

# NARSAD

The Brain and Behavior Research Fund

## Research *Quarterly*

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## Letter from the President



*Benita Shobe, NARSAD  
President & CEO*

I am privileged to both be introducing myself as NARSAD's President and introducing NARSAD's campaign for the Decade of Brain and Behavior Research. I came to NARSAD with a career of 25 years of building and leading organizations focused on supporting healthcare breakthroughs through research and services. I am privileged to begin my service to NARSAD at a time when it is on the threshold of support for new achievements aimed at great breakthroughs in mental health.

On October 30th, the founding and continuing president of our Scientific Council, Herbert Pardes, M.D., announced at our National Gala Dinner and Prize Award ceremonies that NARSAD would initiate an effort in 2010 to be called the Campaign for the Decade of Brain and Behavior Research. In 1990, the President of the United States announced that the then new decade would be called the Decade of the Brain. The aim of that announcement was to marshal the government's resources to achieve greater understanding and treatment for brain disorders through research. Dr. Pardes noted that this decade was a highly productive period, developing new strategies and understanding led by the National Institute of Mental Health and other government agencies. NARSAD-sponsored research was a new factor in 1990, only in its third year of providing research grants.

Now, 20 years after the inception of the Decade of the Brain, NARSAD has established philanthropic leadership in the broad fields of psychiatric research, having funded 3,776 research grants for over \$256 million, having established the leading prizes for lifetime achievement in the major fields of psychiatric research, and supported key research information media. With this background of philanthropic leadership in research, Dr. Pardes declared that NARSAD would become the cornerstone of the structure of the Decade of Brain and Behavior Research. He announced the NARSAD Board of Directors has set a goal for the new decade of doubling the funds raised in NARSAD's first 23 years, aiming for \$500 million philanthropic support by the year 2020.

The record of achievement by NARSAD leads me to enthusiastic optimism for my service to this organization. Contributors to NARSAD's research effort in 2009 demonstrated their continued support notwithstanding a period of economic and personal financial pressures. We met our goals in providing research grants through sustained fundraising. Dedication and commitment to our goals of better treatments and cures for the severe mental illnesses will move NARSAD ahead rapidly and importantly.

The continuing support of scientists is central to our effort. It is demonstrated by the growth of our remarkable all-volunteer Scientific Council, whose membership last year rose to a new high of 116. Their breadth of expertise on every aspect of brain and behavior research is unparalleled. They give us the opportunity to find and support the present and the next generation of leaders in the research which will bring the most needed breakthroughs.

I am deeply honored to be given the responsibility for NARSAD's operations. With the considerable experience and talent of the organization's staff and the support of its knowledgeable Board of Directors, I look forward to accelerated achievement in the interests of better lives for those afflicted by mental illness.

Sincerely,

A handwritten signature in cursive script that reads "Benita Shobe".

Benita Shobe

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# NARSAD's 22nd Annual Awards Dinner

The Pierre  
New York City



*Senator Pete and  
Mrs. Nancy Domenici*

At its 22nd annual New York awards dinner, held Friday, Oct. 30, at The Pierre, NARSAD recognized eight prominent scientists for lifetime achievement in research for their work in the areas of schizophrenia, bipolar disorder and depression, childhood disorders and cognitive neuroscience. Their work has led to new understanding of these illnesses, and in many instances better pathways to treatment.

Considered among the most coveted awards in psychiatry and neuroscience, the prizes were selected by special committees of NARSAD's 116-member Scientific Council, a volunteer body of leading experts in mental health research, and presented at the 22nd annual New York City Awards Dinner Celebration on Friday, October 30, at the Pierre Hotel, in Manhattan.

The dinner's special guest was Pete Domenici, U.S. Senator from New Mexico, who delivered the introduction. A major leader in issues relating to mental illness, Senator Domenici was the guiding force behind the Mental Health Parity Act of 1996, and the resulting law that now requires insurance companies to provide parity between mental health and medical and surgical benefits. He is also responsible for authoring legislation that created the Projects for Assistance in Transition from Homelessness (PATH) Program, which provides support services to individuals with a severe mental illness, who are homeless or at risk of homelessness. Senator Domenici received NARSAD's Humanitarian Award in 1995, and the first NARSAD Paul Wellstone Leadership Award, in 2005, for his efforts on behalf of people suffering from mental illness.

**The Lieber Prize for Outstanding Achievement in Schizophrenia Research** was awarded to two co-recipients, the husband-and-wife team of **Raquel Gur, M.D., Ph.D.**, and **Ruben Gur, Ph.D.**, who together lead neuropsychiatric studies at the University of Pennsylvania, and the Philadelphia Veterans Administration Medical Center. The Gurs apply a range of expertise that includes genetics, brain imaging and studies of gender differences to their explorations of brain function and mental illness, particularly schizophrenia.

**The Falcone Prize for Outstanding Achievement in Mood Disorder Research** was also awarded to two co-recipients, representing both the East and West coasts: **Eric J. Nestler, M.D., Ph.D.**, of Mount Sinai School of Medicine, a world renowned neuroscientist, molecular biologist and psychiatrist whose studies of the ways in which the brain responds and adapts to experiences such as depression, stress and addiction has transformed understanding of the areas in the brain involved in reward and motivation; and **Lewis L. Judd, M.D., D.Sc. (Hon.)**, of the University of California, San Diego, who heads a broad program of clinical and basic research. Dr. Judd operates centers in mood disorders, late-onset psychoses, neurobehavioral aspects of HIV infection and child and adolescent services, among other programs.



*The Prizewinners l-r: Drs. Raquel Gur, Daniel Wolf, Eric Nestler, Lewis Judd, Brenda Milner, Ruben Gur, E. Jane Costello, Adrian Angold and Herbert Pardes, President of NARSAD's Scientific Council.*

**The Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research** was presented to one other husband-and-wife team of researchers, **Adrian Angold, M.D.**, and **E. Jane Costello, Ph.D.**, who co-direct the Center for Developmental Epidemiology at the Duke University Medical Center. At this center, researchers from different disciplines are working to advance understanding of the origins, course and prevention of mental illness across the life span. Drs. Angold and Costello conducted the Great Smoky Mountains Study — a long-term assessment of psychiatric care, substance abuse disorders and access to mental health care in young Americans living in the southeastern United States.

**The Goldman-Rakic Prize for Outstanding Achievement in Cognitive Neuroscience** was presented to **Dr. Brenda Milner, C.C., Ph.D.**, of McGill University, who has been breaking new ground in the study of cognitive functioning for more than 60 years, studying the brain mechanisms involved with thinking, reasoning, learning and remembering. Still active at the age of 91, Dr. Milner leads the Montreal Neurological Institute's Cognitive Neuroscience Unit in explorations of the anatomical basis of cognition. NARSAD Scientific Council member and Nobel Laureate Eric Kandel described her work as having created the field of cognitive neuroscience by merging neurology and psychology.

**The Sidney R. Baer, Jr. Prize** is traditionally selected by the year's Lieber Prize recipients — who select an early-career scientist who is conducting promising research on the genetic and neural causes of schizophrenia. The 2009 recipient of the prize was **Daniel H. Wolf, M.D., Ph.D.**, of the University of Pennsylvania, whose interest focuses on the functional changes within the brain that effect the so-called negative symptoms — the social and emotional deficits — as well as the cognitive deficits experienced by people with schizophrenia.

The awards dinner culminated a day that began with the 21st Annual New York Mental Health Research Symposium, held at The Times Center, which presented talks by the 2009 NARSAD prizewinners in the morning and six outstanding NARSAD Young Investigators in the afternoon. NARSAD Scientific Council member **Robert M. A. Hirschfeld, M.D.**, organized and moderated the symposium as he has done every year since its inception. Dr. Hirschfeld is the Titus H. Harris Chair and **Harry K. Davis, M.D.** Professor in the department of psychiatry and behavioral sciences at the University of Texas Medical Branch at Galveston. He was previously head of the National Institute of Mental Health's Mood and Anxiety Disorders Research Branch and is internationally recognized for his research on depression, bipolar disorder and anxiety disorders. A full report on the symposium begins on page 6.

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## Introducing NARSAD's Productive Lives Award

A critical and widely ignored challenge for our society is the need for constructive employment of the millions who suffer from mental disabilities. Whether it is depression, bipolar disorder, schizophrenia, autism or anxiety disorders such as post-traumatic stress or obsessive-compulsive disorders, millions are denied occupational opportunity. Researchers estimate that at least 6 percent of the work-eligible U.S. population cannot find normal employment because of these conditions and that 85 percent of people with serious mental illnesses are unemployed.

People with these brain disorders are denied all the benefits of productive lives: income, personal fulfillment, companionship, social integration and intellectual stimulation. This tragedy has not been overcome despite the great improvements in psychiatric care and the development of ever more effective medications. A fundamental downfall of our society is that we have not adequately addressed this challenge. It has been easier to allow a mentally disabled person to wander the streets, confused and too often incarcerated, ghettoized at great cost in institutions or — at best — isolated with family caregivers and aides rather than to provide supportive employment programs.

After years of effective work on the causes and treatment of mental illness, researchers are turning increasingly to finding ways to improve rehabilitation and productivity for people with these disorders. We still have only a limited understanding of the cognitive problems that affect people with mental illness, and of the best approaches to help them overcome those problems. But there has been significant progress. NARSAD alone has funded over 200 different scientists in the areas of cognitive, behavioral and employment rehabilitation.

As research scientists develop new insight and treatments, employers are beginning to take note. Some enterprises have created environments and systems where people with mental disabilities can achieve high degrees of productivity, often exceeding that of people without these illnesses. Their success belies the prejudice and stigma against the mentally disabled. In these workplaces, they have shown outstanding levels of consistent performance, cooperative effort and institutional loyalty. These examples provide the model for a new era of enhanced productive lives in employment.

