH.D.
CIBERSAM- Centro de Investigación en Red de Salud Mental, Spain

"The work conducted by previous recipients of this grant has had a tremendous impact on my research and has helped me to advance the understanding of cognitive function in psychosis. Being one of those recipients today feels like a decisive achievement."

Dr. Rapado-Castro will lead efforts to develop a new treatment for the cognitive symptoms of psychosis, which do not respond strongly to current antipsychotics. Dr. Rapado-Castro's team will test a combination therapy: a drug targeting glutamate, the chemical that drives much of the communication in the brain, plus auditory training based on the brain's ability to adapt.

THOMAS WEICKERT, PH.D.
University of New South Wales, Australia

Dr. Weickert will study the role of the body's immune system in schizophrenia. He will test for anti-schizophrenia effects of a drug that reduces levels of a protein the body releases as part of its immune response. This protein has previously been linked to schizophrenia and related symptoms, including an inability to experience pleasure, memory impairments, and social dysfunction. Dr. Weickert's team predicts that the drug will reduce symptoms and cognitive impairment in people with schizophrenia by regulating specific brain activity. Such findings would confirm their target drug as a viable new treatment for schizophrenia among patients who show irregular immune responses.

TODD WOODWARD, PH.D.
University of British Columbia, Canada

Dr. Woodward will test a combination treatment for delusions in schizophrenia. The treatment combines a technique called metacognitive training, where schizophrenia patients must question the reality of everyday experiences, and electrical stimulation of particular brain regions. Dr. Woodward predicts that simultaneous electrical stimulation will make metacognitive training more effective. His team will also test whether the brain regions targeted by electrical stimulation respond with a difference in activity. They hope their findings will expand and encourage the use of non-pharmacological treatments for psychotic symptoms in schizophrenia.

New Technologies

Depression

VINCENT P. FERRERA, PH.D.
Columbia University

"My goal is to see focused ultrasound based brain stimulation used routinely for treatment of psychiatric and neurological disorders. Foundation funding will help me take a huge step in that direction."

Dr. Ferrera will study a non-invasive brain therapy that holds promise for treating different psychiatric conditions, including depression that does not respond to usual forms of treatment. This non-invasive therapy, called focused ultrasound, uses targeted sound waves to stimulate or limit the activity of brain cells. Dr. Ferrera's team will investigate the mechanisms underlying focused ultrasound's ability to improve performance on a decision-making task in monkeys.

Eating Disorders

NADIA MICALI, M.D., PH.D., M.SC.
Icahn School of Medicine at Mount Sinai

"Anorexia nervosa is a chronic disorder and has the highest mortality amongst psychiatric disorders, but our treatment options are limited. This study will lay the foundations for understanding the neurobiology that predisposes to anorexia nervosa and will likely contribute to developing new early intervention and prevention strategies."

Dr. Micali will study girls at high risk for the eating disorder anorexia nervosa due to family history, in the hopes of identifying biological signs that can help predict development of the disease. Her team's work will be the first to look for features of brain structure, brain connections, and cognitive performance that may serve as biological predictors of anorexia in girls aged 10 to 15, specifically those whose mothers have had the illness and may pass down genetic susceptibility. Dr. Micali's team predicts that these high-risk girls will show impairments in processing visual and spatial cues, controlling their behaviors, and understanding social situations.

PTSD

DANIELA KAUFER, PH.D.
University of California-Berkeley

Dr. Kaufer aims to identify one of the biological bases of post-traumatic stress disorder that can help predict the development of the disease. She will use a rat model of PTSD to compare brain activity in rats that have not been exposed to trauma, rats that have been trauma-exposed but have not developed PTSD, and rats that have PTSD as a result of trauma. She predicts that PTSD symptoms will be linked to an excess of myelin, fatty material that facilitates communication throughout the brain. They will investigate how this material may overdevelop in the pathology of PTSD, whether this overproduction can predict PTSD, and the potential for reversing overproduction as a treatment. ■

New Biotypes Classify Psychosis Cases According to Measurable Biological Features

TAKEAWAY: Using a panel of brain-based tests, scientists have placed patients with psychotic disorders into groups that may be more biologically meaningful than current diagnostic categories.

