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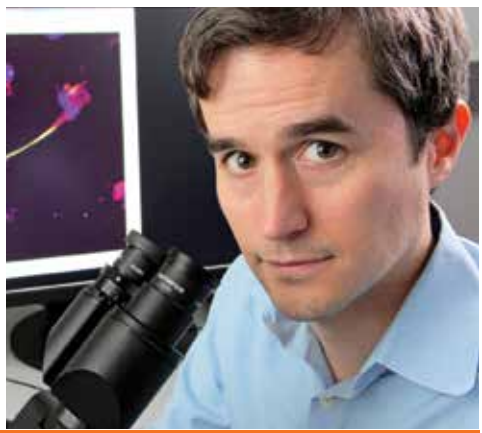

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Advice on Caring for Children and Adolescents with Bipolar Disorder

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A Breakthrough in the Effort to Develop a Fast-Acting Antidepressant

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NOVEMBER 8

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PRESIDENT'S LETTER

Jeffrey Borenstein, M.D.

President & CEO
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This issue of the *Quarterly* highlights our 2016 Klerman & Freedman Prizewinners for exceptional clinical and basic research conducted by NARSAD Young Investigator Grantees. Our Young Investigator Grants fund new and "out of the box" ideas of early career scientists. Equally important, these grants help launch neuroscience and psychiatric research careers by providing the initial support needed to gather crucial pilot data necessary for future funding.

Our Scientific Council selects the scientists who receive Young Investigator Grants and has an excellent track record of funding innovative projects and promising young scientists.

The Klerman & Freedman Prize recipients, featured in this issue, demonstrate just how critical your donations can be to the success of a scientist like Klerman Prizewinner Katie McLaughlin, Ph.D., a University of Washington clinical psychologist who is exploring the links between childhood maltreatment and the risk of developing anxiety disorders and depression. Dr. McLaughlin, like many of our other prize recipients, has said that her NARSAD Young Investigator grant was pivotal to her career and has opened up new opportunities for funding and the long-term pursuit of her groundbreaking theories.

Two Foundation Grantees and Outstanding Achievement Prizewinners who have dedicated their careers to research on psychiatric illness in young people are Francisco Xavier Castellanos, M.D. and David Miklowitz, Ph.D. In his lab at the NYU Child Study Center, Dr. Castellanos, a 2005 Distinguished Investigator and the 2015 recipient of the Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research, aims at explaining the neuroscience of ADHD through structural and functional brain imaging studies. In this issue, he discusses the advances and key findings from his research on brain imaging research (page 8). Dr. Miklowitz who serves as Professor of Psychiatry in the Division of Child and Adolescent Psychiatry at the UCLA Semel Institute, and is a 1987 Young Investigator Grantee, 2001 Distinguished Investigator Grantee and 2011 recipient of the Colvin Prize for Outstanding Achievement in Mood Disorders Research, offers advice to parents caring for a bipolar child in our parenting column (page 4).

On page 30 we feature a very moving article about how the tragic loss of a beloved daughter moved one family to dedicate their efforts to mental health research funding. Linda and Mario Rossi have dedicated their lives to helping remove the stigma of mental illness and raise awareness to mental health issues.

I very much appreciate the generosity of our donors and ask you to consider just how significant your support to the Foundation can be to a new idea, a new scientist, or a new treatment aimed at providing a child with a healthy future.

Sincerely,

Jeffrey Borenstein, M.D.
President & CEO

FEATURE

Parenting

TYPICAL TEEN BEHAVIOR OR SOMETHING MORE?

Advice on Caring for Children and Adolescents with Bipolar Disorder

David Miklowitz, Ph.D. is Professor of Psychiatry in the Division of Child and Adolescent Psychiatry at the UCLA Semel Institute, and a Senior Clinical Research Fellow in the Department of Psychiatry at Oxford University. His research focuses on family environmental factors and family psychoeducational treatments for adult-onset and childhood-onset bipolar disorder.

Among his many honors, he is a NARSAD Young Investigator (1987); Distinguished Investigator (2001); and in 2011 was the Foundation's Colvin Prizewinner for Outstanding Achievement in Mood Disorder Research. He has published over 250 research articles and eight books, including *The Bipolar Teen: What You Can Do to Help Your Child and Family* (with Elizabeth George) and *The Bipolar Disorder Survival Guide*.

Photo: Luke Porter

Symptoms of bipolar disorder aren't the same in adults and children. Can you start by describing the disorder in adults?

In adults, bipolar disorder is characterized by swings from severe states of depression to states of either mania or hypomania (a less intense form of mania). A full manic episode usually lasts at least a week, although for some people it can last several weeks. The person becomes elevated in mood or extremely irritable, and they feel grandiose—they have all sorts of ideas about things they're going to accomplish or powers that they have acquired. They sleep very little or not at all, and don't feel tired the next day. They are loaded with energy, and they speak fast. They often do very impulsive things—like spend a lot of money, or have sex with a lot of partners. And then these episodes swing to the other extreme, depression. They lose interest in everything. They become very fatigued, and they're often suicidal.

What about in adolescents or younger children?

About 1.8 percent of children under age 18 have some form of bipolar disorder. The majority of cases emerge between ages 15 and 19, but there's quite a bit of variability, anywhere from childhood up to later adulthood. Adolescents have longer periods with "subthreshold" symptoms than adults, or more frequent switches between depression and mania. Children and adolescents also develop more of what we call mixed episodes, or combinations of mania and depression. Here's a scenario: The child comes in irritable and says, "There's no point in the world and my life is terrible," but they're also talking rapidly and moving a mile a minute. Some people describe it as a "tired but wired" feeling. When adolescents have depression and anxiety, we also worry about suicide, because adolescents can be impulsive.

With younger children—four, five and six years old—the disorder is not very common, but there's enough cases on record that we know it can occur. The children usually have a family history of bipolar disorder. In addition to problems with sleep, increased activity, and impulsiveness, they may go from explosive and aggressive to hyper-sexual—even five-year-old children have been known to say and do inappropriate things. And once in awhile we see delusional thinking, things like, "I have 100 brothers and they live on the moon." When we have a child who shows those signs, we often don't know whether it's bipolar or some other disorder, or even a developmental transition. Mania is often confused with attention deficit disorder, and both poles can have a significant anxiety component.

Bipolar disorder has a strong genetic component. What do you tell parents who blame themselves for their child's disorder?

Among women who have bipolar disorder, the rate of the disorder in their children is around 10 to 15 percent. But there's no clear agreement on what exactly is inherited. It's probably not bipolar illness per se but something like vulnerability to mood swings when under stress. After all, the majority of people whose parents have bipolar disorder don't actually develop it themselves. This is what I tell parents: "There are many genes and they are inherited in complex ways. We don't know the actual mechanisms, but we suspect it's a combination of genes, environmental factors, and changes in cells and circuits in our brains. It's not like blue eyes or blonde hair. None of us can control what genes we bring into this world, or how those genes get translated into illness in our children."

Some typical teen behavior—such as unstable moods and risky behavior with drugs or sex—can also be expressions of bipolar disorder. How can a parent tell the difference?

This is one of the toughest problems for parents. The key is the clustering of unstable moods with other symptoms. Let's use the example of a child who goes snowboarding, jumps off a cliff, and breaks his leg. Is that a manic symptom? Well, does he also have a decreased need for sleep? Is he saying grandiose things like, "I'm the best snowboarder in the world?" Is he staying up late at night and talking faster? Does his behavior stand out, even among his friends?

If parents suspect a problem, they should first talk to the child and say, "Here's what I'm seeing. Do you think you need to talk to somebody?" The child will probably say no. Then you go a little further and say, "Why do you think you're more irritable? It must be hard to get through the day with such little sleep." If you suspect that he or she does have a mood disorder, get an evaluation with a psychiatrist or a psychologist—a diagnostic evaluation that includes a full medical history. Ask for recommendations on next steps—knowing that no one doctor has all the answers.

If there are questions about whether your son or daughter's behavior is healthy or not, it may be best to just do "watchful waiting" for a while, before insisting on medications or therapy. If your child has expressed any suicidal ideation and depression, get rid of any weapons in the house and make sure alcohol or prescription medication are not easily available.

David Miklowitz, Ph.D.

You emphasize the importance of monitoring moods. What are the best ways to do that?

Keeping a record is often the first step in knowing whether a child needs treatment. There are all sorts of mood charts you can download as apps (for example Mood Reporter or IMoods). They let you record what time you woke up, and when you went to bed. You record your mood at various times during the day on a scale, say from negative five—depressed—to plus five, which is hyper-activated or overly happy. Ideally the child keeps the chart, but if they won't this is something the parents can monitor as well.

When you take a look at the end of the week, you will find patterns. For instance, the child's parents are divorced, and over three weeks you notice that her mood goes down right before she's about to go to the other parent's house. You can also use a chart to track whether a new medication is working or causing agitation and sleep loss.

What are some common triggers for mood episodes?

One common trigger is a change in sleep-wake cycles. You'd be amazed by the number of phone calls we get at our clinic in the first couple weeks of the high school semester. Suddenly children have gone from sleeping until 10 or 11 a.m. to getting up at 6 a.m., and it's counter to their natural biological rhythm. Sleep is so important in teens that we tell parents it's important to have family rituals around bedtime—certain times when you start getting ready for bed, when all electronics are shut off, and when the lights go out.

Interestingly, both positive and negative life events can be triggers for mood episodes. Breaking up with a girlfriend, loss of a grandparent, high levels of criticism from a parent—those can all trigger depression. In addition to changes in sleep, positive events can trigger mania, such as getting a date to the prom or getting elected class officer. Look for evidence that the teen is "revving up" after these events or sleeping less and less.