In the U.S., the economic and social ramifications for constructive employment and rehabilitation are staggering. Current research suggests that attaining reasonable levels of employment for Americans with mental disabilities can generate billions of dollars in potential income for them annually. Additional billions can be saved if caretakers and support institutions are no longer needed, or the need for services is at least reduced. A recent Dartmouth Medical School study showed that “Highly significant reductions

in [mental health] service use were associated with steady employment” of people with psychiatric disorders.

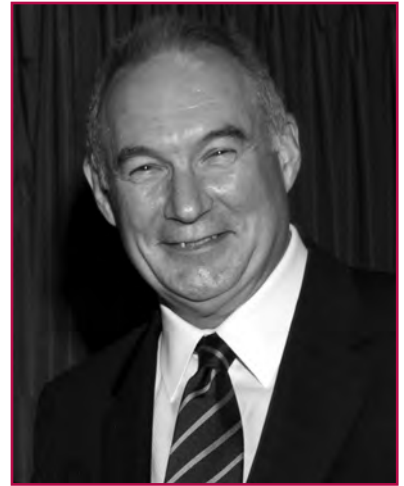
### Honoring J. Randolph Lewis and Walgreens

To honor those who are creating new workplace opportunities for people with brain and behavioral disorders, NARSAD has inaugurated a Productive Lives Award. We were very pleased to present the first to J. Randolph Lewis, Senior Vice President of Supply Chain and Logistics for Walgreens, who has made that company a world leader in providing new opportunities for people with these illnesses.

Walgreens is a winner when it comes to Productive Lives. This major U.S. retailer of pharmacy, healthcare and wellbeing supplies has taken great steps to succeed in creating an inclusive environment that embraces workers of varying abilities to lead productive lives. They have developed distribution center facilities where more than 30 percent of the workforce is made up of people with disabilities. These include not only mental disorders, but a range of physical, cognitive, and developmental problems, from autism and mental retardation to hearing and physical impairments.

Walgreens employees with disabilities have been trained to work side-by-side with other team members: They have the same productivity goals and earn the same pay. The impact is transformative. “For many, this is their first fulltime job,” says Randy Lewis. “For a parent to finally see their son or daughter experience what it’s like to hold a job, be responsible and actually look forward, can fulfill a lifelong dream.”

NARSAD is proud to honor Walgreens with its first Productive Lives Award.



*J. Randolph Lewis,  
Senior Vice President,  
Supply Chain & Logistics, Walgreens*

## THREE STEPS *to* BRAIN HEALTH

### *Step 1:* **SCIENCE**

*Clarifying malfunctions of the brain*

### *Step 2:* **MEDICATIONS**

*Development and application of pharmacology*

### *Step 3:* **TRAINING**

*Cognitive and behavioral therapy help the brain adapt from disability toward normalcy*

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# NARSAD's 21st Annual Mental Health Research Symposium

The Times Center  
New York City



*Robert M. A. Hirschfeld, M.D.,  
Titus H. Harris Chair and  
Harry K. Davis, M.D. Professor,  
Department of Psychiatry  
and Behavioral Sciences,  
University of Texas Medical  
Branch at Galveston.*

On Friday, October 30th, NARSAD welcomed hundreds of attendees to its 21st annual National Mental Health Research Symposium. The day's program typifies what NARSAD is all about — supporting the work of scientists who are at the forefront of the search to better the lives of people living with mental illness.

This year, the morning session was devoted to presentations by the recipients of NARSAD's 2009 awards for outstanding achievements in research on schizophrenia, mood disorders, child and adolescent psychiatry and cognitive neuroscience. Their prizes, which are highlighted in this issue, are among the most prestigious honors in the field. One of the honorees, Dr. Brenda Milner of McGill University, still at work in the lab at the age of 91, is a legendary pioneer whose work has spanned the entire arc of modern neuropsychiatric research.

The afternoon session was devoted to presentations by NARSAD-funded Young Investigators, grantees chosen from among hundreds of applicants each year who show promise of becoming the scientific leaders of the future. The six singled out to speak at the symposium have initiated novel and innovative projects aimed at understanding, treating and preventing a range of mental-health disorders. They are all recipients of a 2008 NARSAD Young Investigator Award.

Once again, NARSAD Scientific Council member Robert M. A. Hirschfeld, M.D., organized and moderated the symposium as he has done every year since its inception.

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## Session 1: RESEARCH BREAKTHROUGHS by NARSAD's 2009 Outstanding Achievement Awardees

### Neurobiology of Schizophrenia: Then and Now

#### **Raquel E. Gur, M.D., Ph.D.**

*Rickels Professor and Vice Chair for Research Development,  
Departments of Psychiatry, Neurology and Radiology  
Director, Neuropsychiatry Section  
University of Pennsylvania Medical Center  
2009 NARSAD Lieber Prize Awardee*

Where does one start with a disorder so challenging, and so clinically heterogeneous? I've seen thousands of people with schizophrenia over the years and each one is different. How do you generalize when each is unique? You try to come up with features that are common. Schizophrenia affects multiple domains — memory, attention, mental flexibility, language, emotion processing. How do you focus when so many areas are affected? And of course, finally, schizophrenia presents a treatment challenge. We have treatments for the positive symptoms, the delusions and hallucinations, but what about the cognitive deficits, the negative symptoms that affect motivation, volition, the ability to form relationships, to enjoy life? We have no good treatment for those devastating aspects of the illness.

#### **A Lifelong Journey**

There seems so much to do and so relatively little we know. How do you get going? You get going by deciding what the most important questions are and how one result can lead to another. It's a lifelong journey, just as the illness is. All of this is done to advance treatment. For if at the end of the day, with all of our efforts, if we do not make more effective treatments, we have failed in our mission.

In the study of schizophrenia, as with any serious mental disorder, several perspectives require integration. We can start from the behavior that we see in the clinic and try to understand the underlying brain processes, the aberrations and abnormalities in these processes that can lead to deviation in behavior. We try to have these interactions lead to basic biological studies in animals. Genetic strategies are paramount for examining hypotheses about the genetic contribution to schizophrenia. Neuroimaging is a linking ring between brain behavior, biology as it can be done in animals and humans and genetics.



*Raquel E. Gur, M.D., Ph.D.,  
co-recipient of NARSAD's 2009  
Lieber Prize.*

On receiving the award, Dr. Gur remarked: It's an honor and pleasure to be here. I fell in love with [the study of] schizophrenia at about the same time that I fell in love with Ruben as an undergraduate at the Hebrew University of Jerusalem. Through an abnormal psychology course, we were asked and encouraged to follow one individual with schizophrenia. And this event led to an interaction with a family of a young man that convinced me ... this was in the 70s ... that [schizophrenia] is a brain disorder. And led me, with Ruben, to come to the United States, pursue training in medical school, both in neurology and psychiatry, and witness the growth of technology and the information available, reaching to the point where we can integrate basic and clinical science, and convince colleagues from different disciplines that the disorder that we care about is worthy of the best talent in the field.

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Schizophrenia is a disorder of complex behavior. What calls individuals who suffer from the disorder to our attention are disruptions in normative behavior. So we go from the clinical phenotype — what we see in the clinic — to animal models. While mice do not develop schizophrenia, they can be made to depict important features of the disorder, as, for example, memory deficit.

## Genetic Vulnerability

What we try to do is evoke the phenotype, the behavior, and look at endophenotypes, intermediate quantitative measures that can be related to brain behavior and to genetics and can be reliably measured in humans. We look at brain structures and neurons, at proteins, RNA and DNA. Or we can begin by asking what is relevant in gene expression that can explain a cognitive or emotional deficit prevalent in people with schizophrenia. For example, we know that neuregulin, dysbindin and other genes have been implicated, and we now have the possibility of doing genome-wide association studies that focus on specific genes.

One of the promising areas that has emerged from pharmacological studies has to do with the deficit in people with schizophrenia of the neurotransmitter glutamate, a hyperfunctioning that results in less glutamate release and disruption of the excitatory and inhibitory process so important in brain regulation. This disruption leads to the cognitive and emotion deficits that we see in the phenotype of patients, the schizophrenia syndrome. This process occurs before birth; people are born with this genetic vulnerability. However, as we have learned from twin studies and other research, not everybody born with this predisposition is going to manifest schizophrenia, but some who experience prenatal stress that might be related to poor nutrition or infection in the mother or decreased oxygen during delivery, when added to their genetic vulnerability, are more likely to have this circuitry affected resulting schizophrenia.

## The Uses of Brain Imaging

Our effort is directed toward looking at the underlying circuitry that can cause the disruption in behavior. To do that we look at brain structure, which now we can do with MRI, and at brain

physiology with functional MRI (fMRI). We know that individuals with schizophrenia have difficulty focusing attention. They might be easily distracted by internal stimuli like auditory hallucinations, for example, or by external stimuli. For people with schizophrenia it is hard to focus attention.

In one functional MRI study, we train schizophrenia patients to perform a relatively simple test — to look at a target — to activate the brain's attention system. They perform the task and they do activate the system, but less so than healthy controls. The less they activate, the more poorly they perform when asked to pay attention. Then, when a novel stimulus is introduced, the patients are overwhelmed, whereas the healthy subjects ignore it and keep looking at the target they were instructed to look at. With the schizophrenia patients, the novel stimulus causes an activation in the brain that distracts them from the target, which demonstrates abnormalities that mimic what happens in real life when patients can't focus. We want to train them to focus and see if we can normalize brain activity, if they can be trained to focus and ignore things that are irrelevant. This has not been done yet, but the field is open to this type of research.

