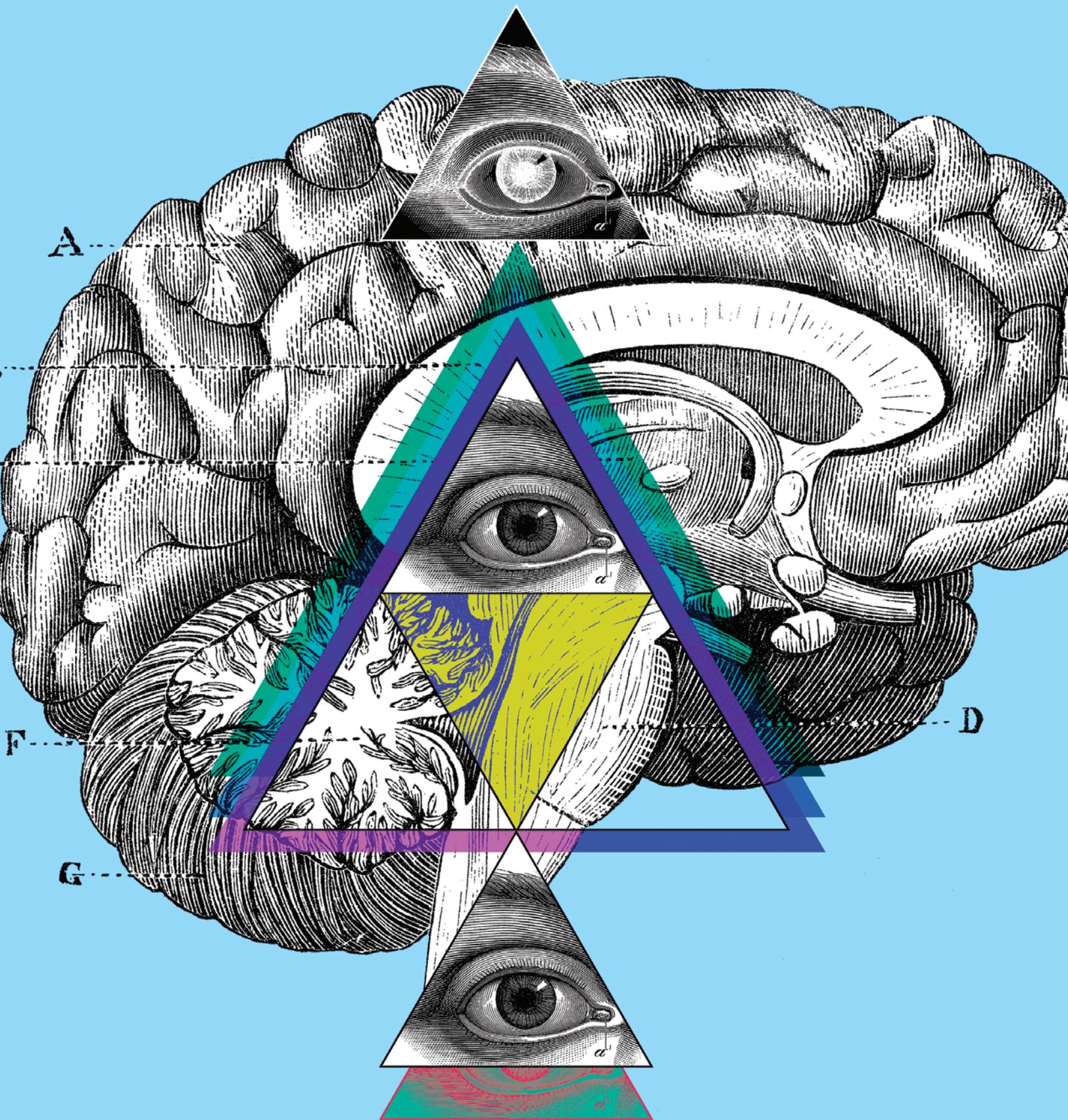


# PROGRESSNOTES

MUSC'S MEDICAL MAGAZINE // SPRING 2018



## Upcoming CME Conferences

The following conferences, sponsored by the Medical University of South Carolina, will be held in Charleston unless otherwise noted.

Visit [www.musc.edu/cme](http://www.musc.edu/cme) for a complete list of CME conferences.

April 14, 2018	Spine Conference 2018 – Controversies in Spine Care <i>Kiawah Island Golf Resort</i>
April 17-21, 2018	MUSC Pathology Multi-Specialty Symposium <i>Kiawah Island Golf Resort</i>
April 20-22, 2018	South Carolina Rheumatism Society 2018 Annual Meeting <i>Hyatt Place Charleston</i>
April 26-28, 2018	47th Postgraduate Course in Surgery <i>Hyatt Place Charleston</i>
April 28, 2018	5th Annual Lowcountry Sickle Cell Disease Symposium <i>MUSC Drug Discovery Building Auditorium</i>
May 24-26, 2018	2018 Evidence-Based Drug Therapy Update <i>Crowne Plaza Hotel, North Charleston</i>
June 1-2, 2018	18th Annual Charleston Magnolia Conference <i>Hyatt House Charleston</i>
June 6-9, 2018	42nd Annual Cardiology Update <i>The Francis Marion Hotel</i>
June 11-16, 2018	Family Medicine Update <i>Kiawah Island Golf Resort</i>
July 13-15, 2018	The Charleston Course: 8th Annual Otolaryngology Literature Update <i>Kiawah Island Golf Resort</i>

## MUSC Health Medical Video Center

[MUSChealth.org/medical-video](http://MUSChealth.org/medical-video)

### A sampling of current videos:

#### The COMPASS Trial

MUSC Health neurointerventional radiologist **Aquilla S. Turk, D.O.**, discusses preliminary findings from the COMPASS trial, a head-to-head comparison of the direct-aspiration, first-pass technique, pioneered at MUSC Health, and stent retrievers for thrombectomy.

#### What's New in the 2018 AHA/ASA Guidelines for Acute Ischemic Stroke?

**Edward C. Jauch, M.D.**, interim chair of the Department of Emergency Medicine and one of the authors of the recent guidelines, discusses updates in recommendations for stroke care.

#### New Techniques for Treating Secondary Effects of Intracerebral Hemorrhage

MUSC Health neurosurgeon **Alejandro M. Spiotta, M.D.**, discusses minimally invasive surgical techniques for evacuation of hematoma in patients with intracerebral hemorrhage.

#### Deep Brain Stimulation

MUSC Health neurosurgeon **Istvan Takacs, M.D.**, discusses how deep brain stimulation controls symptoms and improves quality of life in patients with Parkinson's disease, essential tremor and dystonia.

#### Laser Ablation for the Treatment of Temporal Lobe Epilepsy

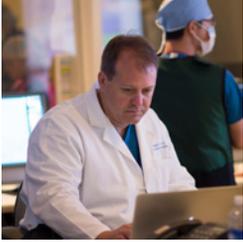
MUSC Health neurosurgeon **William A. Vandergift, M.D.**, discusses an alternative to traditional surgery for patients with medication-refractory temporal lobe epilepsy.

#### Pineal Gland Surgery

**Sunil J. Patel, M.D.**, chair of the Department of Neurosurgery, explains that some pineal cysts are in fact pineocytomas and that their removal provides relief from a novel constellation of symptoms.

# PROGRESS NOTES

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Minimally invasive therapies provide good seizure control for patients with medication-refractory focal epilepsy

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## Restoring Poetry to Motion

While not a cure, deep brain stimulation can alleviate some of the most debilitating symptoms of advanced Parkinson's disease, essential tremor and dystonia to improve quality of life

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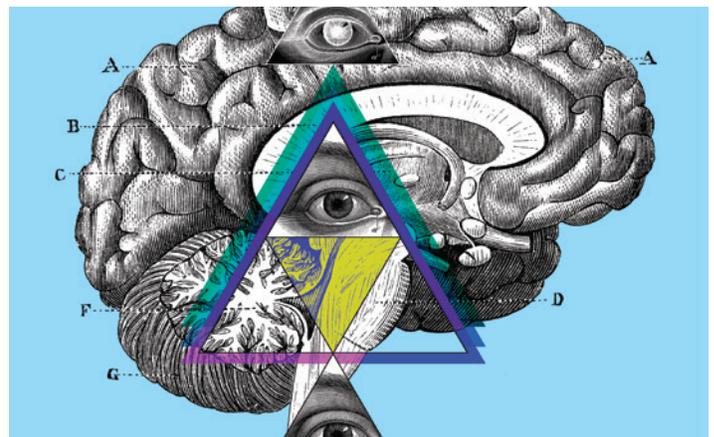
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## Pineal Cysts: Worth a Second Look

MUSC Health neurosurgeon identifies a novel constellation of symptoms that resolve upon excision of pineal lesions

On the cover: Stylized brain image depicting the pineal gland as a vestigial third eye. Illustration by Emma Vought





Dr. Aquilla Turk (front left) in the angiography suite

## CLINICAL RESEARCH

# Aspiration as Good as Stent Retrievers for Large-Vessel Clots

An interview with a principal investigator for the COMPASS trial

Neurointerventional radiologist **Aquilla S. Turk, D.O.**, is one of the principal investigators (PIs) for the COMPASS trial, a head-to-head comparison of the direct-aspiration, first-pass technique (ADAPT), pioneered at MUSC Health, and stent retrievers for thrombectomy of large-vessel clots. The other PIs for the trial are J. Mocco M.D., MS, of the Icahn School of Medicine at Mount

Sinai and Adnan Siddiqui, M.D., Ph.D., of the Jacobs School of Medicine and Biomedical Sciences at the University at Buffalo.

Stent retrievers, the current standard of care for mechanical thrombectomy in patients with acute ischemic stroke, are cage-like devices that are used to “engage” and then remove the clot. ADAPT, developed at MUSC Health by Turk,

fellow neurointerventional radiologist **M. Imran Chaudry, M.D.**, and neurosurgeons **Alejandro M. Spiotta, M.D.**, and **Raymond D. Turner, M.D.**, uses a large-diameter aspiration catheter (ACE68™, Penumbra) to remove the clot in its entirety.

Preliminary findings from the trial were presented at the International Stroke Conference in Los Angeles in January 2018. They showed that comparable functional outcomes and revascularization rates were attained by ADAPT and stent retrievers in stroke patients with large-vessel clots. ADAPT was also shown to reduce procedure times and to be more cost effective. The full results of the COMPASS trial, including the economic data, will be presented at the annual Society of Neurointerventional Surgery meeting in San Francisco in July.

*Progressnotes* sat down with Turk to learn more about ADAPT and the COMPASS trial results.

### PN: How is aspiration used to remove large-vessel clots?

Aspiration is something that we happened upon back in 2013. The seminal case for us was one where we actually did a thrombectomy using a large catheter with a stent retriever through it. We pulled the stent retriever through it. We pulled the stent retriever out, and there was nothing on it, but the catheter was clogged. So we pulled the catheter out, thinking that we would have to go back up and do it again, and the large clot was embedded in the end of the catheter. So a light bulb went off for us. That's what started us trying to use aspiration alone.

Before that, the company (Penumbra) sold the catheters, but they had these little wires with stoppers on the end that they used to break up the clot and then clear the end of the catheter. But that just fragmented the clot and sent more of it downstream. And we'd have to work our way through the vascular tree to open one-sized vessel, and then go to the next smaller, and the next smaller. With aspiration alone, we were able to pull the entire clot out without breaking it up the majority of the time.

So it gave us an idea — if we can just take a catheter, drive it to the clot, turn on suction and then pull the clot out, or have it get sucked out through the catheter, that would be much simpler and really a home-run way to go.

### PN: Can you describe the preliminary findings of the COMPASS trial?

The COMPASS trial randomized patients with a large-vessel occlusion to either aspiration or stent retrievers as a first approach. After three attempts, any measure could be used to open the blood vessel.

The preliminary results seem very encouraging. There was a French study doing the same trial design, ASTER, which was released this past year. The ASTER investigators showed that stent retrievers and aspiration had similar outcomes clinically and that there wasn't a significant difference

angiographically. From what we've seen so far, our results are almost identical. Our primary end point was functional outcome — whether the patients were able to be functionally independent (defined as a modified Rankin score of 0-2). In the ADAPT arm, about 51 percent of patients had a modified Rankin score of 0 to 2, whereas, in the stent retriever group, 49 percent of patients were functionally independent. So, there was not a significant difference between the two.