Anything that's a stimulant—cocaine and amphetamines—can trigger mania. Alcohol is more associated with depression. We have no evidence that marijuana causes manic or depressive episodes, but smoking marijuana regularly will interfere with the effectiveness of mood stabilizers. Another problem with marijuana is that people tend to go off their mood stabilizers, thinking marijuana will work as a substitute. But it doesn't, and it can interfere with sleep. We ask parents to be aware of possible early warning signs of mania or depression, and they might be very subtle things. For example, the child may be hiding food under their bed, watching TV to see if their name is called, or calling relatives they haven't spoken to in years. When parents notice, *that's* a time to call the physician, and maybe get a change in medications to stave off the need for hospitalization. They may not be able to prevent their child from having a mood swing, but they may be able to prevent her from having a full manic or depressive episode. If we can reduce the severity, their lives are going to be easier.

How can parents find the right doctor?

Try to find a psychologist or psychiatrist who knows about childhood mood disorders. If all they tell you is that they look for unacknowledged childhood traumas, then you're not in the right place. And you probably don't want to see a psychiatrist who just has a general practice. It's best to go to a child psychiatrist who has some experience with mood disorders. Beyond that, I think it's a question of finding a doctor you can communicate with, one you'd be comfortable calling in an emergency, and most importantly, one your child wants to talk to.

What role should parents have in the child's medications?

The parent's job is to get their child in for an evaluation. The doctor is the one who says, "I think you should start taking this medication." A parent should know what the treatment options are, and then discuss it with the child. If the child is only five years old, obviously they aren't in a position to decide on their own medications. But when the child is 15 or 16, you don't want to force it, because if you force them to take medicine they're just going to refuse them later. You need the child's buy-in, and the best way to get buy-in is to let the child play a role in the negotiation of medication and dosages.

It's also very important for both parents to be on the same page, and that's often the hardest thing. I can't tell you how many times I've seen children or adolescents who just go off their medications one day, and the parents come in for a family session and they tell you, "I don't know why he went off his medications." When I explore a little more, I almost always find that at least one parent didn't believe the medication was a good idea, and the child knew that.

If the child still resists medications, I think it's the job of the therapist or the psychiatrist to find out what the issue is. It could be side effects—they don't like what it does to their body—or the stigma of diagnoses like depression or bipolar disorder. They may enjoy the high or manic feelings. Parents also need to acknowledge the side effects and not play them down—side effects like weight gain or acne can be real problems for children.

You recommend "family-focused treatment" for children with bipolar disorder. Can you explain what that involves?

It's therapy for the family—the parents, the child, and sometimes siblings as well. It has three components: psychoeducation, communication training, and problem-solving skills training, and there is a long history of using therapies with a similar structure to treat other disorders, like schizophrenia. It's weekly at first and then switches to biweekly. When we combine family-focused treatment with medications, the outcomes are much better than if we use medications alone.

In psychoeducation, we get the child to explain what the episodes are like. We ask the parents the same questions. We get them to have meetings every week to discuss what issues in the family are playing a role in the child's mood episodes, either positively or negatively. We end psychoeducation with what we call a relapse prevention plan, where we have the family and child list signs that an episode is starting, and plan what to do when this occurs, and what obstacles they foresee. It's best to make these plans when the child is well and able to look back and see what would have been helpful during the episode buildup.

Then we move on to communication training. We teach people to listen actively, to make requests, to balance positive feedback with negative. That's done with role playing. For disagreements, I recommend parents use what's called the "three-volley approach." If you set some sort of limit, that's volley one. If the child responds, "That's not fair," that's the second volley. You say, "Let me explain again why I think this is fair," that's three volleys. Now, if the child then comes up with another argument, you say, "I explained myself. We can discuss it some other time, but for now, the discussion is over." And you stop talking.

At the end of treatment we move into a phase where we identify problems that are not getting solved in the family. That might be cleanliness, or money, or taking care of the family pets, or getting back to school. We give the family a structure for solving problems and evaluating solutions, so they feel like they have some control over the things that are happening to them.

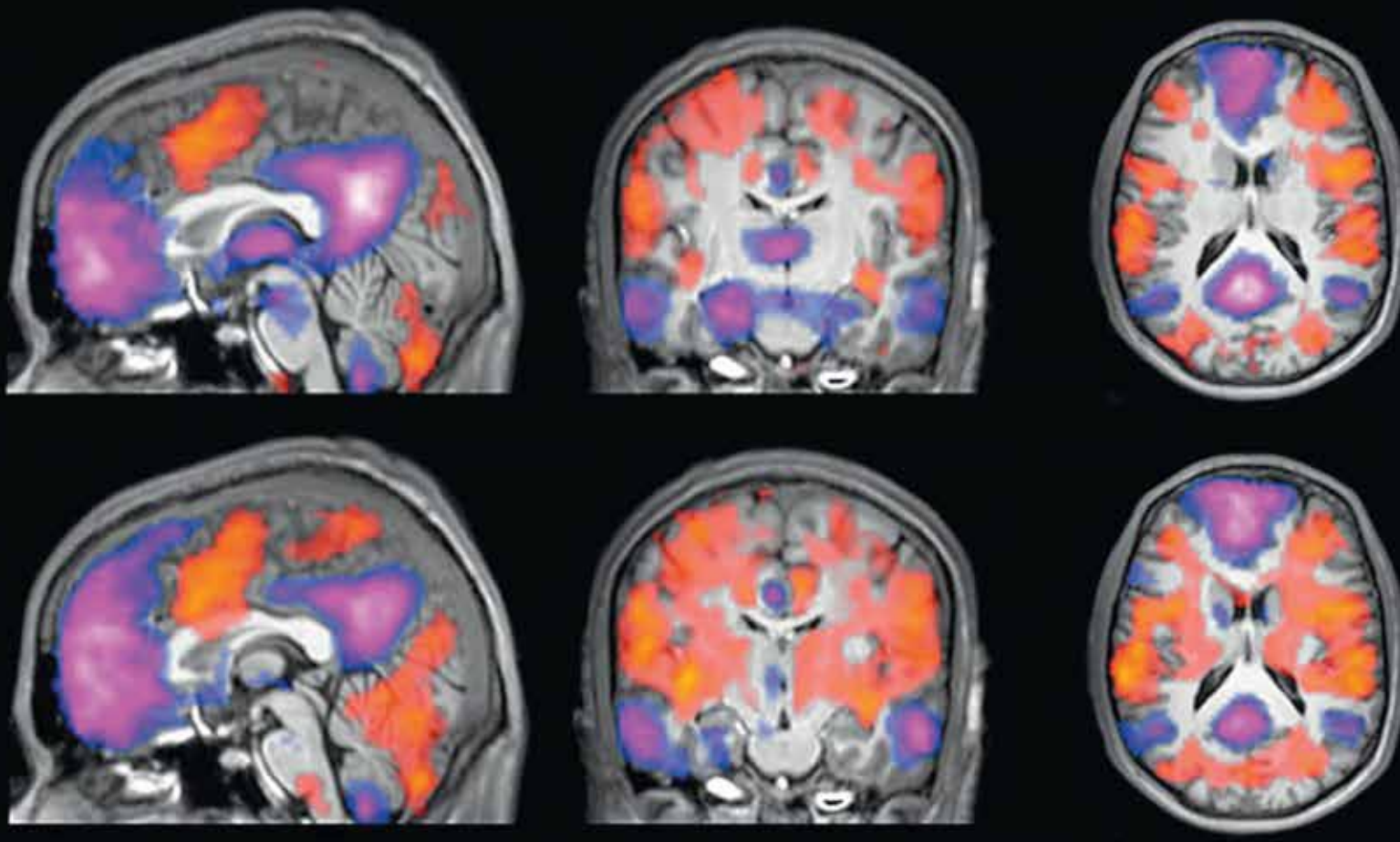
How can parents best advocate for their children at school?

First, you have to ask if the child's at the *right* school. If there's a problem at school, is it being driven by the mood disorder, or is it that the school system is not a good fit? It's good to set up an IEP, which is an individualized educational program. The school does an evaluation, and you sit down with the teachers and the administrators and develop a plan specifying the kind of classroom, the classes, the length of the school day, and more. That's a legally binding document that the school is obligated to follow. Then the parents meet with the school every couple of months to see how it's going.

Remember that the child wants to feel normal. My sense is that peers are getting more familiar now with what it means to have psychiatric problems, and there are a lot more children on medications and IEPs now, but nevertheless children feel very stigmatized. Parents should help their child avoid thinking that they're crazy or are not likable. And that's where a therapist can be of help too.

Speaking of stigma, do you think children should tell their friends about the diagnosis?

Children have a tendency to tell everybody, and don't really think through the implications. A child will be heartbroken when a friend's mom won't let him play because she's afraid of the bipolar disorder. It's OK to tell someone if you have a goal in mind. For instance, a friend can recognize when your son or daughter is getting agitated and call you. A teen might decide to disclose the illness to a new girlfriend or boyfriend. But I also tell them to be aware of the ways that information can be used against you, by peers, teachers or school administrators, and prospective employers. It's sad, and it's what we're fighting against, but it's also the truth. ■



Patterns of Activity in the 'Resting Brain' Shed Light on ADHD

by Peter Tarr, Ph.D.

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NYU School of Medicine

Research Psychiatrist
Nathan Kline Institute for Psychiatric Research

2015 Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research

2005 NARSAD Distinguished Investigator

"IT'S *YOUR* JOB TO FIGURE OUT WHAT ADHD IS." These words, spoken decades ago, helped shape the career of F. Xavier Castellanos, M.D., a leader in the field of functional brain imaging. The command—offered more as friendly encouragement—was given by his mentor, Judith Rapoport, M.D., a longtime member of the Foundation's Scientific Council and Chief of the Child Psychiatry Branch at the National Institute of Mental Health.

Today, while Dr. Castellanos modestly insists that the study of the brain is still in its infancy, he and colleagues have made great progress toward fulfilling Dr. Rapaport's wish. Last year, his many achievements were recognized by the Foundation when he was named co-winner of the Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research.