Another example where imaging is helpful is in the study of emotion. People with schizophrenia have difficulty reading faces. This is a relatively recent finding in the laboratory. We put healthy people and people with schizophrenia in the scanner and instruct them to look at faces that express different emotions. You tell them that when they see a happy face, push a button for happy, a sad face, for sad, for angry and so forth. Healthy people activate the emotional system when they see the faces; in fact, the ability to read emotion is present by the age of one or two. The people with schizophrenia understand the test perfectly well, but they cannot easily identify the emotions on the face. Some people with schizophrenia have difficulty not just in reading emotions, but in expressing it on the face, comparable to what you see in autism. Some of the genetic findings in autism have also been found in schizophrenia, especially in males.

Clinical observations and imaging feed the basic science in the schizophrenia research center, and

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because the dysbindin gene has been found in linkage studies in schizophrenia and is related to glutamate expression it is potentially important genetically. We have a large collection of brains donated by family members of people with schizophrenia who were followed through life. We compare these with postmortem brains from healthy people. Because people with schizophrenia have deficits in memory, we look at the hippocampal system. In the healthy brains we see that there is much less expression of dysbindin in a region of hippocampus called the dentate gyrus, important in memory formation, than we see in the brains of people with schizophrenia.

### **The Need to Zoom In and Zoom Out**

So we zoom in on functions and regions related to behavioral deficit and then go to a more molecular level where we can become very specific and create animal models. Genetic studies of schizophrenia up to now have been done on the phenotype, the clinical description. In the neurobiologic studies in both animals and humans, which we are vigorously pursuing, we look at endophenotypes, or intermediate phenotypes that show a similar pattern in family members, but not to the same severity, and are heritable. What we are looking for are biomarkers.

The initial vulnerability of mental disorders, including schizophrenia, is the combined genetic vulnerability and early environmental insult; but as noted before, susceptibility doesn't inevitably lead to schizophrenia, which doesn't usually manifest itself clinically until adolescence or early adulthood. We need better measures to identify, early in childhood, individuals who might be at risk for schizophrenia. We need to establish those markers reliably in human and animal studies for early identification and intervention. By intervention I don't mean necessarily medication for every person; it can be a booster of cognitive remediation, social interactions similar to what is done in autism, and in many kids quite successfully.

We have a convergence of methods — behavior, imaging, electrophysiology, animal studies, genetics, cellular and molecular biology — a blessing we need to take advantage of. We face many challenges. We need to zoom in and focus within schizophrenia with the multiple levels of analyses that I have tried to illustrate, and we need to zoom out and look at other disorders, such as autism, that might show similar abnormalities with some genetic overlap. What might be good for intervention in autism might be good for schizophrenia, and vice versa.

*Schizophrenia is  
a disorder of  
complex behavior.*

*It affects multiple  
domains — memory,  
attention, mental  
flexibility, language,  
emotion processing.*



Ruben C. Gur, Ph.D., co-recipient of NARSAD's 2009 Lieber Prize.

On receiving the award, Dr. Ruben Gur remarked: As soon as we came to Penn, we realized that we were at the place where neuroimaging was born and was being developed ferociously. So I positioned myself with the people who were developing these technologies as they came. And being raised as a psychologist who was trained to believe that if we can just understand the stimuli and the responses, we don't need to know anything about a black box. And that theory got shattered immediately, as soon as I began seeing actual patients and people who were suffering from severe mental illness.

## How Cognition Became Neurocognition

### Ruben C. Gur, Ph.D.

*Professor, Departments of Psychiatry, Radiology and Neurology  
Director, Brain Behavior Center and Center for Neuroimaging  
in Psychiatry  
University of Pennsylvania Medical Center*

You heard from Raquel how the anatomy drives the physiology and the physiology drives behavior. But how do we measure behavior? Over the years, psychologists working with individuals who suffer from various brain disorders developed a battery of neuropsychological tests, so called because each test has been linked through careful research to a particular brain system.

Attention requires cooperation between frontal and parietal areas of the brain. People who have lesions in either area have deficits with attention. In the tests for attention, developed before the advent of brain imaging, we get a score by comparing patients' performance to the way healthy people perform, and use what is called Z score. You take the average of any particular test, you subtract it from the average of what is normal, you divide it by the standard deviation, and so you know how much off someone is. If the score is minus 1, you are one standard deviation below normal, plus one you are one standard deviation above normal. And by looking at the pattern of abnormalities in this battery, this neuropsychological battery, we can gauge where the lesion would be.

When we first started to study schizophrenia as a brain disorder, we said, "Well, let's see how they compare to people with other types of brain disorder, like strokes, or tumor, or epilepsy." We put together this neuropsychological battery that scans the brain, and studied a large group, first of all, of healthy people, to establish what is the average on abstraction and flexibility, attention, verbal memory, spatial memory, language, spatial processing, sensory and motor skills. Then we asked what happens when you give this battery to people with schizophrenia.

### The Magnitude of Cognitive Deficit in Schizophrenia

Our first study, in 1991, published in the *Archives of General Psychiatry*, created quite a stir because the magnitude of the deficit we documented in people with schizophrenia was comparable and sometimes exceeded what we see in people with stroke and epilepsy, or other verifiable brain disorders. Our critics said that it was probably because they are were symptomatic; in the first study, we took only people who were off medication at first presentation. So we studied them again after treatment when they were in remission. The symptoms were fine, but the cognitive deficits did not budge; they remained as impaired with only some tiny improvement in

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spatial memory and verbal memory. The medication did not touch the underlying brain disorder, did not improve the cognitive deficits.

When imaging appeared, we started scanning the brain, giving tasks that activate different brain regions, and we were able to come up with much more efficient, faster computerized tests. But when looking at all these domains, we realized that one domain very important in psychiatric disorders was totally missing from any standard neuropsychological battery, the domain of emotion. This wasn't our fault; psychology had relegated emotion to the role of a sort of orphan child. We did a great job with cognition, but really did not pay much attention to emotion, even though some of the giants of the field called attention to it. Charles Darwin thought that all psychology is to study emotion, and so did William James, but there weren't any good tools for studying it.

### **Studying Emotion as Darwin Advised**

Charles Darwin said that to study emotion, go to the face. Darwin also pointed out that emotions are expressed very similarly not only within species, but across species. An angry dog, and an angry human literally activate the same muscles on the face. Emotions not only communicate within our species, but also across species. We decided to follow Darwin's advice, but the problem was that we didn't have good stimuli to study emotions. So we turned to a community of actors in the Philadelphia area, enlisting the help of Aaron Posner, the son of the renowned neuroscientist Michael Posner. Aaron founded and is the artistic director of the Arden Theater, in Philadelphia, and he was able to bring us 140 actors ranging in age from teenagers to I think the oldest was 91, who also represented the ethnic diversity of the city.

Our colleagues in the School of Computer Science helped us by adapting a program developed for NASA, where you can take pictures from different angles and create a three-dimensional model, so that our actors could move around. We took their three-dimensional pictures as they expressed happiness, sadness, anger, fear, disgust — emotions that are easily recognized. Again, we went to healthy people and looked at differences, and found, as you undoubtedly know, that women

recognize emotions faster and more accurately than men. When we put men in the scanner and ask them to recognize emotions, they have literally a limbic storm; the entire emotional part of the brain goes into overtime, trying to figure out what the emotion is, whereas women just activate the visual area in the amygdala, and can tell what it is.

Putting together all those computerized tests that we used in the scanning, we came up with a complete battery looking at all the same domains we can now measure in an hour that used to take a day to measure. We test for abstraction and flexibility, attention, face memory, verbal memory, spatial memory, and emotion processing. What is also nice about this format is that the computer can faithfully record every response and how many milliseconds it took to arrive at an answer. As you may know, performance is a bull with two horns; one is accuracy, the other is speed. We can decompose the performance of the patients, and see that they are impaired in both areas, implicating frontal temporal regions.

Now, we can look at children and compare, in healthy subjects, younger children to early adolescents and later adolescents, and we find that there are two areas where adolescents are impaired. One is attention — I guess most people who have adolescents know that — and the other is emotion recognition. If we then compare them to children who are at risk for psychosis, either because they have first-degree relative with psychosis, or they are prodromal (with early-warning symptoms), their impairment is much more severe. They're also impaired in abstraction and flexibility, face memory, and very importantly, emotion processing. So we are beginning to see targets where we can intervene early and start teaching them.

### **The Hope of Early Intervention**

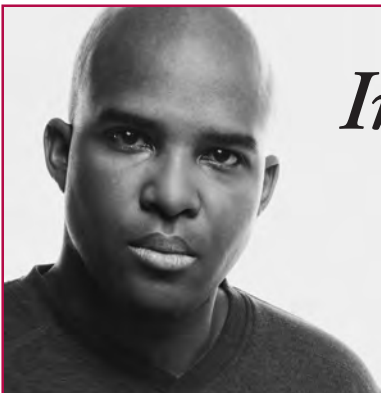
As an analogy, we now know that heart disease is not genetically coded, but there are a lot of endophenotypes that are: cholesterol level, blood pressure, type A personality, all those things. If you have the genes for those and you don't do anything about it, then you'll get heart disease. But you may have all those things and not get heart disease if you exercise and eat healthy food. We now find out there is hypercholesterolemia in

children. So a child who is discovered with high cholesterol will get treated for it immediately. In the same way with disorders such as schizophrenia, we are hoping to find the genetic predisposition and the endophenotypic markers of that predisposition as early as possible so that we know the problem is schizophrenia. If we find memory deficit early, we can teach children tricks to deal with it. Similarly, it turns out that flat affect, having difficulty expressing emotions and perceiving emotions, is a devastating symptom in schizophrenia, actually much more so than hallucinations and delusions.

