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Bridging Clinical and Neurobiological Approaches in Psychiatry: OCD as a Prime Example

Contributing faculty: **Helen B. Simpson, MD, PhD**

In 1982, the Anxiety Disorders Clinic at the New York State Psychiatric Institute (NYSPI)/Columbia University Medical Center was one of the first research clinics in the country established to study the pathophysiology and treatments



of anxiety and related disorders. The Anxiety Disorders Clinic continues to study these disorders and improve treatment outcomes by developing new therapeutic strategies, using imaging technologies to elucidate the brain mechanisms underlying their symptoms, and applying evidence-based practices to patient care.

"Psychiatry is undergoing major changes through the integration of clinical and

neurobiological research," says Helen Blair Simpson, MD, PhD, Professor of Clinical Psychiatry at Columbia University College of Physicians and Surgeons and Director of the Anxiety Disorders Clinic at NYSPI. "We are bringing together the expertise of psychiatrists, psychologists, neurologists, neurosurgeons, and neuroscientists. Our goal is to advance not only science, but also patient care."

A case in point is Dr. Simpson's research program on obsessive-compulsive disorder (OCD). OCD affects more than two million adults in this country, with symptoms often appearing in childhood or adolescence. The disorder can be debilitating – preventing individuals from working, completing day-to-day responsibilities, or enjoying a normal lifestyle.

"OCD is more prevalent than schizophrenia and, tragically, 25 percent of cases are diagnosed by age 14," says Dr. Simpson. "It typically has a chronic waxing and waning course with a very high proportion of serious and moderate cases. Not the most common anxiety disorder, OCD is arguably among the most severe."

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Balloon-Assisted Coil Embolization Does Not Increase Periprocedural Complications

Contributing faculty: **Y. Pierre Gobin, MD, and Athos Patsalides, MD**

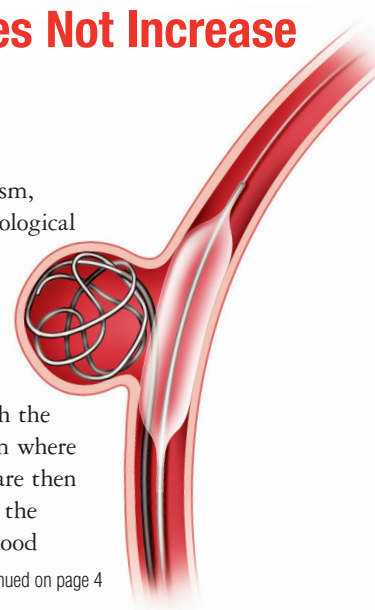
Two decades ago, Y. Pierre Gobin, MD, now Director of Interventional Neuroradiology at NewYork-Presbyterian/Weill Cornell, performed the first case in France of coil embolization of an intracranial aneurysm. Since that time, Dr. Gobin, who came to Weill Cornell in 2001, has improved the technique using balloon-assisted coil embolization.

Today, coil endovascular treatment is considered a first-line treatment for the management of most intracranial aneurysms. It is generally used in

patients with small neck aneurysm, multiple aneurysms, severe neurological grade, posterior fossa location, and early vasospasm.

In conventional coil embolization (CCE), the coil is introduced through a micro catheter that is threaded through the artery directly into the aneurysm where the coils are released. The coils are then packed into the aneurysm up to the point where it arises from the blood