Carol A. Tamminga, M.D., Scientific Council, 1998, 2010 DI
Brett A. Clementz, Ph.D., 2000 II
Elena I. Ivleva, M.D., Ph.D., 2010 YI
Matcheri S. Keshavan, M.D., 1997 II
Godfrey D. Pearlson, M.D., Scientific Council, 2000 DI
John A. Sweeney, Ph.D., 1997 II

Scientists have assembled a panel of biological assessments to classify patients with psychosis into biologically distinct groups that they call biotypes. The advance is an encouraging step toward developing biomarker-based diagnostic strategies that could guide treatment decisions better than current methods, which rely entirely on patients' clinical symptoms.

Patients with psychotic disorders are usually diagnosed with either schizophrenia or bipolar disorder—but the symptoms of these disorders often overlap, as do the associated genetic risk factors. Many patients are difficult to diagnose because they do not clearly fit the criteria for either diagnosis, and individuals who share the same clinical disorder may benefit from different treatments, especially if their symptoms have distinct biological causes. For these reasons, neuroscientists and clinicians are in need of new tools to classify psychotic disorders in a more biologically meaningful way.

The new approach is described in a paper published December 8, 2015 in the *American Journal of Psychiatry*. Led by Foundation Scientific Council Member and 1998 and 2010 Distinguished Investigator Carol A. Tamminga, M.D., at the University of Texas Southwestern Medical Center, and 2000 Independent Investigator Brett A. Clementz, Ph.D., of the University of Georgia, the research team looked for patterns of neurobiological traits among patients with psychosis regardless of their clinical diagnoses. The team also included 2010 Young Investigator Elena I. Ivleva, M.D., Ph.D.; 1997 Independent Investigator Matcheri S. Keshavan, M.D; 2000 Distinguished Investigator and Scientific Council Member Godfrey D. Pearlson, M.D.; and 1997 Independent Investigator John A. Sweeney, Ph.D.

To define the biotypes, the researchers used a panel of brain-based tests to assess 711 people who had been diagnosed with schizophrenia, bipolar disorder, or schizoaffective disorder, as well as 883 first-degree relatives of those individuals and 278 healthy, unrelated controls. The assessment measured a range of features associated with brain function and psychosis, and included cognitive tests, studies of eye movements, and electroencephalogram (EEG) measures of brain wave activity.

Without considering the patients' clinical diagnoses, the researchers used the results of those tests to place the study participants into three biologically distinct groups based on the features above. Interestingly, the biotypes did not match clinical diagnoses: each of the newly defined groups included patients diagnosed with all three conditions.

The team acknowledges that more research is needed to determine whether the categories they defined will be useful diagnostic tools. But some evidence already suggests the groupings reflect the biological origins of different disorders. Brain scans of the participants (which were not used in developing the biotypes) revealed that individuals within biotypes shared certain anatomical features. Some of the features used to define the biotypes were also found among first-degree relatives of psychosis-affected participants, supporting the idea that the new categories are biologically relevant and influenced by genetic factors. ■

Early Childhood Depression May Impact Brain Development in Later Years

TAKEAWAY: Young adolescents who were diagnosed with depression in their preschool years have less gray matter in brain areas important for emotional processing than children unaffected by the disorder.



Joan L. Luby, M.D., 1999 YI; 2004, 2008 II
Deanna M. Barch, Ph.D., 1995, 2000 YI; 2006 II; 2013 DI
Kelly N. Botteron, M.D., 1997 YI; 2005 II

Over the past decade, it has become clear that even very young children can suffer from clinical depression. Now, research published December 16, 2015 in the journal *JAMA Psychiatry* suggests that early childhood depression can impact the course of brain development, underscoring the importance of identifying and treating children with the disorder.

According to the study, which followed children diagnosed with major depressive disorder between the ages of three and six, early childhood depression is associated with disruptions in brain development that continue into early adolescence. Periodic brain imaging revealed that in comparison with children unaffected by the disorder, children who had suffered from depression in their preschool years had lower volumes of gray matter—which contains the neural connections through which brain cells communicate—in the cortex of their brains. This change may have a lasting effect on emotional processing and make a child vulnerable to problems later in life, the researchers say.

