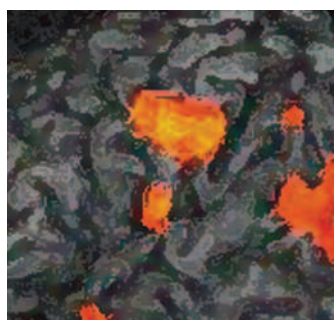


# NewYork-Presbyterian Psychiatry

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## Functional Neuroimaging Reveals Circuitry Dysfunction of Psychiatric Disorders



**A**lthough there has been significant work characterizing negative affective processing in depression, there has been much less focus on the positive emotional and motivational circuitry of the brain. Researchers at the Functional Neuroimaging Laboratory (FNL) at NewYork-Presbyterian Hospital/Weill Cornell Medical Center are developing and applying novel neuroimaging techniques to localize and characterize brain circuitry dysfunction underlying major psychiatric disorders.

David A. Silbersweig, MD, and Emily Stern, MD, recently led an interdisciplinary team of researchers from Weill Cornell Medical College using functional magnetic resonance imaging to test the hypothesis that patients with major depression would not activate the ventral striatum in response to positive emotional stimuli (*Am J Psychiatry* 2006;163:1784-1790). Findings revealed that patients who suffer from depression activated the ventral striatal regions of the brain significantly less than control subjects in response to positive emotional stimuli, correlating with a lack of interest and pleasure in work or activities. The study offers initial evidence for positive emotion-related dysfunction in the region of the nucleus accumbens, with clinical correlation to a core feature of anhedonia.

The interdisciplinary research team was comprised of psychiatrists, neurologists, radiologists, electrical engineers, computer scientists, mathematicians, statisticians, psychologists, and a clinical coordinator. Psychiatrists Jane Epstein, MD, and James Kocsis, MD, as well as image analysis scientist Hong Pan, PhD, were among the researchers involved. The team is planning follow-up studies to further characterize the dysfunction, but these initial findings help to clarify a biological underpinning for an important feature of depression, and provide

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important information for the refinement of brain circuit models of depression.

“A broader approach is to use these sorts of functional brain imaging techniques to characterize the abnormal circuit functioning in key circuits of the brain in a number of major psychiatric disorders to identify final common pathways of disease expression, and ideally to lay a foundation for more targeted diagnostic and therapeutic approaches,” said Dr. Silbersweig.

A particular focus of the FNL is fronto-limbic modulation across the neuropsychiatric spectrum. The group plays a leading role in a National Institutes of Mental Health grant that uses a translational research approach to study mechanistic hypotheses of fronto-limbic fear circuitry dysfunction that may underlie core elements of anxiety disorders.

“Fronto-limbic subcortical circuits are viewed as particularly relevant by a range of investigators because those are the core emotional circuits of the brain as well as the regulatory or control circuits of the brain,” said Dr. Silbersweig. “A lot of the dysfunction that one sees across the various psychiatric disorders represents different domains of emotional and/or regulatory dysfunction.”

In addition to studying major depression and anxiety disorders (including post-traumatic stress disorder and panic disorder), the team has identified neural circuitry abnormalities associated with major psychiatric disorders, including schizophrenia (specifically the positive psychotic symptoms of schizophrenia), geriatric depression, bipolar disorder, and borderline personality disorder.

## “Ideally the field is moving from systems-level pathophysiology to ... treatments and interventions.”

—David A. Silbersweig, MD

“Each of these illnesses is turning out to have certain characteristics that are seen in that disorder, but there are some themes and common denominators that are emerging that we’re very interested in as well.”

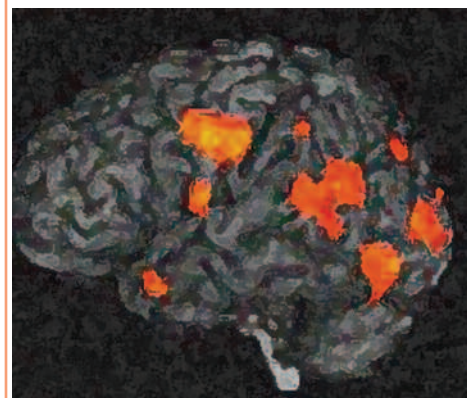
Dr. Silbersweig has also conducted studies with Tracy Butler, MD, a member of the group, to examine the neural circuitry associated with psychiatric aspects of epilepsy. Such studies, he said, “are testing hypotheses about overlap in the brain regions and how that may account for some of the psychiatric phenomenology, above and beyond having a so-called ‘psychological reaction’ to having these conditions.”

