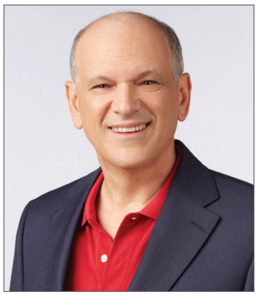
Icahn School of Medicine at Mount Sinai

The Friedman Brain Institute

FALL 2017 | DIRECTOR'S REPORT | www.mountsinai.org/fbi

Building a World-Class Epilepsy Program



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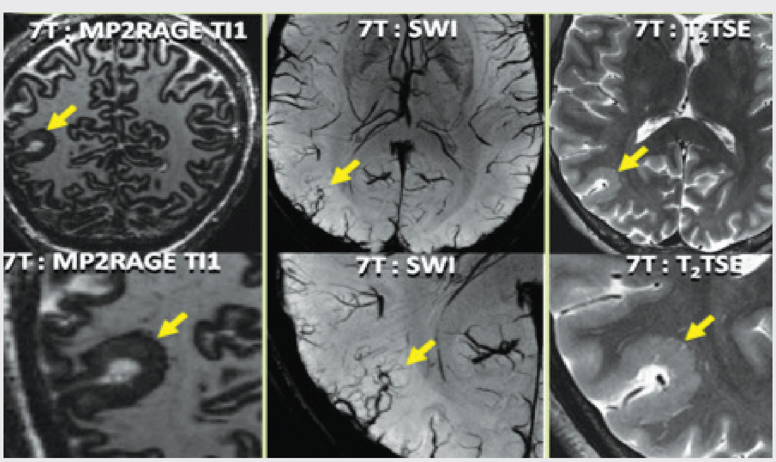
Epilepsy describes a collection of neurological disorders that are characterized by episodes of excessive brain activity manifesting as seizures. Classic seizures—called generalized or tonic-clonic seizures—are the most severe, as individuals lose consciousness and their entire bodies shake.

Many other types of seizures can present in very different ways, including focal seizures that affect more limited parts of the brain and body, in some cases presenting with predominantly psychiatric symptoms.

Epilepsy can be caused by brain trauma, brain tumors, localized congenital abnormalities in the brain, metabolic derangements, and rare genetic mutations, but most cases have no known cause. More common among children with a range of other neurological or psychiatric symptoms, epilepsy is often disabling and incompatible with normal social and occupational function. Unfortunately, today's range of anti-seizure medications works fully in only approximately 70 percent of all affected patients. Surgical treatments that remove the site in the brain where seizures originate can lead to dramatic improvements, but the challenge is to optimize identification of this site. Clinicians would also need a better understanding of which patients would respond best to surgical treatment.

The Mount Sinai Epilepsy Program—through clinical and research efforts under way at three of our hospital campuses—aims to build one of the world's foremost epilepsy treatment and research programs by integrating efforts across neurology, neurosurgery, radiology, neuropathology, psychiatry, and basic neuroscience. Our strategy is to break down the barrier between laboratory and clinic to obtain the most penetrating information about individual patients, and to use that information—along with studies in animal and cell models—to devise the most effective personalized treatment, at the same time driving an improved understanding of brain function under normal and pathological conditions.

A Brave New World for Epilepsy Treatment



7 Tesla MRI showing the area of cortical dysplasia (yellow arrows) on the MP2RAGE image, with abnormal vasculature on the SWI, and again on the T_2TSE.

The Mount Sinai Epilepsy Center, co-directed by Madeline Fields, MD, and Lara Marcuse, MD, cares for several thousand individuals every year based upon a precision medicine approach developed in large part by Mount Sinai's world-class research programs in basic and translational neuroscience, which continue to advance individualized understanding of disease pathogenesis and pathophysiology.

