

Departments of Neurology and Neurosurgery

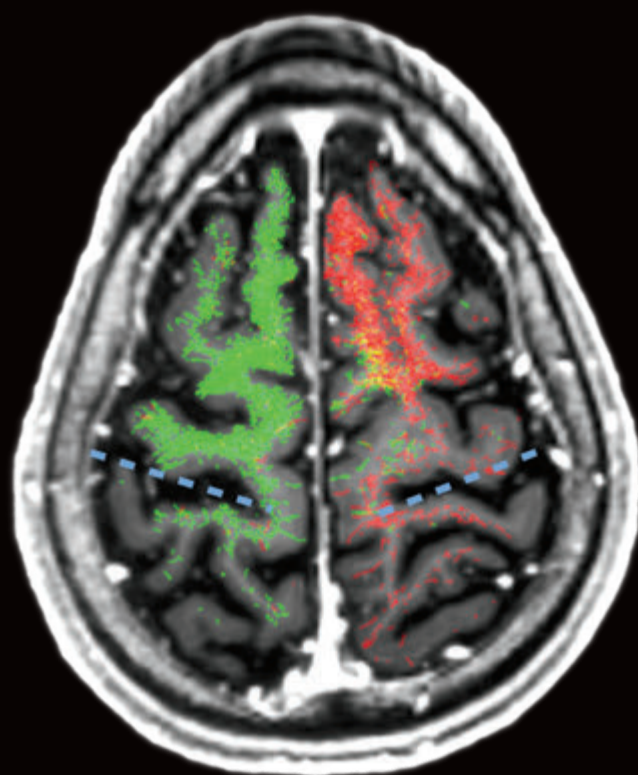


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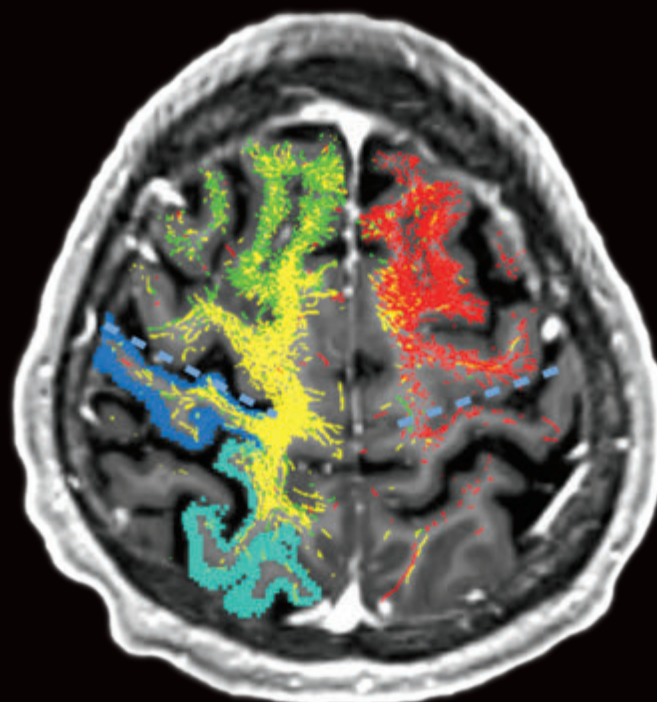
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Utilizing Magnetic Resonance Tractography to Individualize Deep Brain Stimulation Therapy

Patient 1



Patient 2



- Post-Central
- Right Contact 1
- Left Contact 1
- Sup. Parietal
- Right Contact 1 (explanted)

Images above show a comparison of the tractography from caudal zona incerta deep brain stimulation (DBS) in Patient 1 (responder) and Patient 2 (non-responder). It can be appreciated that electrode stimulation in both patients project to similar areas of the frontal cortex, particularly the motor and premotor areas. The approximate location of the central sulcus is indicated by the dashed blue line and demonstrates that stimulation of Patient 2's explanted lead (yellow) is associated with a greater number of white matter fibers terminating in the sensory cortex than with the revised implants (red, green). Based on the results of imaging, Patient 2 underwent a successful tractography-guided DBS lead revision.

Magnetic Resonance Tractography for Deep Brain Stimulation

Although most patients at the Mount Sinai Health System's Center for Neuromodulation respond to medications for Parkinson's disease (PD), obsessive-compulsive disorder, and other neuropsychiatric disorders, some require surgical therapies—specifically, deep brain stimulation (DBS)—when medical treatments fail to alleviate symptoms.