As both a neurologist and a psychiatrist, Dr. Silbersweig is drawn to the intersection of the workings of the brain and the mind. Recently he gave Grand Rounds at the Department of Psychiatry and Human Behavior at Brown University Medical School, where he discussed “Ventral Striatal Dysfunction in Major Depression and Pre-Menstrual Dysphoric Disorder.”

“Ideally the field is moving from being able to understand systems-level pathophysiology to providing a foundation for clinically relevant approaches to these disorders that can help to subtype patients and guide treatments and interventions,” he added.

In regards to treatment of various psychiatric disorders, the FNL continues to be involved in translational research.

“There is interest in the implications of work such as ours for some cases of psychiatric disorders that are severe and refractory, where deep brain stimulation/neurosurgery is being developed to target the regions to try to modify or modulate the activity in those circuits,” he said.



And in terms of other treatments, such as cognitive behavioral therapy or medication, Dr. Silbersweig added, “As one identifies and understands more about the dysfunction on the systems level of the circuit mechanistically, one can zero in on specific regions and functions, selectively targeting them to modulate them more directly and more specifically, with fewer side effects.”

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# Psychiatry Researchers Awarded Top Honors

**T**wo of New York-Presbyterian Hospital's most notable psychiatrists—Jack D. Barchas, MD, and Jeffrey A. Lieberman, MD—have recently received top awards for their contributions to psychiatric research.

In October 2006, the Institute of Medicine honored Dr. Barchas with the 2006 Rhoda and Bernard Sarnat International Award in Mental Health, a prize that includes both a medal and \$20,000. The award reflects Dr. Barchas' work on fundamental and behavioral neurobiology, particularly on neuroregulators. Since the mid-1960s, he has studied how these compounds modulate interactions between nerve cells, investigated how they are metabolized, documented their genetic foundations, and pioneered research related to how the brain's biochemistry affects behavior and vice versa.

As a medical student, an influential faculty member told him bluntly that there was no connection between biochemistry and psychiatry. "Biochemistry is like a locomotive, and a locomotive isn't changed by the wind, meaning behavior," Dr. Barchas recalled being told. "What we found was that the wind really does change the locomotive."

With much persistence, he completed the first study to demonstrate how neurotransmitters, in this case serotonin and norepinephrine, respond differentially to physiological stress in rats. The published study (Barchas JD, Freedman DX. *Biochem*

**“There may be dozens of forms of depression just like pneumonia ... each of which has to be treated differently.”**

—Jack D. Barchas, MD

*Pharmacol* 1963;12:1232-1235) laid the groundwork for decades of influential research, including his discoveries that stress and exercise can influence endorphin levels in the brain and body.

Today, Dr. Barchas believes that increasing knowledge about neurobiology and its relationship with behavior will continue to lead to new treatment strategies, including both pharmacotherapy and psychotherapy. "Scores of neuroregulators have barely been studied," he said. "There may be dozens of forms of depression just like there are so many of pneumonia, which can be both bacterial and viral, each of which has to be treated differently."

In addition to his role as a mentor for both young and senior faculty members at New York-Presbyterian/Weill Cornell Medical Center, Dr. Barchas is currently a researcher for the Pritzker Neuropsychiatric Research Consortium, a multisite study group that aims to uncover the genetic and neurobiological roots of mood disorders and schizophrenia.

Also in October, the National Alliance for Research on Schizophrenia and Depression presented its Lieber Prize for Schizophrenia Research to Dr. Lieberman. The \$50,000 prize honored Dr. Lieberman for his investigations into the natural history and pathophysiology of schizophrenia (Figure), as well as his work to elucidate the mechanisms and efficacy of antipsychotic medications.