### PN: What are the advantages of ADAPT?

ADAPT is very simple to do. Whether neurointerventionalists, cardiologists, peripheral interventionists or vascular surgeons — we all drive catheters over wires through blood vessels. And if the goal is just to take a catheter and drive it to the level of occlusion, and that's all you have to do to get it open, that's about as easy as it gets. So that also implies speed and safety because you're not having to deploy multiple devices. And it implies lower costs. It's just one of those common sense approaches across the board. If it's that simple, it should be the easiest way to go.

So for me the COMPASS trial was just the final, validating study that gives us Level 1 evidence that, in a head-to-head trial against stent retrievers, aspiration is at least as good. And certainly, to me, aspiration is the way to start doing a thrombectomy procedure. I say that because you simply drive the catheter to the face of the clot. You attempt aspiration a couple of times. If it doesn't work, then you add a stent retriever. If you do that approach, you'll have at least as good a success as you would using a using a stent retriever first approach, but it will be cheaper and faster.



**Watch the interview with Dr. Turk on the Neurosciences page of the MUSC Health Medical Video Center (MUSChealth.org/medical-video).**

## COLLABORATION

# The Charleston Summit

Since 2011, MUSC has hosted The Charleston Summit of Advanced Ideas and New Technology, an influential meeting where key opinion leaders in stroke surgery can discuss future directions in the field in a safe forum.

Attendees include the leaders of major national and international scientific organizations and endovascular neurosurgeons, interventional radiologists and interventional neurologists from top-flight health care institutions, such as Mayo Clinic, Cleveland Clinic and Johns Hopkins University. There is a good mix of established authorities and young leaders in the field. Attendees sign a non-disclosure agreement to ensure positive, open dialogue without fear of compromising intellectual property. Unlike typical scientific meetings, no industry representatives are present, further encouraging open, frank dialogue.

A popular topic of the summit is developing new scientific trials. Trial ideas generated at this meeting have garnered approximately \$20 million in research support, including funding for the COMPASS (NCT02466893), POSITIVE (NCT01852201) and LARGE trials.

"It's really exciting that, one day a year, Charleston, South Carolina is the center of the world when it comes to stroke surgery," said **Raymond D. Turner, M.D.**, host of The Charleston Summit and chief of the Neuroscience Integrated Center of Clinical Excellence at MUSC Health.

Although usually held in January, this year's meeting has been postponed until May 5 due to inclement weather in January. —MATTHEW GRESETH



## CLINICAL CARE

## Striking a Nerve

Treatment reverses pediatric complications of botulinum toxin therapy

BY SVER AUNE

Physicians at MUSC reported the first pediatric use of a treatment to reverse complications from botulinum toxin therapy in a study published online in December by *The Journal of Pediatrics* (doi: 10.1016/j.jpeds.2017.11.013). Botulinum toxin is used to treat nerve disorders and a variety of other neurological conditions.

In the study, physicians recognized immediate and delayed complications early and treated patients with the maximum dose of pyridostigmine appropriate for their weight.

Early treatment is critical for patients who experience complications from botulinum toxin therapy, because symptoms can progress to difficulty swallowing or breathing, according to **Lucinda A. Halstead, M.D.**, an associate professor in the MUSC

Department of Otolaryngology-Head and Neck Surgery and senior author on the study.

“We see a profound effect in people who can’t swallow. We give pyridostigmine and the effect is within hours,” said Halstead. “Patients are eating normally again within days.”

Botulinum toxin blocks the nerves that control muscle tone, causing muscles to relax. This makes it a useful tool for neurologists and otolaryngologists who treat a group of nerve disorders called *dystonias* — problems with muscle tone — that affect the head and neck.

In a rare but serious complication, botulinum toxin can sometimes travel backward up nerves and cause unintended paralysis of nearby or distant muscles. In those cases,

pyridostigmine can reverse paralysis by encouraging muscles to contract. The official antidote to botulinum toxin is difficult to procure quickly and takes several days to work, while pyridostigmine begins to relieve symptoms within hours.

In the first case, physicians treated a one-year-old female patient having difficulty swallowing. The patient had a history of aspiration pneumonia, wherein food or saliva is inhaled into the lungs rather than passing into the esophagus, and she was dependent on an abdominal gastrostomy tube for nutrition. During swallowing, one set of muscles called the *pharyngeal constrictors* must contract to push food toward the esophagus, while another muscle called the *cricopharyngeus* must simultaneously relax for food to pass into the esophagus. Physicians observed a poorly relaxing cricopharyngeus and injected the muscle with botulinum toxin to force it to relax so the patient could keep food down.

The next day, however, the patient was admitted to the hospital with choking, vomiting and difficulty breathing. A swallow study revealed that her cricopharyngeus had indeed relaxed, as intended, but that the pharyngeal constrictors had also relaxed. As a result, she was nearly unable to swallow.

The patient was given pyridostigmine through her gastrostomy tube to oppose the effects of botulinum toxin, with the idea that the toxin had spread unintentionally to her neighboring pharyngeal constrictors, causing them to relax. Two days later, she was breathing normally, and she was released on day thirteen after admission.

In the second case, an eight year-old female patient was given an injection of botulinum toxin into her salivary glands to treat excessive salivation. She had displayed an excellent response to the same treatment six months earlier. Seven days after the injection, however, she returned to the hospital, unable to eat or drink without choking. A

swallow study showed that her pharynx was not completely clearing itself of food during swallowing. The patient was given oral pyridostigmine and began to rapidly improve. Within a week, she was eating normally again.

This is the first report of physicians treating complications from botulinum toxin therapy with pyridostigmine in pediatric patients. Pyridostigmine is a widely available medication for myasthenia gravis, a disorder that causes muscle weakness. It is safe, but it can cause slowing heart rate in patients with a history of heart problems. It is not an antidote to botulinum toxin, but it does oppose its effects by preventing the breakdown of acetylcholine, which is needed for muscle contraction. In both patients, the drug was given in doses similar to those used to treat myasthenia gravis.

This study emphasizes the need for physicians to be alert to complications from botulinum toxin therapy in children and adults, recognizing that such problems might not arise immediately and can appear in muscles distant from the injection site. This recognition is critical in patients who have difficulty swallowing or breathing.

“When a patient has had too much botulinum toxin, there is a point when symptom management strategies are no longer beneficial to the patient,” said Halstead. “Pyridostigmine is an active intervention to modulate the effects of botulinum toxin therapy.”

## NEWS

## How do extended space missions affect the brain?

BY CINDY ABOLE

NASA astronauts have experienced altered vision and increased intracranial pressure (VIIP) during flight aboard the International Space Station. The VIIP syndrome is thought to result from the redistribution of body fluid toward the head during long-term microgravity exposure; however, the exact cause is unknown.

In the November 2, 2017, issue of the *New England Journal of Medicine* (doi: 10.1056/NEJMoa1705129), **Donna R. Roberts, M.D.**, associate professor in the Department of Radiology and Radiological Sciences, reported the findings of a study comparing brain MRI scans from NASA’s Lifetime Surveillance of Astronaut Health program for two groups of astronauts: 16 astronauts who had been in space short-term aboard the space shuttle and 18 astronauts who had been in space for longer periods of time, typically three months, aboard the International Space Station.

Roberts’ team evaluated the cerebrospinal fluid (CSF) spaces at the top of the brain and CSF-filled structures, called ventricles, located at the center of the brain. The team also paired the preflight and postflight MRI cine clips from high-resolution 3-D imaging of 12 astronauts from long-duration flights and six astronauts from short-duration flights and looked for any displacement in brain structure.

Study results confirmed a narrowing of the brain’s central sulcus, a groove in the cortex near the top of the brain that separates the parietal and frontal lobes, in 94 percent of long-duration flight astronauts and 18.8 percent of the short-duration flight astronauts. Among the long-duration flight astronauts only, cine clips also showed an upward shift of the brain and narrowing of the CSF spaces at the top of the brain.

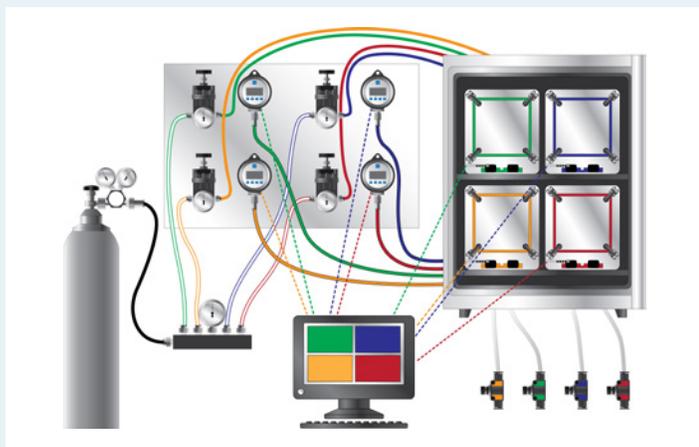
These findings suggest that significant changes in brain structure occur during long-duration space flight and that symptoms of VIIP syndrome would be expected to worsen the longer an astronaut stays in space. The parts of the brain that are most affected — the frontal and parietal lobes — control movement of the body and higher executive function.

With NASA’s Mars expedition mission set to launch in 2033, it is urgent for researchers such as Roberts to continue to collect data about astronauts and understand the basics of human space physiology.

## TECHNOLOGY

## Modeling pressure-induced cellular injuries in the brain

SCHEMATIC DRAWING BY EMMA VOUGHT



Elevated intracranial pressure (ICP), present in almost every category of brain injury, causes cellular injuries and additional neurological deficits beyond the initial insult. Yet little is known about ICP-mediated effects on cellular functions and the mechanism by which ICP-induced injuries occur, in large part because methods to study them have been lacking.

A team of investigators led by **Ramin Eskandari, M.D.**, director of pediatric neurosurgery at MUSC Children's Health, has developed an *ex vivo* model of ICP-induced cellular injury

Schematic drawing of the Pressure-Controlled Cell Culture Incubator (PC<sup>2</sup>I).

for understanding early cell-injury mechanisms and identifying biomarkers associated with pathological pressure in multiple brain injury etiologies. Eskandari's

group reported their findings in the January 1, 2018 *Journal of Neuroscience Methods* (doi: 10.1016/j.jneumeth.2017.10.004).

"The novelty of this model is we are able to simulate elevated ICP and examine this influence on nervous system cells suspended in a 3D matrix, which attempts to recapitulate early-injury scenarios to brain parenchyma not easily assessed in the clinical setting," said **Michael E. Smith, Ph.D.**, assistant professor of neurosurgery at MUSC and first author on the article.

The *ex vivo* system devised by Smith and Eskandari, called the Pressure-Controlled Cell Culture Incubator (PC<sup>2</sup>I), consists of separate acrylic chambers inside a cell culture incubator under a regulated and adjustable pressure. The originality of this *ex vivo* system is the ability to expose a 3D matrix of brain cells to extended periods of sustained as well as pulsatile pressure conditions while having complete control over all other parameters of the cell culture system. This allows for systematic and reproducible assessments of pressure effects at the cellular level. —NOUHOUBRAHIM

## Targeting pediatric brain cancer

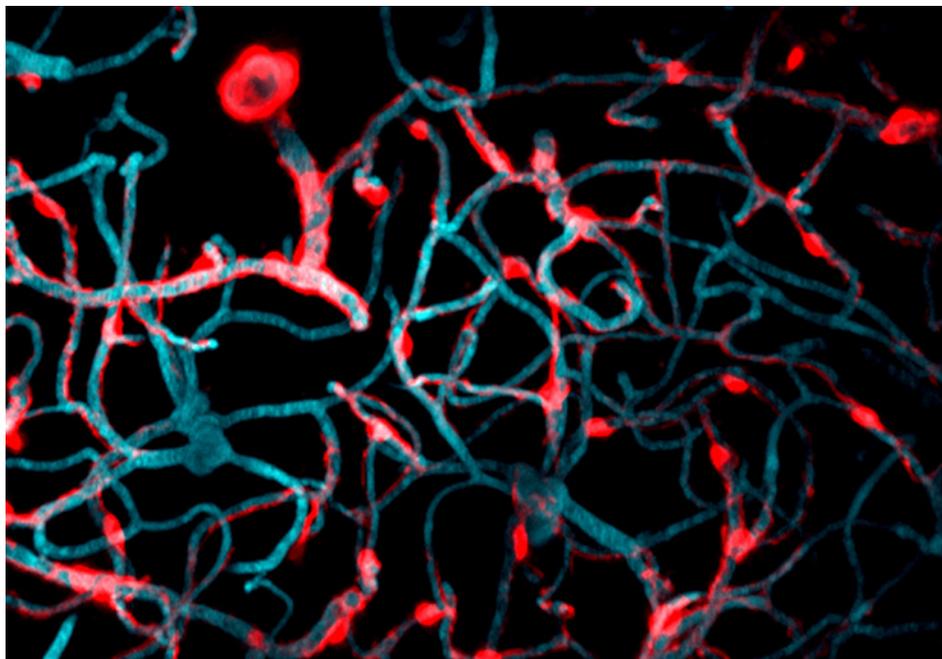
Juvenile pilocytic astrocytoma (JPA), while rare, is the most common pediatric brain tumor. This type of tumor develops in astrocytes — star-shaped cells that surround and protect nerve cells — and is often benign and slow growing. Research into this type of tumor is difficult due to the lack of an established cell line. **Ramin Eskandari, M.D.**, director of pediatric neurosurgery at MUSC Children's Health, and his team have solved this problem. In 2016, Eskandari removed a brain tumor from five-year-old Mary Scott Gallus. He then received permission from Mary Scott's parents to use the resected tumor for research.