The Center's director, Brian H. Kopell, MD, Associate Professor of Neurosurgery, Neuroscience, Psychiatry, and Neurology, at the Icahn School of Medicine at Mount Sinai, is a leader in these surgical treatments. He and his team, including Jonathan J. Rasouli, MD, PGY-6, are using advanced MRI techniques to place electrodes in selectively targeted areas of the brain that are generally inaccessible by conventional surgical methods.

The two patient histories that follow help illustrate how advances in neuroimaging—specifically, fiber tractography—are used to diagnose anatomic variations in white matter tracts and guide a DBS lead revision in a previously implanted patient with suboptimal clinical results. Dr. Kopell believes that this approach, which the Center refers to as “Connectomic DBS,” has the potential to serve an important role in accurate and patient-specific DBS targeting.

Patient 1 (responder): In 2015, a 65-year-old right-handed man with a 20-year history of medically resistant tremor-predominant PD was referred for DBS evaluation. The patient's tremor was severe enough to impair his daily living, and he had exhausted all medical treatment options. Surgery for bilateral DBS lead placement in the caudal zona incerta (cZI) was performed without incident. The patient's tremor and PD symptoms remain well controlled more than two years after surgery.

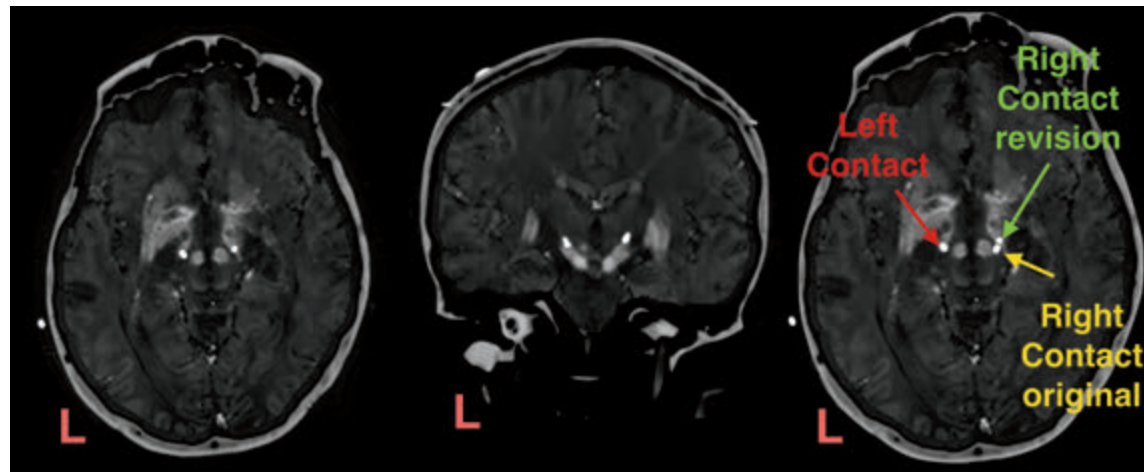
Patient 2 (non-responder): Similarly, in 2015, a 61-year-old right-handed man with a 15-year history of medically refractory tremor-predominant PD was referred for DBS evaluation. His right-hand tremor was well controlled with carbidopa/levodopa for many years; however, he began noticing that the medication was taking longer to have effect and that sudden wearing off was becoming more common. Bilateral DBS lead placement in the cZI was performed without incident (see figure at right). Initially, the patient demonstrated >90% reduction in baseline tremor, and his stimulation parameters were well tolerated. However, he experienced

episodic disabling dystonia of his left lower extremity and significant dysarthria. Even with close follow-up and maximal adjustment of the DBS device settings, he continued to experience these symptoms. Revision of his right-sided DBS lead was recommended.

Advanced MRI revealed that the connections between the targeted region to the superior parietal and postcentral gyri were found to be more prominent in this patient's troublesome electrode (see cover images). Given the known role of the excessive sensory cortex activation in dystonia, it was felt that it could explain the dystonic response associated with stimulation at that site. With the observation that stimulation of the explanted lead induced the dystonic side effects, the team hypothesized a link between these connections to the sensory cortex and the observed dystonic symptoms. Projection of stimulated fibers to the postcentral and superior parietal gyri may represent a potential imaging marker that can be used to predict and avoid this side effect prospectively.