Balloon-Assisted Coil Embolization, continued on page 4



Using Digital Trend Analysis of EEGs to Capture Pediatric Seizures

Contributing faculty: **Cigdem I. Akman, MD**

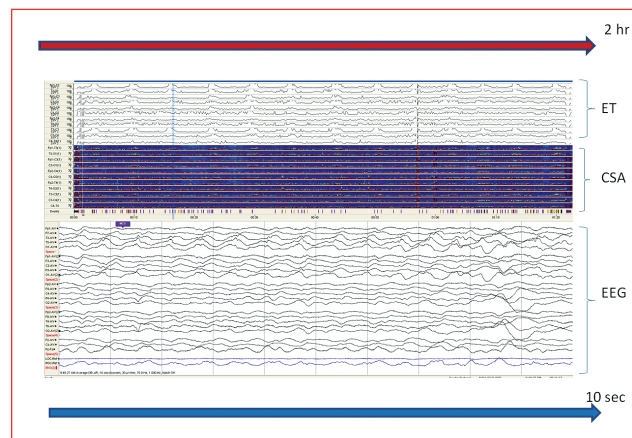
When evaluating seizure activity in critically ill children in the Pediatric Intensive Care Unit (ICU) or the Newborn ICU, it is critical to read the EEG in a timely manner. Using the conventional method to review a 12-hour-long EEG takes about 25 minutes. “EEG monitoring is important for the early detection of seizures during the course of critical illness,” says Cigdem I. Akman, MD, Director of Pediatric Epilepsy at NewYork-Presbyterian/Morgan Stanley Children’s Hospital. “However, the logistics of real-time EEG interpretation is challenging for neuro-physiology and critical care medicine teams.”

To determine if this process can be accelerated, Dr. Akman and her colleagues conducted a study evaluating digital trend analysis (DTA) and factors that might affect its usefulness for rapid identification of seizures. DTA provides a compressed EEG analysis in a graphic format that condenses EEG data compiled over several hours on to a single page. By clicking on an area questionable for seizure, the clinician can obtain more specific information to determine if a seizure did occur, particularly in children who have no clinical manifestations. However, compressing the time span may obscure brief clinical or EEG events and result in inexperienced users identifying artifacts that mimic seizures.

The research team identified newborns and children between 2007 and 2009 who underwent EEG video monitoring, evaluating 166 seizures. “We used two methods to

evaluate this data – each with advantages and disadvantages,” explains Dr. Akman. “One method, compressed spectral array [CSA] analysis, converts raw EEG waveforms to condensed color displays that clarify patterns in long-term recordings. The second method – envelope trend [ET] – looks at changes and variations in the mean amplitude of the EEG potentials. Together, they determine EEG power, which is a function of the frequency and amplitude of the activity. We then compared the conventional EEG data to the computerized EEG.”

The researchers found that a number of factors affected accurate seizure detection, including the interpreter’s experience, display size, and type of DTA methods used for analysis. “Envelope trend was more dependent on user experience,” says Dr. Akman. “Display size and multimodal DTA application, in our case CSA and ET combined, increased the sensitivity of seizure detection for the experienced user compared to inexperienced users. Without the presence of a conventional EEG recording, however, artifacts were reported as seizures regardless of the user’s experience.”

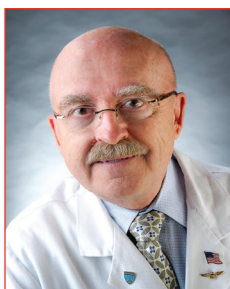


ET and CSA depict an entire EEG study on a single page. EEG demonstrated repetitive seizures with low amplitude arising from the left hemisphere in a newborn. Trend methods revealed the cyclical appearance of seizures, which were better visualized using ET compared to CSA trend.

In addition, the study demonstrated that the maximum spike amplitude, seizure duration, and seizure frequency were other important determinants for accuracy. ET was better at detecting electrographic seizures with shorter duration; both ET and CSA readily detected repetitive seizures. “While DTA does facilitate identification of seizures,” says Dr. Akman, “we believe the overall accuracy of seizure detection increases when multimodal trending is used simultaneously. The conventional EEG recording remains indispensable to identify the electrographic feature of seizures. Once this is established, digital trending analysis can help neurophysiologists to review EEG files timely in selected populations of patients with critical illness.”