Now, because this battery of tests we have is computerized and quick, we can employ it in large-scale studies. In a collaboration with colleagues at Pittsburgh, we administered the tests to 1,200 controls, a little under 1,300 schizophrenia patients, 1,500 first-degree relatives of people with schizophrenia and approximately 560 more distant relatives. One of the things we were struck by was that first-degree relatives have the same impairment as patients if not quite as bad, yet they do well. In one case, a patient who has been

hospitalized most of his life with severe psychosis has a brother who is a successful lawyer. The brother shows exactly the same neurocognitive profile, the same memory deficit. We asked the brother, “Do you know you have memory problems?” With a big smile on his face he said, “Of course.” He opened his bag which was full of gadgets he uses to overcome his memory problems.

That is what we hope we can do with patients; identify them early enough so that we can ameliorate the cognitive deficit. It would be like early treatment for hypercholesteremia, which doesn't necessarily mean you're cured, but you can live with it. This is basically the paradigm we are pursuing. Our hope is that in the future, by using this combination of careful behavior assessment with understanding the genome with understanding the brain regions involved in the different processes, we will be able to close in on schizophrenia and start treating it like heart disease, where you have genetic vulnerability and you have environmental stresses, but you can work with the environment to help the resilient part of the individual achieve a fully productive life.



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## The Long-term Course of Manic Depressive Illness: Implications for Treatment

### Lewis L. Judd, M.D.

*Mary Gilman Marston and Distinguished Professor of Psychiatry  
Chair, Department of Psychiatry  
University of California, San Diego*

We learned from the pioneering Framingham study of coronary artery disease the benefits that can accrue from the study of an illness over a long period of time. I'm going to talk about what the study of the long-term course of manic depressive illness tells us about the way individuals with this disorder ought to be managed and treated over their lifetime.

My colleagues and I followed people who entered our study in the late 1970s and early 1980s over a period of 20 years. As we studied them, the first thing we noted was the sheer chronicity of the disease. We had known that manic depressive illness was chronic in the sense that people have repetitive episodes of mania and depression, but just how chronic it was no one at that time was aware. It begins early in life, in the early 20s, half the people will experience their first episode before the age of 20. But what really struck us was the degree of symptomatology. We noted the weeks that people were ill from their symptoms — subsyndromal symptoms, minor and hypomanic symptoms and manic and major depressive symptoms. The bipolar I patients, those with mania and major depression, were depressed a little less than half the time; the bipolar II patients, those with hypomania and major depression, were ill from depression 56 percent of the time. This said to us that, yes, people have episodes, but between the episodes they still are frequently symptomatic.

### Importance of Between-Episode Symptoms

We divided the symptomatic periods into the depressive spectrum and the manic spectrum and found that the patients moved from one category to another frequently; they go back and forth in these categories over time in a highly changeable, very dynamic way. And, even though this disorder is defined by episodes of major depression and mania — and those episodes have been the major focus of research — between episodes people were symptomatic. In fact, we found bipolar I patients were experiencing major depression or mania 12 percent of the week, but they were symptomatic at the sub-threshold level 35 percent of the time. What that says is that these are legitimate treatment targets and you don't have to wait for someone to be ill at the most severe level.

The other thing that we noticed was that despite the fact that this illness is said to be manic depressive illness, about 95 percent of all the research has been on manic episodes and their treatment.



*Lewis L. Judd, M.D., co-recipient of NARSAD's 2009 Falcone Prize.*

I'm truly honored by the Falcone Prize, and I want to thank NARSAD for sponsoring this prize. I'm deeply committed to NARSAD. I have been ever since the beginning. As one of the founding members, along with Herb [Pardes] and Jack [Barchas] and some other people in the room, we have recreated what the National Institutes of Health spent millions of dollars to do, and that is to create a peer-review system. The Scientific Council is one that we have created here with NARSAD essentially without much in the way of money, except devotion of the scientists to the purposes of NARSAD.

At UCSD we were able to give an empirical description of the course of illness in major depression. From our studies, we found that depression was an extremely important part of bipolar illness, and in fact it was more prevalent than manic symptomatology on a three-to-one basis. And that it was important that we attend to this aspect of bipolar disorder, and to treat it and study it with the same degree of rigor and priority that we were studying manic episodes. This is a chronic illness — and the paradigm that one should use should be for the treatment of a chronic illness. And the goal is to keep patients symptom-free throughout their lifetime.

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So what we did was divide the weeks ill into two categories, those with symptoms in the depressive spectrum from subthreshold to full syndromal level of major depression, and weeks in the manic spectrum subthreshold on up to mania, and compare them. And what we found was that the weeks symptomatic with depression occupied 31 percent of the weeks, and the weeks involved with mania were 10 percent. The ratio of depression to mania was three to one in bipolar I, but that is not the way we have been studying it. Since publishing our results a number of years ago, there has been a wide variety of studies confirming them, and indicating that depression makes up most of the course of the illness, and we really ought to be attending to it in at least equal status with mania.

Now, something interesting happened when we looked at bipolar II illness, which has been kind of a throwaway diagnosis seen as the lesser of the two bipolar subtypes. It turns out it is rather a serious illness in its own right. These individuals spend the vast majority of their time with depressive symptoms and episodes, and only a small percent of their time, a little blip, with hypomania, and subsyndromal hypomania: a ratio of 37 to 1. In effect, what we found was that bipolar II is essentially a chronic depressive illness.

Here is the data that we found on the levels of disability: when a patient was fully asymptomatic, they had no symptoms or impairment; when the patient experienced subsyndromal symptoms, there was a small but highly significant increase in impairment; when the patient had minor and hypomanic symptoms, again, a small, less significant increase in impairment was noted; and at the syndromal level, impairment is between mild and moderate, and at moderate, slightly more than moderate. Impairment — how they're getting along with their spouse, how they're doing at work or school, etc. — paralleled the degree of symptomatic severity: as effective symptoms increased in severity, so did the impairment. What was encouraging to us, and to the field, was that when all symptoms were removed, and the patient was asymptomatic, no impairment was noted. That says that we can remove psychosocial impairment and disability by effectively treating the symptoms of bipolar illness.

Before the study, there had been a feeling in the field that manic episodes and symptoms were far worse than the depressive ones. It turns out that they're basically the same. To establish that we looked across the spectrum, and averaged levels of impairments through the entire course of illness, and compared bipolar I and bipolar II.

Next, in an attempt to reduce chronicity, we looked at patients going through an episode. Those whose quality of recovery was a little bit better seemed to have a better course in the future. A group we defined as asymptomatic recoverers had eight consecutive weeks with no symptoms; those with eight consecutive weeks with minimal, mild symptoms we called residual symptom recoverers. Then we looked at the first well interval to the time of the next episode, relapse or recurrence. We found much to our surprise, a rather striking difference between these two components of recovery that are in standard use in the field today. The people who recovered with residual symptoms relapsed to the next episode five times faster than those with asymptomatic recovery.

And so we are proposing that patients should be treated for their episodes until they are as symptom-free as possible. Currently it's standard in pharmaceutical studies to call a medication effective when there's a 50 percent reduction of symptoms. But that still leaves people with a lot of symptoms. We feel that this is absolutely wrong, and should not be utilized. We also found that if you recover with residual symptoms, you will be symptomatic for 58 percent of the weeks in the future, whereas if you recover asymptotically you will be symptomatic 36 percent of weeks in the future, and this was highly significant.

### **Changing the Concept of Manic Depressive Illness from Episodic to Chronic**

What we've now done, as well, is aggregate all the findings from these long-term studies to recommend a way to manage patients, not regarding selection of drugs or psychosocial treatment, but as to the matrix in which management is offered. The first thing we are recommending is a change in the concept of manic depressive illness, and of major depressive disorder, as well, from that of an illness that has some isolated episodes to

that of a chronic illness, like diabetes or arthritis. We have championed a shift to a new paradigm of this illness as a chronic disorder that is often lifelong in nature.

As a part of that, treatment must be initiated to include a thorough education of the patient, the family, the significant other. As to the characteristics of the course of illness; that it is chronic and that a person is given to repeat episodes and frequently are symptomatic between those episodes. We recommend that the early warning signs of a pending episode be identified, because it's now become clear that patients enter into an effective episode with similar signal symptoms. If you know those, you can educate the patient to them making them aware to come in to see the physician.

We emphasize the need to adhere to treatment. Bipolar patients frequently go off. They enjoy being manic at times, at least the early phases of it, before it becomes disorganizing and psychotic in nature. One has to adhere to treatment management and frequently needs maintenance

treatment. The one thing that we have pushed is that physician care should be ongoing in nature. It's not uncommon for patients with a manic episode to be treated, and then have the physician say, "Okay, you're well now, come back and see me if you have problems in the future." This is absolutely inappropriate.

Our studies show that if you treat a patient, you have to treat them into as full abatement as possible of the symptoms, because if there are residual symptoms remaining, they are associated with disability and they put the patient at risk for an early relapse. To prevent that, it's important to continue the treatment beyond the episode, and move to maintenance treatments to ensure that a stable state of recovery is achieved.

What we're recommending is that the physician see the patient in an ongoing way, treat the episodes and control them, and if there are symptoms between the episodes that they're legitimate treatment targets. The goal is to try to keep patients as symptom free as possible throughout their lifetime.

## Schizophrenia Research Forum

The Schizophrenia Research Forum (SRF) is designed to help researchers in their quest for causes, improved treatments, and better understanding of schizophrenia.