Eskandari gave part of the tumor to **Arabinda Das, Ph.D.**, assistant professor in the Department of Neurosurgery. Das was able to purify and culture this low-grade tumor — the first-reported cell line for JPA. They named this brand new cell line MSG after Mary Scott Gallus.

Eskandari's group also works on high-grade tumors and has developed a novel experimental treatment model targeting pediatric medulloblastoma that is detailed in the March 2017 *Child's Nervous System* (doi: 10.1007/s00381-016-3305-x). When low-dose X-ray radiation was combined with immunotherapy (targeting HER2 or VEGF), T-cell-mediated cell death improved.

High-grade tumors are notorious for evading the body's immune system. To combat this, Eskandari's new treatment model uses a two-pronged approach. The first prong uses low-dose radiation that doesn't kill tumor or brain cells; however, it shocks the immune system into recognizing the tumor as a foreign object. The second prong uses antibodies targeting proteins on the cell surface to enhance the immune cells' ability to recognize the tumor. These *in vitro* results are tantalizing and warrant further investigation.

—MATTHEW GRESETH



The long arms of pericytes (shown in red) appear draped over capillaries in the brain (shown in blue). Image courtesy of Dr. Andy Shih.

## DISCOVERY

# Mystery Cells

New snapshots of a little-understood brain cell type

BY SVER AUNE

Pericytes, a little-understood cell type on brain blood vessels, grow into the empty space left when neighboring pericytes die, report scientists at MUSC in the January 2, 2018 issue of *Cell Reports*. (doi: 10.1016/j.celrep.2017.12.016). Such growth is a kind of brain plasticity that might be harnessed to fight age-related vascular disorders such as Alzheimer's disease and stroke.

Pericytes die in large numbers during Alzheimer's disease and stroke, but scientists do not know how many distinct types of pericytes there are or what functions the different types perform, according to **Andy Y. Shih, Ph.D.**, assistant professor in the MUSC Department of Neuroscience and principal investigator on the project. "They're probably the least understood of

the cells that comprise the neurovascular unit, which forms the blood vessel walls in the brain," said Shih.

Shih is interested in why pericytes appear so vulnerable to Alzheimer's disease and stroke. In the study, adult mice were genetically modified so that their brain pericytes glowed brightly under a powerful two-photon microscope. Using this technique, Shih and graduate student **Andrée-Anne Berthiaume**, who performed the experiments, were able to take detailed pictures over several weeks to see what happened to the brain when pericytes were lost.

In live mice, the pericytes were seen as oval cell bodies often located near junctions where two capillaries intersected, with long tentacle-like arms called *processes* extending

outward along the capillaries. These unusual cells blanketed much of the capillaries.

To study what happens when a pericyte is lost, Shih's team used a precision beam of laser light to ablate — or burn off — a single pericyte at a time. As they ablated more pericytes over time, they observed a curious pattern: over a period of days to weeks, the processes of neighboring pericytes grew to cover the capillaries where pericytes had been ablated. When their neighbors were lost, the surviving pericytes seemed to compensate for the job of keeping capillaries toned, a feature that is essential to maintain healthy blood flow in the brain.

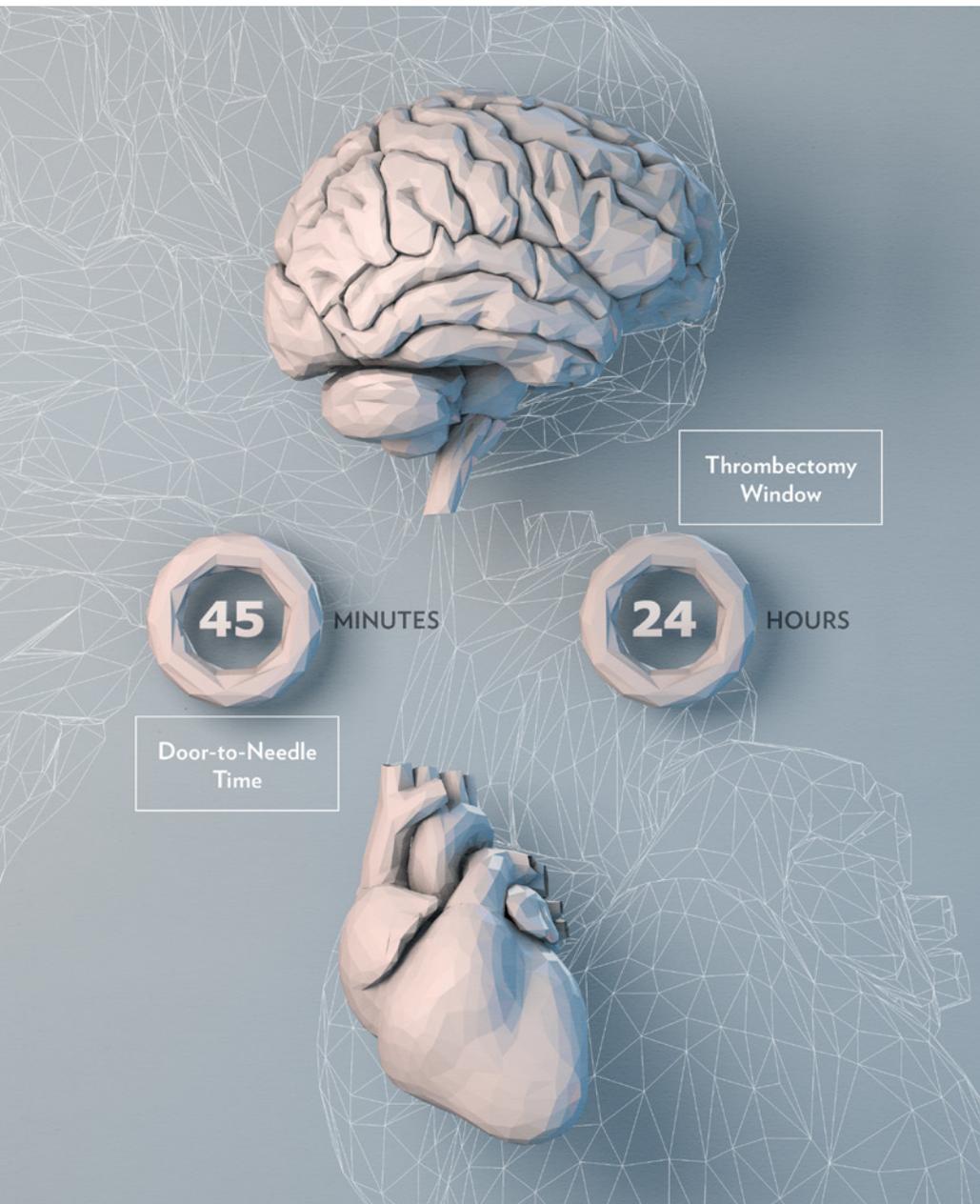
The images captured by Shih's group of pericytes extending their arms to cover exposed capillaries are the first of their kind. Although these findings show that pericytes can take over the job of supporting capillary tone when a single neighbor is lost, it is still not clear what happens when larger numbers of pericytes die, as they do in Alzheimer's disease and stroke.

Solving that puzzle could reveal ways to facilitate new pericyte growth, which in turn could combat the type of blood vessel dysfunction observed in Alzheimer's disease and stroke. The Alzheimer's Association is funding Shih's next plans to test the health of blood vessels in the brain when larger numbers of pericytes are ablated.

"Are there ways to augment this plasticity, to protect it and stabilize it if we need to? There are mechanisms driving this that we need to understand," said Shih.

# What's New in the 2018 AHA/ASA Guidelines for Acute Ischemic Stroke?

An interview with Dr. Edward C. Jauch, one of the guidelines' authors



The first all-inclusive update to the AHA/ASA Guidelines for Acute Ischemic Stroke was released in January at the International Stroke Conference in Los Angeles. *Progressnotes* spoke with **Edward C. Jauch, M.D.**, interim chair of the Department of Emergency Medicine at MUSC and one of the national authors of the 2013 guidelines and subsequent revisions, about what's new in the latest update.

## PN: Why was an update to the guidelines needed?

Acute stroke has been rapidly evolving over the last five years largely due to the development of endovascular therapies, where catheters are inserted through the arteries to go up and directly remove the clot using special devices. The other thing that is changing in stroke care in general is the development of regional stroke systems of care. We are recognizing that hospitals within a region need to collaborate to manage stroke patients most effectively. So we are emphasizing the importance of stroke capability credentialing, stroke recognition in the pre-hospital setting, understanding the severity of the stroke and getting the patient to the most appropriate hospital based on that stroke severity.

GRAPHIC: EMMA VOUGHT

**PN: What are the new guideline recommendations for thrombolytic therapy?**

Some years back, we expanded the treatment window for alteplase out to 4.5 hours for carefully selected patients. We have also started to remove some of the absolute contraindications to the drug based on 20 years of experience, so more people are eligible for treatment. More importantly, we have recognized that door-to-needle (DTN) time, as we call it — how quickly we administer the drug once the patient has entered the emergency department — is very important in terms of the patient's outcome. So we are developing these systems of care to ensure that we minimize any delays that could prevent the patient from actually getting the medication. Building these systems of care within a region and within a hospital to effectively deliver this in a timely fashion has become an important part of the guidelines. And so we have established some new time benchmarks. It used to be that we wanted patients treated within 60 minutes of arriving at the emergency department. Now we want to administer alteplase even quicker, since we realize it is an attainable goal. So now we want DTN to be under 45 minutes, and ideally you could probably drive it down to 30 minutes. And for every 15 minutes you decrease it, more patients will have a good outcome and survive their stroke.

**PN: What are the new guideline recommendations for endovascular therapy?**

Endovascular therapy as standard of care really came about in 2015 with the publication of five positive clinical trials. Based on those results, we issued a guideline update at that time recommending endovascular therapy with stent retrievers out to six hours. But now, as we are using more advanced imaging such as MRI and computed tomography (CT) perfusion, we are able to

identify tissue that is still salvageable in the brain beyond the traditional six hours. So now we can get patients who wake up with a stroke or are found down with a stroke in the last 24 hours and — if the imaging that we perform shows that there is still salvageable brain — then we are able to go up into these large arteries and perform mechanical embolectomy with these new devices. Patients beyond 4.5 hours are not eligible for the drug alteplase but are now potentially eligible, if they have a large clot and salvageable brain, to have the catheters remove the clot directly.

**PN: What do the guidelines say about optimal in-hospital care?**

We have created all sorts of new processes that are more effective in getting patients through the entire in-hospital system of care. That starts with Emergency Medical Services (EMS) bringing the patient to the right hospital based on the severity of the patient's symptoms. It starts with them telling the receiving hospital they're coming through advanced notification. With that notification, we can take patients straight to the CT scanner, because that is a rate-limiting factor in determining eligibility for therapies. We give alteplase to all patients who come in within 4.5 hours of symptom onset and meet criteria. And then, based on the recent DAWN and DEFUSE 3 trials, we very quickly perform additional imaging to see if there is a large vessel within the brain obstructed by a clot, if it's in an area from which we can actually retrieve it and if there is still brain that can be salvaged. If so, and it's still within 24 hours of symptom onset, then we rapidly get the patients to the neurointerventional suite, where they undergo an embolectomy. But there has to be salvageable brain — opening up a blood vessel to dead brain doesn't do any good.