"My research has led to the understanding that schizophrenia is a progressive disease. The best chance to prevent its disabling effects is to identify people early and to treat them aggressively," said Dr. Lieberman. "Episodes of psychosis are like brain attacks. They have a progressive pathologic effect on the parts of the

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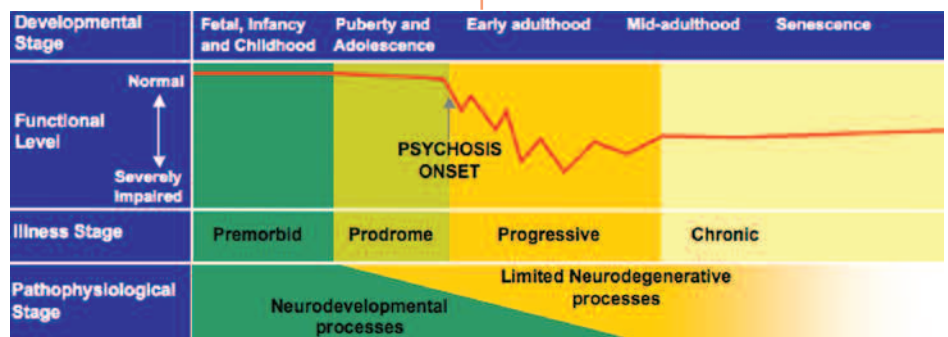


Figure. Natural History of Schizophrenia



# Genetic Variation To Rx Response Suggests Individualized Therapy

**W**ith its role in neuronal survival, differentiation, and synaptic plasticity, brain-derived neurotrophic factor (BDNF) stands out as a likely factor involved in genetic predisposition toward neuropsychiatric disorders. New research by Weill Cornell psychiatrist Francis S. Lee, MD, PhD, suggests that a single-nucleotide polymorphism within BDNF, known as Val66<sub>Met</sub>, may be key in identifying which patients will respond to particular antidepressant medications.

Val66<sub>Met</sub> has previously been associated with abnormally low hippocampal volume and memory deficits. But Dr. Lee's study, published in *Science* (Chen ZY, et al. 2006;314:140-143), links this genetic variation to anxiety-related behavior and resistance to the selective serotonin reuptake inhibitor fluoxetine.

"This is 1 of the first studies to suggest that BDNF might be involved in complex behavior, much more along the lines of emotionality models of anxiety and fear. Before, BDNF was considered important for memory and other types of learning paradigms," said Dr. Lee.

Dr. Lee and researchers conducted the study in mice. He pointed out that although BDNF is found in all vertebrate species, the Val66<sub>Met</sub> variation appears only in humans, which suggests a late-evolving genetic alteration.

After generating a transgenic mouse in which Val66<sub>Met</sub> was expressed, Dr. Lee and his colleagues assessed heterozy-

gous, homozygous, and wildtype mice—all genetically brothers. Mice carrying the BDNF<sub>Met</sub> allele, either 1 or 2 copies, had decreased hippocampal volume, as well as differences in individual dentate gyrus neurons, such as decreased dendritic arbor complexity and greater distances to cell soma. Predictably, these mice also showed memory impairment.

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**"In the future, psychiatrists may be able to offer treatment that is tailored for individual patients, based on genetic information."**

—Francis S. Lee, MD, PhD

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When it came to anxiety-related behaviors, however, mice homozygous for BDNF<sub>Met</sub> were affected by their genetic make-up far more than were their heterozygous counterparts. Compared with their littermates, the homozygous mice had decreased exploratory behavior. In conflict tests, they also showed increased anxiety behavior. Mice with 2 copies of the variant gene showed decreased response to long-term treatment with fluoxetine.

Currently, Dr. Lee is planning the next phase of his research. One option is to test whether temporary stress puts mice at greater risk for developing anxiety later in life. The mice with either 1 or 2

copies of the variant BDNF<sub>Met</sub> would be exposed to stress and evaluated. Another possible route would involve the opposite approach, Dr. Lee said. "Laboratory mice live in essentially unenriched environments. Could various enrichment strategies, like toys and a running wheel, rescue mice with this phenotype and make them less anxious?"