AANS Awards the 2012 Harvey Cushing Medal to Dr. Donald Quest

Over the past 35 years, Donald O. Quest, MD, the J. Lawrence Pool Professor of Neurological Surgery at Columbia University College of Physicians and Surgeons, has led a distinguished and multifaceted career. In recognition of his many years of outstanding leadership and contributions to the field of neurosurgery, Dr. Quest was awarded the 2012 Harvey Cushing Medal, the highest honor granted by the American Association of Neurological Surgeons. After completing his residency in general neurosurgery in 1976 at Columbia’s Neurological Institute, Dr. Quest went on to specialize in carotid artery surgery and cervical and lumbar spine disease. Pursuing his interests in neurosurgical training, he was elected a Director of the American Board of Neurological Surgeons, becoming



Dr. Donald O. Quest

Secretary and Chairman of the organization. He was also appointed to the American Council of Graduate Medical Education’s Residency Review Committee for Neurological Surgery, where he served as Chairman for six years. Today, Dr. Quest is an Assistant Dean of Students at Columbia University, serving as advisor, mentor, and advocate for each medical school class. Throughout his tenure, Dr. Quest – who continues as a practicing neurosurgeon with the Spine Center – has held a number of leadership positions, serving as Vice Chairman and Acting Chairman of Neurological Surgery at Columbia University Medical Center and as President of the Congress of Neurological Surgeons, the Academy of Neurological Surgeons, and the American Association of Neurological Surgeons.

Bridging Approaches, continued from cover

"For patients of today, we examine how to combine and sequence pharmacotherapy and psychotherapy and explore novel treatment strategies to maximize outcome," says Dr. Simpson. "For patients of tomorrow, we collaborate with experts in neuroimaging, genetics, and basic science to study the underlying brain mechanisms of obsessions, compulsions, and anxiety. Our goal is to identify novel targets for treatment development."

According to Dr. Simpson, the content of obsessions and compulsions varies among individuals, which raises several questions: Do all patients with OCD have the same underlying neurobiology? How do medications or psychotherapy affect the brain in a causal way and improve symptoms? Can a patient's brain be rewired to improve their functioning in the world?

First-line treatments for OCD are 1) medications called serotonin reuptake inhibitors (SRIs) and 2) cognitive behavioral therapy involving exposure and response/ritual prevention (EX/RP). EX/RP consists of confronting feared situations without performing rituals. Acute treatment usually consists of about 20 sessions, with assignments between sessions. "With successful treatment, patients learn not to fear these situations and stop spending hours ritualizing," says Dr. Simpson. "EX/RP can transform peoples' lives."

Dr. Simpson and her colleagues have found that EX/RP for OCD can be superior to SRIs when delivered intensively by skilled therapists to patients without significant depression. They have also found that providing EX/RP to OCD patients with a partial SRI response can help many then achieve minimal symptoms (i.e., remission). "One question for future research," says Dr. Simpson, "is whether patients on SRIs who attain remission after the addition of EX/RP can maintain remission if they then discontinue their SRI."

Dr. Simpson is funded by the National Institutes of Mental Health (NIMH) to address this important clinical question, and her team is currently recruiting adults on SRIs who might be interested in participating; if eligible, all will first receive EX/RP (at no cost to the patient) delivered by Dr. Simpson's expert team. "Another important question is why, even when we give people our best two treatments, some, but not all, achieve remission," says

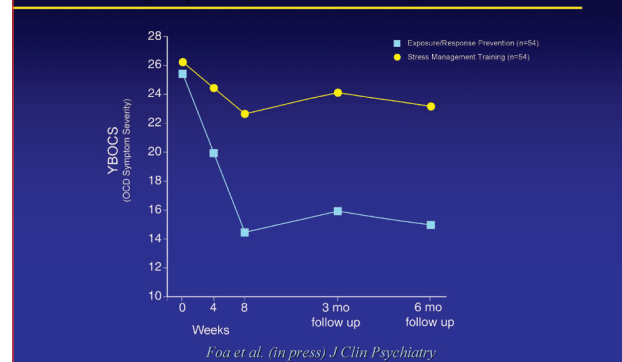
Dr. Simpson. To address this question, Dr. Simpson and her team are studying novel treatments. For example, she is collaborating with Drs. Moira Rynn and Dikoma Shungu to examine the effects of medications that modulate the glutamate system in pediatric OCD patients on SRIs. In adults with OCD, Dr. Simpson and her team are also studying intravenous ketamine, which is thought to affect the glutamate system, and transcranial magnetic stimulation.