Attention deficit hyperactivity disorder is the most common neurodevelopmental disorder, affecting at least five percent[1] of children and adolescents, and possibly as many as 9.5 percent.[2] Dr. Castellanos can point to an experiment in the late 1990s that changed the direction of his research on the disorder.

At the time, he and a colleague decided to conduct a simple eye-tracking experiment. ADHD was already well described in the clinic by doctors who had been diagnosing it for decades, but it was not very well understood biologically. Its characteristic symptoms—a child's difficulty in focusing, the tendency to act impulsively, and sometimes to be hyperactive—were thought to reflect deficiencies in what brain researchers call executive function. Since stimulants like the drug methylphenidate (Ritalin) were often effective in curbing ADHD symptoms, it was further assumed that the disorder might involve irregularities in the brain's reward system and with the message-carrying neurotransmitter dopamine.

In collaboration with the late Daniel Hommer, M.D., Dr. Castellanos selected two groups of children who were placed, one at a time, in a dark room and seated at a computer screen. Half the children had been diagnosed with ADHD; the others did not have ADHD. "We asked them to look at a lighted dot at the center of the screen until it went off. We didn't tell them how long that was going to be, but the interval was set for 21 seconds," Dr. Castellanos recalls. In that fraction of a minute, "the kids who did not have ADHD looked away from the screen an average of once. The kids with ADHD looked away an average of 11 times."

F. Xavier Castellanos, M.D.

The relationships between the default network and the networks that control our cognitive faculties underpin lapses in attention and behavioral regulation in the disorder.

This was an interesting if not unexpected result, since children with ADHD have trouble paying attention. But then something curious happened when the scientists repeated the experiment with children in the ADHD group. "The kids whose eyes were wandering all over the room in the first trial were mostly focused on the screen the second time; those who had been focused the first time now did poorly. Almost none of the kids had the same result in both trials! It really drove home how variable the kids with ADHD were," Dr. Castellanos says.

Fortuitously, around the time of the experiment, he had been introduced by a colleague to a new area of research that involved using magnetic resonance imaging (MRI) to study the human brain in what is called the "resting state"—when it was *not* engaged in a conscious task. Previously, "functional MRI" had been used to see which parts of the brain "lit up" when a person was asked to do a specific mental task—like focusing on a dot in the center of a computer screen, or adding a column of numbers. Such task-related brain activity produces local changes in how much oxygenated blood is delivered to specific brain regions, and in fMRI this is translated into a visible signal.

PHOTO TOP OF PAGE 8: Brain networks are inversely correlated: When the brain is not working on a task, the default network dominates (blue and purple colors); when engaged in specific tasks, the default network subsides and specific brain areas involved in the task become active (yellow and orange colors). In the graph to the right, when the blue line is high, the orange line is low, and vice-versa. (*Trends in Cognitive Sciences* January 2012: 22)

First performed in 1995, resting-state fMRI scans (R-fMRI) revealed something unexpected. The "resting" brain was also active, and active in highly characteristic ways–in patterns that were virtually identical in different individuals, of different ages, across the sexes.

R-fMRI showed that large swaths of the brain fluctuate—in synchrony—at very slow speeds. The timescale of most "task-related" brain signaling is in hundredth-of-a-second increments. Astonishingly, in the resting-state brain, signals generated *within* and *between* large-scale neural networks fluctuate over many seconds, sometimes in waves lasting more than half a minute.

All of this ran against prevailing theories of how the brain works. Looking at how much energy the brain used in the resting state was, for Dr. Castellanos, a crucial revelation. The brain consumes about 20 percent of the body's energy even though it accounts for a tiny fraction of its mass, and it became clear that it devotes most of that energy to maintaining itself in the resting state. "The brain invests so much in this intrinsic activity that it has to be indicative of something profound," he says.

It turns out that the human brain is something like a computer with a power-hungry operating system running constantly in the background, on top of which specific "apps" are launched. When such tasks are undertaken—for example, when the brain receives data from the senses and processes it—parts of the brain that make up the resting state's "default network" are repressed somewhat. But they never cease their activity, which tends to wax again when the brain pauses before re-engaging on the next task.

The inconsistency in the ability of children with ADHD to focus that Dr. Castellanos saw in his 1990s experiment, along with other behavioral symptoms of the disorder, including pronounced variability on tests measuring reaction time, led him to image the ADHD-affected brain. Popular theories of the disorder had pointed to dysfunction in circuity connecting the prefrontal cortex (executive function), the striatum (reward system) and the cerebellum (motor control). In 2007 he and colleague Edmund Sonuga-Barke, Ph.D. made an influential suggestion that ADHD pathology goes well beyond this circuitry. They proposed that it involves a number of different large-scale, resting-state networks. Specifically, they suggested that portions of the default network were falling out of synchrony—activating out of phase with one another and giving rise to symptoms.

In the intervening years, functional imaging has made "a quantum leap" forward in technological terms, in Dr. Castellanos' words. Images obtained using functional MRI today are the equivalents of what high-definition TV is to grainy, black-and-white TV technology. Resolution is greatly enhanced, and researchers have been inspired to assemble vast data sets consisting of scans of large sets of people. As a result, functional brain imaging today is poised as never before to help explain pathology in disorders, not only ADHD but perhaps depression, anxiety and other conditions.

The imaging projects that have been completed so far have raised fascinating questions, including what it means to be considered "normal." The scans reveal what scientists call inter-individual variation in exquisite detail, and have already prompted some experts to wonder whether understanding the brain in terms of the functioning of large-scale neural networks will change the way disorders are diagnosed and classified.

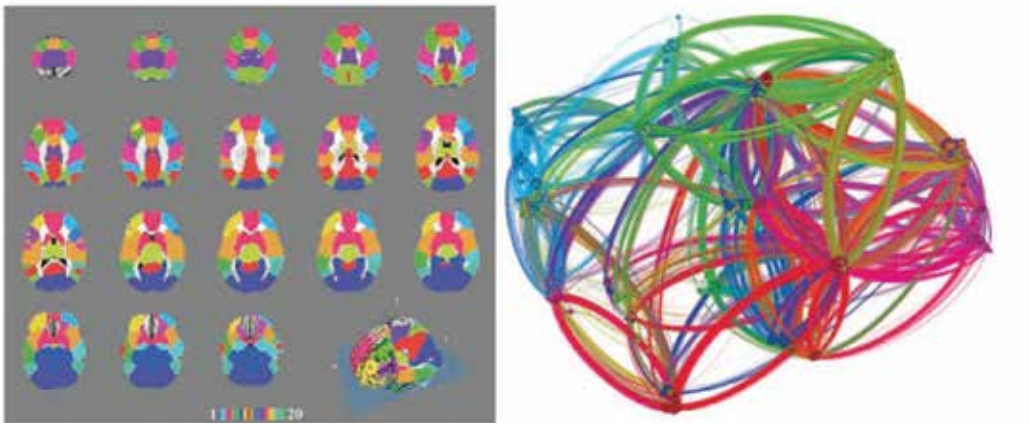
The considerable body of work on ADHD and resting-state fMRI that has been published over the last decade has led to a few interim conclusions. One conclusion is that a diminished *suppression* of default-network activity, while the brain is faced with specific tasks requiring attention, appears to be related to *lapses* in attention that are among ADHD's telltale symptoms.

Another interesting set of findings concerns brain scans of ADHD patients being treated with stimulants. These have shown that among those taking the medicine, suppression of the default network returns to normal levels in two important parts of the brain, the prefrontal cortex and posterior cingulate cortex. This suggests why the drug is able to help some patients. Separately, other research has shown that youths with ADHD who were scanned while off their medication did *not* deactivate their default network unless they were offered strong behavioral incentives to perform a given task.

As Dr. Castellanos has noted, both of these results "point to dysregulation of the default network rather than its fundamental impairment" in ADHD. This is an important distinction suggesting that what is out of sync can be brought back into sync with treatment, as opposed to a mechanism that is not functioning at all.

As research moves forward, investigators continue to study the most important theory emerging from resting-state imaging of ADHD: The relationships between the default network and the networks that control our cognitive faculties underpin lapses in attention and behavioral regulation in the disorder. "We believe it is likely that interactions among functional networks we have identified will form distinguishable neurobiological patterns that can provide the basis for meaningful subtyping of this condition, which varies so markedly from person to person," Dr. Castellanos says.

1 Polanczyk et al 2007, Am J Psychiatry 164:943-48
2 CDC 2010 estimate of prevalence in US, MMWR 59: 1439-43



Left: A color-coded whole-brain functional connectome, as revealed by functional MRI. Right: A version showing connections between networks. (*Cerebral Cortex* August 2012: 1866)

INTERVIEW WITH A RESEARCHER / SIDEBAR

Needed: A Growth Chart for the Brain

When he was in residency training, Dr. Castellanos divided his time evenly among two specialties, which meant regularly switching attention between pediatric and child psychiatry. It was 25 years ago, and the separation of the two fields was quite pronounced, more than is the case today.

Dr. Castellanos recalls being asked in those early days to consult on a case involving a newborn failing to thrive, apparently because of her mother's difficulties in breast feeding. Nurses suggested the baby be given formula, but the mother resisted. "You're a psychiatrist," they pleaded with Dr. Castellanos, "surely you can convince her to change her mind."

Instead, he decided to give the mother a chance to do what she felt was best, but within supervised limits: He would take a standard infant growth chart and plot against its curve the progress—or lack thereof—of the struggling infant. Everything would hinge on the comparison of the baby's weight relative to well-established norms. If the baby continued to not thrive, she would be put on formula out of concern for her health and tests could be run to check for an undetected illness.

Dr. Castellanos tells the story for two reasons. One is to suggest how satisfying a simple observation can be: Breast feeding continued and the child began, at last, to gain weight. "With that single sheet of paper [showing a normal growth curve], which cost less than a penny, and a couple of pencil marks [plotting the baby's weight as the days passed], I saved maybe $30,000 worth of tests," he says.