**PN: How have the criteria for evaluating stroke care changed?**

In the past, we have looked at hospitals in terms of being stroke centers

based on their infrastructure. What I mean by that is that we would say: "Do you have a CT scanner? Do you have an emergency department? Do you have a stroke expert either in-house or now by telemedicine?" But that's just really telling us if you have the infrastructure. It doesn't tell us how well you use it. So we are evolving fairly quickly across the country with our credentialing and with guidelines to look at patient-centric outcomes. We are looking not only at whether you have those tools and resources, but also whether they produce meaningful outcomes for the patients. If you have all of the resources but don't use them effectively, the patients suffer. So we are going toward a more public reporting of your performance. The Centers for Medicare and Medicaid Service are wanting this. The public wants this. And it will help regional areas understand how well individual hospitals work within that region. For a Comprehensive Stroke Center like MUSC, it will help us identify hospitals in our region that may need our help. And for health care systems, it will tell them where they need to place additional resources. And when that becomes publicly available at the state level, that will help EMS agencies understand where's the best hospital to take stroke patients.



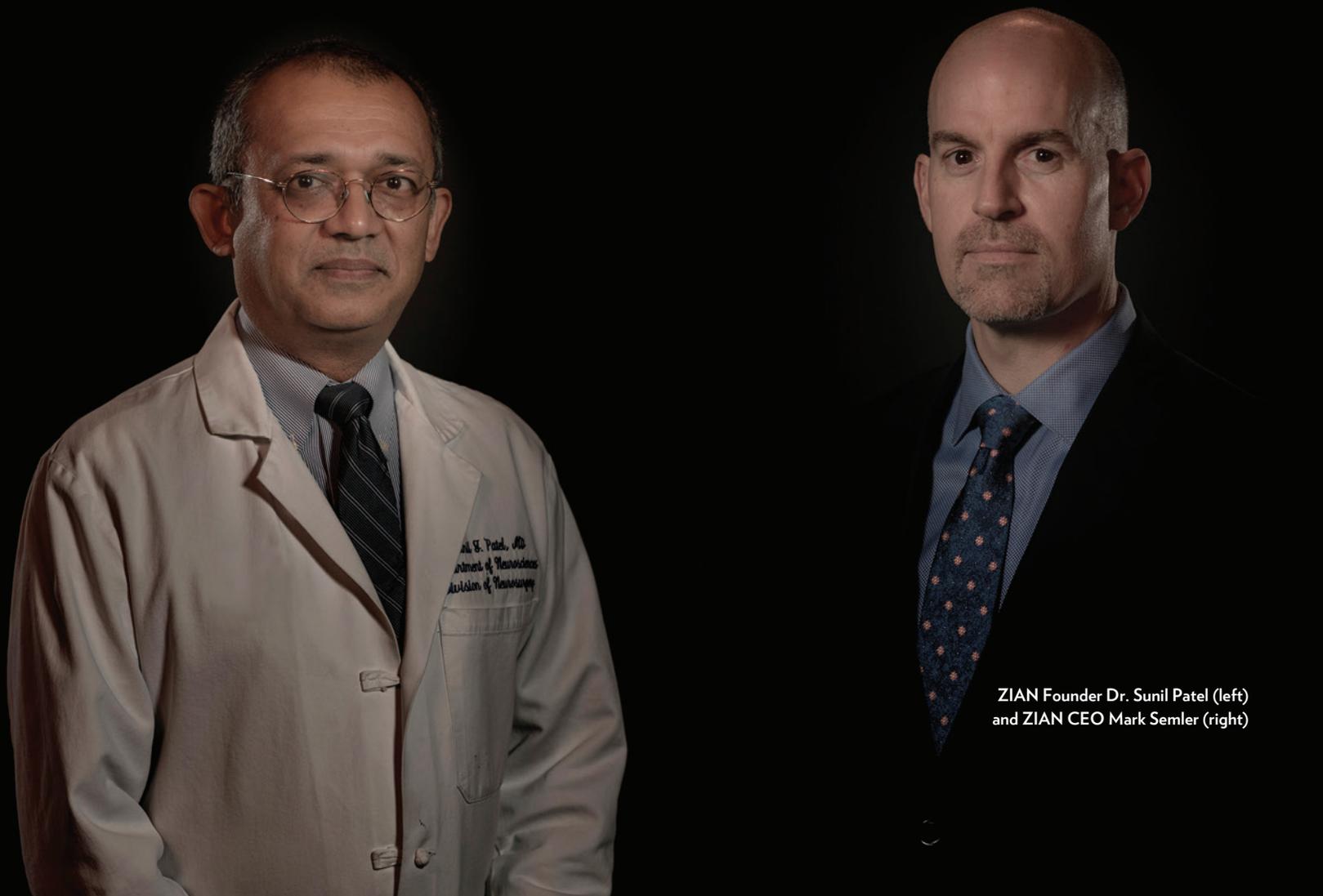
Dr. Edward C. Jauch

 **For an unabridged version of this interview, visit the Neurosciences page of the MUSC Health Medical Video Center ([MUSChealth.org/medical-video](https://MUSChealth.org/medical-video)).**

# A Bold Experiment

The Zucker Institute for Applied Neurosciences brings together the worlds of engineering and medicine to speed the translation of innovative technology into the clinic

BY KIMBERLY MCGHEE



ZIAN Founder Dr. Sunil Patel (left)  
and ZIAN CEO Mark Semler (right)

Founded in 2012, the Zucker Institute for Applied Neurosciences (ZIAN), a technology accelerator embedded in MUSC, is a bold experiment in bringing the worlds of medicine and engineering together to speed the translation of technological innovation in the neurosciences into the clinic. ZIAN taps into the creativity of clinicians and provides them access to the expertise in engineering, intellectual property and business development needed to develop their ideas into viable products. The vision of ZIAN's founder, **Sunil J. Patel, M.D.**, chair of the Department of Neurosurgery at MUSC, is for this to be a self-sustaining model of innovation, in which the licensing of inventions provides the funds needed for the development of new technologies. On a trajectory to achieve sustainability, ZIAN offers a model of successful translational research that could be adopted by other specialties.

### The genesis of ZIAN

When Jerry Zucker, a prominent Charleston businessman, received a diagnosis of glioblastoma in 2006, he and his family were surprised at how few treatment options were available. This led to a series of conversations with Patel about why the pace of innovation in medicine was so slow and how it could be accelerated. Patel explained that obstacles to innovation existed in both academia and industry. Physicians, who are involved with patient care every day, often have ideas for new technology, but most abandon these ideas because they do not have the time or support to carry them forward. In contrast, industry has the engineering and product design know-how as well as the business expertise needed to bring a technology into the clinic, but that technology is often less than ideal because it is designed with little input from frontline clinicians.

Zucker and Patel thought there had to be a better way. "We wanted to bring these two worlds together and change the culture," said Patel. After Zucker's death in 2008, Zucker's wife, Anita, donated the money to make that happen, and ZIAN was born.

Patel had witnessed firsthand that bridging the divide between these two worlds could spur innovation while working as a fellow under the famed neurosurgeon and inventor Kenichiro Sugita, M.D. "In his OR, in addition to junior faculty, residents and students, he always had a couple of engineers working on how to improve this and that," said Patel. That memory stuck with Patel and would become one of the inspirations behind ZIAN.

One of Patel's first tasks in establishing ZIAN was finding an engineer with a passion for medical innovation and deep industry experience. Enter **Mark Semler**, who serves as ZIAN's chief executive officer. While in high school, Semler lost both parents and, like

Zucker, became frustrated at the slow pace of innovation. "I watched my parents die in hospital rooms full of equipment," remembered Semler. Later, when he worked on his first medical device as an engineer, he knew he had found his calling. "I wondered whether I could affect this equipment so that I could have kept my parents alive," said Semler. Rounding out the ZIAN team are **Jesse Goodwin, Ph.D.** vice president for development, and biomedical engineer Chris Hapstack.

### A model of clinical innovation that works

The ZIAN offices are embedded in the neurosurgery department, so clinicians can easily stop by between cases to brainstorm ideas for devices. Each of the ZIAN offices has an entire wall painted to serve as a large white board. Many of ZIAN's products have begun as a sketch on Semler's wall.

ZIAN sparks innovation by encouraging clinicians and engineers to learn to converse with one another. "Engineers speak a language I don't understand and vice versa," said **Jessica Barley, Ph.D., CNIM**, one of the ZIAN inventors. "I had to bring the engineers into the operating room to show them what the real issue was. There's a translation that has to occur between two worlds." But when that translation occurs, magic happens and medical devices are designed that are grounded in the clinical realities of care.

Because ZIAN wants to focus its efforts on devices that will help as many patients as possible and is mandated to be self-sustaining, it must be selective in the ideas it decides to take forward. To be chosen, inventions must address an unmet clinical need, be buildable at a competitive cost, have a clear path to intellectual property and have a wide market. "We don't want to just create a 'me too' device," said Goodwin. "We want to push the limits of what's possible." Thus far, of the more than 150 ideas that have been pitched, ZIAN has pursued only seven. This selectivity has paid off; one of the technologies has been FDA approved, two more are licensed and a fourth is being licensed (see Box).

### De-risking

That impressive track record is due in part to the care with which ZIAN "de-risks" its products to make them more attractive to potential licensors. Intellectual property rights are secured, market analysis is performed, a clear pathway to regulatory approval is defined and manufacturable prototypes are created. "Those all reduce risks that could kill a project," said Semler. "If we've done our work in those areas, the device is more attractive to companies because there's very little risk they can't get it into the market."

Perhaps most important of all, the ideas have been thoroughly vetted as inventors pitch to their fellow clinicians, to ZIAN and finally to a shark tank of local investors. “When you go in front of a shark tank, you are going to show up with a better analysis, business model and pitch,” said Semler.

### Culture change

ZIAN has helped create a new culture of innovation in the neurosurgery department. “Medical science is supposed to be done to bring solutions to patients, but often it remains science,” said Patel. “With ZIAN, we developed a more solution-driven science, and that has changed the culture and the way our faculty and trainees think.” Due to that culture of innovation, the department is receiving residency applications from some of the most inventive minds in the country. “We are beginning to see applicants that I would never have

dreamed possible,” said Patel. “We just finished interviewing about 30 potential residents — they all knew about ZIAN and were creative people, some of whom already had patents themselves.”

### The road forward

Once it attains sustainability, ZIAN is a model that could be rolled out to other clinical departments at MUSC. “In my mind, every academic department — surgical or nonsurgical — needs to have an entity like this, where an engineer can give feedback on how to make the innovation impactful,” said Patel. In addition to assisting clinicians develop their innovative ideas into viable products, ZIAN also plans to serve as a think tank for industry, providing early clinician feedback about products in development. ZIAN views this as the best way to fulfill its mission of helping patients benefit sooner from innovative, clinically relevant technology.

## ZIAN’s Seven Current Technologies \*\*See [ianeuro.org](http://ianeuro.org) for more details

Name	Clinician-Inventor	Licensing Status	Description
<b>Blink Reflexometer™</b>	Nancey Trevanian Tsai, M.D.	Licensed	A portable device for measuring the blink response
<b>HEALx™</b>	Bruce M. Frankel, M.D.	Being licensed	An expandable corpectomy device
<b>NaviCap™</b>	Raymond Turner, M.D., Alejandro Spiotta, M.D., Aquilla Turk, M.D., Imran Chaudry, M.D.		A “screw-less” cranial anchoring port system
<b>SIMelectrode™</b>	Jessica Barley, Ph.D., and Jonathan Edwards, M.D.	Licensed	An improved needle electrode for intraoperative neurophysiological monitoring
<b>Sinu-Lok®</b>	Bruce M. Frankel, M.D.	FDA-approved	A novel replacement for a standard rod implant used in lumbar spine surgery
<b>TranZform™</b>	Stephen P. Kalthorn, M.D.		A novel interbody device that expands both vertically and horizontally
<b>VayuClear™</b>	Stephen P. Kalthorn, M.D.		A surgical suction wand declogging device



CLINICIAN-INVENTOR:  
Stephen P. Kalthorn, M.D.



CLINICIAN-INVENTOR:  
Nancey Trevanian Tsai, M.D.



CLINICIAN-INVENTORS:  
Jessica Barley, Ph.D., CNIM (pictured)  
and Jonathan Edwards, M.D.

## TranZform™

**“If we know there is an unmet clinical need — if a patient is hurting and needs help — it motivates the whole team to get moving and get this product to market to help patients.”**  
— Stephen P. Kalthorn, M.D.