Developing the next generation of clinician-scientists who take a translational approach to clinical research is a significant goal of Dr. Simpson's program. Her team includes MD and PhD level clinicians and scientists, research assistants, and volunteers, all working to develop novel treatments based on emerging findings in neuroscience. For example, Anthony Pinto, PhD, an Assistant Professor at Columbia University, is studying obsessive compulsive personality disorder and its relation to OCD. Carolyn Rodriguez, MD, PhD, an Assistant Professor at Columbia University, who leads the ketamine study described above, is also designing innovative approaches for people with hoarding disorder.

The "New" Psychiatry

Looking forward, Dr. Simpson wants to uncover the root cause of abnormal behavior. To date, her work has focused primarily on investigating neurochemical abnormalities in fronto-striatal brain circuits that have been hypothesized to underlie OCD. In collaboration with Anissa Abi-Dargham, MD, Chief of Translational Imaging in the Department of Psychiatry, Dr. Simpson explored the long-standing theory that abnormalities exist in the brain's serotonin system. Collaborating with Drs. Dikoma Shungu and Lawrence Kegeles, she has also examined the main excitatory and inhibitory neurochemicals in the brain: glutamate and GABA. One method uses positron emission tomography imaging and radio-tracers to target different aspects of the serotonin system. Another uses magnetic

Durability of response as augmentation



OCD patients on SRIs who received exposure and response prevention for 8 weeks had a clinically significant decrease in their OCD symptoms as measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score and maintained this response at 6-month follow-up.

resonance spectroscopy to measure glutamate and GABA metabolites. These imaging studies can determine whether OCD patients have abnormalities in these neurochemical systems and the impact of treatment on the brain.

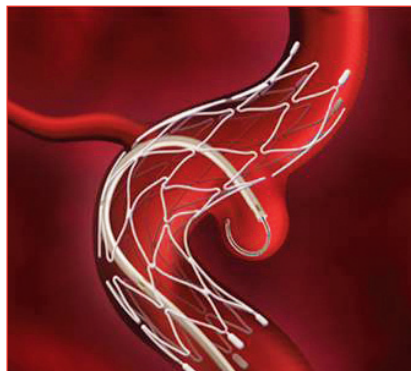
With more questions than answers, Dr. Simpson has taken her research to a more basic level – hoping to bridge clinical and neurobiological approaches by collaborating with basic scientists who are developing animal models of OCD-like behaviors. Working with Susanne E. Ahmari, MD, PhD, and others in the Department of Psychiatry, Dr. Simpson uses preclinical data to guide human studies, and human data to guide animal modeling, by identifying markers of neural dysfunction in humans for use in animals, studying genes associated with OCD in mice, and investigating brain circuits implicated in OCD in animals. With funding from the NIMH, Dr. Ahmari is developing a mouse model with the gene with the strongest associations to date with OCD in humans.

"The field of psychiatry is poised to establish bridges between clinical and neurobiological approaches," says Dr. Simpson. "The New York State Psychiatric Institute, together with Columbia University Medical Center at Columbia University, is a research powerhouse with basic scientists and clinical researchers housed under the same roof. Integration of basic, translational, and clinical research between psychiatry and the neurosciences holds the key to an exciting future for clinicians and patients alike."

For more information on clinical trials, visit www.Columbia-OCD.org.

Balloon-Assisted Coil Embolization, continued from cover

vessel, preventing blood flow from entering the aneurysm. “When there is a small neck aneurysm, we can put the catheter into the aneurysm and just fill it with coils,” explains Dr. Gobin. “An



Stent-assisted coiling

aneurysm with a large opening cannot be treated as successfully with the conventional approach, and an additional device, such as a stent or a balloon, may be needed to help keep the coils in place. Stent-assisted coiling involves placing a stent in the vessel adjacent to the aneurysm to provide a scaffolding

of support that keeps the coils within the aneurysm sac. But the stent remains permanently in place, requiring the patient to be on blood thinners. Balloon-assisted coil embolization involves placing a balloon adjacent to the aneurysm while coils are positioned in the aneurysm. When a balloon is inflated into the vessel, we are able to pack more coils into the aneurysm. The balloon is then removed. The procedure is a little more complex, but much more effective.”

