

ADVANCES IN ADULT, CHILD, AND ADOLESCENT PSYCHIATRY

Affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medical College

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Changing the Course of Schizophrenia Through Early Detection and Intervention

An emerging understanding of schizophrenia has led to an innovative care model developed for individuals with first-episode psychosis that aims to foster recovery and prevent disability. The model maintains that effective treatment targeting the early stage of illness has the greatest potential to limit the progression of the illness and maximize achievement of age-appropriate advances in social development, education, and functioning in the workplace.

"The time is right for early intervention, for early detection, and optimal treatment for people with diseases like schizophrenia," says Lisa B. Dixon, MD, MPH, Director of the Center for Practice Innovations, Columbia Psychiatry, New York State Psychiatric Institute. As principal investigator of the Recovery After Initial Schizophrenia Episode – Implementation and Evaluation Study (RAISE-IES), funded by the National Institute of Mental Health of the National Institutes of Health, Dr. Dixon, along with co-investigator Jeffrey A. Lieberman, MD, Chairman of Psychiatry at Columbia University College of Physicians and Surgeons and Director of the New York



State Psychiatric Institute, described their work in the August 2013 issue of the *Journal of the American Medical Association*.

"Our study builds on evidence that if we intervene and treat as early as possible after the onset of psychosis with optimized services, we may be able to fundamentally change the trajectory of the illness," says Dr. Dixon, whose work over the last 30 years has

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Timing Therapies for Anxiety Disorders in Adolescence: A Vertically Integrated Translational Approach

Disorders of anxiety and stress are among the most common of the psychiatric disorders, with about 20 percent of the population affected over their lifespan. The prevalence of anxiety disorders in youth is particularly high, affecting as many as one in 10.

"Adolescence is a life stage during which the differential developmental trajectories of regions of the brain that generate fear responses and those that regulate them are imbalanced," says B.J. Casey, PhD, Director of the Sackler Institute for Developmental Biology at Weill Cornell Medical College. "Anxiety disorders actually peak during this period. One of my goals has been to try to understand what is going on in the adolescent brain that might make

an individual more susceptible to an anxiety disorder and, more importantly, to predict who is going to respond to treatment."

Dr. Casey – a cognitive neuroscientist – is not alone in her quest. She is joined in this effort by Francis S. Lee, MD, PhD, Vice Chair for Research for the Department of Psychiatry and a basic molecular neurobiologist, and Charles E. Glatt, MD, PhD, a clinical psychiatrist and basic human geneticist. Their work, recently published in the *Annual Review of Medicine*, has been focused on what they identify as a fundamental issue in psychiatric medicine – the lack of empirical evidence indicating when, during development, a treatment will be most effective for a patient.

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Changing the Course of Schizophrenia Through Early Detection and Intervention

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focused on developing and implementing quality services for people with schizophrenia, bipolar disorder, and other serious mental illnesses.

Schizophrenia, which affects one percent of the population, is clinically manifested by psychosis and cognitive symptoms that typically emerge in adolescence and early adulthood. It follows a course often characterized by recurrent exacerbations and remissions, which can result in an ongoing state of residual symptoms and functional impairment.

The National Institute of Mental Health funded the RAISE Connection Program study as part a nationwide effort to develop an optimal early intervention strategy for treating people experiencing a first episode of the psychotic symptoms of schizophrenia. The study included a team of researchers from Columbia University Medical Center, University of Maryland, University of North Carolina, UCLA, Dartmouth College, and Harvard University whose goal was to develop an evidence-based strategic intervention for early psychosis that can be facilitated both in community-based and public mental health settings, and in private clinical practice settings. Since failure of clinicians to engage people with psychosis in treatment is a major problem in providing effective treatments for people with schizophrenia, the intervention emphasizes shared decision making and engagement in treatment.

The New York State Office of Mental Health, a partner in the RAISE program, has helped to establish fully dedicated multidisciplinary first-episode psychosis teams that provide approximately two years of treatment services tailored to meet each person's needs.

Among the services offered are illness management, medication, family psycho-education, substance abuse treatment, and supported employment and education.

"Historically, schizophrenia was thought to have devastating consequences," says Dr. Lieberman.

"However, the advent of anti-psychotic drugs, the development of psychosocial treatments, and accounts from individuals diagnosed with schizophrenia who have recovered have begun to change the perceptions and expectations of clinicians and the public. In addition, a growing body of research in the last two decades has increasingly justified optimism for the development of a comprehensive strategy with the potential to minimize, if not prevent, the cumulative morbidity of this once debilitating disease."



Dr. Jeffrey A. Lieberman

The new care model is designed for patients with first-episode schizophrenia and offers multi-element and multidisciplinary treatment. "This includes medications that are prescribed within the context of what we call 'shared decision making,' so that we are really working with the individual to help him or her make decisions," says Dr. Dixon. "You start with the lowest possible doses because these individuals are both highly sensitive to side effects, and, typically, highly responsive to treatment."