TranZform™ is a new type of expandable interbody device that could improve outcomes for patients undergoing lumbar spinal fusion surgery. Interbody devices are implanted between vertebrae and grafted with bone to encourage the bony ingrowth that is required for a stable spinal fusion. Unlike static interbody devices, expandable ones are small enough to be introduced during minimally invasive surgery but can be expanded once in place.

Although there are expandable interbody devices currently on the market, they expand only vertically or horizontally and do not fill the disk space adequately or provide enough of a graft window for the needed bony ingrowth. As a result, short-term and long-term patient outcomes suffer.

TranZform™, which expands both vertically and horizontally, provides a class-leading graft volume for bony ingrowth, facilitating better spinal fusion.

“I think this will have a tremendous benefit for patient outcomes, and we will be able to help patients in a less invasive way and give them a more durable and consistent solution for their problem,” said Kalthorn.

## Blink Reflexometer™

**“It is wonderful when you have a team behind you that says ‘Thank you for sharing your idea. We will take it from here and develop it and you can be as involved as you want.’”**  
— Nancey Trevanian Tsai, M.D.

The Blink Reflexometer™, which has been licensed to BLINKtbi (Charleston, SC), is a portable device that uses high-speed video to capture and quantitatively analyze a series of blinks that it stimulates with puffs of air. The blink reflex has been shown to be sensitive to a number of neurological conditions, including traumatic brain injury, Parkinson’s disease and Huntington’s disease, suggesting that it could be a useful tool for neurological assessment. The device analyzes the recorded blinks to determine whether the patient has experienced neurological insult.

The device could make it possible to include the blink reflex as a metric or vital sign in medical examination. Because it is portable, it could be taken into the field for on-site neurological assessments. Potential uses are field-side assessment of athletes for concussion or field sobriety tests for marijuana intoxication. The device was recently awarded the 2018 Technical Team Project of the Year by the Charleston Engineers Joint Council.

“When you can provide quantitative, objective data, it’s a game changer,” said **Nancey Trevanian Tsai, M.D.** “It’s analogous to the difference between saying someone is feverish and measuring the patient’s temperature with a thermometer.”

## SIMelectrode™

**“You don’t go into this thinking you are going to get a home run, but when it happens, it is a feeling of accomplishment that I cannot even begin to describe.”**  
— Jessica Barley, Ph.D., CNIM

SIMelectrode™ solves a serious safety problem with intraoperative neurophysiological monitoring (IONM) — the risk of needle sticks. As many as 60 disposable needle electrodes are taped to the patient — from the scalp to the feet — so that neurological function can be monitored during surgery. Although IONM is crucial to patient safety, the needles can stick personnel as they dislodge the electrodes or move the patient. Needles can also become snagged in the many wires that connect the electrodes to the IONM specialist’s computer, making accidental sticks more likely.

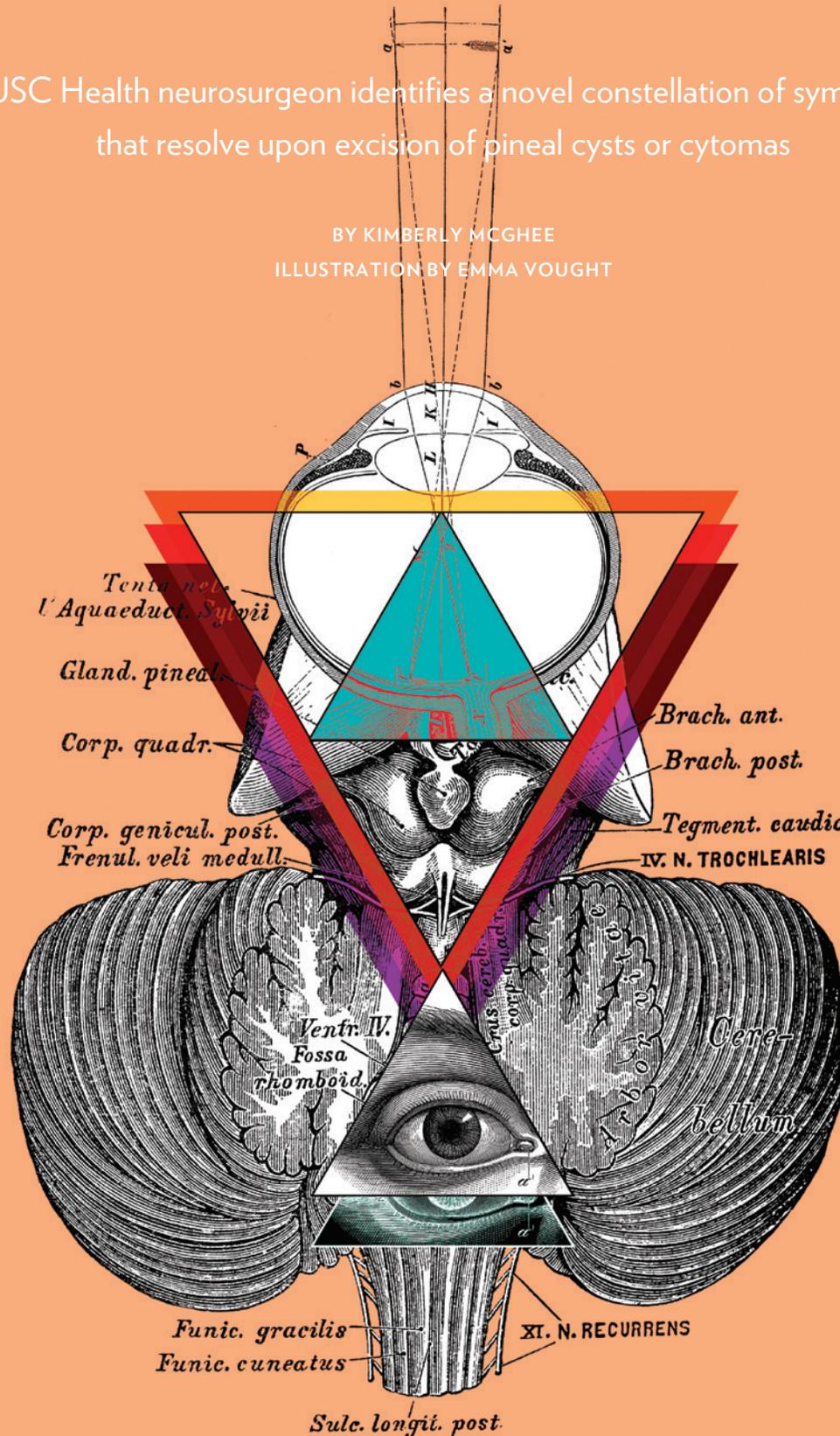
The innovative design of SIMelectrode™ solves these problems. The needles are covered in a protective sheath and retract immediately after use. The market for the device is substantial, since intraoperative monitoring is used by neurosurgery, orthopaedic surgery, urology, radiology and cardiac surgery.

# Pineal Cysts: Worth a Second Look

MUSC Health neurosurgeon identifies a novel constellation of symptoms that resolve upon excision of pineal cysts or cytomas

BY KIMBERLY MCGHEE

ILLUSTRATION BY EMMA VOUGHT



The pineal gland, a fingertip-sized structure located deep in the center of the brain, is found in almost all vertebrates, and yet its function, if any, remains a mystery. Philosophers and mystics have sometimes magnified its importance, while physicians have tended to underestimate it. Seventeenth-century philosopher René Descartes thought it to be the seat of the soul, while nineteenth-century mystic Madame Blavatsky believed it to be an atrophied third eye. In contrast, medical science has long dismissed it as unimportant — a vestigial gland of little significance, the neurological counterpart of the appendix. For generations, neurosurgeons have been taught to discount imaging evidence of a pineal cyst as inconsequential, in part because resection of the gland in cases of pineal tumor has led to no functional loss.

This has left little clinical recourse to patients with pineal cysts who are experiencing symptoms such as headaches, double vision or nausea for which there is no other neurological explanation. Some patients are referred for psychiatric evaluation with the suspicion that the symptoms are psychosomatic. Others are left to seek relief for their symptoms one by one by seeing a variety of specialists.

Like most other neurosurgeons, **Sunil J. Patel, M.D.**, chair of the Department of Neurosurgery, had been taught to dismiss pineal cysts as clinically inconsequential. Then, five years ago, a patient's story and a resident's question led him to re-examine that assumption. A patient presented with imaging evidence of a pineal cyst and a set of neurological symptoms that caused her to leave a very successful career and become virtually house-bound, unable to care for her children. Her symptoms were not consistent with a pineal tumor, and no other neurologic or metabolic cause for them could be found.

Having rounded on the patient, Patel was ready to hand down to a new generation of providers the long-held assumption that pineal cysts are clinically insignificant, when a resident raised the question whether it wasn't possible, in the absence of all other explanations, that the pineal cyst was causing the patient's problems. "It takes a young mind to question you," said Patel. "It was a young resident who asked 'Why not try removing the cyst/gland? How do you know that's not causing her symptoms?'"

For the first time, after discussion with the patient, Patel opted to excise the cyst. The results shocked him. When the patient came in for a follow-up visit several weeks later, her symptoms had vanished. What's more, the pathology report revealed that the excised mass was not a cyst at all but rather a benign tumor known as a pineocytoma.

Patel has since identified a constellation of symptoms — headaches, insomnia, episodic cognitive deficits such as speech or vision difficulties or lapses in short-term memory, and, rarely, numbness in limbs and problems with balance — that are associated with

pineocytomas and that resolve upon their excision. He has also come to recognize certain changes on MRI that are indicative of pineocytomas. He highly suspects a pineocytoma when both characteristic symptoms and MRI changes are present. If the symptoms are interfering with a patient's quality of life and all other causes have been ruled out, Patel recommends surgery to remove the suspected pineal lesion.

Patel, who is one of only a handful of surgeons in the world who resects pineal cysts, has now performed more than 40 of these surgeries. In most cases, the pineal cyst has turned out to be, as expected, a pineocytoma. Ninety percent of these patients have achieved complete symptom resolution, and all achieve at least partial resolution. In patients with comorbid conditions, such as migraine, the symptoms associated with the pineocytoma resolve, but those that are migraine-specific, for example, do not.

**“The majority of the symptomatic pineal cysts have turned out to be benign tumors, and removing them does provide relief of symptoms.”**

**— Sunil J. Patel, M.D.**

What does all of this mean for physicians? First, it's worth taking a second look at MRI findings of a pineal cyst, because it could in fact be a pineocytoma. Even patients with small cysts who are not experiencing symptoms should undergo monitoring with MRI every year or so in case it turns out to be a cytoma and starts to grow. Second, patients already experiencing some of the telltale symptoms of the syndrome should be referred to a neurosurgeon with experience in intracranial masses for evaluation, because surgery could provide them complete or partial relief.

“Not all pineal gland cysts are asymptomatic and not all of them are nonneoplastic,” said Patel. “The majority of the symptomatic pineal cysts have turned out to be benign tumors, and removing them does provide relief of symptoms.”



**To watch a video interview with Dr. Patel about pineal gland surgery, visit the Neurosciences page of the MUSC Health Medical Video Center ([MUSCHealth.org/medical-video](https://www.muschealth.org/medical-video)).**



To watch a video interview with Dr. Vandergrift, visit the Neurosciences page of the MUSC Health Medical Video Center ([MUSChealth.org/medical-video](https://MUSChealth.org/medical-video)).



Placement of the electrodes for stereotactic electroencephalography. Photograph by Brennan Wesley.

# Retuning the Brain

Minimally invasive therapies provide good seizure control for patients with medication-refractory focal epilepsy

BY KIMBERLY MCGHEE

Epilepsy affects an estimated 3.4 million Americans, whose quality of life and sense of independence can be decreased and chances of self-injury increased by seizures. “When you have a seizure, the electrical activity of the brain, which is usually in harmony, becomes out of tune,” explained **William A. Vandergrift, M.D.**, a neurosurgeon at the MUSC Health Comprehensive Epilepsy Center, the only level 4 epilepsy center in South Carolina.

Although most patients achieve good seizure control with pharmacological therapy, one in three does not. Surgery to remove tissue from the epileptogenic zone — the area from which the seizure originates — has been shown to provide good seizure control in 75 percent of patients with medication-refractory focal epilepsy. However, some patients are reluctant to undergo open brain surgery.