But even more impressive, and instructive for his subsequent career, was a second lesson: "When you know *what* to measure, and you measure it, it is incredibly powerful," Dr. Castellanos says. It all depended, in this case, on the robust science that produced the curve of "normal" growth. "That chart was made on the basis of data collected from more than 50,000 children," over a period of years, he says. "It is only the average of data from tens of thousands of individuals in the past that enables us to make *predictions* today."

The brain imaging research to which Dr. Castellanos has devoted the better part of his career takes this lesson to heart. Imaging is used to show the human brain as it operates in living people. There is not yet anything like the equivalent of a "growth chart" for different parts of the brain as they develop from the period in the womb all the way to the end of adolescence. But that is one among a number of tools of "Rosetta Stone" importance, Dr. Castellanos says, that he and others in the functional imaging field are in the midst of developing.

"We're still in the very early stages of quantifying brain structure and function. We are still in the phase of trying to learn what to measure, what is relevant," he says. "It's a huge challenge. But…wow! What we have learned so far is breathtaking!" ■

Have A Question?

Send questions for F. Xavier Castellanos, M.D. to **asktheresearcher@bbrfoundation.org.**

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

ASK THE RESEARCHER

Robert Freedman, M.D.

Chair of Psychiatry
University of Colorado

Editor-in-Chief
The American Journal of Psychiatry

Foundation Scientific Council Member

We have a history of schizophrenia in my family. Should I consider taking a choline supplement when I get pregnant, or is it better to just eat lots of foods that are rich in choline?

Either approach would work in principle. But if you chose the two foods highest in choline, you would need two servings of beef liver or eight large eggs every day, plus a normal diet with meat and eggs and other proteins, to equal the supplementation that we used in the clinical [choline] trial. Earlier experiences with folate supplementation have shown that supplements are more effective for most people than efforts to eat a better diet alone.

Do you think widespread choline supplementation will actually lead to fewer cases of schizophrenia, or will it just make symptoms of the disease less severe in people who develop the illness?

We will need to wait for two to three decades for the children whose mothers took choline to grow into adulthood to be able to answer this question. So far, all we know for sure is that children at four years of age whose mothers received choline during their pregnancy do not have the kinds of difficulty with paying attention and making friends that children who develop schizophrenia typically have. We are working to establish a social media platform that will allow mothers to tell us what happens to their children as they grow into adulthood, regardless of whether or not they took choline supplements during their pregnancy.

Have you been testing drugs to see which ones might be useful in treating adult schizophrenia, including drugs that stimulate alpha-7 nicotinic receptors, as you mentioned in your interview?

Yes, we have. One drug, 3-2.4 dimethoxybenzylidene anabaseine, was first synthesized at the University of Florida based on a chemical found in a worm from Puget Sound. The drug helps patients with schizophrenia and autism spectrum disorder pay attention more effectively. Several pharmaceutical companies have tried to copy it, but they have chosen to make much longer-acting drugs that have not proven to be quite as effective. We are hoping that they will understand that the biology of alpha-7 nicotinic receptors better accommodates shorter acting drugs. Alpha 7-nicotinic receptors are naturally stimulated by acetylcholine, and clozapine is particularly effective at increasing acetylcholine levels in the brain. For now, clozapine is the best way to increase alpha-7 nicotinic receptor stimulation.

From the way you described inhibition in the brain, I'm wondering if problems with inhibition are involved in other mental illnesses beyond schizophrenia. And if so, would choline supplementation help with those illnesses as well?

Problems with inhibition and alpha-7 nicotinic receptors have been found in ADHD, autism spectrum disorder, psychotic bipolar disorder, and schizophrenia. It is possible that all these disorders might be benefited in children whose mothers take choline during pregnancy. ■

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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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FEATURE

A Breakthrough in the Effort to Develop a Fast-Acting Antidepressant

by Peter Tarr, Ph.D.

CARLOS A. ZARATE, M.D.
Chief, Section on the Neurobiology and Treatment of Mood Disorders
Chief of Experimental Therapeutics and Pathophysiology Branch
National Institute of Mental Health

Clinical Professor of Psychiatry and Behavioral Sciences
George Washington University

2011 Colvin Prizewinner for Bipolar Mood Disorder Research

2005 NARSAD Independent Investigator

1996 NARSAD Young Investigator

Photo: Thanun Buranapong

"IMAGINE YOU HAD A COMPOUND that does what ketamine does, but without its side effects or risk of addiction," says Carlos A. Zarate, M.D., a senior scientist at the National Institute of Mental Health. He's referring to a drug that has been shown in recent years to almost miraculously relieve deep depression—the kind that resists other forms of treatment—within hours, and sometimes, though less frequently, in minutes. The problem is that it can generate serious side effects and is also addictive when misused.

This "improved" version of ketamine, Dr. Zarate explains, could similarly act rapidly to relieve treatment-resistant depression. It could help people in the midst of a suicidal crisis to stop thinking of ending their lives. Like ketamine, this new drug could also be effective in treating the depressive phase of bipolar disorder. And like ketamine, it could relieve anhedonia, the inability to experience pleasure that is seen in millions of depressed people, not only the most severely afflicted.

Indeed, says Dr. Zarate, "ketamine is an exciting drug" for all of these reasons, and he has been involved in some of the preclinical and clinical trials in animals and people that have documented its potential. Since 2009, when he founded the Experimental Therapeutics and Pathophysiology Branch (ETPB) at the Division of the Intramural Research Program at the NIMH, he and his colleagues have been trying to find out exactly how ketamine works, in the hope of learning how to engineer a safer alternative.

This alternative drug that would have all or even some of ketamine's benefits but not cause its most troublesome side effect, dissociation (a variety of perceptions in which one feels detached from one's immediate surroundings, or feels a distinct separation between one's body and mind). A future ketamine substitute also would not be addictive. Indeed, ketamine, originally an anesthetic used in veterinary medicine, is also known on the street as a "party drug," called Special K.

The wait for this improved ketamine may be nearing an end. On May 4, Dr. Zarate and colleagues at the NIH, along with a team at the University of Maryland led by Todd Gould, M.D., (a NARSAD 2013 Independent Investigator and 2004, 2010 Young Investigator) published a paper in the journal *Nature* that turned heads. They presented powerful evidence suggesting that ketamine did not work primarily as most scientists had previously postulated. Even more important, they showed that ketamine's desirable effects are likely due to one of the chemicals generated when the drug is metabolized by the body.

Progress on a ketamine substitute is a triumph of basic and clinical research.

This report shook the field because it suggested that it may be possible to administer the metabolite, called HNK (or "Hank"), separately as a drug in its own right. This metabolite, importantly, does not appear to be addictive or to generate dissociative effects. "If you have something without ketamine's side effects and addictiveness, you could totally change how treatment is given for depression, suicidal thinking, and anhedonia," Dr. Zarate says. "You could intervene very rapidly, and very early in the course of treatment."

It could mean "rapidly and early" not only in the most severe cases of depression, he adds. If a safe drug based on HNK is as effective as hoped—"and we shouldn't jump the gun, there's plenty of work to do," he stresses—it could be prescribed conceivably "for everybody" with life-impairing depression. He means the millions who currently take drugs in the Prozac class, called SSRIs, which affect the brain's serotonin system. About half of those who take SSRIs are not helped by them, and those who are helped often must wait weeks or months to see any improvement in mood.

"We could decrease the length of every episode of depression, which ranges on average from three to nine months. So over the course of a lifespan one could significantly lessen the time spent 'in depression' and in this way decrease the harmful impact depression has on the brain and body. It could get people back to their normal lives very quickly, minimizing the disruption," Dr. Zarate says of a drug with ketamine's benefits and lacking its downsides.

A recipient of a Young Investigator grant in 1996, an Independent Investigator grant in 2005, and the Brain & Behavior Research Foundation's Outstanding Achievement Award for Bipolar Mood Disorder Research in 2011, Dr. Zarate, an Argentinian by birth, came to the NIMH in 2001. He organized the ETPB precisely to work with drugs like ketamine that were already known to have a beneficial effect on psychiatric illnesses, but for one reason or another were not suitable for use in large numbers of patients. He likens his approach to reverse engineering, which has been very much in evidence in the years of work culminating in the new paper on ketamine and HNK.

Carlos A. Zarate, M.D.

He and his colleagues arrived at the new findings by trying to take apart or isolate different aspects of ketamine—ranging from what became of the compound once it entered the body to where it acted in brain cells to generate its beneficial antidepressant effects. An early clue was an experiment that tested the long-held theory that ketamine works by blocking docking ports called NMDA receptors on the surface of nerve cells. This blockade was thought to spur the release of a neurotransmitter called glutamate, which helps cells carry messages from one neuron to the next.

But when the team used a different compound to block NMDA receptors—one that did so much more powerfully than ketamine—they noticed very weak or no impact on depressive symptoms in mice. This led them to look for other mechanisms behind ketamine's beneficial effects.

Knowing from their own work and that of others that ketamine generates stronger antidepressant responses in female mice than male mice, Dr. Zarate and colleagues looked closely at the drug's metabolites. They noticed that one, HNK, was about three times more prevalent in the brains of female rodents given the drug compared with males, while other metabolite levels did not differ among the sexes. HNK thus seemed a good place to focus.

In meticulous experiments that can be compared, roughly, with taking a computer and subtracting parts until it malfunctions, the scientists tested a version of ketamine that did not break down into HNK. This version of ketamine was *not* effective in reducing depression in mice. They then tested two versions of HNK, and identified the one that most effectively and rapidly treated depressive symptoms and reversed the mouse equivalent of anhedonia.