Joan L. Luby, M.D., a 2004 and 2008 Independent Investigator and Young Investigator in 1999, now at Washington University in St. Louis, has led research establishing that depression can occur in children as young as three years-old. Like adults with major depressive disorder, preschool-aged children with depression experience changes in sleep, appetite, and activity level and an inability to experience pleasure. These symptoms often continue later in childhood.

In the new study, Dr. Luby and her team, including 2013 Distinguished Investigator Deanna M. Barch, Ph.D., (also a 1995 and 2000 Young Investigator, 2006 Independent Investigator), along with 1997 Young Investigator and 2005 Independent Investigator Kelly N. Botteron, M.D., also at Washington University, wanted to understand whether those early experiences of depression impact brain development.

To find out, the researchers followed a group of 193 children, including 90 diagnosed with major depressive disorder during their preschool years, for up to 11 years. The scientists used magnetic resonance imaging (MRI) to watch how activity in each child's brain changed as he or she aged. Up to three scans were collected for each child, beginning between the ages of six and eight and with the final scan occurring between the ages of 12 and 15.

The brain's gray matter begins to form before birth, but continues to develop during childhood, reaching its greatest volume around puberty. After this peak, cells are pruned back to eliminate redundant connections, reducing gray matter volume. The research team observed this normal and expected decline in gray matter in all the children in their study, but it was most dramatic in those who had suffered depression. What's more, the decline was steepest in those whose depression symptoms had been most severe.

The researchers stress that further research is needed to identify effective ways to treat depression in young children and to determine whether early intervention can restore normal patterns of brain development. ■

Onset of Psychotic Disorders Differs Among Ultra-High Risk Groups

TAKEAWAY: Using data from 33 prior studies, researchers have discovered that individuals who experience brief, limited, and intermittent psychotic symptoms are more likely to develop a psychotic disorder than other ultra-high risk subgroups.







Paolo Fusar-Poli, M.D., Ph.D., 2014 YI

Cheryl Corcoran, M.D., 1999, 2002 YI

Patrick D. McGorry, M.D., Ph.D., 1998 DI, 2015 Lieber Prize

Philip K. McGuire, M.D., Ph.D., 2010 DI

Barnaby Nelson, Ph.D., 2008 YI, 2015 II, 2015 Sidney R. Baer Jr. Prize

Scott W. Woods, M.D., 1998 II, 2005 DI

Alison R. Yung, M.D., 2003 II

The onset of schizophrenia and other psychotic disorders is preceded by a period during which individuals begin to experience some psychotic symptoms—but these symptoms can also occur in people who will never develop a psychotic disorder. Thus, researchers are still trying to develop reliable methods to determine who is most in need of interventions that prevent or delay the onset of these disorders.

For more than two decades, individuals whose symptoms and genetic profile match any of three sets of criteria have been considered at "ultra-high risk" for psychosis; about 30 percent of the individuals in this group develop a psychotic disorder within two years. Now, an international team led by Paolo Fusar-Poli, M.D., Ph.D., at King's College London, whose 2014 Young Investigator helped fund the work, has found that the risk of psychosis varies significantly among three different groups of ultra-high risk individuals. Recognizing the distinctions between the three groups will be important for the design of future research studies, the scientists say, and could help researchers identify biomarkers that can be used to predict which at-risk individuals will develop psychotic disorders.

The scientific team that conducted the analysis included 1999 and 2002 Young Investigator Cheryl Corcoran, M.D.; 1998 Distinguished Investigator and 2015 Lieber Prize winner Patrick D. McGorry, M.D., Ph.D.; 2010 Distinguished Investigator Philip K. McGuire, M.D., Ph.D.; 2015 Independent Investigator, 2008 Young Investigator, and 2015 Sidney R. Baer Jr. Prize winner Barnaby Nelson, Ph.D.; 2005 Distinguished Investigator and 1998 Independent Investigator Scott W. Woods, M.D.; and 2003 Independent Investigator Alison R. Yung, M.D.

To be considered ultra-high risk for a psychotic disorder, an individual must have one of the following: attenuated or weak psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), or genetic risk combined with functional deterioration (GRD). Psychosis symptoms can include feeling paranoid, having false ideas about what is taking place or who one is, and seeing, hearing, or feeling things that are not there. Using data from 33 prior studies on psychosis risk, which together included more than 4,000 individuals, the team of scientists compared how many patients within each group developed a psychotic disorder within six, 12, 24, and 36 months, as well as within follow-up periods of four years or more.