After undergoing revision, the patient experienced significant improvement in his left-sided dystonic symptoms and tremor. More than two years postoperatively, he is doing well with resolution of his symptoms.

In utilizing fiber tractography for image-guided DBS, the team has found that ideal targets correspond to areas of the brain that contain the highest concentrations of primary and supplementary fibers from the frontal cortex. In general, most patients have stereotyped anatomy; however, regional variations can exist. These variations can sometimes warrant adjustments in final target selection in order to stimulate the greatest number of motor fibers. The team believes that new investigations will further clarify the role of tractography for image-guided DBS. ■



Axial and coronal postoperative images demonstrate satisfactory caudal zona incerta electrode placement in Patient 2 (non-responder). The axial image on the right demonstrates the pre- and postanatomic electrode placement after the right-sided electrode was removed and subsequently placed more anteriorly based on the patient's advanced imaging results.

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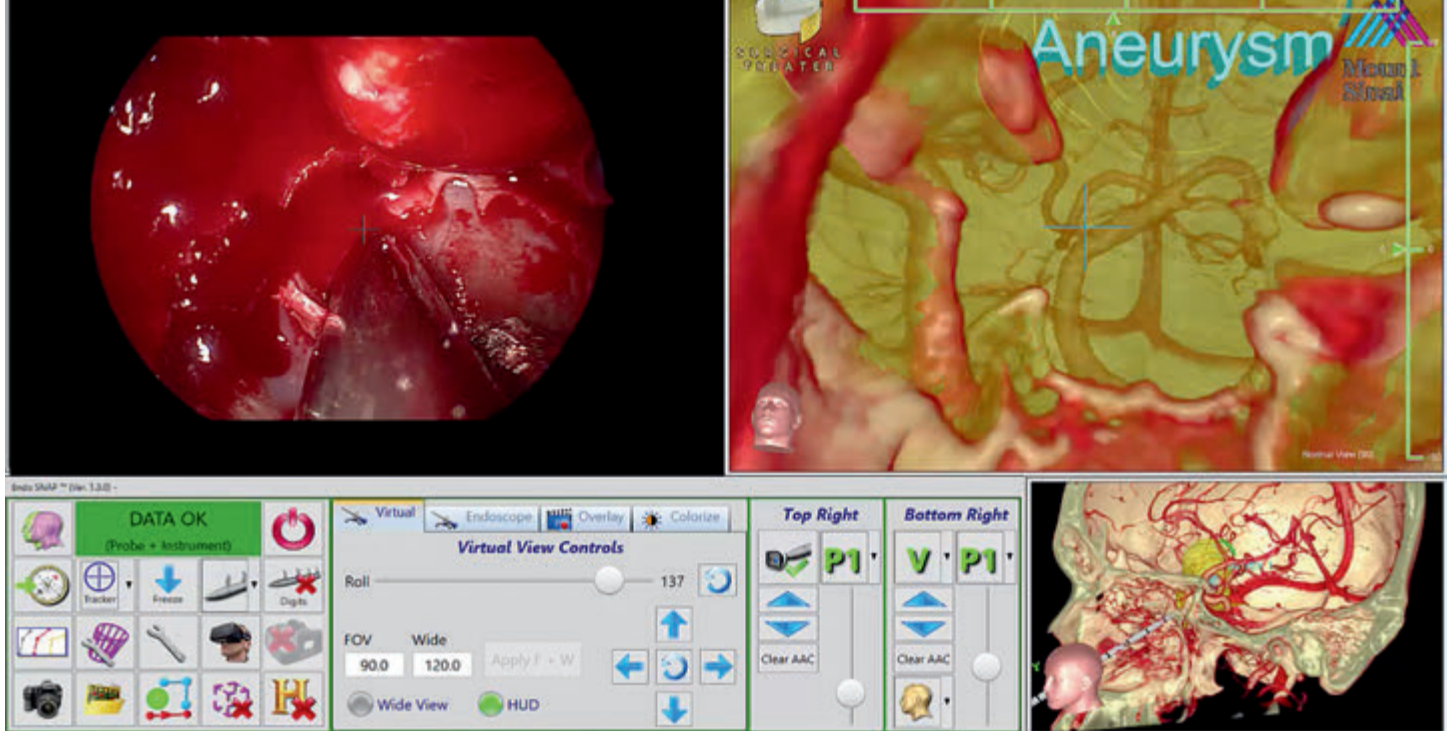


Figure 1, clockwise, from upper left: intraoperative view of tracked endoscope; simulation navigation in real time with tracked instrument; overview of 3D simulation for reference of all anatomical relationships; and a display of tools utilized to manipulate simulated images for more or less information intraoperatively.