Fortunately, a growing number of minimally invasive therapies designed to “retune” the brain’s electrical field are available for these patients at the MUSC Health Comprehensive Epilepsy Center. A team of epilepsy specialists, including neurosurgeons, neurologists, physician assistants, nurse practitioners, dietitians and speech pathologists, guide patients to the therapy that is best for them.

### Identifying the epileptogenic zone

Surgery and the less invasive laser ablation, which uses heat to destroy seizure-generating brain tissues, can only be performed in patients with a clearly identified epileptogenic zone, the removal or ablation of which would not compromise memory, language or other critical neurological functions. Clues about the origin of the seizure are provided by the symptoms associated with its onset and by brain imaging such as MRI, PET scans and/or SPECT scans.

In addition to these traditional tools, MUSC Health also uses high-definition scalp electroencephalography (EEG) as well as surgically placed intracranial stereotactic EEG (SEEG) to precisely locate the origin of the seizure. In high-definition EEG, a cap with as many as 256 electrodes is placed on the scalp to provide detailed information about potential trouble spots. This information is then used to define the targets for SEEG, the definitive method for localizing the epileptogenic zone, which involves placement of deep electrodes in the areas of the brain thought to be generating seizures. “It is not possible to have intracranial SEEG covering the entire brain,” said **Leonardo Bonilha, M.D., Ph.D.**, an epilepsy neurologist at MUSC Health who chairs the working group on high-definition EEG for the American Clinical Neurophysiology Society. “We use high-definition EEG to localize where SEEG goes. High-definition EEG can enable people to get SEEG and sometimes get surgery or ablation that otherwise could not.”

### Laser ablation

Laser ablation offers a minimally invasive treatment option for patients who refuse or are not candidates for surgery. A thin fiberoptic wire sheathed in a protective catheter is inserted through a very small burr hole in the patient’s skull and directed to the mesial structures of the temporal lobe. A laser is used to heat and destroy the targeted tissue in the epileptogenic zone; carbon dioxide in the catheter cools the wire to ensure that heat is administered only to the targeted region. Magnetic resonance thermography, which provides a real-time heat map of the brain, enables the surgeon to very precisely ablate the appropriate tissue. For a few patients, in which the source of the seizure extends beyond the hippocampus and amygdala to the surrounding temporal tissue that is not ablated or removed, laser ablation may not achieve adequate seizure control. These patients are still eligible to undergo open surgery if laser ablation does not lead to a cure.

### Electrical stimulation

Responsive neurostimulation (RNS) and vagus nerve stimulation (VNS) both involve implantation of a device that delivers electric stimulation to prevent the onset or spread of a seizure. For RNS, the neurostimulator is placed in the patient’s skull and is attached to electrodes in up to two suspected epileptogenic regions of the brain. For VNS, a stimulator is implanted in the chest and is attached to leads that are wrapped around the vagus nerve in the neck, a nerve known to be important for autonomic function. Responsive neurostimulation is a closed loop system — after a training period, the device can monitor for changes that indicate the onset of a seizure and deliver an electrical charge to disrupt it. In contrast, VNS delivers electrical stimulation at regular intervals, whether or not a seizure is imminent. If the patient implanted with a VNS system or a family member senses the approach of a seizure, he or she can wave a special magnet over the stimulator to generate an additional pulse in the hopes of preventing it. An investigational closed-loop VNS system that delivers electrical stimulation in response to increases in heart rate, which often occur before and during seizure, is in development.

### What it means for patients

“Having SEEG and laser ablation and these new vagus nerve stimulators and responsive neurostimulators help us help patients without subjecting them to antiquated epilepsy surgery,” said Vandergrift. “The exciting thing is that we can take someone who is debilitated by seizures and put them through a minimally invasive process and return them back to a full life.”



# Language Lost and Found

New language discoveries inform therapies for aphasia after stroke

BY SVER AUNE

ILLUSTRATIONS BY EMMA VOUGHT

Clinical management of aphasia after stroke is being refined with breakthroughs in understanding the networks of language in the brain. Advances in brain imaging show that the dynamically changing neurological environment after stroke can be harnessed to enhance recovery of language in patients with aphasia.

The language impairments of aphasia are observed in nearly a third of all stroke patients.<sup>1</sup> Communication is such a vital part of life that its loss after stroke can be personally and professionally devastating.

**Leonardo Bonilha, M.D., Ph.D.**, an associate professor of neurology in the MUSC College of Medicine and director of MUSC's aphasia clinic, leads a team that is studying how the brain changes after stroke. The researchers seek an understanding of how brain *plasticity* — the ability of the brain to compensate for areas that are lost to stroke — can support recovery of language in patients affected by aphasia.<sup>2</sup> Their hypothesis is that new approaches for aphasia must engage the compensatory potential of brain regions that remain intact after stroke.

## Treating the whole brain

Bonilha's group is using diffusion tensor imaging, which measures white matter tracts, and functional magnetic resonance imaging (fMRI), which displays the areas of the brain that use oxygen during a given language task, to demonstrate that the regions responsible for language are not just unconnected outposts. Rather, they form a continuum, with different regions of gray matter crucial for language connected to one another through a complex network of white matter tracts.<sup>3</sup> A specific area of the brain is not solely in charge of one part of speech, then, but relies on concerted interaction with other areas to function.

According to the new neuroanatomy of language, aphasia syndromes are being classified based upon which component of the language process is impaired, in addition to which areas of the brain are affected.<sup>4,5</sup> Such an approach examines the brain regions and connections that were lost after stroke and how they determine the symptoms of aphasia. This methodology also reveals the networks that are preserved after stroke and how they support *plasticity*.<sup>2</sup>

Traditionally, aphasia has been linked to the location of the stroke lesion in the brain — a method called *lesion symptom mapping*.<sup>4</sup> Specific areas of the brain are paired with the behavior that is lost when that area is damaged by stroke.

"That's one of the few ways in which you can determine for sure that a brain region is crucial for a behavior," said Bonilha.

Stroke affecting the left middle cerebral artery (MCA), one of the most important arteries supplying blood to the brain, can cause damage to Broca's area and lead to Broca's aphasia, with symptoms of non-fluent, halting speech and difficulty finding words. Other strokes affecting the MCA can cause Wernicke's aphasia, wherein patients often speak fluently but tend to pepper their sentences with words that have no context or meaning. From these symptoms, Broca's area of the brain is known to be necessary for word production, while Wernicke's area is needed for word comprehension.<sup>5</sup> The poet Ralph Waldo Emerson suffered what was likely Broca's aphasia caused by a stroke; on one occasion, he was able to describe an apple but was unable to say the word.<sup>6</sup>

Advances in neuroimaging with MRI are improving upon traditional models that explore the areas that control language in the brain. When the brain performs a task that engages a certain language step — say, naming an object — it is possible to examine all areas of the brain that are connected — both the gray matter

**“The individual connectome is a complex chart of the patient’s brain. With our research, we can ensure that individual differences are taken into account for recovery.”**

**— Dr. Leonardo Bonilha**

regions affected by stroke and the white matter regions connecting them. One stroke survivor may have damage to several brain areas responsible for breaking down spoken language into thoughts, for example, while another may have damage to brain regions needed to plan the motor functions required to speak.<sup>7</sup>

Studying all the language regions and how they are connected enables researchers to explore the brain’s *connectome*, which is the comprehensive map of the entire brain’s wiring pattern and its relationship to communication.<sup>3</sup> Bonilha’s research is showing that brain networks are dynamic and adaptive to change — *plastic* — and that different areas of the brain can be trained by specific speech therapy to compensate for the areas lost to stroke. “We have to understand how the brain processes language and also how the brain changes itself in the context of learning how to speak again,” said Bonilha.

### Leaders in aphasia clinical trials

The new neuroanatomy of language is guiding clinical trials designed to place patients in therapy tailored to their specific aphasia. Speech and language therapy remains the standard of care for aphasia, but it is not effective for all patients. There are still questions about how the timing, duration and type of aphasia therapy can affect recovery in different patients.

Research efforts are focused on tailoring speech and language therapies, along with other experimental therapies, to the individual patient. As part of this effort, Bonilha leads the Brain Connectivity Supporting Language Recovery in Aphasia study (NCT02416856). Bonilha’s team will look for specific brain activation patterns that correlate with better recovery of language during speech therapy. The researchers are using fMRI during speech and language therapy to study cerebral blood flow and white matter connectivity in the brains of patients with post-stroke aphasia lasting at least six months.

In a recent high-profile clinical trial, patients who had post-stroke aphasia lasting at least six months experienced significant

improvements in verbal communication with three weeks of intensive speech and language therapy.<sup>8</sup> Bonilha’s study at MUSC will build on this positive result and serve as a model for testing different speech therapies based on their length, intensity and timing after stroke. In the future, these data could be used to predict which therapy will be most effective in a given patient based upon their initial post-stroke fMRI brain patterns.

“The individual connectome is a very complex, rich dataset, a very complex chart of the patient’s brain,” said Bonilha. “With our research, we can ensure that individual differences are taken into account for recovery.”

In addition to studying the mechanisms of language production in the brain, Bonilha leads the MUSC arm of the Center for the Study of Aphasia Recovery (C-STAR), an \$11.1 million program project based at the University of South Carolina (USC) and sponsored by the National Institutes on Deafness and Other Communication Disorders. The center’s goals are to maximize patient recovery from acute or chronic aphasia after stroke. C-STAR’s several research projects enlist stroke and language experts from MUSC, the University of California at Irvine and Johns Hopkins University.

The partnership in aphasia research between MUSC and USC is strategic, since South Carolina is part of the nation’s “stroke belt,” where the incidence of stroke is higher than the national average. Joining efforts in this way is a boon to aphasia research, according to Bonilha. “There’s a network of collaboration within the state that is important,” said Bonilha. “This is a multi-institution, collaborative effort.”

The research partners recently investigated new treatments designed to stimulate the brain during speech and language therapy. The five-year Brain Stimulation and Aphasia Treatment phase 2 clinical trial (NCT01686373) at MUSC and USC assessed whether brain stimulation during speech therapy could improve patients’ performance during language tasks. Patients with post-stroke aphasia lasting at least six months were treated with a method called transcranial direct current stimulation (tDCS), which involves passing a weak electrical current through the brain, along with computer-controlled speech therapy.

The group enlisted the expertise of **Mark S. George, M.D.**, Distinguished Professor of Psychiatry, Radiology and Neuroscience and Layton McCurdy Endowed Chair in Psychiatry at MUSC, and the MUSC Data Coordinating Unit to handle extensive fMRI data processing in the trial. On the basis of preclinical data, the team speculated that tDCS would stimulate patients’ cerebral cortex plasticity and boost their ability to recall words lost to stroke. The promising results of the trial will soon be published.

Bonilha's collaborator, Julius Fridriksson, Ph.D., SmartState™ Endowed Chair of Memory and Brain Function at USC and principal investigator on the C-STAR grant, is leading C-STAR's team of researchers. Fridriksson heads the Modeling Treated Recovery From Aphasia phase 2 clinical trial (NCT03416738), which began enrolling chronic stroke patients with aphasia at USC and MUSC in January. In the trial, Fridriksson's and Bonilha's teams will examine how biographical factors such as age and gender and factors such as the extent and location of stroke damage affect patients' abilities to respond to different kinds of speech and language therapy.

"Why is it that some patients respond much better than others to a given type of therapy?" asked Fridriksson. "We are trying to find the best predictors of treatment response in patients."

In a study with broad implications for future aphasia treatment, Bonilha is working with Chris Rorden, Ph.D., SmartState™ Endowed Chair of Neuroimaging at USC and co-investigator at C-STAR, to evaluate the individual connectomes of patients with acute or subacute forms of aphasia, lasting one month or three months, respectively. Using fMRI, Rorden's team will obtain data-rich pictures of aphasia patients' brains during a wide range of speech and language tasks. The goal is to look at the fine-grained structural connectivity of the entire brain after stroke —the location of the stroke damage in gray matter regions as well as the surrounding white matter tracts that have been interrupted.