As an example, a 26-year-old man with refractory, focal epilepsy that could not be controlled even with multiple medications presented to Mount Sinai. Standard magnetic resonance imaging (MRI) was initially negative. However, as part of a research protocol with Priti Balchandani, PhD, the patient received a high-resolution MRI with a 7 Tesla instrument—Mount Sinai is one of only a few academic medical centers in the northeast United States to have this high field magnet. This more powerful image revealed

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› A Brave New World for Epilepsy Treatment

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Priti Balchandani, PhD
Associate Professor, Radiology, and Neuroscience

Madeline Fields, MD
Associate Professor, Neurology

Saadi Ghatan, MD
Chair, Neurosurgery, Mount Sinai West, and Mount Sinai St. Luke's

Patrick Hof, MD
Professor, Neuroscience, and Geriatrics and Palliative Medicine

Lara Marcuse, MD
Associate Professor, Neurology

Nadejda (Nadia) Tsankova, MD, PhD
Assistant Professor, Pathology, and Neuroscience

James (Jake) Young, MD, PhD
Chief Resident, Epilepsy, and Neurophysiology

a right temporal occipital cortical dysplasia (see figure, page 1). As his seizures were not localizable by use of scalp EEG recordings, neurosurgeon Saadi Ghatan, MD, implanted more than 120 electrodes intracranially using both a standard MRI and the 7 Tesla MRI to guide the placement. The electrodes revealed seizure onsets primarily from the right temporal parietal cortical dysplasia area, as well as some independent onsets.

With the intracranial electrodes in place, the patient underwent a "scenes memory task," where the individual views a series of abstract pictures and is asked to recall certain features of them, as part of a research study headed by James (Jake) Young, MD, PhD. Performance on the task is analyzed in concert with simultaneous intracranial recordings. Dr. Young and collaborators are using this approach in epilepsy patients and continuing to advance this research in laboratory animals to understand the neural basis of episodic memory—the memory of persons, places, and things (see sidebar below). Results from this particular patient indicated that his primary seizure onset zone does not participate in normal memory tasks.

With intracranial electrodes still in place and after seizures were captured, the patient was restarted on medications. At this time, the clinical epileptologists performed bedside brain mapping—stimulating electrodes in pairs while the patient's neurological status is evaluated. This makes it possible to identify areas of so-called "non-eloquent cortex," the sections that could be surgically removed without loss of function. In this patient, stimulation of the right superior temporal gyrus caused him to hear an intonation of a religious prayer from a distance. A neighboring pair of electrodes caused him to hear an echo of what the examiner had just said. This phenomenon has been termed "palinacousis" and has rarely been reported. The examiners then asked the patient to think of a word. Stimulation in that same location—but not in any other location—caused him to "hear" the word again. This is the first reported case of palinacousis elicited with stimulation after a thought.[1]

After this careful analysis, the patient underwent neurosurgery to remove his primary seizure focus—the area of right cortical dysplasia—although it was not possible to remove other, more minor areas of seizure onset. Since surgery, the patient has improved dramatically in his overall functioning. He has had only rare, brief seizures that have not been disabling.

Brain tissue from this patient and those like him are used by several of our scientists to gain a better understanding of the molecular, cellular, and circuit defects that characterize epilepsy. For example, Patrick Hof, MD, and his laboratory examine the morphology of the neurons within and near the seizure focus including their precise synaptic connections, while Nadejda (Nadia) Tsankova, MD, PhD, and her colleagues perform single cell RNA-sequencing to examine abnormalities in gene expression. In parallel, the 7 Tesla imaging data are being analyzed further by our brain-imaging team who found decreased u-fiber density in epilepsy patients compared to control subjects, suggesting that u-fibers may play a role in increasing inhibitory tone and preventing seizures.[2]

The Mount Sinai Epilepsy Center is now working to formalize this type of highly unique and tightly integrated clinical and research approach for all epilepsy patients, including children and adults. The goal is to characterize every patient's epilepsy based on data spanning neural circuit functioning, detailed neuroanatomy, genome-wide maps of gene expression, and DNA sequence, to better understand that patient's clinical phenotype and to devise a targeted treatment program tailored for that individual.

1. Fields MC, Marcuse LV, Yoo Ji-Yeoun, Ghatan S (2017) Palinacousis: seven new cases. Journal of Clinical Neurophysiology, in press.

2. O'Halloran R, Feldman R, Marcuse L, Fields M, Delman B, Frangou S, Balchandani P (2017) A method for u-fiber quantification from 7T diffusion-weighted MRI data tested in patients with nonlesional focal epilepsy. Neuroreport 28:457-461.