Using Augmented Reality to Resect Giant Pituitary Tumor

In the summer of 2016, when a 65-year-old male presented with four to five months of peripheral visual field loss, Mark J. Kupersmith, MD, discovered a giant pituitary tumor. Dr. Kupersmith, Professor of Neurology, Ophthalmology, and Neurosurgery, at the Icahn School of Medicine at Mount Sinai, and Director of Neuro-Ophthalmology, sent the patient for urgent evaluation to Joshua B. Bederson, MD, Professor and Chair of Neurosurgery for the Mount Sinai Health System. MRI and MRA revealed the tumor was located between carotid artery aneurysms on both sides. It was agreed to delay treatment of the aneurysms.

With the assistance of ENT surgeon Alfred M.C. Iloreta, Jr., MD, Assistant Professor of Otolaryngology, Dr. Bederson was able to plan and execute the resection of the giant tumor from around the aneurysms by using 3D virtual-reality simulation during preoperative planning—along with a specific combination of other neurosurgical tools—allowing for greatly improved situational awareness during surgery.

The neurosurgical team prepared the patient for computer-assisted volumetric resection to create a 3D simulated view of the patient's anatomy. Standard pituitary sequence isotropic MRI and contrast CT sequences were obtained, loaded, and fused to one another using Brainlab's Curve™ Image-Guided Surgery and Surgical Theater's EndoSNAP technology. This was followed by segmentation of operative pathology and critical structures.

Following a transnasal endoscopic approach, integrated augmented reality was utilized to obtain maximal exposure while protecting the bilateral carotid artery aneurysms. The endoscopic view alongside the simulated view allowed the surgeon to see past the visual field to the critical anatomy. Throughout the procedure, navigation integrated with augmented reality was used to guide and update position information in real time to enhance the surgical team's awareness of the relative boundary locations of the lesion and aneurysms.

The tumor was safely resected under concurrent endoscopic and augmented reality visualization while the operating microscope was used interchangeably throughout the case. A "heads-up" display also allowed the surgeon to see preoperatively the painted structures overlaid into the eyepieces of the microscope in real time on the patient's anatomy (Figures 1 and 2).

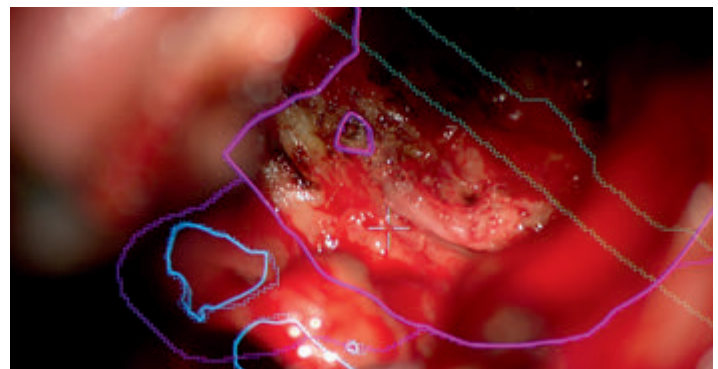


Figure 2: A heads-up display during surgery outlining the tumor as the pathology and the vessels in blue and green. The solid outline is the in-plane view of the microscope where the dotted outline shows deep structures. The surgeon is aware of the bilateral aneurysms; the outline of preoperatively planned objects gives an idea of location during resection.

Postoperative scans confirmed near-complete resection and decompression of the optic chiasm, resulting in improved vision for the patient.

The application of navigation-integrated augmented reality in neurosurgery is an emerging paradigm. The use of these tools is expanding greatly due to their minimal impact on surgical workflow while providing augmented visual field information in the service of patient safety. ■

Dr. Bederson owns equity in Surgical Theater, LLC.

Barbara G. Vickrey, MD, MPH Joshua B. Bederson, MD



We are excited about the rapid transformation of clinical practice that is being driven by stunning new advances in technology and groundbreaking research aimed at making us all better physicians able to treat our patients' more challenging conditions quicker and with far more precision.