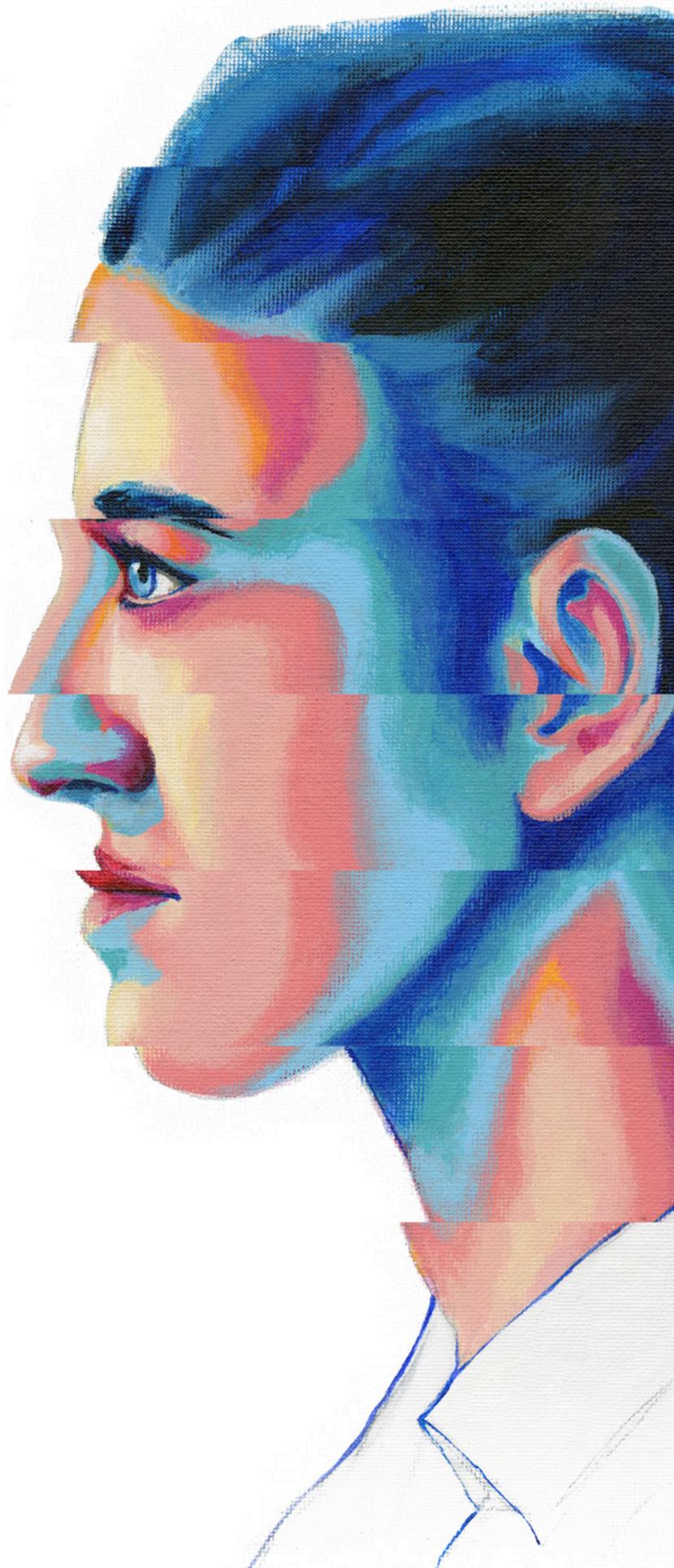
## Language Regained

By working collaboratively with partners in aphasia research, investigators at MUSC are refining clinical care of aphasia by tailoring speech and language therapy to stimulate plasticity in the intact brain after stroke. Data is being used to predict response to treatment, thereby enabling speech therapy to be personalized based on each patient's brain profile obtained with fMRI and language performance.

The end goals are to help patients regain their social and professional lives. In the future, researchers hope that patients with aphasia can regain their language that was once lost to stroke.

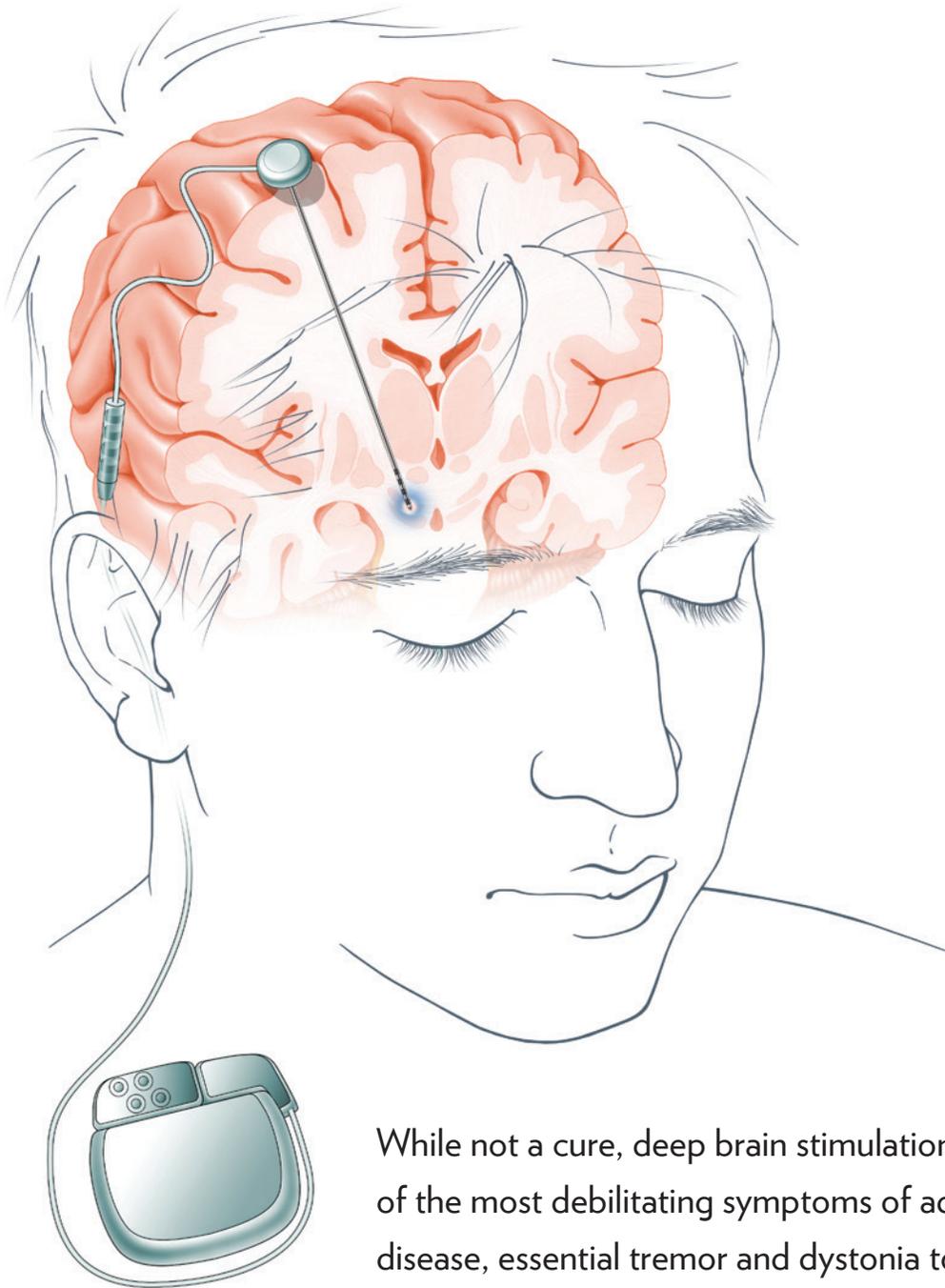
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# Restoring Poetry to Motion:

## Deep Brain Stimulation for the Treatment of Movement Disorders



While not a cure, deep brain stimulation can alleviate some of the most debilitating symptoms of advanced Parkinson's disease, essential tremor and dystonia to improve quality of life.



SUBJECT MATTER EXPERTS: ISTVAN TAKACS, M.D.; GONZALO J. REVUELTA, DO; AND NATHAN C. ROWLAND, M.D., PH.D.

BY KIMBERLY MCGHEE

ILLUSTRATION BY EMMA VOUGHT

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### On completion of the article, the reader should be able to:

- Summarize evidence showing the efficacy of deep brain stimulation (DBS) for alleviating symptoms of advanced Parkinson's disease, essential tremor and dystonia.
- Discuss the benefits and risks of DBS in patients with movement disorders and recognize when to refer appropriate patients for evaluation by a movement disorders specialist.

For select patients with movement disorders, deep brain stimulation (DBS) can be life-changing. Though not a cure, DBS can alleviate some of the most debilitating symptoms of advanced Parkinson's disease (PD),<sup>1-3</sup> essential tremor (ET)<sup>4-6</sup> and dystonia,<sup>7-8</sup> often dramatically improving quality of life. Optimal DBS candidate selection can be facilitated with evaluation by a movement disorders specialist.

During lead implantation, the movement disorders neurologist and neurophysiologist work with the functional neurosurgeon to map the target region. A microelectrode targeting relevant basal ganglia structures is inserted through a burr hole in the skull. In traditional DBS, patients are placed in a stereotactic headframe and are awake for lead implantation; the team can get direct feedback on symptom control, monitor for possible side effects of stimulation and make necessary adjustments immediately. For patients who are intimidated by the headframe, smaller "frameless" platforms that are still bolted to the skull but do not surround it like the frame are available.

In a second operation, a pulse generator, a sort of pacemaker, is implanted below the collar bone to drive the system. Some weeks after implantation, allowing for wound healing, the DBS is activated and, over a series of follow-up visits, calibrated to best effect.

### Parkinson's Disease

The cardinal symptoms of PD — bradykinesia, tremor, rigidity and postural instability — are associated with reduced striatal dopamine. Drug therapy is centered around dopamine replacement, in one of many formulations. Initially, levodopa (L-DOPA) helps patients maintain a predictable "on" period when most of their symptoms are well controlled. However, over time, the response to medication becomes less reliable. To address these fluctuations, the dosage is

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adjusted, and adjunctive dopaminergic therapies are added, raising the L-DOPA equivalent daily dose and subsequently raising the risk of L-DOPA-induced dyskinesias.

For PD patients experiencing motor fluctuations and dyskinesias, DBS can offer more predictable symptom relief. It can also be used to treat refractory tremor in patients with PD. The two primary DBS targets in PD are the subthalamic nucleus (STN) and the globus pallidus internus (GPi).

### Improved quality of life

Multiple clinical trials have shown greater improvements in PDQ-39 scores (lower scores = improvement), a quality-of-life measure, with DBS than medical therapy alone. In a landmark trial by Deuschl et al



DBS lead placement.  
Photograph by Brennan Wesley

in 156 patients with advanced PD younger than 75 (NCT00196911),<sup>1</sup> the PDQ-39 score decreased by 10 points, a 25 percent improvement, six months after DBS, whereas almost no change was seen in the medical therapy group. In another randomized trial of 255 patients with advanced PD (NCT00056563) reported by Weaver et al in 2009,<sup>2</sup> quality of life improved significantly more in the DBS arm than the medical therapy alone arm at six months, as evidenced by improved scores on the overall PDQ-39 and on seven of eight individual quality-of-life metrics. The multi-center PD SURG trial (Current Controlled Trials, number ISRCTN34111222),<sup>3</sup> which enrolled 366 patients with advanced PD, showed a five-point improvement in the PDQ-39 summary score at one year in the DBS plus medical therapy group vs. 0.3 in the medical therapy group. The study is important as it shows lasting benefits for quality of life beyond the “honeymoon” period in the months just after surgery.

### Improved symptom control

These trials also reported better control of motor symptoms, as well as greater gains in “on” time per day in the DBS plus medical therapy group. “On” time is defined as a period of good symptom control and mobility without dyskinesias. In the Deuschl trial,

Unified Parkinson’s Disease Rating Scale (UPDRS) III motor scores improved by 41 percent in the DBS plus medical therapy group but remained virtually unchanged in the medical therapy alone group.<sup>1</sup> In the Weaver trial, motor function improved meaningfully (i.e., by at least five points) in 71 percent of DBS patients but only 32 percent of best medical therapy patients.<sup>2</sup> Gains of 4.5 hours and 4.6 hours of “on” time were reported by Deuschl and Weaver, respectively, in the DBS plus medical therapy group, with little or no change in the medical therapy group.

### The timing of DBS

The Early STIM trial<sup>9</sup> showed that DBS, initially considered a last-resort measure, can be effective earlier than once thought in patients with advanced PD. Most trials of DBS vs. medical therapy alone have enrolled patients with advanced PD who are 11.1 to 13.8 years from diagnosis. In contrast, the EARLY STIM trial, which evaluated quality of life at two years, enrolled patients who were on average 7.5 years from diagnosis and experiencing early motor complications. PDQ-39 scores improved by 7.8 points in the DBS group but decreased by 0.2 points in the medical therapy group. Motor disability, activities of daily living, motor complications and “on” time with no dyskinesia all were significantly better at two years in the DBS-treated group than in the medical therapy group.