Bidirectional Translation Is Key to Understanding The Brain

Synchronous oscillations of electrical fields have been shown in animal models to support diverse brain processes such as language, movement, memory, and learning. However, little is known about which types of synchronous oscillations are needed for which process, particularly in humans. The Mount Sinai Epilepsy Center team performed invasive recordings of electrical activity in patients undergoing surgical management for epilepsy while the patients performed memory tasks that have been well characterized in non-human primates. The researchers recently identified a novel brain network, focused in the temporal lobe,

Epilepsy Leader **Nathalie Jetté, MD, MSc,** Joins Mount Sinai

Nathalie Jetté, MD, MSc, a neurologist, epileptologist, and health services researcher of international prominence, recently joined the Icahn School of Medicine at Mount Sinai and the Mount Sinai Health System as Vice Chair for Clinical Research and Chief of a new Outcomes/Knowledge Translation Research Division in the Department of Neurology.

Dr. Jetté studies the appropriateness and quality of care, treatment outcomes (especially surgical), psychiatric comorbidities, and implementation science for those with neurological conditions. She is involved in the development of online tools and apps to improve neurological care. For example, she and her team recently created a web-based tool (http://toolsforepilepsy.com/) aimed at helping physicians identify epilepsy patients who would benefit most from a surgical approach, and developed an app to help caregivers of persons with dementia.

Dr. Jetté also works extensively with patient, community, physician, and research organizations to ensure that her research is informed by the needs of those living with neurological conditions and that key discoveries and best practices are translated into community settings in a timely manner.

Prior to joining Mount Sinai, Dr. Jetté was Professor of Neurology and Community Health Sciences, Director of the Epilepsy Clinic, Leader of the Hotchkiss Brain Institute Epilepsy NeuroTeam, and Leader of the Neurology and Mental Health Research Clinic Initiative at the University of Calgary in Alberta, Canada. She is past President of the Canadian League Against Epilepsy, and current Chair of the North American Commission of the International League Against Epilepsy (ILAE) and the ILAE Guidelines Task Force. She has been the recipient of more than 50 research, teaching, and clinical awards, including the 2017 ILAE Ambassador for Epilepsy Award.

which is organized by synchronous oscillations in the theta range of frequencies (4-7 Hz). The activity in this network correlates with performance in an episodic memory task, whereas, by contrast, this brain network organized by theta oscillations is not activated during the performance of non-episodic memory tasks. By comparing brain activity in humans during tasks that have been well-described in non-human primate models, Mount Sinai researchers are providing uniquely powerful insights into the underlying neural circuitry in the brain that supports memory in humans.

Thank You, Donors!

Generous Support for Neurology and Alzheimer's Disease

The Department of Neurology received a **$1 million** gift to support strategic priorities from the **Estate of Anita Kert Ellis Shapiro.** Ms. Shapiro was the widow of former Icahn School of Medicine at Mount Sinai faculty member Mortimer F. Shapiro, MD. Dr. Shapiro joined Mount Sinai as an adjunct neurologist in 1948 and had a long career, ultimately becoming an Associate Attending and Associate Clinical Professor Emeritus in Neurology.

Philanthropist **Leroy Schecter**'s most recent gift of **$1 million** will support the Alzheimer's disease research enterprise and fund three annual fellows in the Neuropsychology Program. For more than a decade, Mr. Schecter has been a major benefactor to Mount Sinai and has supported many strategic research projects.

FBI Research Scholars Partnership

The Friedman Brain Institute is pleased to announce that through their generous philanthropy, **Richard and Susan Friedman, Josh and Beth Nash, Michael and Elizabeth Fascitelli, Ram Sundaram and Preethi Krishna, and Dr. Jane Martin and Stuart Katz** have helped fund the third round of the FBI Research Scholars Partnership program. This is a pilot grant program for innovative and collaborative projects aimed at establishing new avenues for basic, translational, or clinical brain and spinal cord research. Projects are designed with a goal of developing new therapeutic models that would generate the preliminary data needed to secure external funding. Recipients are named "FBI Scholars" and receive a one-time grant of up to **$50,000**. With this generosity, The Friedman Brain Institute will increase the program to 10 recipients in 2018.

Interested candidates are asked to submit a letter of intent to apply, including a brief description of the proposed project not to exceed one page by Tuesday, October 31, 2017, to FBIScholars@mssm.edu. Please include an investigator National Institutes of Health-style biosketch that includes other funding support as part of a single PDF with the letter of intent.