Helping Individuals and Families to Stay On Track

While ensuring adherence to the pharmacologic regimen is critical, says Dr. Dixon, medications alone are insufficient. "There are a

number of other components to treatment, including family support and education," she says. "Individuals with these disorders tend to be between the ages of 15 and 30. While this is a time of maturing and separation from family, the family still tends to be quite involved. Also, the teenager is most likely living with the family, which can create a real crisis for all involved. It's very important to work with the family on behalf of the young person who is experiencing this. Intervention also includes individual therapy and support, helping the person to understand what is going on."

Dr. Dixon also directs OnTrackNY/Connections, a New York State Office of Mental Health treatment program at the Center for Practice Innovations for adolescents and young adults who are experiencing their first episode of psychosis. "Participants work actively with the entire treatment team, which includes a psychiatrist, nurse, social workers, mental health clinicians, and an employment specialist," says Dr. Dixon. "Our aim is to help these young people stay on track and to achieve their goals for school, work, and relationships. Everybody is at the table together problem-solving and trying to figure out what is best for the individual."



Dr. Lisa B. Dixon

Other key elements of the care model for proactive treatment include cognitive behavioral approaches, including skills-based stress management, and supported employment and supported education. "These interventions give the young person the help they need to stay in work or school," says Dr. Dixon. "This support could involve just talking through their anxiety about dealing with co-workers or explaining long absences. We are really good at engaging people; we lose very few people in our program. If you engage them and work with them, in many cases, you can keep them out of the hospital."

"I think the most important thing about this approach is that it is oriented around the notion that people can achieve and people can adapt," adds Dr. Dixon. "We believe there is evidence to support that if you approach people with a sense of promise, hope, and shared decision-making they can achieve and learn to manage their illness whatever it turns out to be. It's a very different approach than a traditional medical model."

As the RAISE grant comes to a close, Columbia University, in collaboration with the New York State Office of Mental Health, is continuing the OnTrackNY/Connections clinical program and will also oversee its rollout in three other sites in New York State.

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Timing Therapies for Anxiety Disorders in Adolescence (continued from page 1)

The Intersection of Mouse Studies and Human Applications

Drs. Glatt and Lee work predominantly in the mouse model; Dr. Casey's work is more translational. Their goal is to understand some of the same circuitry, as well as the effects of the same genes examined in mouse models, in the developing human brain. "B.J., Charles, and I have been able to come up with an organized way of thinking about this, which is to go from the bottom up," says Dr. Lee. "We study genes and make mouse models together, and we collaborate on which genes to target for these various mouse models. Then we do parallel studies between mice and humans. Each step of the way in the preclinical studies, we gain greater confidence in that we're studying something that is relevant to humans, but that is also grounded in reproducible, basic neuroscience findings."

In both the human and mouse studies, Drs. Casey, Lee, and Glatt actually showed that adolescents, unlike children or adults, don't seem to extinguish fear as readily. "These data are really provocative," says Dr. Casey. "They suggest that adolescence is a period of time when you may need to try an alternative approach to alleviate their anxiety. If patients present in the clinic in childhood, that's a good time to start cognitive behavioral therapy; however, if they come in as a teenager, CBT may not be the most effective approach. So, this might be a point at which medications may be

necessary. What's important is that we establish the foundation for evidenced-based, novel treatments."

Dr. Casey's work is informed, in part, by the imbalance model of adolescence, which links structural and functional brain changes in brain circuitry mediating emotional reactivity and regulation to their behavioral consequences. "While the amygdala, a subcortical structure that mediates fear learning and reactivity, appears to be functionally mature early in life, the prefrontal cortex,

which is involved in emotion regulation, continues to develop well into young adulthood," explains Dr. Casey. "These distinct region-specific developmental trajectories may lead to an imbalance in how these structures drive behavior during adolescence. As a result, teenagers show elevated emotional reactivity that is more



Dr. B.J. Casey

difficult to regulate. We needed to think of this at a circuitry level, which we can do with neuroimaging, and not just focus on a single brain region."

What has helped the Weill Cornell researchers and others in this line of research is that certain aspects of how fear is regulated is actually

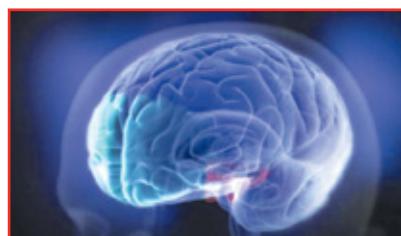
preserved across many species – from mice, to rats, to primates, to humans. "There's almost a one-to-one correspondence in the circuitry," says Dr. Lee. "We could also study the mice through the stages of infancy, childhood, adolescence, and adulthood – within six to eight weeks – because the lifespan of a mouse is so short. This enabled us to map behaviors and generate hypotheses about the impact of a variant across developmental stages."