The majority of high-risk individuals included in the analysis—85 percent—fell into the APS category. Another 10 percent had experienced BLIPS and five percent were classified as high-risk based on GRD.

The team's analysis, published in *JAMA Psychiatry* on December 30, 2015 showed that after the first year, individuals who had been considered at ultra-high risk due to brief limited intermittent psychotic symptoms were significantly more likely to develop a psychotic disorder than those who had experienced attenuated psychotic symptoms. At two years, those with BLIPS were about twice as likely to have developed psychosis as those with APS.

Those with genetic risk and deterioration, on the other hand, were no more likely to develop a psychotic disorder than individuals in a control group, who had not been classified as at high risk for psychosis. ■

With this issue, the *Quarterly* begins coverage of recent news bearing on treatments for psychiatric and related brain and behavior conditions.

A Better Form of Electroconvulsive Therapy?

Researchers have been working for years to improve the effectiveness of electroconvulsive therapy (ECT) while reducing its side effects, including memory loss. The therapy, which uses small electrical currents to induce a brief seizure across the brain, has been shown to have therapeutic effects in people with severe depression who have not responded to other therapies. In the February 19 issue of *AJP in Advance (The American Journal of Psychiatry)*, Maria Semkovska, Ph.D., of Trinity College, Dublin, and her colleagues reported the results of a randomized clinical trial testing two versions of ECT: the more commonly used bitemporal ECT, in which one electrode is placed on each side of the head, and a variant called high-dose unilateral ECT, in which both electrodes are placed on one side and a higher dose (i.e., current) is administered. In this trial of 138 patients, who were treated twice weekly, the team concluded that unilateral ECT "was no less effective" than bilateral ECT, either in terms of reducing symptoms or risk of relapse after six months. Most promising about the trial was its finding that patients who received unilateral ECT had fewer side effects: they recovered more quickly from the disorientation typically experienced immediately following treatment and had greater recall of personal memories months later. The researchers suggested their results "justify considering high-dose unilateral ECT as the preferred ECT option for treating depression and may help improve acceptability and availability of this effective treatment."

Abstract:
http://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2015.15030372

Opioid Medication Combo for Patients Who Don't Respond to Antidepressants

A significant percentage of people with depression do not respond adequately to treatment with antidepressants. Adding certain opioid medications specifically designed to have low addiction potential as an adjunct to depression treatment could help this group of patients, finds a study published February 12 in the *American Journal of Psychiatry*. Opioids act on biological systems in the brain that may play a role in depression but are not affected by conventional antidepressants. Although opioids have been used historically to treat mood problems, their use is limited today due to their addictive potential. In the new study, Maurizio Fava, M.D., of Harvard Medical School and his colleagues developed a drug combination made of buprenorphine, an opioid medication, and samidorphan, which can block those effects of buprenorphine that are linked with its addictive potential. More than 140 people with major depression who had not responded well to antidepressants participated in the randomized trial and either had buprenorphine/samidorphan added to their antidepressant treatment or received only antidepressants and placebo. After four weeks of treatment, those participants who had received the additional treatment with buprenorphine/samidorphan showed greater improvements than their peers in the placebo group. Moreover, the participants didn't show symptoms of opioid withdrawal after finishing the treatment course. The findings suggest that the buprenorphine/samidorphan combination may be a promising candidate to consider in the treatment for people with hard-to-treat depression and should be investigated further in future research.

Abstract:
http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2015.15070921

Brain Scans from Teenagers with Psychiatric Problems Help Predict Risk of Future Symptoms

In some people, behavioral problems in childhood are early signals of psychopathology in adulthood—but is there a way to predict that risk? In a new study published February 23 in *Molecular Psychiatry*, researchers led by Mary L. Phillips, M.D., of the University of Pittsburgh School of Medicine, add to growing evidence that brain imaging of teenagers with behavioral and emotional problems could at least partly predict the risk of worsening of symptoms in the future. Eighty adolescents participated in the study and played a game on the computer as their brain activity was being monitored. The team focused on the activity of certain brain areas involved in reward processing, the degree to which these areas work together, as well as integrity of the neural fibers that connect them. The severity of the participants' behavioral and emotional problems was measured through parents' reports at the time of the scans and then at an average of 14 months later. The results showed that brain imaging could predict part of the change in the severity of the symptoms in the future, and help partly predict how likely the symptoms are to worsen a year later. Although brain scans are still far from being able to show which individuals are going to develop more serious symptoms, the findings are a step toward identifying neurobiological measures that together with other tools could help predict future risk in adolescents, say the scientists. However, future studies are required to confirm and improve the findings.