NEW APPOINTMENTS



Helen S. Mayberg, MD, Named Founding Director of Mount Sinai's Center for Advanced Circuit Therapeutics

Helen S. Mayberg, MD, a neurologist renowned for her study of brain circuits in depression and for her pioneering research in deep brain stimulation—which led to one of the first hypothesis-driven treatment strategies for a major mental illness—has been appointed founding

Director of the Center for Advanced Circuit Therapeutics at the Icahn School of Medicine at Mount Sinai. She has also been named Mount Sinai Professor in Neurotherapeutics, with senior faculty appointments in Neurology, Neurosurgery, Psychiatry, and Neuroscience.

Under her direction, the Center will build a platform for collaborative translational research that will bring together clinical colleagues in neurology, neurosurgery, and psychiatry with experts from

Today, the once complex procedure is becoming simple, the once inaccurate test or diagnosis is now precise, and the once overwhelmed patient is reassured.

At the departments of Neurology and Neurosurgery at the Icahn School of Medicine at Mount Sinai, we continue to lay the technological and research groundwork to considerably advance treatment in movement disorders, multiple sclerosis, neuro-ophthalmology, stroke, and epilepsy.

An entrepreneurial environment on our Mount Sinai Health System campuses, and at the Icahn School of Medicine at Mount Sinai, now celebrating its 50th anniversary, is pushing new efforts in clinical modeling, simulation, prototyping, and robotics.

For Mount Sinai clinicians and researchers, the once unexpected now is allowing us to be strategically prepared. The once impossible is now possible. ■

neuroscience, imaging, engineering, bioinformatics, neuroengineering, and computational neuroscience. The goal is to strengthen Mount Sinai's global role devising novel transformational treatments for depression and other neuropsychiatric disorders, as well as to refine and optimize current neuromodulation strategies for movement disorders and epilepsy now routinely practiced. Key to the success of the Center will be a close partnership with Brian H. Kopell, MD, a pioneer of deep brain stimulation and Director of the Center for Neuromodulation within the Department of Neurosurgery, whose work is featured in this Report.

Immediately prior to joining Mount Sinai, Dr. Mayberg was Professor of Psychiatry, Neurology, and Radiology, and held the inaugural Dorothy C. Fuqua Chair in Psychiatric Neuroimaging and Therapeutics, at Emory University School of Medicine. ■

Prominent Epileptologist and Researcher 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 Division of Health Outcomes and Knowledge Translation Research 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 (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. ■



Diet and Multiple Sclerosis Symptoms: A New Approach

Neurologists have long suspected a link between diet and symptoms of multiple sclerosis (MS), but today, Ilana B. Katz Sand, MD, Assistant Professor of Neurology at the Icahn School of Medicine at Mount Sinai, and Associate Medical Director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis, is offering fresh insights.

Dr. Katz Sand and a team from the Icahn School of Medicine are currently conducting studies aimed at understanding the role of gut bacteria in inflammation and neurodegeneration. A recent publication of which Dr. Katz Sand is a co-author suggests that gut microbial composition in individuals with MS differs from that in healthy controls. Because gut bacteria communicate heavily with the resident immune system in the gut, as well as secrete molecules that can have distant effects, Dr. Katz Sand and colleagues hypothesize that changes in gut microbiota may contribute to the development of MS and other autoimmune diseases and also may influence disease course once MS is established. If further research confirms this, investigators like Dr. Katz Sand believe it may be possible someday to offer patients microbiome-based therapy to keep the bacteria in check.

One of the biggest drivers of gut microbial composition is diet, and it is this potential mechanistic link that led Dr. Katz Sand to begin studying dietary factors in MS. She says, “We want to better understand the inflammatory process, the neurodegenerative process, and the effect that diet has on MS symptoms. Our findings could be very important in understanding the onset of MS and how to treat it.”

Until recently, developing a methodology to study the possible connection between diet and MS has proved challenging because a double-blind randomized controlled trial doesn't lend itself to studying diet. Dr. Katz Sand, who has pursued this clinical interest since she was a fellow, designed what she believes is a scientifically sound methodology that may help lay the groundwork for future clinical trials in this area.

She has developed a study to begin evaluating the hypothesis that a modified Mediterranean diet—which includes fresh fish, fruits, vegetables, nuts, whole grains, and avocados, and eliminates meat, dairy, and processed foods—may reduce inflammation characteristic of MS, whereby immune cells attack the myelin insulation that surrounds and insulates nerve fibers, causing problems with vision, balance, muscle control, cognition, and other debilitating symptoms.