The original questions about ketamine—how did it work and where did it act in the brain?—had to be applied to this desirable version of HNK. Perhaps it was HNK that blocked NMDA receptors, leading to a glutamate surge and accounting for ketamine's effects. In a wonderful example of why a rigorous scientific approach is needed, the team demonstrated that HNK by itself *does not block* NMDA receptors. This experiment was important because it suggested that both ketamine and HNK administered alone rapidly relieved depression, but those benefits did not come from blocking NMDA receptors.

When the team blocked another type of glutamate receptor called AMPA in mice, HNK did *not* relieve depression-like symptoms. In other words, HNK's rapid antidepressant action requires the vigorous activation of AMPA docking ports and a surge of glutamate signaling in nerve cells. Further experiments, using EEG brain-wave measurements and other methods, suggested to Dr. Zarate and the team that HNK relieves depression by causing more AMPA docking ports to appear at the synaptic junctions that connect nerve cells in the brain.

Will we see a drug based on HNK in the very near future? Not immediately. But Dr. Zarate says his team, in conjunction with the National Center for Advancing Translational Sciences (NCATS)—a section of the NIH created to assist in the development of therapeutics based on government-funded research—is already working hard to get to a drug that pharmaceutical companies would then test in large-scale human trials.

"Our results are very exciting, but we need to know more," Dr. Zarate emphasizes. Since HNK is generated when ketamine is given to seriously ill patients, it is "proven" safe in at least limited dosages. But no one yet knows the dose to use to achieve the best results if HNK is given separately.

"We are conducting such tests right now," says Zarate. "If we find that higher doses are needed than those generated naturally in ketamine administration, then we have to establish safety very carefully. We have to show how effective and how safe it is when taken over longer periods of time. We also have to test other metabolites of ketamine, repeating much of the same work with them, to see if any of them are important in ketamine's 'good' effects. None of these steps can be skipped."

The team hopes to move from preclinical tests in animals to Phase 1 and 2 trials in humans. If successful, then a partnering approach with the industry is possible in the near future, Dr. Zarate says. ■

Drugs That Mimic Natural Resilience Suggest New Treatment for Depression

TAKEAWAY: Three drugs that open specific ion channels in a part of the brain called the VTA experimentally reversed neural and behavioral changes associated with depression in mice.





Ming-Hu Han, Ph.D., 2015 II, 2007 YI
Dipesh Chaudhury, Ph.D., 2014 YI
Allyson K. Friedman, Ph.D., 2014 YI
James W. Murrough, M.D., 2009 YI
Rachael L. Neve, Ph.D., 1997 DI

Researchers have developed a new therapeutic strategy for treating depression. As described in a paper published May 24 in *Nature Communications*, the new approach seeks to mimic in people the neuronal state of rodents that are naturally resilient to stress.

Just like people, individual rodents react to stress differently. Some are much more resilient than others, while still others are notably vulnerable to stress. For years, researchers have used mouse models of stress-induced depression with the aim of identifying what makes some people susceptible to depressive episodes.

In previous research, a team led by Ming-Hu Han, Ph.D., a 2015 Independent Investigator grantee and 2007 Young Investigator grantee from the Icahn School of Medicine at Mount Sinai, explored how the brains of resilient and depressed animals differ. They found that resilience in the brain is an active state—in other words, not simply the absence of depression. In resilient animals, specific genes are switched on in a brain region called the VTA (ventral tegmental area). These genes are inactive in VTA neurons of depressed animals.

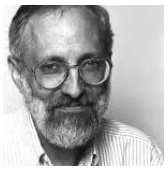
When these genes are active in resilient animals, ion channels—tiny pores on the surface of neurons that open and close when signals are being relayed—are significantly more often open and active. Observing this, the researchers wondered what would happen if they could open such channels in VTA neurons in animals that were depressed. Would there be a therapeutic effect?

The team, which also included Icahn School researcher Allyson K. Friedman, Ph.D., a 2014 Young Investigator grantee and first author of the new paper, sought to open a particular subset of potassium ion channels called KCNQ ion channels in non-resilient animals. These are the channels encoded by the gene, called *KCNQ3*, that was turned on much more in the VTA of resilient animals than in depressed animals. Overexpressing this gene led to more ion channels, whose activity had the effect of quelling the neuronal hyperactivity in the VTA that corresponds with depression. The animals became more resilient with fewer and less intense symptoms of depression-like behavior.

This experimental success suggests a brand new therapeutic approach for depression. There are three known drugs that open KCNQ ion channels. One of these, retigabine (also marketed as ezogabine), is already FDA-approved for the treatment of epilepsy. The research team tested it and the other two channel-opening agents in mice, and found that all three reduced neuronal hyperactivity in the VTA as well as symptoms of depression in the animals. The team is now working to see if similar treatments might *prevent* depression in susceptible animals if administered prior to stressful situations. ■

Marriage Reduces the Risk of Developing an Alcohol Use Disorder

TAKEAWAY: A study of more than three million people suggests that marriage protects against the development of alcohol use disorders, particularly among those with a family history of alcoholism.



Kenneth S. Kendler, M.D., Scientific Council, 2010, 2000 DI, 1995 Lieber Prizewinner

Married people are significantly less likely than unmarried individuals to develop alcohol use disorders, according to a new analysis of more than three million Swedish people. The study, published May 16 in the *American Journal of Psychiatry*, found that marriage protects against such disorders, and that its protective effect is strongest among people with a family history of alcoholism.

Researchers have noted previously that married people tend to consume less alcohol and have lower rates of alcohol abuse disorders than people who are unmarried. But the reasons for this association have been unclear. It has been difficult to determine whether marriage protects against alcohol abuse, or if people who are already at risk for alcohol use disorders are less likely to marry and to stay married.

In the new study, researchers used official medical, pharmaceutical, criminal and government records to look for associations between marital status and first reports of alcohol abuse. Their aim was to find out whether marriage influences a person's risk of developing such a disorder. The research was led by Kenneth S. Kendler, M.D., a 2010 and 2000 Distinguished Investigator, 1995 Lieber Prizewinner, and Scientific Council Member from Virginia Commonwealth University. In Sweden, the research was led by Drs. Jan and Kristina Sundquist at Lund University.

Analyzing the records of more than 3.2 million individuals over time, the team determined that more than 72,000 people—about three percent of men and one percent of women—had alcohol use disorders. When they compared those data to an individual's marital status, the researchers found that the disorders were significantly more likely to arise in single individuals than in those who were married.

Men were 60 percent—and women 71 percent—less likely to develop an alcohol use disorder if they were married, the researchers found. What's more, the protective effect was strongest among those with a family history of alcohol use disorders.

Not all marriages had this effect, however. The researchers noted that while marriage to a spouse without alcohol problems protects against alcohol use disorders, being married to a spouse with alcohol use problems, perhaps not surprisingly, has the opposite effect.

The team considered the impact of several factors that might influence both one's likelihood of developing an alcohol use disorder and their marital status, but the reduction in risk among married people could not be attributed to any of these factors, including variations in socioeconomic status, histories of criminal behavior or drug abuse, or family histories of alcoholism. They also observed the protective effect of marriage on risk for alcohol problems when comparing close relatives, where one was married and the other was not. The researchers concluded that marriage itself, through its social and psychological impacts, likely protects against alcohol use disorders. ■

New Technique Recreates Large-Scale Genetic Errors Linked to Neurodevelopmental Disorders

TAKEAWAY: A new method for introducing disease-associated variations into cells expands opportunities to investigate causes and new treatment approaches for autism, schizophrenia, and other disorders.

James F. Gusella, Ph.D., 2007 DI

Michael E. Talkowski, Ph.D., 2012 YI

Genetic abnormalities called copy number variations (CNVs) are thought to be among the most common causes of neurodevelopmental and psychiatric disorders. CNVs occur when segments of DNA are either overrepresented or are missing entirely from a person's cells. Now, researchers have devised a way to recreate specific copy number variations—including those linked to autism and other neurodevelopmental disorders—in human cells grown in the lab. This important achievement paves the way for studying exactly what goes wrong in cells that carry these defects, and could help researchers find ways to correct the problems they cause.

Considered large-scale mutations in the human genome's structure—as opposed to "point" mutations involving changes in single DNA "letters"—CNVs can span one or even dozens of genes, altering activity levels for some or all of them. These changes can range from extreme overactivation where genes are multiplied in number, to no activation at all where genes are missing entirely. Geneticists have had difficulty teasing out exactly how different CNVs affect bodily processes and functions.

2007 Distinguished Investigator James F. Gusella, Ph.D., and 2012 Young Investigator Michael E. Talkowski, Ph.D., who are both at Harvard University and Massachusetts General Hospital, led the development of the new method, which they call SCORE (Single-guide CRISPR/Cas targeting of repetitive elements).

As they and their colleagues reported in the February 1 issue of the journal *Nature Neuroscience*, the team has used SCORE to create human stem cells that carry too many or too few copies of chromosomal regions known as 15q13.3 and 16p11.2. CNVs in these regions are associated with autism, schizophrenia, and intellectual disability.

SCORE is an application of CRISPR (Clustered regularly interspaced short palindromic repeats), a molecular research tool that in recent years has taken the biology world by storm. CRISPR is an adaptation of a genome defense system native to bacteria. (Bacteria use a CRIPSR-like system to cut out the unwanted DNA of viral intruders.) It enables scientists to edit genomes—including the human genome—with unprecedented precision and ease.

The team led by Drs. Gusella and Talkowski recognized that they could use CRISPR to create human cells with specific CNVs, those that are caused by errors in repetitive DNA sequences that flank the CNV itself. SCORE is an efficient way to introduce into lab-grown cells duplications or deletions that precisely match those that occur in people with particular disorders.