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*SRF is supported by NARSAD and NIMH*



*Eric Nestler, M.D., Ph.D.,  
co-recipient of NARSAD's 2009  
Falcone Prize .*

On receiving the award, Dr. Nestler remarked: It really is a great honor to receive the Falcone Prize, and a great honor to share it with Lew Judd. My lab studies the molecular mechanisms of depression and drug addiction. In the case of depression, that means studying how chronic stress changes the brain in bad ways to lead to depression. And in some individuals, why chronic stress produces very different types of changes that protect those individuals from the bad effects of stress, in other words, mediating resilience.

Now all of our work is carried out in rats and mice, and that highlights one of the major challenges that we have in psychiatry. Obviously, many features of depression will always remain inaccessible in rats and mice. Nevertheless, we think that animal models for depression and other mental illnesses are improving, and they've taught us a great deal about the brain and emotional control under normal conditions, and what might go wrong in people who get depressed.

I'm an optimist — I believe the difficulty in finding the cures is related solely to the complexity of the brain and the complexity of these illnesses. And I remain as positive as ever that we will reach the time when we discover the causes of mental illness and figure out how to treat it and eventually cure it.

## Epigenetic Mechanisms of Depression

### Eric Nestler, M.D., Ph.D.

*Nash Family Professor and Chair, Department of Neuroscience  
Director, Brain Institute  
Mount Sinai School of Medicine*

It's impossible to overstate the impact of depression, which the World Health Organization has determined to be the number one cause of morbidity worldwide. Yet despite its impact, we still know very little about its underlying neurobiology. We know that roughly half the risk for depression is genetic, but we have not yet identified specific causative genes. We know that chronic stress is involved in some people but probably not in others, which has led to the view that depression is not a disease, it's a syndrome, a heterogeneous collection of many disparate illnesses that manifest themselves in some similar ways. Although we don't know much about the neurobiology, we do have some very effective treatments, but all these treatments were discovered by serendipity, by luck, and studies have shown that about half the people treated with the best treatments currently available don't get fully better. So we need better treatments.

Abnormalities of depression fall into several domains — abnormalities in mood, cognition and what are called neurovegetative functions. When you can make the same diagnosis of major depression whether a person eats too little or too much, loses or gains weight, sleeps too little or too much, has low energy or too much energy, you know you have a problem with diagnosis, again emphasizing that we do not yet know enough about depression.

Over the last decade or so, we've learned a great deal about regions of the brain important in the control of mood in normal individuals and regions that work abnormally in people with depression, areas called limbic regions, the emotional centers of the brain. Very recently we've obtained unique insight into brain areas important in depression by virtue of neurosurgical treatments. Using a treatment developed for Parkinson's disease called deep brain stimulation, in which electrodes are placed in the brain, it's been found that stimulating these limbic regions elevates mood in normal people and alleviates symptoms of depression in severely ill people. These regions are an area called SG 25 and another called the nucleus accumbens, which I will focus on.

### Mouse Models of Social Stress and Depression

My lab studies depression in animal models, based on the fact that all advances in biomedical science have come from basic research in animal models. The question is, what are animal models for depression? This highlights the fundamental challenge we have in psychiatric research. Unlike every other medical specialty where animal

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models are straightforward, animal models of psychiatric illness are limited. Clearly, there are aspects of depression that will remain inaccessible to animal models. Nevertheless, other symptoms, namely loss of pleasure or an impairment in reward, abnormalities in sleep and appetite, which are part of those neurovegetative symptoms I mentioned earlier, can easily be modeled in a rat or mouse.

One particular animal model of depression we've used is called social defeat. What we do is take a normal mouse and put it in the home cage of a big, mean, aggressive mouse. Instantly, fighting occurs — the large mouse does not like having an intruder in its cage. We allow the fighting to continue only for a couple of minutes so there is no physical injury. For the remainder of the day, we keep the test mouse in the cage of the mean mouse separated by a screen, safe from physical injury but subjected to all the sensory cues of the aggressive mouse. We repeat this process every day for 10 days. Each time the test mouse is exposed to a different aggressor mouse.

By taking a normal mouse and subjecting it to this horrendous social stress, we found that we induced a behavioral syndrome, aspects of which are essentially permanent. They include anhedonia-like symptoms, including decreased interest in drinking a sugar solution or eating a sweet treat or having sex; anxiety-like symptoms of increased stress hormones and disrupted circadian rhythms; a metabolic syndrome characterized by obesity and profound social avoidance. We believe this test is relevant to certain human stress-related disorders, such as aspects of subtypes of major depression and post-traumatic stress disorder.

We then place the test mouse in another cage. When that cage is empty and we put a control mouse or a mouse subjected to defeat in the cage, they move normally. When we place another mouse in the cage, the control mouse spends a lot of time interacting with the newly introduced mouse, whereas the mouse subjected to defeat shows profound social avoidance, hovering in the corners of the cage. This quantifies the finding showing less social interaction in animals subjected to defeat. We've now shown that it persists at least six months — it's essentially lifelong. It can be treated with antidepressants. A single dose

of imipramine or fluoxetine, two antidepressants used in humans, does not affect the symptoms, but chronic administration of the drugs fully treats the abnormalities.

## Susceptibility and Resilience

Interestingly, when we examined large numbers of mice we found dramatic variation in their response to this social stress. About two-thirds show the social avoidance I just described. We call them susceptible. But we were struck by the fact that about one-third behave similarly to control animals. We call those mice resilient. During the recovery period, when the animals are no longer subjected to any stress, the resilient mice slowly gain weight as normal mice do, whereas there is a dramatic increase in weight by the susceptible mice. We essentially induce in normal mice a long-lasting obesity as a consequence of chronic social stress. They eat too much and show signs of early diabetes, elevated glucose and insulin levels, elevated bad cholesterol, and even abnormal liver metabolism. In medicine this is called the metabolic syndrome. It shows that depression is not located solely in the brain. It's generated in the brain, but it has effects throughout the body. We have used this information to try to understand some of the underlying neurobiology involved in mediating the consequences of chronic social stress in this mouse model. We've done it by focusing on genes in the brain reward area I mentioned earlier, the nucleus accumbens.

## Gene Chips and the Mechanisms of Susceptibility and Resistance

Each cell in the body has about two meters of DNA, all of which is somehow exquisitely packaged within a cell nucleus. Epigenetics refers to the way in which genes are turned on or off to change gene activity without changing the DNA itself. We use a technology called a gene chip, a piece of silicon the size of a thumbnail that contains every gene in a mouse, which is pretty much equivalent to every gene in a human. With it we can identify the genes that are regulated by stress, understand how that regulation occurred, and why the changes in gene expression last so long. It makes it easy to examine all the genes in the nucleus accumbens affected by chronic social

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defeat stress; to show very long-lasting molecular changes in the brain as a consequence. This gives us new insight into the ability of chronic antidepressant treatment to undo or repair most of those changes.

We gain insight into mechanisms underlying susceptibility and resilience, using gene chips to show how those same genes look in resilient animals, both in the nucleus accumbens, and in another brain reward region, which connects to the nucleus accumbens, called the VTA. One aspect of our findings is that resilience is associated with many changes in gene expression not seen in susceptible animals, suggesting that resilience is not the absence of bad things happening in this mouse, but actually represents an active, positive adaptive process that protects these animals from the bad effects of stress. We can study the individual genes that make up this list to understand mechanisms of resilience.

It became clear to us that among the many genes uniquely regulated in resilient animals are those that encode ion channels, proteins that regulate the electrical properties of nerve cells. As you may know, each nerve cell is like a tiny battery, and its function is controlled by its electrical activity. This led us to the notion that regulating the electrical activity of these VTA neurons may be key for resilience. And, in fact, that is the case, as we've shown in two complementary experiments.

In the first experiment we took susceptible mice, subjected them to chronic social defeat stress, and then gave them an ion channel treatment in the brain. This induced in susceptible mice the antidepressant response that occurs naturally in resilient animals. We can also do the reverse. We can take resilient mice, mice that after defeat behave normally, prevent the ion channel response and induce depression. This is a long way from a new treatment in humans, because what we've done in these mice is use a technique called viral-mediated gene transfer, where we inject a virus expressing ion channels or blockers of ion channels, in particular nerve cells in the brain. Nevertheless, this gives us unique insight into changes that we can now pursue in humans to induce or promote resilience.

## **A Potential New Approach to Antidepressant Treatment**

Let me show you one further finding, generalizing this to many genes. A lot of changes are associated with resilience, or susceptibility involving about 1,200 genes. The genes that are increased in defeat but reversed by imipramine treatment come to even more, 1,300 or 1,400. We see that there is a large degree of overlap between mechanisms of resilience and mechanisms of antidepressant action. That suggests that some of the way antidepressant treatments work is to induce some of the changes that occur naturally in animals who are more inherently robust and resilient. We believe the same thing occurs in humans.

So let me conclude by saying that we believe that the social defeat model is just one model of depression, or stress-related disorders in humans, and it's giving us insight not only into susceptibility to stress, but also resilience to stress. By studying gene and chromatin arrays, chromatin being the ways in which genes are packaged into a cell nucleus, it's possible to understand changes that occur in the brain that mediate susceptibility and resilience, as well as antidepressant action. Another word to describe chromatin is epigenetic.

We're particularly struck, as I mentioned, that mechanisms of resilience and antidepressant action overlap, which has raised the possibility of a fundamentally different way to approach developing new antidepressant treatments. Most such work to date has looked for ways to prevent the bad effects of stress on the brain. What I'm suggesting as another approach is to find the ways more robust individuals avoid the bad effects of stress and reproduce those more positive adaptations in people who are more vulnerable. The goal of all of this work, of course, is to improve the clinical picture, to identify better diagnostic tests and treatments, and ultimately to effect cures.