In order to assess the possibility of Val66<sub>Met</sub> being a biomarker for drug resistance, Dr. Lee suggests future research examine patients with 2 copies of the variation. "In many clinical trials, researchers cannot segment which patients do or do not respond. This study hints at which people might need to have a more personalized treatment plan," he said. "These findings provide 1 possible avenue of how, in the future, psychiatrists may be able to offer treatment options that are tailored for individual patients, based on genetic information."

Until clinical studies are complete, Dr. Lee stressed that his findings have limited applicability to humans. There is no commercially available blood test for this biomarker, so patients cannot request to be genotyped by their physician. "More important than proving whether this variant confers drug resistance, this study points to the possibility of some lab finding a novel compound to rescue this drug resistance," he concluded.

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# Cognitive Remediation Program Enhances Neurocognitive Skills



*In the Neuropsychological and Educational Approach to Remediation model, patients work in groups on neurocognitive exercises that emphasize personalized, contextualized learning.*

Psychiatric disorders such as schizophrenia, bipolar disorder, anxiety, and depression can cause not only emotional problems but cognitive problems as well. These impairments in memory, attention, and other skills may occur during episodes of mental illness or persist long after recovery, affecting a patient's quality of life and sense of independence.

To serve the needs of this unique population, the Columbia Day Treatment Program is launching a Cognitive Remediation Program. The new services will complement the many therapies already available through Columbia's Day Program, established in 1983 and located in midtown Manhattan on East 60th Street. The facility offers dialectical behavioral therapy, cognitive-behavioral therapy (CBT), insight-oriented groups, and programs for substance abuse and eating disorders, all of which allow patients to tap into a diverse selection of experts for an individualized treatment plan. The Day Program treats patients from 18 to 60 years of age who are from a variety of backgrounds. Some are mid-career adults who have hit a roadblock. Many patients are college students. Columbia can now offer support for the cognitive issues that students often face, in addition to addressing possible emotional and social problems.

"Frequently, when kids leave home, they've had problems all along but the separation from parents really brings those problems out," said Betty Jeanne Kass, LCSW. "We try to keep people from just seeing themselves as psychiatric patients. A huge thrust of our program is keeping people at work or school. We try to schedule our program so that people can maintain classes or employment, or take on a volunteer position on a part-time basis while receiving the support or therapy they need."

Columbia's Cognitive Remediation Program employs the Neuropsychological and Educational Approach to Remediation (NEAR), a method developed in the late 1980s by Alice Medalia, PhD, which has since been used in programs throughout the United States and in Australia, Japan, and Europe. The approach emerged from Dr. Medalia's background in neuropsychology, clinical psychology, and education. It is based on the idea that learning is a function of motivational and instructional styles as well as ability.

On June 1, 2007, Columbia University College of Physicians and Surgeons and the New York State Psychiatric Institute will co-host a conference called Cognitive Remediation in Psychiatry. The event is open to mental health professionals involved in the research and treatment of people with psychiatric conditions who have cognitive deficits.

"My model is designed to enhance people's intrinsic motivation to learn," said Dr. Medalia. "The severe psychiatric disorders impact not only cognition but also motivation. One of the hallmarks of schizophrenia and depression is that people lose their enthusiasm for doing things."

In the NEAR model, patients work in groups on neurocognitive exercises that emphasize personalized, contextualized learning. For example, rather than doing repetitive attention drills where the task is to respond to a circle that turns red, a patient might use a computer program that simulates the activity of driving a truck to make deliveries, and is required to monitor a simulated dashboard that sends warning signals. According to Dr. Medalia, cognitive remediation differs from the similarly named CBT in several key areas.

"The idea in CBT is to temper emotional reactions by thinking through a situation, being aware of thoughts that contribute to your behaviors," Dr. Medalia explained. "Cognitive remediation is focused on the neurocognitive skills that allow you to think clearly: the ability to pay attention, to remember, to hold things in your mind as you are working toward a goal. You actually need those skills to engage in therapy and also to engage in work or even social interactions."