The team demonstrated the new technique by replicating two specific copy number variations implicated in psychiatric disorders. But their approach can be readily applied to produce other mutations of the same type. They and other researchers can explore the effects of any copy number variation by engineering cells that carry the mutation and comparing them to cells that are genetically identical save for that particular mutation. Such an approach, it is hoped, will illuminate biological pathways that are disrupted by copy number variations and how those disruptions contribute to psychiatric disorders. ■

2016
KLERMAN & FREEDMAN PRIZES FOR EXCEPTIONAL RESEARCH BY NARSAD YOUNG INVESTIGATOR GRANTEES

Six Young Investigators received the Annual Klerman & Freedman Prizes on Friday, July 29th in New York City, in recognition of their exceptional research.

These two prizes pay tribute to Gerald L. Klerman, M.D. and Daniel X. Freedman, M.D., whose legacies as researchers, teachers, physicians, and administrators have indelibly influenced neuropsychiatry. These prizes recognize exceptional clinical and basic research by young scientists who have been supported with NARSAD Young Investigator Grants—our hallmark program which enables aspiring young scientists with innovative ideas to garner the pilot data needed to often times go on to receive further funding once they have "proof of concept" for their work.

The prizewinners are selected by committees of the Foundation's Scientific Council, an all-volunteer group of 164 distinguished scientists across brain and behavior research disciplines. This early recognition of their work by the Foundation's Scientific Council often serves as a precursor to further accomplishments, awards, and prizes as well as to their establishment as Independent Investigators at their institutions.

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The Klerman Prize was established in 1994 by Myrna Weissman, Ph.D., in memory of her late husband, Gerald Klerman, M.D.

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University of Washington

2013 NARSAD Young Investigator Grant

"The NARSAD Young Investigator Award has been pivotal to my career development as a young scientist. This grant provided the funds for the first large study conducted in my lab and has fueled numerous additional research projects. In particular, this award was instrumental in helping me obtain a large federal grant from the NIMH by providing the pilot data that was necessary for the grant submission. I am certain that I would not have received this larger grant, which will fund my research for the next five years, without the support I received from this award. I am deeply grateful for having been given this opportunity."

KATIE MCLAUGHLIN, PH.D., is a clinical psychologist and an Associate Professor of Psychology at the University of Washington. She is being honored for her work on "Child Maltreatment and Neural Networks Underlying Emotion Regulation: A Neurodevelopmental Pathway to Anxiety and Depression."

For her grant project, Dr. McLaughlin examined how exposure to maltreatment in childhood influences the architecture of the developing brain in ways that increase risk for anxiety and depression.

Dr. McLaughlin's research looks at how environmental experience shapes emotional, cognitive, and neurobiological development throughout childhood and adolescence. Her research uncovers specific developmental processes that are disrupted by adverse environmental experiences early in life and determines how those disruptions increase risk for mental health problems in children and adolescents. Understanding these mechanisms is critical for the development of interventions to prevent the onset of psychopathology in children who experience adversity. Dr. McLaughlin's overarching goal is to contribute to greater understanding of the role of environmental experience in shaping children's development, so as to inform the creation of interventions, practices, and policies to promote adaptive development in society's most vulnerable members.

Dr. McLaughlin has a joint Ph.D. in Clinical Psychology and in Chronic Disease Epidemiology from Yale University. She has published more than 135 peer-reviewed journal articles and has received early career awards from the Society for a Science of Clinical Psychology, the International Society for Traumatic Stress Studies, and the Jacobs Foundation. She has also received the Distinguished Scientific Award for Early Career Contribution to Psychology from the American Psychological Association.

2016 Klerman Prize Honorable Mentions

ERIN C. DUNN, SCD, MPH
Assistant Professor of Psychiatry
Harvard Medical School

Assistant in Research
Massachusetts General Hospital

2013 NARSAD Young Investigator Grant

"Having this grant enabled me to acquire the foundation, tools, and resources to pursue my research, gave me the confidence to know I was heading in the right direction, and put me on a trajectory towards independence. I am tremendously grateful to the Research Foundation and its generous donors for supporting young investigators like me who are passionate about discovering ways to rid the world of depression."

ERIN C. DUNN, SCD, MPH is an Assistant Professor of Psychiatry at Harvard Medical School and an Assistant in Research at Massachusetts General Hospital. She also holds affiliations with the Center on the Developing Child at Harvard University and the Stanley Center for Psychiatric Research at the Broad Institute of Harvard and MIT.

Dr. Dunn is being honored for her grant work looking at "Sensitive Periods Associated with the Development of Depression." Sensitive periods refer to windows of time in the lifespan when the developing brain is particularly vulnerable or sensitive to experience, including exposure to adversity (like maltreatment, neglect, and poverty).

Several novel findings have emerged from her analyses. First, she identified a set of genes that share similar profiles of expression over time, with some sets of genes "turning on" or "turning off" at specific stages of human brain development. She has also identified several developmental stages when exposure to adversity appears most harmful in increasing risk for depression. Lastly, Dr. Dunn has found evidence suggesting that the effect of genes implicated in stress related disorders may vary as a function of the age stage when the adversity occurs.

Through this research, it is Dr. Dunn's hope that she can guide prevention efforts by identifying when adversity is most harmful to people and when public health investments can have the biggest impact on preventing depression.

AVRAM J. HOLMES PH.D.
Assistant Professor of Psychology and Psychiatry
Yale University

2013 NARSAD Young Investigator Grant

"The Foundation has been instrumental in supporting the early phases of my research program and funding my laboratory's first independent research project. This generous support provided me with the momentum to establish my own laboratory at Yale University while initiating a program of research that is currently funded by NIMH."

AVRAM J. HOLMES, PH.D. is an Assistant Professor in the Department of Psychology and Psychiatry at Yale University. He is being honored for his work in "Identifying the Network-Level Fingerprints of Affective Illness and Associated Polygenic Vulnerability in the General Population."

For his grant project, Dr. Holmes established common and unique patterns of dysfunction in people with unipolar and bipolar depression. His work is based on his recent identification of a biological 'marker' of preferential disruption of the frontoparietal control network in individuals with bipolar disorder relative to the general population.

Dr. Holmes's research is focused on discovering the fundamental organization of large-scale human brain networks. The Holmes lab uses a variety of brain imaging techniques, including structural and functional MRI, diffusion tensor imaging, and electrophysiology, along with quantitative and molecular genetic methods. Dr. Holmes is working to establish a new imaging intermediate phenotype of unipolar and bipolar depression risk based on the network-level signatures of each illness, assessed through the analyses of dynamic fluctuations in brain activity. He will then explore the genetic factors that contribute to these network-level profiles in individuals within the general population. He hopes that the knowledge gained through this approach can provide novel biological targets for therapeutic interventions and predictive markers of clinical course.

2015 Freedman Prizewinner for Exceptional Basic Research

The Freedman Prize was established in 1998 in honor of the late Daniel X. Freedman, M.D., a founding member of the Foundation's Scientific Council.

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KAY M. TYE, PH.D.
Assistant Professor

Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences
Massachusetts Institute of Technology

2013 NARSAD Young Investigator Grant

"The NARSAD Young Investigator Award was critical in helping me launch my career as an independent investigator, which allowed me to pursue research on the neural circuitry underlying behaviors relevant to mental illnesses thus providing greater insight regarding the common circuitry that could be involved in comorbidly-expressed disease states. This knowledge will hopefully facilitate the development of treatments that are more efficacious and have fewer side-effects."

KAY M. TYE, PH.D. is an Assistant Professor at the Picower Institute for Learning and Memory and the Department of Brain and Cognitive Sciences at MIT.

For her grant project, "Identifying Unique Neural Circuits for Anxiety Control," Dr. Tye used optogenetics technology to manipulate neurons in specific pathways implicated in anxiety disorders. She then observed the effect on neural activity as well as corresponding behaviors. Dr. Tye ultimately seeks to crack the neural code of anxiety and gain new insight towards effectively treating these disorders.

Dr. Tye's research focuses on understanding the neural circuits important for processing positive and negative emotional valence and how this gives rise to motivated behaviors. Her lab uses a number of neuroscience approaches including optogenetic, pharmacological, electrophysiological and imaging techniques to look at limbic circuits that underlie a range of disease-relevant behaviors including social interaction, feeding, and associative learning.

In the research supported by this Young Investigator award, Dr. Tye used genetically-encodable, light-sensitive proteins that allowed her to manipulate specific neurons or pathways with millisecond precision while leaving adjacent brain tissue unaffected. Dr. Tye made major breakthroughs using optogenetic tools to show that different projections arising from the basolateral amygdala and terminating in different downstream targets—such as the central amygdala, ventral hippocampus, and prefrontal cortex—have different roles in modulating anxiety-related behaviors.

Dr. Tye graduated from the Massachusetts Institute of Technology in 2003 where she majored in Brain and Cognitive Sciences. She received her doctoral training at the University of California at San Francisco Ernest Gallo Clinic and Research Center where she examined the role of dopamine in modulating learning and learning-induced synaptic plasticity in the amygdala. Dr. Tye also worked as a Post-Doctoral Fellow in the Karl Deisseroth Laboratory at Stanford University from September 2009 to December 2011 where she used novel optogenetic techniques to dissect the neural circuitry underlying psychiatric disease.

2015 Freedman Prize Honorable Mentions

KATHLEEN K.A. CHO, PH.D.
Postdoctoral Fellow, Department of Psychiatry
University of California, San Francisco

2013 NARSAD Young Investigator Grant

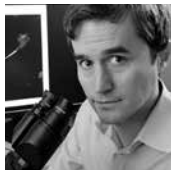
"The Brain and Behavior Research Foundation has upheld the tradition of investing in researchers to advance scientific research in mental illness. Their support has played a critical role in funding my first research project, and as a NARSAD Young Investigator, I was able to investigate the relationships between inhibitory neurons, neural oscillations, and cognitive symptoms of schizophrenia. Through the support of the Foundation, I was also able to obtain additional funding from the National Institute of Mental Health to continue my research into understanding the detailed pathophysiology of schizophrenia and designing novel therapeutic treatments."