Ilana B. Katz Sand, MD, with Amit Blushtein, a clinical trial participant, one of 18 multiple sclerosis patients randomized to follow a special dietary plan.

She and her team have recruited 36 participants, 18 of whom have been randomized to follow this dietary plan for six months. All participants move through the study in small groups according to their assignment. The dietary-arm participants attend monthly meetings, led by Dr. Katz Sand, a nutritionist, and a research coordinator, that include presentations about various aspects of the diet to keep them motivated—one of the challenges of the study. There, they have the opportunity to discuss their experiences with their restrictive diet and to share tips.

Additionally, they are asked to complete questionnaires at the meetings and through regular emails. Certain markers, including salt, fatty acids, and carotenoids, are tested through lab work at the beginning and end of the study, and participants also are tested for the diet's effects on body mass index, blood pressure, cholesterol, and glucose. The research team also employs quality-of-life scales that assess fatigue and measure depression, common MS symptoms. “We've got a nice group dynamic going,” says Dr. Katz Sand.

The non-dietary intervention participants attend study visits occasionally and also are offered seminars on topics of interest to MS patients. At the end of their study period, if they wish to start the diet, they are offered an opportunity to meet with the study's nutritionist.

The study, funded by the National Multiple Sclerosis Society, began in January 2017, and the last group of participants will finish in April 2018. The challenge for Dr. Katz Sand and her team will be to scale the study to include more participants, which Dr. Katz Sand and her team are planning to do in the near future. ■

A clinical trial explores one diet's effect on inflammation.

Advancing Research for Disorders In Neuro-Ophthalmology



Mark J. Kupersmith, MD,
leads NORDIC, the
Neuro-Ophthalmology
Research Disease
Investigator Consortium.

There is a broad spectrum of neuro-ophthalmologic disorders that collectively affect millions of people. Many of these are visual disorders associated with other systemic or neurological conditions, and almost all fit the U.S. government definition of rare diseases. While some of these disorders, such as optic neuritis in multiple sclerosis, afflict larger numbers of people, most—such as idiopathic intracranial hypertension (IIH), nonarteritic anterior ischemic optic neuropathy (NAION), and thyroid eye disease—affect far fewer. Because they infrequently have been the subject of prospective research, there is often little consensus among practitioners on the diagnostic evaluation or therapy for many neuro-ophthalmological disorders.

In 2009, with the support of the National Institutes of Health's National Eye Institute (NEI), other funding agencies, private donors, and industry, Mark J. Kupersmith, MD, Professor of Neurology, Ophthalmology, and Neurosurgery, at the Icahn School of Medicine at Mount Sinai, and Director of Neuro-Ophthalmology, established a renewable clinical trial and

research network to provide a structured organization for prospective clinical research. Known as NORDIC, the Neuro-Ophthalmology Research Disease Investigator Consortium now includes an extensive group of neuro-ophthalmologists and other physicians. The Consortium headquarters, clinical-site and reading-center management, and grant and financial operations are located within the Icahn School of Medicine and The Mount Sinai Hospital.

With \$10.7 million in funding, NORDIC has made advances in several key areas. Its first major study, the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), recently established the therapy and guidelines for management in IIH patients with mild vision loss. The Consortium used 50 clinical sites, three reading centers, and one coordinating center located at major medical institutions in the United States and Canada. IIH is a disorder with an incidence of close to 100,000 per year that principally affects women who are overweight. If untreated, IIH causes severe headaches and double vision, and can lead to total blindness. The IIHTT has produced more than 25 publications since 2014, providing the first prospective data on this illness. "The findings set everyone on their ear by showing that a lot of theories in neuro-ophthalmology need updating," says Dr. Kupersmith.

NORDIC continues to enroll subjects in a major study with industry sponsorship, begun in January 2016, to investigate acute ischemic or vascular injury to the optic nerve. The randomized controlled trial is investigating the first prospective medical therapy for NAION, which causes permanent visual field loss and optic nerve damage. It is also the first trial on acute neuroprotection for optic nerve injury. Recruitment is 70 percent complete and on target at 45 U.S. sites and 45 sites in eight other countries.