Dr. Medalia's research on cognitive remediation spans the effectiveness of the treatment, factors that predict treatment success, and mediators of learning

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# Expansion of Lieber Center Enhances Research and Treatment Programs

**T**homas E. Smith, MD, an innovator in the development of psychiatric treatment approaches and research, has joined Columbia University Medical Center and the New York State Psychiatric Institute (NYSPI) to serve as Director of the Psychotic Disorders Service, which has been expanded to provide comprehensive psychiatric services to a wider population of patients.

Dr. Smith will oversee all clinical services for individuals with psychotic disorders at 3 locations: the NYSPI inpatient Schizophrenia Research Unit (SRU), the outpatient schizophrenia research clinic at NYSPI, and the new Lieber Clinic for Comprehensive Care at Columbia's East 60th Street outpatient faculty practice location.

“My goal is to dramatically increase the number of patients coming into the service,” noted Dr. Smith, referring to both The Lieber Center and NYSPI. Thus, among Dr. Smith's first actions will be to double the size of the SRU at NYSPI to a 24-bed unit, from its current 12-bed capacity. Moreover, with the expansion of services, the Department will be able to follow patients after discharge from the inpatient unit via the Lieber Clinic and the East 60th Street facility.

On the clinical side, the goal is to bring together the 3 sites and create an integrated service that provides comprehensive diagnostic evaluations, second opinions, psychopharmacology consults, and state-of-the-art treatment.

Physicians can also seek out the services of the Center for intensive psychosocial rehabilitation as an adjunct to current treatment. “Our goal is to accommodate everyone who needs our help,” noted Dr. Smith.

there are no fees or limitations on length-of-stay. Moreover, patients can get extended consults and evaluations when they participate in research protocols investigating the treatment and underlying physiology of schizophrenia.

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**Long-term, Dr. Smith sees the Center as offering unparalleled academic clinical programs that are heavily involved in research, with researchers' findings bringing new treatment possibilities to the clinical service.**

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The changes within the Psychotic Disorders Service have been made possible by the recent \$9 million endowment from Constance and Stephen Lieber. The funding has allowed Dr. Smith to return to the NewYork-Presbyterian Hospital after 5 years as the Medical Director at Hall-Brooke Behavioral Health Services, the Columbia-affiliated, 80-bed psychiatric hospital in Westport, CT, where he designed and implemented the Hall-Brooke/St. Vincent's Medical Center (Bridgeport) integrated psychiatry service. Before going to Hall-Brooke, Dr. Smith headed the schizophrenia rehabilitation program at the Payne Whitney Westchester Division of NewYork-Presbyterian Hospital.

According to Dr. Smith, the inpatient unit and outpatient research clinic at NYSPI form the “perfect union,” as

The expanded Lieber Center also boasts the prodromal clinic for people in their late teens and early 20s, run by Cheryl Corcoran, PhD. The clinic serves as a valuable resource for clinicians looking for a consult and evaluation for young patients.

Dr. Corcoran has published extensively on the prodromal phase and early lead-up to schizophrenia, specifically on the “risks of being at risk,” (including exposure to medication and stigma among false-positives). Her research focuses both on ethics and confidentiality issues for patients, families, and institutions. She has also examined the etiology and onset of “the stress cascade” and schizophrenia, and has done qualitative research on the evolution of symptoms in prodromal patients. She has looked at the biological effects of

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stress mediated by the hypothalamic–pituitary–adrenal axis, reviewing its neural effects.

The Center will offer a particularly strong psychosocial rehabilitation service; Alice Medalia, PhD, will enable the Center to offer a combination of cognitive remediation and social cognition skills training that are unique to NewYork-Presbyterian Hospital (see interview with Alice Medalia, PhD, page 5).

David Kimhy, PhD, who is on staff at the Center, is an award-winning cognitive-behavioral therapist. Dr. Kimhy uses cognitive-behavioral therapy to work with people in persistent psychotic states, and is “currently one of only a few clinicians in the tri-state area to advance this treatment,” according to Dr. Smith. The Center will also support the services research work of Susan Essock, PhD, especially her work on organization of services for people with schizophrenia, another example of research that is fundamental to the Center.