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## What We've Learned From Children About Mental Illness

### Adrian Angold, M.D.

*Associate Professor of Psychiatry and Behavioral Sciences  
Center for Developmental Epidemiology  
Duke University*

### What is Developmental Epidemiology?

Jane and I call ourselves developmental epidemiologists. Okay, so what is that? Epidemiology is the study of the distribution of diseases in time and space, and development encompasses the history of individuals over time. Our key interest is in trying to relate aspects of individual development on the one hand, and the development of disorders and diseases, particularly mental illnesses, on the other.

One of the projects we've been engaged in is the Great Smoky Mountain Study, in which we've been following kids for about 16 years. The study is located in North Carolina, in an 11-county region with the Cherokee reservation bang-slap in the middle of it. We started out with about 1,400 kids ages nine, 11 and 13. As epidemiologists tend to do, we measure everything under the sun. We've just put in a grant to follow them up to when they're 30. The kids involved are ordinary people. We think it's important to study these things in the general population, given that most people with mental illnesses never present for treatment, or if they do it's long after their problems began.

The general notion that there's a group of people who have mental illnesses, and there's a group who don't is probably wrong. At any one time, about 10 to 15, maybe 20 percent, of people suffer from some sort of psychiatric disorder. Some estimates are even higher than that. The group of people who have mental illnesses at some point or another is probably all of us. I want to suggest that just as all of us at some point or another have physical illnesses, I think probably most or perhaps all of us at some point or other will have something that would meet the criteria for a mental illness.

### Disorders Begin Earlier Than We Thought

But what happens if you follow a group of people over multiple observations? What does the picture look like? When should we be thinking these disorders begin? We know some things are uncommon before adolescence, disorders like schizophrenia or classical mania or panic disorders. But some others start earlier than we used to think. With our excellent colleague Helen Egger, M.D., another NARSAD awardee, we've been looking at psychiatric disorders in two- to five-year-olds, pursuing this work in



*Adrian Angold, M.D.,  
co-recipient of NARSAD's  
2009 Ruane Prize*

On receiving his award, Dr. Angold remarked: It's a great pleasure to be here, and a huge honor to win this award. I just want to say our program has also benefitted from [the NARSAD Independent Investigator] program. He shares the Ruane Prize with his wife and colleague, E. Jane Costello, Ph.D.

One piece of the work that we've been doing recently is to suggest amongst other things that the entire treatment system is upside-down, and that we're completely ignoring the early stages of psychiatric disorders in much younger children, and we're filling our clinics with kids who have already been having problems for 15 years by the time we ever see them for the first time. So while I think there's enormous progress, I'm also happy to say that though we're doing studies that we hoped we'd be able to do 20 years ago, there's a bit of work for us to do in the next 20 years

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imaging studies. She's also doing imaging studies of children aged six to nine, following up kids who had disorders, particularly anxiety disorders, in the preschool years to see what their brains look like a few years later. This is another exciting new area. She's an example of where NARSAD funding of \$120,000 was absolutely key to her then getting a two and a half million dollar grant from the National Institute of Mental Health (NIMH).

Our study is, I think, the first done anywhere that used standardized diagnostic instrumentation to diagnose preschoolers. What we see is that the rates of disorder already in the preschool years, even for things that we don't think of as beginning that early, like depression, are not very different from what they're going to be in later childhood or even in adulthood. And so I want to suggest that our thinking has been starting much too late. Most of what we think of as prevention programs can hardly be called prevention programs when the disorders started long before anybody was put in them.

I think the history of psychiatry over the last 30 years has been one of recognizing that things start earlier than we thought. When I began my career, early-onset depression meant before 40. Then, 20 years ago, it was before 30, then before 20 and then prepubertal. Now we want to suggest it's preschool. Moreover, if we can see it at age two, it was already there before. The other thing is that our diagnostic criteria are useless in these young children. A one-year-old can't tell you whether or not he feels guilt and anhedonia. How do you make the diagnosis? We haven't even begun to consider how we're going to trace the roots of these disorders in the very youngest children.

When we started the Smoky Mountain Study, we started at age nine. That was too late. When we started this program of preschool research, we started at two. That was too late. The difficulty is that we're really going to have to start from scratch to figure out even what we mean by mental illness in kids younger than that. I think that's a very interesting, exciting task for the future.

With the kids we've been studying, a lot of them who are impaired don't get better; these weren't just little transient problems that went away and everything was fine. Already we're seeing patterns that are very similar to what we'll see at later ages, which is what leads us to argue that these really are genuine disorders.

### **Adolescent Girls and Depression: A Key Finding**

This sounds as though we're saying everything's the same whether you're two or five or 10, but we also have to consider that individuals are developing. As many of you know, unipolar depression really takes off in girls after the age of 13. The rate rises between two and three-fold. One of the things we've been interested in is what this might be due to. This is another point at which we can say thank you to NARSAD. We submitted a proposal to the National Institute of Mental Health. They said it wouldn't work. But NARSAD and another foundation decided that maybe it wasn't completely stupid and funded the work. Well, we put in a grant to NIMH again after the pilot funding, to do a replication of what we'd already done. This time they said it was fantastically innovative, and gave us the money right away. Once again, thank you, NARSAD.

What we found in this research is that what seemed to be the key ingredient in driving that increase in depression was increases in levels of testosterone. It wasn't the other hormones, it wasn't growing breasts, or increases in stress or sensitivity to stress. It was particularly testosterone. The testosterone goes up in puberty. It seems all girls become more prone to get depressed as they go through this developmental transition unless they're American Indians, where you don't see this pattern at all. This again is a new finding that I think we haven't yet reported anywhere else but here. The key point to be aware of here is that maybe not all people are the same, that what we're seeing here are quite important changes.

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## The Great Smoky Mountain Study

### E. Jane Costello, Ph.D.

*Professor, Psychiatry and Behavioral Sciences  
Director, Center for Developmental Epidemiology  
Duke University School of Medicine*

Many of you might wonder, if our concern is the treatment and cure of mental illness, why spending years studying ordinary, normal kids would be a useful thing to do. In fact, there have been people who've talked about the death of epidemiology. They say that just looking at people doesn't set any questions for which we can come up with firm answers that are going to lead to treatments and cures. I want to suggest that that's not necessarily the case.

I want to show you some things we've done as a result of this longitudinal, observational study that do have implications for treatment and maybe can open our eyes to aspects of treatment that aren't immediately involved with sitting in a doctor's office or taking pills. We don't conduct treatment trials, but we can use the longitudinal data in our studies to find out more about who gets treated and strong evidence for who needs treatment but doesn't get it, which is just as important a part of understanding about treatment as looking at the actual treatments themselves. And also looking at other kinds of treatment we might not immediately think of.

Here's an example of what goes on in the real world. I think there has been some quite justifiable skepticism about whether the way mental health services are delivered in the community actually does a whole lot of good. It's very difficult to test because the reality is that the more symptoms you have, the more likely you are to get treatment. If you flip that around, what comes out of your studies is the more treatment you get, the more symptoms you have, which is not very helpful.

What we were able to do with an observational study like this was to take a year or two of observations to select out the kids who had not just little blips of symptoms, but serious symptoms that continued for over a year, and then look at the impact the next year on those who were treated versus those who were not. These were not children in treatment trials in white-coat hospitals, these were ordinary kids going to local mental health practitioners. What we found was that there was a marked effect of treatment in the real world in the community if they had eight or more sessions of what was mostly psychotherapy. Very few of them had medication treatments.

We were able to use an observational study without any interventions to show what the effect was of real treatment that real children are getting in real time. And to show, I believe for the first time



*E. Jane Costello, Ph.D.,  
co-recipient of NARSAD's  
2009 Ruane Prize. Dr. Costello  
shares this prize with husband and  
colleague, Adrian Angold.*

On receiving her award, Dr. Costello remarked: I'm really delighted to be here, because I think it's tremendously important for people whose main interest has been traditionally in treatment and trying to help people with severe problems to see the importance of epidemiology, the study of patterns of disease in time and place — which is what we do.

I've been working on an Institute of Medicine panel on a book about prevention that came to the conclusion after two years, that we really, really, really, have to start with prevention. Because treatment is way too late for most people. Now treatment is necessary for care and protection and help of people with chronic mental illnesses, but we haven't even begun to grasp the nettle of prevention.

Together, Adrian and I are working on ways in which we can use the studies in the general population over time, to help with the treatment of severely mentally ill people. And we're really, really grateful to NARSAD for seeing how this work relates to psychiatry in general.

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ever, that it was working. This I think is really important, because poor old general practitioners and mental health workers in the community have had a bad rap about the quality of their services, while, in fact, if given in sufficient quantity, the treatments were having an effect on these children in our study.

## **The Real-World Environment and Mental Illness**

Here's another kind of treatment that I think we pay too little attention to. We tend to think that mental illness is something where you should go to a doctor and get pills or get psychotherapy from a specialist, and that will or will not cure the disease. We don't think enough about the environment in which people are living.

If putting mice in with aggressive mice can cause the symptoms that look exactly like depression, that's an environmental intervention (Dr. Nestler's presentation, page 16). Well, maybe we should treat the results of this environmental intervention with pills, or maybe we should treat them with an environmental intervention ourselves. But it's hard to do in the general world. It's hard to get public enthusiasm and pressure going for changing people's environments. It's something we seem to be very resistant to.

The kind of observational longitudinal study we've been doing gave us an opportunity to observe a real-world intervention in the environment that we never, ever, even with NARSAD funding, could have been able to do. This is what happened. As Adrian told you, about a quarter of our sample are American Indians, Cherokees who live on a reservation, where, in 1996, they opened a casino.