A comparative effectiveness study on surgery and medical therapy of patients with moderate to severe vision loss, funded with \$19 million by the NEI, begins enrollment this spring. The Surgical Idiopathic Intracranial Hypertension Treatment Trial will include 46 clinical sites, three reading centers, and a nationally recognized coordinating center. ■

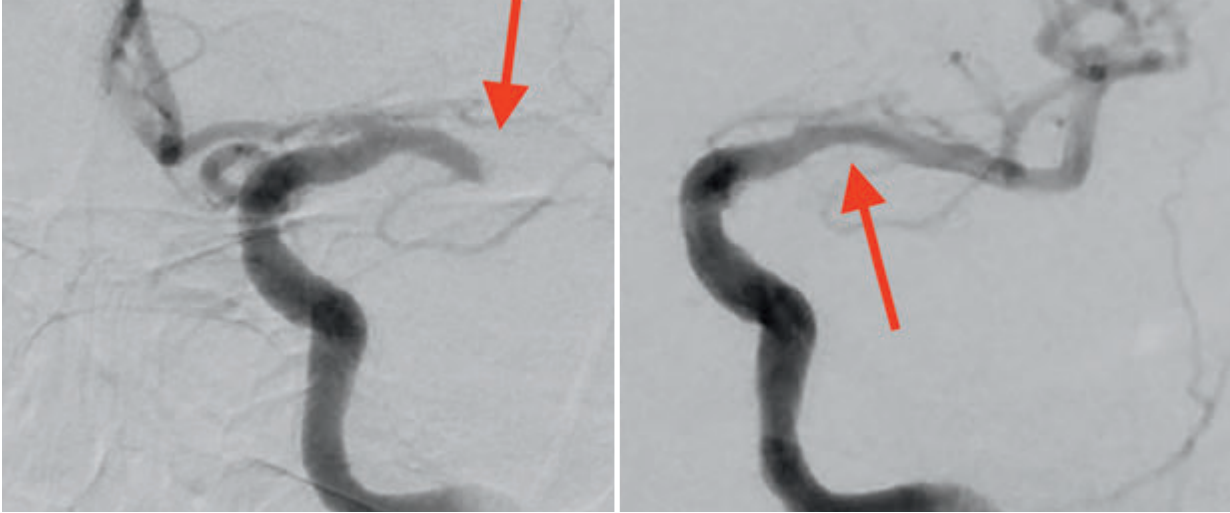
See You in April!

**2018 American Association of Neurological Surgeons
Annual Scientific Meeting**
Ernest N. Morial Convention Center, New Orleans
April 28 – May 2

Mount Sinai Neurosurgery exhibitor April 30 – May 2
Booth #447

American Academy of Neurology 2018 Annual Meeting
Los Angeles Convention Center
April 21 – 27

Mount Sinai Neurology exhibitor April 22 – 25
Booth #509



Left: the initial diagnostic angiogram shows a left M1 occlusion. Right: the angiogram shows the clot has been removed and the vessel is recanalized.

Making Gains in Treating Endovascular Thrombectomy For Stroke Due to Large Vessel Occlusion

Studies suggest that 2 million neurons are lost every minute during a stroke. For decades, tPA was the only treatment available, but in six recent trials, endovascular thrombectomy was shown to be highly effective for patients suffering acute ischemic stroke due to a large vessel occlusion. Still, time remains the most important factor in determining the efficacy of this procedure: typically, the odds of a good neurologic outcome fall by 20 percent for every hour delay in treatment.

Only a small number of hospitals are able to perform endovascular thrombectomy, however. Often, patients are first transported to the nearest hospital, where they are diagnosed with a stroke from a large vessel occlusion and then transferred to a thrombectomy-capable center, a process that costs 110 minutes on average.

By chance, when a 66-year-old man with a medical history of hypertension suddenly developed aphasia and right-sided weakness in May 2017, he was brought by ambulance to The Mount Sinai Hospital emergency room, which has expertise in endovascular thrombectomy. He underwent a CT and CT angiogram that revealed a left distal internal carotid artery occlusion. His symptoms had improved to only a right visual field cut, mild aphasia, and dysarthria, and he was given tPA and admitted for observation. Two hours later, he developed right-sided weakness and worse aphasia. Repeat imaging showed that he now had a left M1 occlusion (see left figure above) and he was taken immediately for endovascular thrombectomy. The clot was successfully removed (see right figure above) in 16 minutes by Thomas Oxley, MD, PhD, Instructor of Neurosurgery, and Reade De Leacy, MD, Assistant Professor of Neurosurgery, and Radiology, at the Icahn School of Medicine at Mount Sinai. The patient immediately improved—he had a right visual field cut and mild aphasia with no weakness or other symptoms.