Additionally, Maria Karayiorgou, PhD, has joined Columbia University College of Physicians and Surgeons from Rockefeller University, where her research focused on the genetics and neurobiology of schizophrenia. This

work sought genes that affect neuronal cell migration abnormalities as well as overactivity of the dopaminergic pathways; she has also researched genes that affect these processes and whose mutations may contribute to susceptibility to schizophrenia. Her work has concentrated on the isolation of specific genes in order to examine and understand their role during normal brain development and function, and their mode of dysfunction in schizophrenia. Her goal is to understand the role of any identified susceptibility genes during normal brain development and function, as well as their mode of dysfunction in the disease. Dr. Karayiorgou has researched the genetics of obsessive-compulsive disorder, sorting out the components of susceptibility genes and environmental influences; she and colleagues have described a gene associated with increased risk for obsessive-compulsive disorder.

The Department has benefited from the groundbreaking work of its Chairman Jeffrey Lieberman, MD, who Dr. Smith calls “one of the leading clinical psychopharmacologists in the world.” Dr. Lieberman is looking at new antipsychotic agents as well as a class of new medications targeting cognitive enhancement, making it a leading institution for the study of

novel pharmacologic mechanisms and treatment approaches in schizophrenia. Long-term, Dr. Smith sees the Center as offering unparalleled academic clinical programs that are heavily involved in research, with researchers’ findings bringing new treatment possibilities to the clinical service, creating the synergy between clinical practice and research.

“I want to ensure that our clinical services are running smoothly, so that we can support our investigators and develop a state-of-the-art clinical operation,” said Dr. Smith. “We will be creating standards and protocols for clinical care and work on developing a clinical center of excellence, while at the same time, getting new research underway.”

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and motivation. For example, a study she published in *Schizophrenia Bulletin* (2005;31:942-953) revealed that illness factors are unlikely to influence the outcome of cognitive remediation. Key variables for success turned out to be both treatment intensity, with twice-weekly sessions being necessary, and the motivation of the patient to learn.

Current studies are investigating the application of NEAR to people with early Alzheimer’s disease and mild cognitive impairment, as well as examining whether people have insight into their own neurocognitive disorders and if this self-awareness can be increased. Additionally, a review of the NEAR method is now in press with the *American Journal of Psychiatric Rehabilitation*.

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brain that mediate perception, cognition, and emotional regulation. If a person experiences psychosis too long and has too many recurrent episodes, then their capacity to recover is diminished.”

Dr. Lieberman carried out 1 of the earliest comprehensive studies of first-episode schizophrenia, using magnetic resonance imaging brain scans to show a progressive loss of brain matter in the temporal and frontal cortices (*Biological Psychology* 2001;50:884-897). The study formed the basis for his subsequent investigation into how first-episode patients fared on haloperidol (Haldol, Ortho-McNeil), the standard regimen, versus olanzapine (Zyprexa, Lilly), a specialized treatment approach. This randomized, controlled, double-blind longitudinal study found that patients on the atypical antipsychotic olanzapine showed less reduction in gray matter, whereas haloperidol-treated patients had significant gray matter loss. Results appeared in the *Archives of General Psychiatry* (2005;62:361-370).

Dr. Lieberman also served as principal investigator of CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness), the National

Institutes of Mental Health (NIMH)-sponsored trial that evaluated the clinical effectiveness of marketed antipsychotics. Initial Phase I results were published in *The New England Journal of Medicine* (2005;353:1209-1223) and have continued to be published over the ensuing 2 years, culminating in a public access database on the NIMH Web site in September 2007.

CATIE is now being extended by the NIMH as the Schizophrenia Trials Network (STN).

“Unfortunately, CATIE found that there’s not nearly as much progress as we’d hoped with the second generation of antipsychotic medications. To remedy this, STN will work to verify how effective any of these new treatments are and to test novel strategies that will produce innovation and advances in the treatment of schizophrenia,” said Dr. Lieberman.

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#### Psychiatry Newsletter

Published by  
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