Abstract:
http://www.nature.com/mp/journal/vaop/ncurrent/full/mp20165a.html

FDA Warns About Opioids

The U.S. Food and Drug Administration (FDA) on March 23 issued safety labeling changes for opioid medications. The advisory pertained most immediately to immediate-release, or IR opioids, and was issued against a backdrop of broader warnings about the marked rise of opioid overdoses and fatalities in the U.S. IR opioids are intended for use every four to six hours. New label warnings are intended to raise awareness of the risks of misuse, abuse, addiction, overdose and death from IR opioids, the FDA said. At the same time, the agency said it was requiring updated labeling for all opioid medicines, whether immediate-release or other types, to include safety information about potentially harmful drug interactions with antidepressant medicines used to treat migraines, among other conditions. The new labels will inform users, for instance, on opioid impact on the body's endocrine (hormone) system. The FDA also said it was investigating "potentially serious outcomes related to interactions between benzodiazepines and opioids." Benzodiazepines are widely prescribed as sedatives, muscle relaxants, and as agents against convulsions, seizures, agitation, and panic, among other conditions.

The FDA warning:
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm491739.htm

NIDA Director Nora Volkow's statement on opioid abuse:
https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2015/prescription-opioid-heroin-abuse

FEATURE

Birth of New Nerve Cells in Adult Brains Suggests New Strategies to Treat Depression and Anxiety

by Peter Tarr, Ph.D.

RENÉ HEN, PH.D.

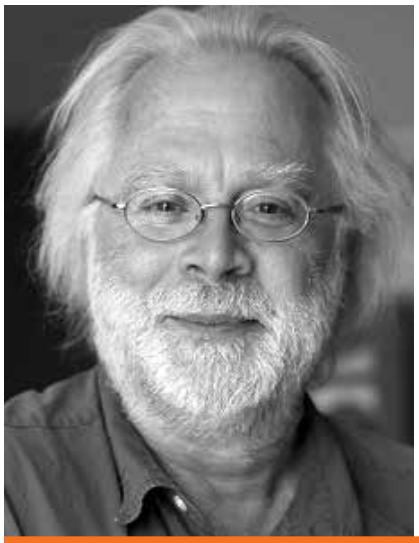
Professor of Psychiatry, Neuroscience and Pharmacology

Columbia University

Director of Integrative Neuroscience

New York State Psychiatric Institute

Image Credit: © Andrii Muzyka for Shutterstock



René Hen, Ph.D.

Every day, new neurons are born in our brains—often in the hundreds per day, and in some people, over a thousand. This process, called neurogenesis, has long been known to be active at a much more intensive level in utero, when the brain is growing very rapidly, and was thought to cease in the first years of life.

Beginning in the 1960s, however, researchers began to explore what was then a radical idea that has since been confirmed: new neurons continue to grow in the already developed brains of adults, almost to the very end of life.

Which then raises a new set of questions. What do these new brain cells do? Is there an impact on our mental state if we don't make enough new cells? And ultimately, what would happen in someone with a brain disorder like depression if we could increase the rate at which these new cells are born?

One pioneer in this field is René Hen, Ph.D., a Professor of Psychiatry, Neuroscience and Pharmacology at Columbia University and Director of Integrative Neuroscience at the New York State Psychiatric Institute. A member of the Foundation's Scientific Council and three-time recipient of NARSAD Grants, Dr. Hen has been at the forefront of the effort to find out what newly born neurons do in the adult brain. In recent work, he and colleagues have sought to parlay the knowledge they have gained over the past 15 years to identify new treatments for anxiety and depression.

In a 2014 article titled "Add Neurons, Subtract Anxiety," which appeared in *Scientific American*, Dr. Hen and his Columbia colleague Mazen Kheirbek, Ph.D. explained that new neurons arise in adults only in two regions of the brain, one affecting our ability to distinguish odors, and one area called the hippocampus, involved in learning, memory and

emotion. It's that latter area, the hippocampus, and specifically a thin wedge of it called the dentate gyrus (DG), where most neuroscientists have focused their attention, for that is where new hippocampal brain cells are born.