Their chief at that time was a very wise woman named Joyce Dugan. She made a deal with the casino company that every member of the community, every registered member of the tribe, would receive a percentage of the profits from the casino. That meant that everybody got it from the day they were born, got it whether they were good or bad, whether they were working or not working, whether they were smart or stupid, whether they were in jail or at home, they all got the money, and it went up as the casino became

more profitable. By the time the casino had been open for four years, the amount was about \$6,000 a year per person.

That's a really serious sum of money. We had been studying these kids since 1992 so it occurred to us, we can look at how they were in the four years before the casino opened, and compare it with how they were after. What we found was that just giving families extra money actually changed children's behavior. We saw that as a result of this income supplement, 14 percent of the families moved out of poverty, as federally defined. Some, even with this extra money, didn't move above the poverty line. And some who weren't poor before, obviously with additional money weren't poor afterwards.

Looking at the impact of this extra money on these three groups what we saw was that in the persistently poor families, the children had high levels of behavior problems beforehand, and eight years later, had high levels of behavior problems. Conversely, the kids who were never poor had low levels before and low levels after. What was dramatic was that in the families who moved out of poverty as a result of this income supplement, the kids had high levels of behavioral problems before the intervention and low levels afterwards. They changed from one group to the other.

We wondered whether this affected all sorts of psychiatric problems or just behavior. We looked at emotional problems, depression and anxiety, and here the effect was much smaller. It was still statistically significant, but at a much lower level. But you still saw this effect, that moving out of poverty, moving this enormous environmental stressor off the families to some extent. I mean moving out above the federal poverty line doesn't solve all your problems, but it helps.

Then we thought we needed to look at the white families, too, and what we saw there was exactly the same pattern as in the Indian families. If by chance, for whatever reason, a white family moved out of poverty over that period of time, we saw the same reduction in both behavioral and emotional symptoms in the children. The natural experiment we were able to observe in the Indians was reflected in the white families.

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We have an intervention that has the same sort of effect on children's symptoms as a drug treatment might or a psychotherapeutic treatment. But it's an intervention on the environment. And I think that tying this, with what Eric Nestler was talking about earlier, is really important because just as environmental stresses can create mental illnesses, so environmental interventions can remove them.

### **Measuring the Effects of Environment**

Finally, I want to talk a bit about what else epidemiological studies can do. Over time we have been able to use the data we've collected to branch out in all sorts of other ways that have other implications. We've been collecting blood every time we see these kids. We get ten drops of blood. Do you remember when your babies were born? Somebody stuck their heel and collected a drop of blood on a piece of paper? Well, that's what we do in the children's own homes. We've collected ten drops every time and stored them away in the freezer. And they've turned out to be enormously useful for all sorts of things.

To see whether we can measure the way environmental stresses affect psychiatric disorders by getting under the skin, as it were, we've been looking at a range of things that are well-established as biomarkers of stress, such as cortisol and C-reactive proteins. We've been looking at whether these actually mediate the impact of environmental stresses on psychiatric outcomes, and we are beginning to show some really interesting data to suggest that we can measure physical responses to environmental stresses in this way. Also, we're beginning to do structural and functional imaging studies, looking at reward systems and decision-making in our subjects who were adolescent drug abusers, but grew out of it, comparing them with those who started using drugs in adolescence and have continued into adulthood, to see if there are brain differences in those two groups.

We now are using these blood drops to do a genome-wide association study where we're looking at 660,000 SNPs in the brain. (A SNP, or single nucleotide polymorphism, is a variation at a single site in the DNA), and the exciting thing is that in collaboration with colleagues who have the same sort of longitudinal data we can map the environmental stresses onto the genes, and look at which genes are expressed in which environments, or which particular polymorphisms are either good or bad in specific environments because we have so much environmental data on these children.

### **The Breadth of Longitudinal Studies**

This is just an example of the different ways in which a longitudinal study can go: genetics, in which we've been looking at cost benefits of treatment; sex and gender differences; ethnicity differences; cognitive patterns associated with psychiatric disorders; various aspects of the environment; at rural-urban differences. All of these spring out of doing this observational, longitudinal study.

From our point of view, it's been a wonderful period to be a developmental epidemiologist. A lot of the studies we're doing now, we couldn't have dreamt of when we started. The technology didn't exist. We can address issues at the level of the community, the family, the individual, the brain, physiology, the genome, in ways that 20 years ago couldn't have happened. And we do finally and honestly want to say that NARSAD's been at the forefront of stimulating a lot of the work in these fields that we've been able to take advantage of, and we're very grateful for that and for the recognition of our work.



*Brenda Milner, C.C., Ph.D.,  
recipient of NARSAD's  
2009 Goldman-Rakic Prize.*

On receiving her award, Dr. Milner remarked: I am greatly honored to be getting this award. I'm really delighted, as are all the other awardees. But for me, this particular award means more than that, because Pat Goldman was my friend for many, many years. I knew her in her very early days at the National Institutes of Health, and I followed her and shared her love of the frontal lobes. I was very fond of her and admired her. So that is particularly important to me about this particular award.

In the beginning, we were doing detective work, which of course I loved. The question was, "Where are [epileptic] seizures coming from?" It was in that situation that I came upon two patients who had severe memory impairment after an operation that wouldn't normally result in this. It was on one side of the brain. We discovered that damage to this structure — the hippocampus and the surrounding cortex — could produce patients who are not able to remember to build up their lives as they live it. I worked with the patient H.M., who died recently at the age of 82, who had, again for the treatment of epilepsy, had operations on the hippocampus in both sides of the brain. The result of that work has been my study of removal of the temporal lobe of the brain for the treatment of epilepsy, which now is a very well-established treatment.

## Reflections on the Field of Brain and Memory: A Tribute to H.M.

### **Brenda Milner, C.C., Ph.D.**

*Dorothy Killam Professor of Neurology and Neurosurgery  
Montreal Neurological Institute  
McGill University*

Following my arrival at McGill from England as a graduate student in psychology in 1944, I began to study one of the patients of Wilder Penfield (a renowned early neurosurgeon and brain researcher) who was undergoing elective surgery for the treatment of epilepsy. It was pioneering surgery in those days, and presented a wonderful opportunity to try to find out something about the temporal lobes of the brain. In those days, we had no way of really seeing into the brain. We were doing clinical detective work, looking for an area from which seizures might arise in order that an operation on the temporal lobe could be carried out. That is when my great interest in the right half of the brain — the right cerebral cortex — began.

For the purposes of this talk, I'm going to equate the left hemisphere of the cerebral cortex with dominance for speech, and the right with the non-speaking hemisphere. These surgeries were unilateral procedures; taking out only one temporal lobe, which led to my interest in the complementary specializations of the two temporal lobes in memory. Why memory? Because some patients told me after the surgery that they were having trouble with memory. Memory was not a fashionable topic for study in those days, but when a patient tells you there's a problem, you don't say, I'm not interested. So I started working on memory. From operations on the right side, what I discovered that was new was a complementary deficit that I call material specific — impairment in memory for faces, places, tunes.

### **Meeting H.M.**

We know now from MRI studies that there is often atrophy in the hippocampus in these patients. Penfield and I had speculated that the reason that some patients had memory impairment when other patients didn't after a unilateral removal was that there was damage we couldn't see before surgery in the hippocampal region, the memory center, of the opposite hemisphere. These are lesions that occur in infancy, or even prenatally. This remained a hypothesis until one such patient, P.B., died 13 years later and was proven to have more atrophy on the right than was caused by the surgery Penfield had done on the left.

Based on the work with P.B., I was invited, in 1950, to study another patient, H.M., in Connecticut. The first challenge was to delineate where the trouble in his memory arose. His I.Q. was fine and had actually gone up after the surgery because he was not having seizures. He could remember and repeat numbers I gave him within a limited time span, but when he tried hard to retain information, he would lose it. We found that H.M. could not keep a visual

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representation going for more than 30 seconds if it were not something he could put into words. As soon as rehearsal in words is impossible, the information, be it visual, be it auditory, is lost in less than a minute.

So the next question was, what can H.M. learn? I would trot over to the psychology department at McGill, pick up a couple of learning tasks, catch the night train to Hartford and spend the next two or three days testing H.M., trying to train him, and most of the tests he failed miserably. I gave him practice on mazes and all sorts of things with no improvement. But I struck oil with one task. In this task the patient looks at a drawing of a star with two borders, a double contour, on an 8 x 10 piece of paper, and he's told to start at point S, up at the top, and to trace a line keeping within the narrow contours of the star until he reaches S again. He sees the star and his hand only as reflected in a mirror, which means, of course, that when you get to the edges you do this kind of back and forth. We all do. Drawing in a mirror for the first time we have all the wrong movements, the wrong habits, but we practice and we improve. And so did H.M.

Over the course of three days H.M.'s performance improved markedly. We tested him for three days, and by the third day he had this beautiful performance. But afterward he had absolutely no memory of these days, these practices. He'd done 30 trials of which he had no memory. As soon as one trial was over and it was out of his mind, he had no memory of it. That was a very, very exciting moment in my research career when I saw this amazing disassociation — that this motor learning, because it was like learning skiing or tennis — must be independent of the medial temporal system.

### **Discovering the Existence of Multiple Memory Systems**

This was very early evidence for the idea of multiple memory systems in the brain. Memory isn't just one big thing depending on how much brain you've got, it's something that involves different systems. People working further with the motor memory system have shown that tests like H.M.'s depend very much on the basal ganglia part of the motor system, and not on the media temporal lobe. That there are many, many kinds of learning was very exciting news. And, yes, I'm still talking about it because people got really interested, and

as you know, everybody now is working on memory at a molecular level and the behavioral level. It was all very exciting and remains so. We learned so much from this patient who never knew me. Over all the years, H.M. never recognized my face.