In this case, the patient was taken quickly to a thrombectomy center and he was able to get the procedure immediately, which contributed to his good outcome. Currently, the Mount Sinai Cerebrovascular Research Team is evaluating

the use of a portable device that could ultimately be used in ambulances and emergency rooms to more quickly and accurately identify patients with severe stroke—versus those with less urgent stroke—to enable rapid triage to capable treatment centers.

Christopher P. Kellner, MD, Assistant Professor of Neurosurgery at the Icahn School of Medicine at Mount Sinai, and Director of the Intracerebral Hemorrhage Program, recently served as the Principal Investigator of the VITAL study, a multicenter evaluation of the VIPS (Volumetric Impedance Phase Shift Spectroscopy) device, developed by Cerebrotech Medical Systems. The device measures bioimpedance over a range of electromagnetic frequencies on the left and right side of the brain, assigning a mean bioimpedance asymmetry to each patient. With large vessel occlusion and other forms of severe stroke, there is higher mean bioimpedance asymmetry than with other forms of stroke and neurologic disease that might mimic stroke.

The VITAL study enrolled 128 patients across four centers between March and July 2017 and pooled data with two other studies. Findings presented by Dr. Kellner at the Society of NeuroInterventional Surgery annual meeting on July 23, 2017, indicate that the device was highly accurate in diagnosing severe stroke, with a sensitivity of 93 percent and a specificity of 92 percent. The device recently was cleared by the U.S. Food and Drug Administration for use in the United States and is CE marked for distribution in the European Union. It is currently in a second phase of testing to validate the findings in a population of patients presenting with stroke codes. If this device continues to demonstrate a high degree of accuracy, Dr. Kellner believes it could serve as an EKG for the brain, allowing physicians and paramedics to triage patients to the right hospital right from the start. ■

Joshua B. Bederson, MD, Chair, Department of Neurosurgery, and J Mocco, MD, MS, Vice Chair, Department of Neurosurgery, and Director of the Cerebrovascular Center, hold equity in Cerebrotech, the study sponsor and developer of Cerebrotech Medical Systems. Dr. Mocco also serves as a consultant for Cerebrotech.

Studying a device to more rapidly identify patients with severe stroke

Innovation, Invention, and Entrepreneurship Drive New Approaches to Neurosurgery

Four years ago, the Department of Neurosurgery at the Icahn School of Medicine at Mount Sinai undertook an ambitious plan to change the way that clinicians and researchers understand, utilize, and interface with the most advanced digital technologies in surgical medicine. First, the Department established the Neurosurgery Simulation Core (NSC), co-directed by Joshua B. Bederson, MD, Professor and Chair of Neurosurgery for the Mount Sinai Health System, and Anthony B. Costa, PhD, Assistant Professor of Neurosurgery, to improve outcomes and reduce complications by coordinating novel simulation and visualization technologies in presurgical planning and patient education, and in the operating room. The program employs these and other modeling tools on a daily basis in the clinical setting, and also helps to develop new technologies—working with industry to improve technology globally; licensing technologies to outside companies; and advancing the field through publication, presentations, and training.

The NSC's capabilities continue to expand and now involve projects throughout many areas within Mount Sinai, including Otolaryngology-ENT, Pediatric Cardiology, Orthopaedics, Plastic Surgery, Radiology, and research institutes. Additionally, the Medical Modeling Core, a fee-for-service group led by Dr. Costa and managed by the NSC, now provides

clinical modeling, which includes patient-specific virtual-reality scenarios and 3D printing services, to physicians throughout the Health System.

Several entrepreneurial projects are also contributing to the program's growth. Key among them is the creation of Monogram Orthopaedics, a New York City medical device startup that makes use of modeling, simulation, prototyping, and robotics to improve implants. It was co-founded by Dr. Costa together with colleagues in the Department of Orthopaedics, medical students, and Mount Sinai Innovation Partners, the institution's technology development and commercialization hub.

Newly launched is Sinai BioDesign, which takes the capabilities of the NSC and integrates them into Mount Sinai's prototyping and engineering facilities—effectively allowing them to serve as project and engineering platforms for converting research into commercially relevant products. Sinai BioDesign is a prototyping, simulation, and modeling facility that has active project management to guide prospective inventors, utilizing Mount Sinai's strengths in mechanical and biomedical engineering, industrial design, clinical research, and surgical medicine to help translate the wealth of Mount Sinai ideas and innovation potential directly to the patient. ■

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