From left, New York City schoolchildren toured the inside of an inflatable model of the brain and examined animal brains at Mount Sinai's Fifth Annual Brain Awareness Fair.

Making Science Fun for New York City Students

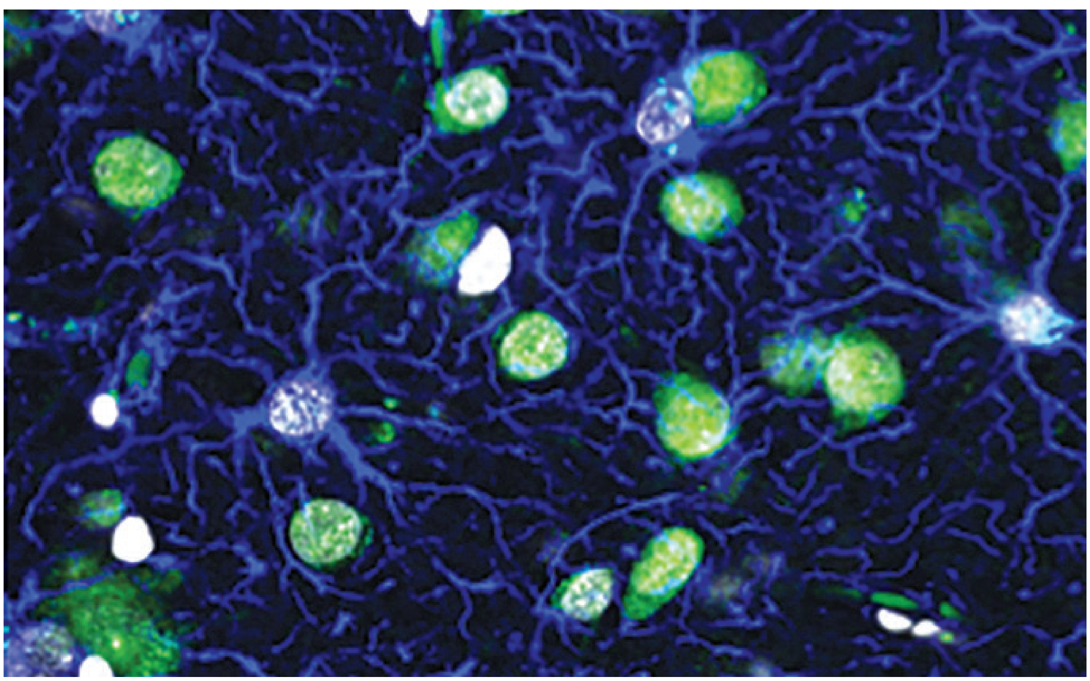
"Today is about making science accessible, not scary or intimidating," said Alyson Davis, LMSW, Program Director of Mount Sinai's Center for Excellence in Youth Education (CEYE), as 500 New York City elementary and middle school students attended Mount Sinai's Fifth Annual Brain Awareness Fair. More than 15 immersive activities provided the students with a fun, tactile learning environment where they were able to view specimens of animal brains, use 3D virtual reality to simulate the experience of performing brain surgery, and control the movement of their peers using electroencephalogram sensors. The Fair was organized by Mentoring in Neuroscience Discovery at Sinai (MiNDS), with support from the Icahn School of Medicine at Mount Sinai's Friedman Brain Institute and CEYE.

PHOTO ESSAY

Reactive Astrocytes Form Part of the Scar in Temporal Lobe Epilepsy

Immunofluorescence imaging of brain cells at a seizure focus that were surgically removed from a patient with medically intractable temporal lobe epilepsy. A glial scar that is composed of abnormal reactive astrocytes (GFAP+, blue) surrounds the epileptic neurons (NeuN+, green).

Credit: Nadejda (Nadia) Tsankova, MD, PhD, Assistant Professor, Pathology, and Neuroscience



Each March, as part of Brain Awareness Week, The Friedman Brain Institute also hosts an "Art of the Brain" exhibition that celebrates the beauty of the brain through images such as this. The educational effort showcases the work of Mount Sinai's leading scientists with a goal to enlighten faculty, staff, and the public about the importance of brain research.