When I returned to Montreal after testing H.M., I had to get back to testing patients with unilateral lesions and would be having conferences about whether a patient was a suitable candidate for surgery. Penfield didn't want to operate on any more patients who had any evidence of bi-temporal abnormality like H.M. Then it was suggested I devise a memory test to screen these patients. We were using already the wider technique of anaesthetizing essentially one half of the brain to test for where speech was in left-handed patients, where speech wasn't necessarily going to be in the left hemisphere. This was a very solid, well-established method of temporarily incapacitating one hemisphere to produce a paralysis of the other side, and if you're injecting into the speaking hemisphere you produce a language disturbance.

I tried it, and it was a remarkable success. I would have a patient whose left side has been paralyzed, and he's naming little pictures I'm showing him, and later I'm testing him after the drug wears off for his memory for the objects. It's turned out to be very useful. So perhaps this is one way in which my work is clinically useful. It has these tests, or modifications of them and used everywhere. I think what is clinically relevant in my work is really in epilepsy diagnosis and treatment.

### **Future Challenge: The Left Brain-Right Brain Conversation**

The new challenge for me now going into my 90s, what I'm really interested in, is how these hemispheres work together. I had the privilege back in the '60s of doing some experiments with Roger Sperry's patients on the West Coast. Roger Sperry got the Nobel Prize for his work on the split brain, sectioning all the pathways that connect the two halves of the brain, and I was able to see the special functions of the two sides. So now we know a lot about hemispheric specialization, but we know little about how those two hemispheres work together, and I think that with all the new imaging techniques, and the clever young scientists that will come and help me, I'm going to try to probe that question a little.

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## Session 2: RESEARCH INSIGHTS by NARSAD-funded Young Investigators



### Linking Brain Development to Mental Illness: Identification of Vulnerable Pathways

**Genevieve Konopka, Ph.D.**

*Postdoctoral Fellow, David Geffen School of Medicine  
University of California, Los Angeles*

Genevieve Konopka is working to understand how disruptions in brain development manifest as disease, particularly in autism and schizophrenia, which share a number of characteristics. In her presentation, she explained that developmental signaling pathways are very important in both disorders, and that through the use of both human cells and tissues it is possible to begin to identify what these signaling pathways are, and through the use of whole genome analyses, to identify novel targets important for neuropsychiatric disease. Her goal is to determine how the expression of thousands of genes within any given cell are co-regulated, and how this co-expression of genes varies from cell to cell and from one brain region to another.

Dr. Konopka's specific point of reference is the development and evolution of language, and how disruptions in language occur in autism and schizophrenia. Toward that end she has been studying the gene for the transcription factor FOXP2. (A transcription factor is a protein that turns gene expression on or off.)

Patients with mutations in FOXP2 have difficulties in spoken and written language. The FOXP2 peak of expression occurs in the human brain about midway through gestation, when the circuitry for neuronal signaling pathways is being laid. In experiments with fetal brain cells, Dr. Konopka and her colleagues have uncovered several hundred genes specifically bound by FOXP2 in the central nervous system.



### Dissecting the Function of an Interesting Gene Family in Developing Neural Circuits

**Julie Lefebvre, Ph.D.**

*Postdoctoral Fellow, Center for Brain Science  
Harvard University*

Julie Lefebvre described as the goal of her research learning how a neuron knows which other neuron to connect with; that is, what is the molecular basis of the specificity. Protocadherin is a neural-specific set of genes that can generate up to 60 different molecules. She and her team are testing the hypothesis that an infinite number of possible recognition specificities are mediated by protocadherins. To do so, they are removing a group of protocadherin genes from neurons in the retina in experimental animals.

Dr. Lefebvre explained that she chose the retina because it functions as a sort of mini-brain,

composed, like the brain, of many different types of neurons organized in different layers. In dissecting this pathway, the researchers were able to show that protocadherins act to promote the survival of neurons, allowing connections between the neurons to follow.

Dr. Lefebvre now plans to investigate the mechanisms by which protocadherins promote the survival of neurons in the developing neural circuit, why there are so many different neural molecules made by protocadherins, and, finally, how this relates to mental illness and neurodevelopmental disorders. Some studies have suggested there may be a linkage to schizophrenia and bipolar disorder. Also, protocadherin-related molecules may be associated with autism, but, she says, "the jury is still out."

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## Structure and Function of a Novel Molecular Target for Schizophrenia

**Javier González-Maeso, Ph.D.**

*Assistant Professor, Departments of Psychiatry and Neurology  
Mount Sinai School of Medicines*

Javier González-Maeso is investigating the structure and function of G-protein-coupled receptors (GPCR), molecules that activate G-proteins, which are important signal messengers in the body. There are more than 2,000 GPCRs, belonging to about 50 families. They are important therapeutically; a quarter of the 100 top-selling drugs, including all the atypical antipsychotics used in the treatment of schizophrenia, activate or modulate the activity of GPCRs.

In his talk, Dr. González-Maeso reported that his group has found that the serotonin 2A receptor, target of the atypical antipsychotics, and the

metabotropic glutamate receptor 2, target of the new glutamate antipsychotics, are expressed or localized in the same nerve cells in the brain.

What was surprising, he said, is that the two receptors form a diamond, which suggests that this complex may be responsible for some psychotic symptoms in schizophrenia, and is the direct target of the two different classes of antipsychotic drugs. He is now focusing on how the complex regulates signaling in brain, with the ultimate goal of new approaches for treatment of schizophrenia.



## Screening for Bipolar Disorders in Primary Care with the Mood Disorder Questionnaire

**Mark Gameroff, Ph.D.**

*Research Scientist, Division of Epidemiology  
New York State Psychiatric Institute, Columbia University*

Marc Gameroff is addressing the fact that bipolar disorder is underdetected. Since many people lack access to specialty mental health care, primary care is a major place to aim detection efforts, but screening for bipolar disorder is comparatively rare. One problem is that patients more often seek care when experiencing a depressive rather than a manic episode, and treating bipolar disorder with antidepressants can have serious consequences. A mood disorder questionnaire (MDQ) exists (developed by Dr. Hirschfeld, the symposium moderator, and colleagues) but is underused. Dr. Gameroff's research question was whether it might be adopted by more physicians if shown that a positive MDQ screen was associated with negative outcomes down the line. He therefore initiated a study in a primary care clinic in

Manhattan in which 518 of the screened patients were followed up four years later.

The results showed that among people who screened MDQ positive, the rate of bipolar disorder was 37 percent versus 9 percent among those who screened MDQ negative. Also, health service use for mental health reasons was much higher in the MDQ-positive group. Dr. Gameroff explained that a positive screen must be followed up with a comprehensive evaluation. While screening positive is not an absolute diagnosis of bipolar disorder, he said, without the MDQ, a patient might not even get to the point of having an evaluation.





## **Inpatient Post-Admission Cognitive Therapy (PACT) for the Prevention of Suicide Attempts**

**Marjan G. Holloway, Ph.D.**

*Assistant Professor, Department of Medical and Clinical Psychology  
Uniformed Services University of the Health Sciences*

Dr. Holloway is working on a suicide intervention program for the military, which is facing a major issue of suicide behavior with no scientific evidence that what is currently being done for these patients is effective. Her overall goal is to test a targeted, brief inpatient cognitive treatment, called post-admission cognitive therapy (PACT), based on earlier studies in which she participated in the University of Pennsylvania laboratory of Dr. Aaron Beck, the psychiatrist widely regarded as the father of cognitive therapy. The findings of those studies indicated that outpatient intervention for individuals who had attempted suicide could reduce the risk of subsequent suicide behavior by almost 50 percent.

The focus of the Dr. Holloway's current project is to adapt the outpatient treatment for use in a military, inpatient setting. This PACT will consist of six 60-minute sessions, focusing on developing a new intervention, writing a treatment guide, conducting pilot and feasibility testing, implementing a training program for the clinicians who are going to administer treatment and developing competency measures to see how well the therapists are doing. The pilot study will be small, Dr. Holloway said, but the Department of Defense is contributing funding to increase the numbers of participants in the coming months.



## **A Novel Pharmacologic Treatment for Bipolar Disorder**

**Brian P. Brennan, M.D.**

*Associate Director for Translational Neuroscience Research  
Biological Psychiatry Laboratory  
McLean Hospital*

Brian Brennan's talk centered on work he has been doing with potential treatment for bipolar disorder targeting mitochondria, organelles in cells that serve as the cellular power plants and uniquely have their own DNA. The brain uses on average ten times more energy than any other organ in the body and, Dr. Brennan explained, deficits in energy production in the brain, even subtle abnormalities, may have extreme effects. Evidence from magnetic resonance spectroscopy (MRS) suggest that there are abnormalities in mitochondria in bipolar disorder.

A number of dietary supplements have been used to treat mitochondrial disorders and have shown to be of some benefit. Dr. Brennan has been

interested in two of these, acetyl L carnitine and alpha lipoic acid, which show some properties that allow mitochondria to be much more physiologically distributed, which is beneficial.

In his study, Dr. Brennan will be looking at 30 participants with bipolar depression, the phase of the disorder patients spend the most time in and that causes the most distress, mortality and morbidity and for which there are not a lot of good treatments. He will work out effective and safe dosage, measure clinical response and use MRS to look at neurochemical changes in the brain to determine whether, if patients are getting better, it is because of enhanced mitochondrial functioning.

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