Studies of BACE for the treatment of complex and wide-neck intracranial aneurysms over the years by a variety of research teams in the U.S. and abroad have demonstrated mixed results related to adverse events. “The procedure is certainly more difficult because in addition to placing the micro catheter into the aneurysm, you also need to insert the balloon into the parent artery that bears the aneurysm,” explains Dr. Gobin.

Dr. Gobin and his team use BACE in approximately 30 percent of their cases of both ruptured and unruptured aneurysms. Their experience with the procedure has minimized its risk, with recurrences after treatment infrequent. “With difficult cases, we use the balloon to pack the aneurysm with coils so it doesn’t recur,” says Dr. Gobin. “Our re-treatment rate is 5 percent versus the nationwide average of 15 to 20 percent.”

In their recent study, published online in the June 22, 2012 issue of the *Journal of Neurointerventional Surgery*, Dr. Gobin and Athos Patsalides, MD, present a retrospective review of their combined experience over the past 10 years with 428 consecutive patients with 491 intracranial aneurysms (274 acutely ruptured and 217 unruptured) treated with CCE or with the BACE technique. Their examination of the two groups revealed the following:

- risk of thromboembolic events and device-related problems was similar between the CCE and BACE groups
- a trend towards a higher risk (not statistically significant) of intraprocedural aneurysm rupture in the BACE group
- no statistically significant difference in the morbidity, mortality, and cumulative morbidity and mortality rates between the two groups

The study is among the very few large studies that provide a comparison of the rate of periprocedural complications in both BACE and CCE groups. The researchers concluded that in this series of patients with acutely ruptured and unruptured aneurysms, the BACE technique allowed aneurysms with unfavorable anatomic characteristics to be treated without increasing the incidence of procedural complications.

BACE: An Indispensable Tool

Dr. Gobin proposes the use of BACE in very small aneurysms with increased risk of rupture. “While some would argue that positioning a balloon across the aneurysm neck when CCE is feasible carries an increased thromboembolic risk, we feel that in the event of rupture, the balloon serves as a safety net that can be used to minimize bleeding and promote intra-aneurysmal thrombosis.”

“There is a risk that during the coil embolization you will puncture the aneurysm and that it will rupture and bleed,” adds Dr. Patsalides, Alvina and Willis Murphy Assistant Professor of Neurological Surgery at Weill Cornell and a co-author on the study. “But if you have a balloon across the aneurysm opening, you can inflate it and immediately stop the bleeding, giving you time to fill the aneurysm with more coils. In a separate study

In the event of rupture, the balloon serves as a safety net that can be used to minimize bleeding and promote intra-aneurysmal thrombosis.

focusing on patients who had aneurysmal rupture during the embolization, we have shown that if a rupture occurs, patients do much better if the balloon is in place because we can control the bleeding immediately.”

“In cases where patients arrive with an acute hemorrhage, the procedure is always more difficult because the wall of the aneurysm is very weak,” says Dr. Gobin. “In these cases, I like to have a balloon on standby. I place the balloon across the aneurysm neck and inside the blood vessel but do not inflate it. I then put the micro catheter into the aneurysm and do the procedure with coiling. If a rupture occurs, I’ll immediately inflate the balloon and the bleeding stops. So it’s an adjunctive tool that I find indispensable.”