With her expertise in neuroimaging in children, adolescents, and adults, Dr. Casey brings to the table the capacity to look at various, discrete transition stages from childhood to adolescence and adolescence to adulthood. "Our first step was to describe findings from human imaging studies that show the changes in neural circuitry that underlie the features of anxiety in healthy individuals during the transition into and out of adolescence," says Dr. Casey.

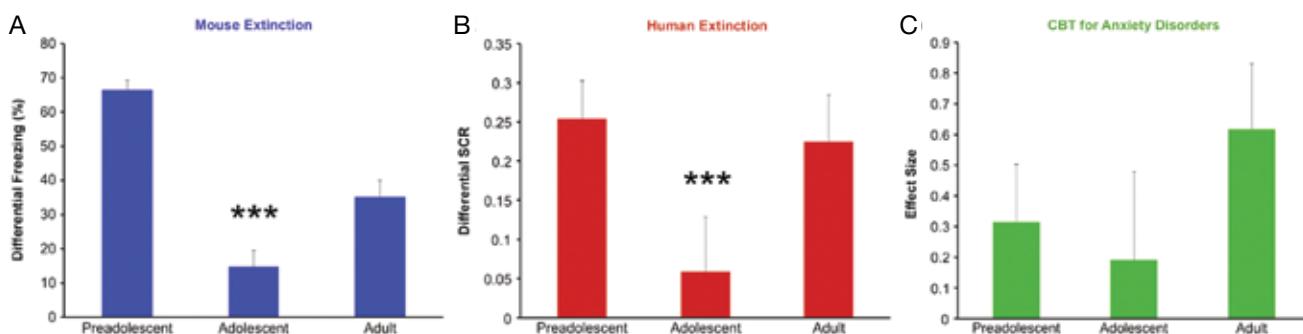
The researchers then sought to provide comparable evidence in humans and in mice for tempering basic fear regulation processes during adolescence and the biological mechanisms that correspond to the human imaging work. From this, they pursued a translational genetic approach from mouse to human to identify individual factors that alter fear regulation and the underlying neural circuitry during adolescence.

"We try to do as much as possible between the mouse and the human," says Dr. Lee. "We can do studies with greater precision in the mouse. For example, we can map the circuitry or do biochemistry within the mouse brain that we obviously can't do in humans. On the other hand, we are able to do many more complex investigations within the human in terms of behavioral and cognitive neuroscience than we could ever do in the mouse."

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Representative illustration of frontolimbic circuitry, highlighting the earlier developing limbic areas (red) and later developing prefrontal cortex (green) suggested by the imbalance model of adolescence (Reproduced with permission from Larkin McPhee)



A) Adolescent mice show diminished extinction learning relative to adults and preadolescents; B) Human adolescents show diminished fear extinction learning as indexed by skin conductance responses (SCR) compared with adults and children; C) Comparing response rates for cognitive behavioral therapy across age groups reveals a nonsignificant pattern in which adolescents show reduced treatment efficacy.

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On the Road to Precision Medicine

Their ultimate goal, notes Dr. Glatt, is to improve treatment for psychiatric disorders through personalized medicine. "There is a general belief that there are genetic components to every psychiatric disorder. If we could identify these it would help us to target treatments to the people who are most likely to respond. That's where the mouse model comes in."

According to Dr. Glatt, the mice are genetically identical except for the one variant they've introduced. Additionally, because it is easier to generate a huge number of mice that are exactly the same age, the researchers can identify the developmental differences much more precisely. "We're constantly going back and forth between the mouse and the human to make sure that what we're seeing in the mouse grounds or constrains the way we look at the human data."

"The next steps are two-fold," says Dr. Lee. "We know that there is a heritable component in anxiety disorders, bipolar

disorders, schizophrenia, and other psychiatric disorders.

What we're trying to do is to gain precision by identifying biological biomarkers that we can study in both mice and humans to see if any of them can act in clinical practice."

"With the three of us working so closely together, all of our respective areas

of expertise really inform each other's work in the pursuit of understanding genetic and developmental variability," says Dr. Glatt. "In my experience, this is a very unique collaboration."

This collaboration has been further enhanced with the appointment of John T. Walkup, MD, as Director of Child and Adolescent Psychiatry at Weill Cornell. Dr. Walkup is a physician-scientist who has conducted definitive trials on anxiety treatment in children and adolescents. Says Dr. Casey, "John is a really caring physician who is constantly keeping us in check, bringing our research back to what he's observing in the clinic – when the treatments are working for teens and when they're not."

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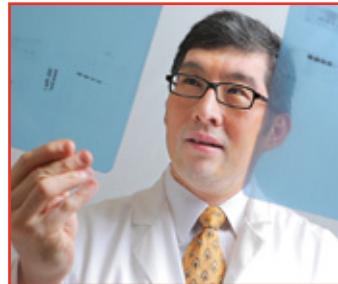
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