After Fred Gage, Ph.D. of the Salk Institute, (Foundation Scientific Council member), proved in 1998 that adult neurogenesis did in fact occur, Ronald Duman, Ph.D. of Yale University, (another Scientific Council member and a multiple NARSAD Grantee) two years later showed that SSRI-class antidepressants like Prozac act indirectly to increase the rate at which new neurons are born in adult brains. Did this account for Prozac's ability to relieve depression and anxiety? What was the relation between adult neurogenesis and mood disorders? The answers are still being explored and debated.

In the early 2000s, Dr. Hen's team looked at what happened to anxious mice treated with Prozac when adult neurogenesis was artificially blocked. In 2003, they published their findings and reported that the drug no longer worked to counteract anxiety in these mice.

While these findings were indeed intriguing, Dr. Hen points out that conditions like clinical anxiety and depression are complex; they affect multiple parts of the brain. Hence, his team's 2003 finding did not by itself prove that when one "added" neurons, one could be assured of "subtracting" anxiety (or vice-versa). It did suggest a relationship, however.

Figuring out the exact nature of the relation between adult hippocampal neurogenesis and mood disorders has continued to be one of the chief goals of Dr. Hen's lab over the past 12 years. In 2015, adding to a long list of research findings they have made on the subject, he and his colleagues achieved their long-sought goal of specifying (in rodents) if the survival of new neurons in the hippocampus was alone sufficient to diminish anxiety or depression symptoms.

The idea was to give adult mice a drug that boosted neurogenesis and then observe how they fared in a battery of behavioral tests, designed to induce anxiety- and depression-like behaviors. While SSRI-class antidepressants like Prozac boost neurogenesis, these drugs affect many parts of the brain and body, which makes their effects are very hard to isolate. Dr. Hen's premise was: what if we had a method that only boosted the rate at which new brain cells in the adult hippocampus survive? Would it act like an antidepressant or anti-anxiety drug?

Mice in the experiment were genetically modified to prevent a normal process in which some newly born nerve cells wither and die before connecting to other brain cells. These mice would have especially robust neurogenesis in the hippocampus. After waiting several weeks for the new cells to "wire up" to the existing neural network, the scientists treated some of the mice with cortisol, a stress hormone.

Results of these experiments were encouraging. Dr. Hen's team did find that increasing the number of new nerve cells in the hippocampus of adult mice was indeed sufficient to reduce anxiety- and depression-related behaviors. The most important qualification: this was true only in mice that were exposed to the stress hormone. The addition of new neurons did not change what the scientists call "baseline" anxiety or depression behavior in the animals.

In other words, while boosting neurogenesis had no impact on baseline behavior, it did protect against the negative impact of subsequent stress. Might a drug that boosts new nerve cell survival in the hippocampus therefore act as a kind of prophylactic against stress? Perhaps, but Dr. Hen reminds us that his team tested only one model of stress. Stress takes other forms which are not modeled by injecting cortisol, and more research needs to be done.

Dr. Hen and another Columbia colleague Bradley Miller, M.D., Ph.D. recently discussed a different candidate drug called P7C3 that they both believe is "exciting," in a paper published in *Current Opinion in Neurobiology*. The drug acts like an antidepressant in rodents, and these effects vanish when adult hippocampal neurogenesis is blocked. If this or a similar drug is proven in future trials to be safe in people, it might serve to do what the experiments just described did: boost new nerve cell survival in the hippocampus.

Drs. Hen and Miller suggest that if such a drug makes it to human trials, it might first be tested on adults in whom neurogenesis is impaired. With this in mind they and others seek to discover a biomarker or to develop an imaging method that can readily measure levels of hippocampal neurogenesis in the living human brain—to help identify people who may benefit from therapies targeted to boost neurogenesis. ■

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Frances and Bob Weisman

Danielle M. Andrade, M.D

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Frances and Bob Weisman have supported a Research Partnership with Danielle M. Andrade, M.D., of the University Health Network at the University of Toronto, a 2010 Young Investigator Grantee.