KATHLEEN K.A. CHO, PH.D. is a Postdoctoral Fellow in the Department of Psychiatry at the University of California, San Francisco.

For her grant project titled, "Investigation of Interneuron and Circuit Dysfunction in a Mouse Model of Schizophrenia," Dr. Cho studied parvalbumin interneurons, an inhibitory type of nerve cell in the prefrontal cortex of the brain. She sought to determine how the properties of excitatory and inhibitory neurons or their interactions might be altered in ways that produce neural imbalance and give rise to abnormal brain-wave oscillations and cognitive defects such as that observed in individuals with schizophrenia.

Dysfunction of the prefrontal cortex (PFC) contributes to cognitive deficits that represent the primary cause of disability associated with schizophrenia. However, currently available antipsychotic medications are only minimally effective for cognitive symptoms, demonstrating the need for better therapeutic targets. Treatments for cognitive deficits in schizophrenia remain underdeveloped in large part because the relevant physiological mechanisms remain unclear.

Dr. Cho hopes to continue to identify critical physiological mechanisms involving fast-spiking interneurons (FSINs) and the gamma-frequency oscillations they generate which may represent promising targets for preclinical drug discovery, and ultimately to develop assays, using mouse models, for testing novel therapeutic interventions.



CONOR LISTON, M.D., PH.D.
Assistant Professor of Neuroscience and Psychiatry
Feil Family Brain and Mind Research Institute
Sackler Institute for Developmental Psychobiology and Department of Psychiatry
Weill Cornell Medical College

2013 NARSAD Young Investigator Grant

"The NARSAD Young Investigator Grant is one of just a few funding mechanisms that is specifically committed to supporting young scientists who are transitioning to independence. This award came at a critical time for me and my research program, enabling me to pursue a promising line of research that was not yet supported by extensive preliminary data, at a time when few other funding opportunities were available."

CONOR LISTON, M.D., PH.D. is an Assistant Professor of Neuroscience and Psychiatry in the Feil Family Brain and Mind Research Institute, the Sackler Institute for Developmental Psychobiology and the Department of Psychiatry at Weill Cornell Medical College.

For his grant project, Dr. Liston studied "Stress Effects on Connectivity in Developing Frontostriatal Circuits," and investigated how chronic stress during adolescence affects the development of neural circuits, assessing whether it has a lasting impact on circuit function in adulthood. Using imaging and optogenetic tools for interrogating neural circuits, his research focused on stress-sensitive brain regions of the medial prefrontal cortex and striatum, known to be central to the regulation of attention and other cognitive processes.

The long-term goals of Dr. Liston's research are to define mechanisms by which specific cellular components of prefrontal cortical (PFC) circuits support cognition and motivated behavior; to understand how they are disrupted in neuropsychiatric disease states; and to advance the development of new strategies for diagnosing and treating depression, anxiety, and other psychiatric disorders.

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Keynote Presentation:
A Search for Balance:
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FREQUENTLY ASKED QUESTIONS

Child and Adolescent Psychiatric Illness

Photo: Linda Ristevski

Q Which psychiatric illnesses are most common among children and adolescents?

A According to the National Institute of Mental Health, about 13 percent of children ages eight to 15 had a diagnosable mental illness in the past year. The most common of these disorders is attention deficit hyperactivity disorder or ADHD (affecting 8.5 percent of these children); followed by mood disorders broadly (3.7 percent); and major depressive disorder (2.7 percent). Anxiety disorders (0.7 percent) and eating disorders (0.1 percent) are among the least common illnesses in this group.[1]

Q When are these illnesses mostly likely to be diagnosed?

A Most mental illnesses are diagnosed in young adulthood. According to data collected between 2005 and 2011, the number of children diagnosed with a mental illness increases among children ages three to 17, with the exception of rates of autism spectrum disorders, which were highest among children ages six to 11.[2] A 2005 study of children in the U.S. found that half of all lifetime cases of mental illness begin by age 14.[3] Many mental illnesses, including schizophrenia, appear in the late teens and early 20s.

Q What are some of the warning signs that a child may have a psychiatric illness?

A Warning signs include mood changes such as sadness or withdrawal that last at least two weeks, or that seem severe; overwhelming feelings of fear or worry that can interfere with daily activities; difficulty concentrating; and behavioral changes such as frequent fighting or expressing a desire to hurt others. Sudden unexplained weight loss or loss of appetite may be a sign to watch for an eating disorder. Self-injury or self-harm, such as cutting or burning oneself, can indicate a mental illness. Children are also more likely than adults to report having physical symptoms of "headaches" and "stomachaches" that correspond to what an adult might call sadness or anxiety.[4]

Q How likely is it that a parent with a psychiatric illness will have a child with the same illness?

A There is a higher risk of any mental illness in children who have a parent with any mental illness, but the complicated mix of genetic and environmental factors that contribute to most mental disorders make it difficult to predict whether children will have the same illness as their parents. Scientists believe that the risk of childhood mental illness is higher when a parent has schizophrenia, bipolar disorder, an anxiety disorder, or depression. This higher risk may stem in part from genetic factors that the parent passes on to a child, and it may also come in part from any fear and stress in the family environment that is a result of the parent's mental illness.[5] Researchers such as Scientific Council Member Myrna Weissman, Ph.D., at the Columbia University College of Physicians and Surgeons, are working on genetic and imaging screening methods to look for markers of these illnesses that could help predict a patient's likelihood of passing on an illness such as major depression to his or her children.[6]

Q Is it all right for children to take the same medicines for psychiatric illnesses that are prescribed for adults?

A A major review of studies looking at antidepressant medicines for children and adolescents, published in 2007, and looking at patients from 1988 to 2006, found that the benefits of these medicines likely outweigh the risks for children with major depression or an anxiety disorder.[7] The review found, however, that four percent of the children treated had an increased risk of suicidal thoughts or behavior after taking common antidepressant medications called selective serotonin reuptake inhibitors (SSRIs). Experts say parents and physicians should monitor children taking SSRIs to watch for signs of suicidal thoughts and behavior—along with any other negative side effects such as agitation and mood instability—that develop or worsen after the child begins taking the drug.

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7. J.A. Bridge et al., "Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-analysis of Randomized Controlled Trials," *Journal of the American Medical Association*, Volume 297, Pages 1683–1696, 2007.

How Exercise Can Help to Alleviate Depression and Bipolar Disorder Symptoms

Two new studies offer more evidence that exercise can help to alleviate certain mental health problems. In one study, published in February in *Translational Psychiatry,* researchers show that exercise when performed along with meditation can relieve symptoms of difficult-to-treat depression by helping people reduce rumination, the mental habit of brooding over one's problems. Over an eight-week period, 22 men and women with depression and 30 people without depression were trained to meditate and then exercise at moderate intensity on a cycle or treadmill. By the end of the study, people with depression reported significantly fewer depressive symptoms and ruminative thoughts. The healthy participants also reported fewer depression-like symptoms. The researchers believe the meditation component of the training may have helped people gain better control over their thoughts and avoid fixating on problems or unwanted memories.

A second study published in May in *Translational Psychiatry* sought to identify brain mechanisms underlying positive effects of exercise in young adults with bipolar disorder—particularly the effects on the brain's executive functions, the ability to pay attention and make decisions, which are impacted in bipolar disorder. The researchers measured brain activity (via fMRI scans) of 50 adolescents completing an attention task, once before and once after 20 minutes of cycling on a stationary bike. Thirty of the participants had bipolar disorder and the first fMRI showed their brain activity patterns during the task differed from the 20 participants who didn't have bipolar disorder. However, after exercising, the brain activity patterns of the two groups appeared more similar. Exercise appeared to restore normal cognitive control in people with bipolar disorder by changing the activity pattern in the brain's reward processing areas, namely the striatum and part of the anterior cingulate cortex.

The study of depression and exercise was led by Tracey Shors, Ph.D., of Rutgers University, a 1999 Independent Investigator grantee and 2014 Distinguished Investigator grantee. The study of bipolar disorder and exercise was led by 2007 Young Investigator grantee and 2014 Independent Investigator grantee Benjamin I. Goldstein, M.D., Ph.D., of the Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada.

FULL TEXT:
http://www.nature.com/tp/journal/v6/n5/full/tp201685a.html
http://www.nature.com/tp/journal/v6/n2/full/tp2015225a.html

Photo: Brandi Redd

Psychotherapy Benefits Moms with Major Depression and Their Children

When mothers suffer major depression, their children have a significantly increased risk of developing childhood psychiatric illnesses. Previous studies have shown that treating mothers with depression with medications improves both mother and child. A new study shows that psychotherapy may be just as effective: researchers treated 168 women who had major depressive disorder with nine sessions of psychotherapy over three months. The treatment not only improved symptoms in the women, it also helped their children (aged seven–18) who had been diagnosed with mood or anxiety disorders, researchers reported in June in the *Journal of the American Academy of Child & Adolescent Psychiatry*. Women in the study were divided in two groups: One group received a general form of psychotherapy while the other group was given therapy specifically focused on the mother's relationship with her child. Both groups showed quick improvement of depressive symptoms, while the children also improved in a few months following their mothers' recovery. The children whose mothers had relationship-focused therapy had a particularly good outcome—they had fewer mental health visits and were less likely to be prescribed antidepressants compared with children whose mothers received general therapy. It is possible that the relationship-focused therapy better equips mothers to help their children improve, the researchers said.

The study was led by 2006 Young Investigator Holly A. Swartz, M.D., and 1998 Distinguished Investigator Ellen Frank, Ph.D., both at the University of Pittsburgh. The team also included 2001 Distinguished Investigator and 2006 Ruane Prizewinner David A. Brent, M.D., at the University of Pittsburgh, and 2002 Independent Investigator John C. Markowitz, M.D., Pharm.D., at Columbia University Medical Center.