### Adverse events

As with any surgery, DBS has its risks, which include intracerebral hemorrhage (ICH), infection and device failure and migration that sometimes require reoperation. In both the Deuschl and Weaver trials, DBS was associated with a higher rate of serious adverse events than the medical therapy group; however, the medical therapy group had more adverse events overall. The most common serious adverse event reported in the Weaver trial was surgical site infection (9.9 percent): 12 DBS-treated patients had 16 infections that resulted in antibiotic therapy and removal of the leads, neurostimulator or both. The rate of infection is quite variable among studies, with some groups reporting infection rates as low as 1.5 percent in first observation.<sup>10</sup> Although most serious adverse events in both trials resolved without permanent sequelae, there was a fatality due to ICH among the DBS-treated group in both the Deuschl and Weaver trials. Two other fatalities — one due to suicide and one to pneumonia — were reported in the Deuschl trial for the DBS-treated group, but not in any other large-scale trials. In EARLY STIM, almost 18 percent of DBS-treated patients experienced a surgery-related adverse event, such as infection or device failure. All but one of these resolved

without permanent consequence, though reoperation was necessary in four patients.

Overall, the data provide strong evidence that DBS can greatly improve quality of life and provide significant relief from some of the most debilitating symptoms of PD, but they also show that DBS is not without risk and that careful patient selection is crucial for best outcomes.

### Patient selection

Deep brain stimulation is most effective for PD patients with motor fluctuations, dyskinesias and/or refractory tremor. For more complicated symptoms such as gait problems, DBS is often very effective at treating them if they are L-DOPA-responsive symptoms.

Contraindications for DBS include dementia and serious comorbidities. Age and psychiatric conditions need to be considered but are not contraindications. Most large clinical trials showing improved quality of life and motor control have involved patients under 70 or 75, and increased surgical complications would be expected in older patients. However, a retrospective cohort study of 1757 patients who had undergone DBS showed that patients older than 75 had the same complication rate at 90 days as younger patients. This suggests that age alone should not exclude patients from treatment.<sup>11</sup>

### Essential Tremor

Essential tremor, one of the most common movement disorders, especially among the elderly, often goes undiagnosed.<sup>6</sup> Referral of patients with tremor to a movement disorders specialist will ensure appropriate management. For medication-refractory ET, DBS to the nucleus ventrointermedius (Vim) of the thalamus effectively controls tremor long-term<sup>4,6</sup> — out to 13 years in one study.<sup>12</sup> Complications are fewer than with traditional thalamotomy. Focused ultrasound, a noninvasive form of thalamotomy that concentrates multiple intersecting beams on targeted brain tissue, was recently approved by the FDA for ET (and is under trial for PD). It offers the advantage over DBS of not requiring permanent implantation of a device. However, unlike DBS, which enables adjustment of stimulation parameters to achieve best outcomes, the effects of focused ultrasound, a type of lesional surgery, are irreversible and can only be performed unilaterally.

### Dystonia

In dystonia, muscles with opposing function contract simultaneously to cause tense abnormal posture and movement. Strong clinical evidence suggests that bilateral neurostimulation to the GPi can improve motor symptoms more than sham stimulation in patients with

generalized primary dystonia,<sup>7-8</sup> with the Burke-Fahn-Marsden Dystonia Scale improving by 14.6 points from baseline at three months<sup>7</sup> and by 25.3 points at one year.<sup>8</sup> Successful DBS in primary dystonia has led patients with secondary dystonia to seek DBS, but results have been variable.<sup>13</sup> For tardive dystonia, GPi DBS can also be very effective, with some symptoms resolving immediately and others, such as neck and trunk dystonia, improving over time.<sup>14</sup> Subjective improvements have been reported in patients with dystonia secondary to cerebral palsy<sup>15</sup>; however, more research is needed to establish the efficacy of DBS in patients with cerebral palsy, especially children.

### Advances in Surgical Treatments for Movement Disorders

Traditional DBS leads stimulate circumferentially. Newer-generation electrodes are directional, enabling the electrical stimulation to be “steered” toward the intended targets and limiting spread of current to surrounding tissue. The Infinity™ System (St. Jude Medical/Abbott, St. Paul, MN), which has directional leads, was approved in 2016, and the Vercise™ System (Boston Scientific, Marlborough, MA), which enables independent control of the current in each contact, was approved in 2017.

Current DBS systems are open-looped — they deliver constant electrical stimulus. Closed-loop systems, such as the RNS® System (NeuroPace, Mountain View, CA) for epilepsy, deliver electrical stimulus only when they sense a seizure about to occur. Research is progressing on closed-loop DBS for PD. One of the closed-loop systems in development relies on changes in the cortical regions of the brain to signal the DBS system to fire. Closed-loop systems remain investigational but are promising and could represent the future of DBS.

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# Interview

## MUSC Health Welcomes Dr. Eugene Hong as New Chief Physician Executive



PHOTOGRAPH BY BRENNAN WESLEY

**Eugene S. Hong, M.D.**, began as the new Chief Physician Executive for MUSC Physicians and MUSC Health in March. In this position, he oversees the practice plan and serves as a senior leader in the health system. Hong is a leading authority on concussions, cardiac issues in athletes, overuse injuries and sports-injury prevention and has worked for decades as a team physician. He comes to MUSC from Drexel University in Philadelphia, PA, where he was an endowed chair and professor in the Department of Family, Community and Preventive Medicine. At Drexel, Hong had a long and distinguished record of leadership, serving as chief of the division of primary care sports medicine, chair of the Drexel University Physician Board and associate dean for primary care and community health. As associate dean, he oversaw the creation of a successful accountable care organization (ACO) lookalike that brought \$3.8 million into the practice plan. *Progressnotes* spoke with Hong in January, as he was preparing to make the move to Charleston.

**PN: What are the greatest strengths of the practice plan at MUSC and the major challenges it faces?**

The major strength of any practice plan is the people — not just the physicians but also the administrators, the staff and everybody who helps deliver patient care, train the next generation of health care providers and advance scholarship. I really enjoyed the people I met during the interview process

and I am looking forward to being a member of the MUSC team. Some of the challenges being faced by MUSC are similar to those faced by other health care organizations — alignment and engagement. Is everybody rowing in the same direction? Is everybody on the bus and, if so, are they in the right seats on the bus? Engagement is a challenge facing many academic medical centers (AMCs). It is very important to address physician morale and wellness at a systems level. My number one, two and three initial plans for addressing these challenges are to listen, listen and listen.

**PN: How did your experience as an associate dean at Drexel help prepare you for your new position?**

One of my modest successes in that position was that we created an ACO lookalike between the hospital and the academic physician group. Payment reform was happening to us and, though we didn't know which way it was going, we tried to read the tea leaves and prepare for what we thought was coming down the pike with this ACO lookalike. That entailed engaging the administration and providers in a shared effort. It was an interesting experience for me as the one trying to pull this thing together, getting everybody in the same room and then having the same conversation. We were able to bring different parts of the health system together and work collaboratively. Over the past five years, this ongoing effort has brought \$3.8 million into the academic practice plan. It's about building sustainable change, something that's not easy to do in big organizations. In this case, I think we had some modest success. This experience taught me the importance of working collaboratively, and that is a lesson I think that will serve me in my new position. I really think we can get further along if we move together as an organization.

**PN: What attracted you to MUSC?**

Nobody across the country knows exactly where health care is going and where reform is going. But some of the things that attracted me to MUSC are the things MUSC is already doing, such as forming an ACO. I also really like that MUSC has already formed its ICCE clinical service lines. That's progressive. So I see MUSC as doing some things that I would consider more progressive for an AMC.

**“We can get further along if we move together as an organization.” — Eugene S. Hong, M.D.**

**PN: How can MUSC Health continue to grow as a health care system?**

A key component for growth in an AMC is what I call “academic entrepreneurship.” It's really thinking like an entrepreneur in an academic health system setting. To elaborate, it means identifying opportunities, developing and initiating strategies and taking calculated risks. We want to create value, and specifically overage, that can then be invested back into the enterprise.

**PN: Can you say something about your clinical practice and research in sports medicine?**

Coming into the Chief Physician Executive role, I plan on continuing to see patients and staying clinically active. I love clinical care, and my own clinical practice has been in sports medicine. As far as the research goes, I've talked nationally and taught in national CME courses on the issues of concussions and mental health in athletes. One area of my research is improving the evaluation and management of sports-related concussions. Another area focuses on the mental

health of athletes. We have published the largest cohort study of depression in college athletes in the literature and still follow that cohort. We found that the prevalence of depressive symptoms in college athletes was comparable to that in the non-athlete population. Athletes are not at decreased risk for mental health issues such as depression. They have their own set of unique challenges that may put them at comparable risk of mental health issues.

**PN: Can you describe your work as a team physician?**

I've been a team physician for a couple of decades now at various levels. For me, being a team physician is a form of community medicine. You take care of a group of people — not just athletes but also coaches, staff and administrators associated with that particular team and community — and you address not just individual issues but also population health issues. My position as a team physician has been incredibly rewarding for me — certainly a privilege and a pleasure.

**PN: Would you like to say a few words about your family?**

I like to say that I married upward. My wife, Mindy Hong, is a lifelong educator. She has been a headmaster of an independent school and is currently running her own educational consulting company. We have two daughters, Katherine and Audrey, and two Weimaraner dogs, Sadie and Welly, who all help keep me grounded and humble.

# New Physicians



## **Eric L. Berman, M.D.**

Board Certification: Ophthalmology // Specialties: Neuro-ophthalmology, oculoplastic surgery // Clinical Interests: Optic nerve disease, pseudotumor cerebri, myasthenia gravis, thyroid eye disease, blepharospasm, hemifacial spasm // Medical School: State University of New York Downstate Medical Center // Residency: State University of New York Downstate Medical Center // Fellowship: University of Minnesota

## **Laura E. Hollinger, M.D.**

Board Certifications: General Surgery, Pediatric Surgery // Specialty: Pediatric surgery // Clinical Interests: Congenital diaphragmatic hernia, ECMO, prenatal therapy and consultation, chest wall deformities, minimally invasive surgery // Medical School: University of Texas Health Science Center at Houston // Residency: Houston Methodist Hospital // Fellowship: University of Texas Health Science Center at Houston



## **Daniel P. Judge, M.D.**

Board Certifications: Advanced Heart Failure and Transplant Cardiology, Internal Medicine: Cardiovascular Disease // Specialty: Cardiology – Heart Failure & Transplant // Clinical Interests: Advanced heart failure, peripartum cardiomyopathy, congestive heart failure, mitral valve prolapse, aortic aneurysm, left ventricular assist device (LVAD) care, cardiac transplantation, neuromuscular disorders, cardiology // Medical School: The Raymond and Ruth Perelman School of Medicine at the University of Pennsylvania // Residency: Johns Hopkins Hospital // Fellowship: Johns Hopkins Hospital





**Meron A. Selassie, M.D.**

Board Certification: Anesthesiology // Specialty: Anesthesia – Pain Management // Clinical Interests: Back pain, pain management, headache, epidural steroid injections, nerve blocks, central and peripheral neuromodulation and neuroablation, trigger point injections, spine injections, arthritis // Medical School: University of Pennsylvania Perelman School of Medicine // Residency: Hospital of the University of Pennsylvania // Fellowship: University of North Carolina at Chapel Hill

**Mario E. Serafini, DO**

Board Certifications: Hospice & Palliative Medicine, Anesthesiology, Anesthesiology: Pain Medicine // Specialty: Anesthesia – Pain Management // Clinical Interests: Complex cancer pain and symptom management // Medical School: West Virginia School of Osteopathic Medicine // Residency: West Virginia University Hospitals // Fellowships: Allegheny General Hospital (interventional pain management) and Dartmouth Hitchcock Medical Center (palliative medicine)



**Aylin Tansel, M.D., MPH**

Board Certification: Internal Medicine: Gastroenterology // Specialty: Gastroenterology & Hepatology // Medical School: University of Miami Leonard M. Miller School of Medicine; University of Texas School of Public Health // Residency: Thomas Jefferson University Hospital // Fellowship: Baylor College of Medicine (two fellowships)



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