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Schizophrenia

Q What is the difference between psychosis and schizophrenia?

A Psychosis is not a separate disease, but is a symptom of the larger disease of schizophrenia. By definition, psychosis is a gross impairment of a person's perception of reality and ability to communicate and relate to others. Psychosis is only one of the symptoms that physicians use to diagnose schizophrenia, although not all people with schizophrenia experience psychotic symptoms at all times during their disease. Psychosis can also be a symptom of other diseases, such as bipolar disorder and depressioon.[1]

Q What are some of the risk factors for schizophrenia?

A Researchers think that there is a mixture of genetic and environmental factors behind schizophrenia. The disease does appear to run in families, but there are probably multiple genes that can be inherited that contribute to the illness. In a major study published in 2014 and led by Foundation 2012 Lieber Prizewinner Michael O'Donovan, M.D., Ph.D., of Cardiff University, researchers found more than 100 places in our genome where variations in the genes can change the odds of a person having schizophrenia.[2] Some of the environmental risk factors for schizophrenia may include a mother's exposure to viruses, malnutrition or stress before birth, birth complications, childhood trauma, and stress and drug abuse during adolescence.[2]

Q What are typical and atypical antipsychotic medications for schizophrenia?

A Typical and atypical antipsychotic medications are sometimes referred to as first and second-generation antipsychotic drugs. First-generation, typical antipsychotics, first developed in the 1950s, include medications such as haloperidol or trifluoperazine. Second-generation, atypical antipsychotics were developed first in the 1980s and include drugs such as clozapine and risperidone.[3] Both types of medications appear to affect the message-carrying neurotransmitter chemicals in the brain, but their common side effects are different. One side effect associated with many typical antipsychotic drugs is muscle spasms and rigidity, caused by the drug's effect on the extrapyramidal system, the brain's nerve network that guides involuntary reflexes and movements. Atypical antipsychotics have a lower risk of this side effect, although patients who use the newer drugs may have a higher risk of weight gain and the development of type 2 diabetes.

Q Why is it important to treat schizophrenia as soon as possible?

A Several studies show that treating a person as soon as he or she has their first psychotic episode in schizophrenia may result in a better response to treatments than those who do not have quick care. A series of studies conducted as part of the National Institutes of Mental Health's RA1SE program suggest that both behavioral therapy and antipsychotic medications are more effective if they are delivered within 74 weeks after a person's first psychotic episode.[4] When patients are treated early for schizophrenia, they may have less severe symptoms, fewer hospitalizations, and less time away from family, friends, work and school.[5]

1. Schizophrenia Working Group of the Psychiatric Genomics Consortium, "Biological insights from 108 schizophrenia-associated genetic loci," *Nature, Volume 511*, Pages 421–427, July 24, 2014.
2. K. Dean and R.M. Murray, "Environmental risk factors for psychosis," *Dialogues in Clinical Neuroscience, Volume 7*, Pages 69–80, March 2005.
3. JC Seida et al., First- and second-generation antipsychotics for children and young adults, Comparative Effectiveness Reviews, No. 39, http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0040944/
4. National Institute of Mental Health, RA1SE: Recovery after an initial schizophrenia episode, http://www.nimh.nih.gov/health/topics/schizophrenia/raise/published-articles.shtml
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FEATURE

"I am absolutely convinced
that there is more pain caused
by the stigma than by the disease.
It's the stigma that prevents
the disease from getting treated."

—LEO WALKER

Hike for Mental Health is a Trek Toward Treatment

One of the most wonderful experiences Leo Walker has at a Hike for Mental Health event is when fellow hikers approach him with a confession: "I have never told anybody this before, but I suffer from mental illness."

Walker, a sales marketing, and operations consultant for companies that work with small businesses, is all too familiar with the stigma surrounding mental health issues.

His mother lived with schizophrenia throughout her adult life. Yet it was something they never talked about at home. "I don't know if my dad really knew what language to use or how to talk about it," Walker says. "The stigma and the embarrassment around it was a huge reason why it wasn't discussed."

When not in the grip of the disease, his mother was a wonderful, loving, funny person, Walker recalls. He believes that she could have led a fuller, happier life, before passing away from cancer 15 years ago, if her schizophrenia had been better understood and treated.