FULL TEXT:
http://www.jaacap.com/article/S0890-8567%2816%2930102-2/abstract

Discovery to Recovery: Therapy Update

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

Statins Combined With SSRIs May Be More Effective Than SSRIs Alone

Adding cholesterol-lowering statins to SSRI antidepressants may lead to better results for people with depression than SSRI treatment alone, suggests a study published in May in the *American Journal of Psychiatry*. Statins are primarily used as lipid-lowering medications but they also have anti-inflammatory effects. This may be useful in treating depression because, as previous research has found, some people with depression show biomarkers in their blood signaling high level of inflammation.

The researchers in Denmark and the United States used a Danish national health care database from 1997 to 2012, which included 872,216 SSRI users, of whom 113,108 (13 percent) also used a statin. Compared with people who took only SSRIs, people who used a statin-SSRI combination were less likely to contact a psychiatric hospital due to depression, or for any other reason. The researchers did not find any adverse effects or an increased risk of suicidal behaviors with the combination of SSRIs and statins compared with SSRIs only. The analysis also found no increase in adverse events with the combination treatment. The new findings provide evidence that reducing inflammation may help treat depression.

The team of researchers included Andrew A. Nierenberg, M.D., of Massachusetts General Hospital and a Independent Investigator grantee in 2000 and 2003, Distinguished Investigator grantee in 2013, and an awardee of the 2013 Colvin Trust Bipolar Mood Disorders Prize.

FULL TEXT:
http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2016.15040463

In Bipolar Disorder, Lithium May Be Most Effective in Reducing Self-Harm

A common symptom in bipolar disorder is the inclination to inflict self-harm, which is in turn associated with an increased risk of suicide. A number of medications are commonly prescribed to stabilize a patient's mood but less is known about their effects on lowering self-harm risk, particularly because clinical trials often exclude those with a history of suicidal behavior. According to a large study published in May in *JAMA Psychiatry*, lithium may be more effective in lowering the risk of self-harm and accidental injury in people with bipolar disorder, compared with other common medications. The researchers, led by Dr. Joseph Hayes, MSc, MBChB of University College London, compared rates of self-harm and suicide in more than 14,000 patients with bipolar disorder between 1995 and 2013. They also looked at rates of unintentional injury (such as falls or car crashes), which is an overlooked but common risk in bipolar disorder.

The people in the study were prescribed lithium, valproate sodium, olanzapine, or quetiapine fumarate to stabilize their mood. Rates of self-harm and unintentional injury were roughly two to three times lower in patients prescribed lithium compared with those prescribed the other medications. The suicide rate was also lower in the lithium group than for other treatments, but the overall number of suicides was too low to draw definitive conclusions. Altogether, the finding adds to previous research finding that lithium use may reduce suicidal behavior, and is consistent with the hypothesis that lithium reduces impulsive aggression in addition to stabilizing mood, the researchers said.

FULL TEXT:
http://archpsyc.jamanetwork.com/article.aspx?articleid=2521461

FEATURE

Chrissy's Wish Fulfills a Promise to a Beloved Daughter

IN THE WEEK FOLLOWING his daughter's suicide, Mario Rossi discovered more than 150 medical books and journals scattered in the basement of her Queens, New York home. Twenty-six year-old Chrissy had been searching for answers in these books, scribbling notes, leaving Post-its® and highlighting passages. But the answers she was looking for could not be found even in the most cutting-edge medical research.

Her mother, Linda, sat on the living room floor, the books in a circle around her. She realized that Chrissy had left them a quest. She made a promise to her daughter that her death would not be in vain. Linda would do something to find the answers her daughter was searching for.

Chrissy was first diagnosed with clinical depression when she was 14 years old, an active and athletic freshman in high school. Since the age of six, Chrissy had been a gifted gymnast, competing in high school-level events, even while in elementary school.

When she developed Bell's Palsy at age 13, her doctors recommended that she take a break from gymnastics. Life for a teenager is difficult enough, with all the normal developmental and emotional undercurrents. In this case, Chrissy was thrown into turmoil after having to leave the one activity and peer group around which her life revolved. She became withdrawn and isolated.

One day Linda got a call from the school counselor. Chrissy had told him she wanted to die, but wouldn't do it because she didn't want her mother to find her.

For the next decade Chrissy drifted from doctor to doctor, therapist to therapist. She was hospitalized multiple times, once after a suicide attempt. Doctors placed her on various medications for her depression, and she often found herself in a whirlwind of severe side effects. Sometimes the drugs would work for a while, and then stop.

Chrissy struggled to lead a normal life. She sought independence, but was trapped by her symptoms and the unwanted side effects of the various drugs she was prescribed.

At 21, she went into a deep depression and drank a bottle of cough medication. It was a cry for help: She called Linda as soon as she did it. After being hospitalized for a few weeks, she was put on high doses of a combination drug therapy. As a result, her eyes were unable to focus, and her hands shook so much she couldn't write. Her tremors were so bad and her eyes so blurry that she failed her final exam after training to become an ultrasound technician. Though disappointed and frustrated, Chrissy fought hard to stabilize her life. For about a year, she worked at a real estate office.

In April 2006, Linda began to realize that Chrissy was slipping back into depression. She encouraged her to go back to a therapist but Chrissy resisted saying, "this time is different." She broke up with her boyfriend, whom she had been planning to marry, saying "he deserved to have a normal life and needed to find someone he could be happy with."

While away on a trip, Linda got a call from Chrissy: "I don't know what to do, I'm just so depressed, I am waiting for you, mom!"

Linda recognized these signs that her daughter was tumbling downward and took Chrissy to see a new psychiatrist who put her on a new medication. From that day forward Linda slept over at Chrissy's each night, while her husband would stay with her during the day.

On July 21, 2006, Chrissy went over to her parents' home and stayed for an hour. She told them her friend Dave was going to stay over that night and reassured them that she was fine. She kissed them goodbye, and told them she loved them. At 10:30 that night, Linda called to check in. Chrissy told her that Dave was coming later. "Momma, you have to let it go." Those were her last words to Linda.

The next morning, unable to get in touch with Chrissy, Linda drove over to her apartment. She found Chrissy on the couch, peaceful. She was alive, but brain dead. She had been saving up her medications, and had taken them all together along with a bottle of Tylenol. The hospital kept Chrissy on life support for three days until her parents decided to let her go.

"We knew Chrissy would never want to live this way, and that she wanted to be free of her lifelong pain, so we set her free," said Linda.

Like Chrissy, 90 percent of those who die by suicide experience mental illness. Linda and Mario set up "Chrissy's Wish Memorial Fund" as a way to fulfill the promise they made to their daughter. It is their hope that they will be able to help tear down the stigma of mental illness and bring awareness to mental health issues, as well as research on our understanding of the brain.

It has been 10 years since Chrissy has passed away. Through the Rossi's annual "Chrissy's Wish" fundraiser, usually attended by 300 people, Linda and Mario have raised more than half a million dollars for brain and behavior research over the past nine years.

Poignantly, Linda Rossi captures the spark of dedication that has made the Foundation so strong over its nearly three decades of existence. She notes that most people who come to the fundraiser held in memory of her daughter share that they, too, have a loved one who has struggled or is struggling with their mental health.

"This is our cause, and one we share with literally millions of others," say Linda and Mario.

The funds raised by Chrissy's Wish have been donated entirely to the Brain & Behavior Research Foundation and its mission of funding mental health research. ■

From Left to Right: Joe Rossi, Diana Rossi, Linda Rossi, Angela Rossi and Mario Rossi

Glossary

Diffusion Tensor Imaging: A magnetic resonance imaging-based technique that allows researchers to visualize the brain's axons and other "white matter" that coordinates communication between different areas in the brain.

Glutamate/Glutamatergic System: The system that regulates glutamate, the most abundant excitatory neurotransmitter in the nervous system of people and other vertebrates.

Hypomania: A mood state in which a person with bipolar disorder may feel elated, irritable or hyperactive, but to a lesser degree than mania.

Optogenetics: A new technology developed with the early support of a NARSAD Grant by Dr. Karl Deisseroth and colleagues that enables research scientists to use colored laser light to switch "on" and "off" individual neurons in the brain. This technology makes possible a new generation of experiments aimed at identifying specific circuits involved in brain and behavior disorders.

Phenotype: The unique way in which an individual's genetic sequence is "expressed," for instance, in the form of traits such as eye color or height or presence or absence of heritable illnesses.

Selective Serotonin Reuptake Inhibitors (SSRIs): Currently the most popularly prescribed class of antidepressant medications. SSRIs keep the neurotransmitter serotonin in the synaptic gaps between nerve cells in the brain by preventing their rapid reabsorption into the neurons that release them, thus promoting signaling between cells.

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Bequests and other planned gifts have a profound and lasting impact on the field of research by funding Young, Independent and Distinguished Investigators around the world.

100% of donor contributions for research are invested in our grants leading to advances and breakthroughs in brain and behavior research. This is made possible by the generous support of two family foundations which cover all of the Foundation's operating expenses.

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100% of donor contributions for research are invested in our grants leading to advances and breakthroughs in brain and behavior research. This is made possible by the generous support of two family foundations which cover all of the Foundation's operating expenses.

OUR MISSION:

The Brain & Behavior Research Foundation is committed to alleviating the suffering caused by mental illness by awarding grants that will lead to advances and breakthroughs in scientific research.

HOW WE DO IT:

The Foundation funds the most innovative ideas in neuroscience and psychiatry to better understand the causes and develop new ways to treat brain and behavior disorders. These disorders include depression, bipolar disorder, schizophrenia, autism, attention-deficit hyperactivity disorder, anxiety, borderline personality disorder, chemical dependency, obsessive-compulsive disorder and post-traumatic stress disorders.

OUR CREDENTIALS:

Since 1987, we have awarded more than $360 million to fund more than 5,000 grants to more than 4,000 scientists around the world.

OUR VISION:

To bring the joy of living to those affected by mental illness—those who are ill and their loved ones.

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