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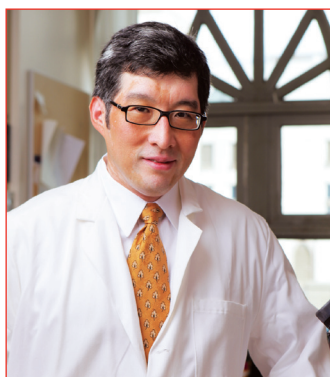
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Investigating Neuronal Cell Biology to Improve Care of Neuropsychiatric Disorders

Contributing faculty: **Francis S. Lee, MD, PhD**

Understanding the cell biology of the nervous system is the focus of research by Francis S. Lee, MD, PhD, Vice Chair for Research in the Department of Psychiatry at Weill Cornell Medical College. In his basic science laboratory, Dr. Lee is investigating the basic molecular and neural mechanisms of depression, anxiety disorder, and



Dr. Francis S. Lee

other mental illnesses. His work, which calls on genetic models to delineate the role of growth factors in complex behaviors related to the pathophysiology and treatment of these disorders, is addressing basic cell biology questions of how a family of growth factors, neurotrophins, are sorted in and secreted from neurons.

Dr. Lee has shown that a common single nucleotide polymorphism (SNP) in brain-derived neurotrophic factor (BDNF), leads to defective BDNF trafficking in neurons. "In humans, this genetic alteration has also been associated with alterations in brain anatomy and memory, but its relevance to clinical disorders is unclear," says Dr. Lee.

Using a novel "knock-in" mouse model of this BDNF SNP, Dr. Lee determined that this SNP may lead to increased forms of anxiety that are resistant to standard drug treatments. The findings suggest that this BDNF SNP may predict patients' responses to drug treatment and could lead to diagnostic testing to guide the treatment of depression,

replacing the current "trial-and-error" method.

Most recently, in collaboration with Weill Cornell's B.J. Casey, PhD, Director, The Sackler Institute for Developmental Psychobiology, and John T. Walkup, MD, Vice Chair of Psychiatry and Director of the Division of Child and Adolescent Psychiatry at Weill

Cornell, Dr. Lee has been

studying the impact of this polymorphism in both mice and humans on fear-based behaviors across development.

Dr. Lee's laboratory has identified a novel form of brain plasticity in fear learning during early adolescence that may prove informative for understanding endogenous mechanisms to suppress unwanted fear memories. "By examining fear conditioning in mice as they transitioned into and out of adolescence, we found that a suppression of contextual fear occurs during adolescence," says Dr. Lee. "Although contextual fear memories were not expressed during early adolescence, they could be retrieved and expressed as the mice transitioned out of adolescence."

In parallel studies, Dr. Lee and his colleagues also examined fear-extinction learning across development in mice and humans. Currently, the only evidence-based behavioral treatment for anxiety and stress-related disorders involves desensitization techniques that rely on principles of extinction learning. However, 40 percent of patients do

not respond to this treatment. "Prior research has focused on individual differences in treatment response, but have not examined when, during development, such treatments may be most effective," says Dr. Lee. "Our studies revealed attenuated extinction learning during adolescence, suggesting that a lack of synaptic plasticity in the prefrontal regions during adolescence is associated with blunted regulation of fear extinction. This provides insight into when exposure therapies during adolescent development may be most effective."

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NewYork-Presbyterian: A Member of NeuroNEXT

NewYork-Presbyterian Hospital is one of 25 sites in the United States selected to participate in NeuroNEXT – the Network for Excellence in Neuroscience Clinical Trials. Created to conduct studies of treatments for neurological diseases through partnerships with academia, private foundations, and industry, NeuroNEXT is expanding the capabilities of the National Institute of Neurological Disorders and Stroke in therapeutic research.

At NewYork-Presbyterian, NeuroNEXT is led by site principal investigators Karen S. Marder, MD, MPH, Sally Kerlin Professor of Neurology and Psychiatry and head of the Division of Aging and Dementia, and Claudia A. Chiriboga, MD, MPH, Interim Director,

Division of Pediatric Neurology, both at NewYork-Presbyterian/Columbia, and Claire Henchcliffe, MD, DPhil, Director of the Parkinson's Institute at NewYork-Presbyterian/Weill Cornell.

The unique endeavor provides a robust, standardized, and accessible infrastructure to facilitate rapid development and implementation of protocols in neurological disorders affecting adult and pediatric populations. NeuroNEXT is expected to expand the pool of experienced clinical investigators and research staff prepared to lead multicenter clinical research trials and decrease the time and cost between trial design and trial completion.



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