This is a big reason why he co-founded Hike for Mental Health in 2011 with partners Tom Kennedy and Nancy Kozanecki. The three met by chance at a hotel in New Jersey while Walker was on a business trip. They discovered that they all enjoyed the outdoors and had some connection to mental illness through family and friends.

"We were all at a similar point in our careers and at a place where we wanted to give back," he says.

Thus was born a nonprofit with a dual mission: foster an appreciation for wilderness trails through fundraising hikes, and direct those donations towards research into the causes and cures for brain and behavior disorders.

Initially the core group only worked with long-distance backpackers on the Appalachian or the Pacific Crest trails, turning their hikes into fundraising efforts. Walker, who by then had moved to New Jersey, also began organizing a few local day hikes. As he shared these events through social media, word spread and people from across the country began to reach out to him. Through the help of a supporter in New Hampshire, the team set up a hike in Mt. Washington, which has since become their largest annual day hike fundraiser.

Since 2011, the organization has grown into a nationwide movement, supporting hikes from New Hampshire to as far west as California and several places in between. Donations come in through the online sponsorship pages set up by participants. This past year alone, Hike for Mental Health has arranged more than 20 different events around the country.

Getting away from the stress of daily life and connecting with nature can be a re-grounding experience with a significant positive impact on mental well-being. However, Walker knows that for those battling mental illness, it takes more than a walk in the woods to achieve balance.

Hike for Mental Health's core team realized that if they raised money for direct care, it would help some people but "not on a very large scale and not necessarily in a lasting way," says Walker. The group wanted to make a bigger, longer-lasting impact by "funding research that would lead to breakthroughs in our understanding of the brain and behaviors that would lead to better treatments and eliminate the stigma," he says.

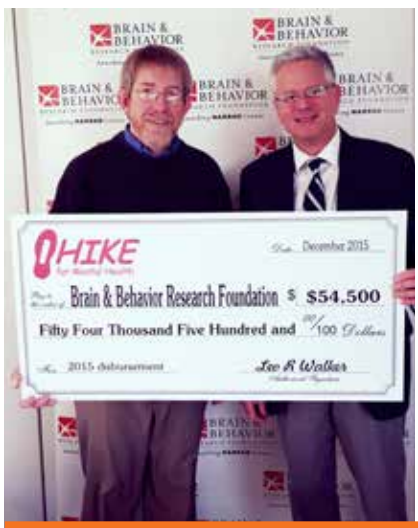
He approached the Brain & Behavior Research Foundation with his first check for $6,187 in 2012 when Hike for Mental Health was a small grassroots organization. Since then, it has become a nonprofit 501c3 and the Brain & Behavior Research Foundation has received the majority of all funds raised by Hike for Mental Health, totaling almost $130,000.

"Like us, the Brain & Behavior Research Foundation funds themselves separately from the donations they receive—we receive a dollar from our donor and we pass the full dollar through, directly to the research. Every way we looked at it, it made sense for us that BBRF is the right organization to work with to have the kind of impact we wanted to have," Walker explains.

A big part of what Walker hopes to achieve through his nonprofit is to eliminate the stigma of mental disorders.

"I am absolutely convinced that there is more pain caused by the stigma than by the disease. It's the stigma that prevents the disease from getting treated," Walker says.

With one in four adults experiencing mental illnesses, we all know someone who is affected. On trails, Walker often meets hikers who tell him that hiking has saved their life. "They mean that literally. That's been one of the most heartwarming aspects of what we've done." ■



Leo Walker presenting Dr. Jeffrey Borenstein with a donation in December 2015

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Glossary

Extrapyramidal system: The neural network within the central nervous system that controls involuntary movements and reflexes, affected by first generation antipsychotic medications.

Microbiome: The collection of microbes—including bacteria, fungi and viruses—that live in and on the human body. Some are helpful or neutral to human health, while others can cause disease. Our microbiome may be as large as 100 trillion cells—about three times the number of human cells in the body.

Neural inhibition: The brain's ability to dial down the strength of signals being exchanged among excitatory nerve cells.

Preoccupation: Recurrent intrusive thoughts that resemble obsessions. These thoughts may concern true events, unlike the delusions sometimes experienced by patients with schizophrenia.

Psychosis: A gross impairment of a person's perception of reality and ability to communicate and relate to others.

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