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Minimally Invasive, Robotic-Assisted Surgery for Diagnosis and Treatment of Epilepsy

Epilepsy surgery remains vastly underutilized, in large part because many patients with epilepsy who might potentially benefit from diagnostic or therapeutic surgery are not referred to a comprehensive epilepsy center. A comprehensive evaluation by a multidisciplinary group of epilepsy physicians is recommended for patients who are not completely seizure-free after having tried two medications, for those who have lesional epilepsy, and for those who have medication side effects that reduce their quality of life. The evaluation process can be complex and may be daunting to both referring physicians and patients, who in addition may fear the possibility of surgery. Recent advances in epilepsy surgery, however, are making both diagnostic and therapeutic surgeries less invasive and more effective.

Diagnostic surgery most often has been accomplished in the United States though open craniotomy for subdural grid placement. Four years ago, R. Mark Richardson, MD, PhD, director of the Epilepsy and Movement Disorders Surgery Program at the University of Pittsburgh, began performing stereo-electroencephalography (SEEG), the percutaneous placement of multiple depth electrodes, in order to diagnose the seizure onset zone in appropriate patients. This minimally invasive approach is more comfortable for patients but it traditionally required a lengthy operation due to the use of a stereotactic frame, which can also limit electrode placement.

UPMC Presbyterian recently became the first hospital in western Pennsylvania to use robotic assistance to improve this procedure. The Robotic Stereotactic Assistance (ROSA) system has a robotic arm with six degrees of freedom — an architecture that simulates movements of a human arm, allowing the rapid and precise alignment of multiple trajectories for electrode placement (Figure 1). The robot does not do anything to the patient, but it reduces the operative time by half while removing frame-based geometrical limitations for electrode placement. At UPMC, we are using these

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Figure 1: The ROSA robotic arm in the "home" position, after placement of several right temporal depth electrodes during a recent SEEG case. Julie Pan, MD, PhD, an epilepsy neurologist, evaluates the intracranial recordings in the background.

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Chairman's Message

When is Progress Real?

Every few years we see the incorporation of novel technologies into our surgical and therapeutic armamentarium. As these technologies become available, we must ask ourselves, "when does technology provide progress, and when is it a gimmick?" This is a key question that we must evaluate using objective parameters.

We must ask ourselves: 1) Is the "advancement" better than what it is trying to replace? 2) Is the "advancement" safe with clear clinical benefits? 3) Is the cost of developing and implementing the "advanced" technology worth any added expense? These are some of the critical questions that clinicians and hospital administrators must wrestle with. In the age of value-based medicine, these are serious questions.

At last October's White House Frontiers Conference, when I saw President Barack Obama shaking hands with the first human able to gain a sense of touch through a robotic arm, I could only think of where this advanced technology would take us. This groundbreaking work of Andrew Schwartz, PhD, of the Department of Neurobiology — collaborating with a robust group of scientists and clinicians at Pitt, including our department's **Elizabeth Tyler-Kabara, MD, PhD** — is opening an exciting window into the future.

Similarly, we see robotic assisted advancements in the operating room — as described in our cover article — cutting surgical times in half and allowing neurosurgeons to operate with greater skill and accuracy, ultimately providing better outcomes for our patients.

At the University of Pittsburgh Department of Neurological Surgery, we not only embrace real progress, but we also help to develop that progress. Recent examples include developing advanced imaging modalities, safer approaches to complex brain lesions, enhancing the diagnosis of traumatic brain injury, developing and improving minimally invasive brain and spinal surgery, developing new applications for Gamma Knife radiosurgery, and implementing the most advanced robotic surgery techniques. Our department is very proud of making our contribution in advancing research and therapy for patients with neurological disease.

Last year, faculty and residents in our department received 21 major national awards for making advancements in their field. These awards reflect the culture of innovation that is woven into this department.

The progress is real. The benefits are real.

Robert M. Friedlander, MD, MA
Chairman and Walter E. Dandy Professor of Neurological Surgery
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Surgery for Diagnosis and Treatment of Epilepsy

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advanced SEEG capabilities to inform decisions on traditional resective surgery, as well as two other minimally invasive options: laser thermal ablation (LTA) and responsive neurostimulation (RNS).

LTA is a procedure, like open resection, that may potentially cure a patient's epilepsy. Rather than removing the seizure focus, however, the focus is ablated, using heat generated from laser light concentrated at the tip of a very thin probe. Several months ago, UPMC Presbyterian became the first hospital in western Pennsylvania to perform LTA for epilepsy. Dr. Richardson now routinely employs the Monteris NeuroBlate® System for LTA via an interventional-MRI approach. Procedurally similar to the placement of electrodes during asleep DBS surgery, MRI scans are used to guide alignment of the trajectory and insertion of the probe in real time. Additionally, the ablation itself occurs under MRI guidance. Special MRI scans are used to report the temperature of the target tissue and to create a continuous visual representation of the ongoing ablation. In mesial temporal lobe epilepsy, for instance, the ablation is confined to the hippocampus and amygdala, without affecting adjacent brain tissue (Figure 2). In this way, appropriate patients can leave the hospital the next day with a single absorbable stitch closing a tiny entry site in the scalp. Although the rates of cognitive side effects in our resection cases are low, an additional benefit of LTA over traditional open resection is to further reduce the chance of cognitive side effects from surgery.

Robotic-assisted SEEG is also being used at UPMC Presbyterian to map an individual patient's seizure circuit for RNS electrode placement. RNS is a brain modulation device that detects seizure activity and delivers therapeutic stimulation in response. This treatment option is appropriate for patients who have one or two localized seizure foci that are not amenable to resection, such as seizure onset in the eloquent cortex or bitemporal seizure onset. More efficacious than vagal nerve stimulation, the RNS device provides a personalized window into the brain for each patient by constantly recording brain activity. When a seizure is detected, the device immediately delivers safe levels of electrical current to disrupt seizure spread and reduce seizure duration.

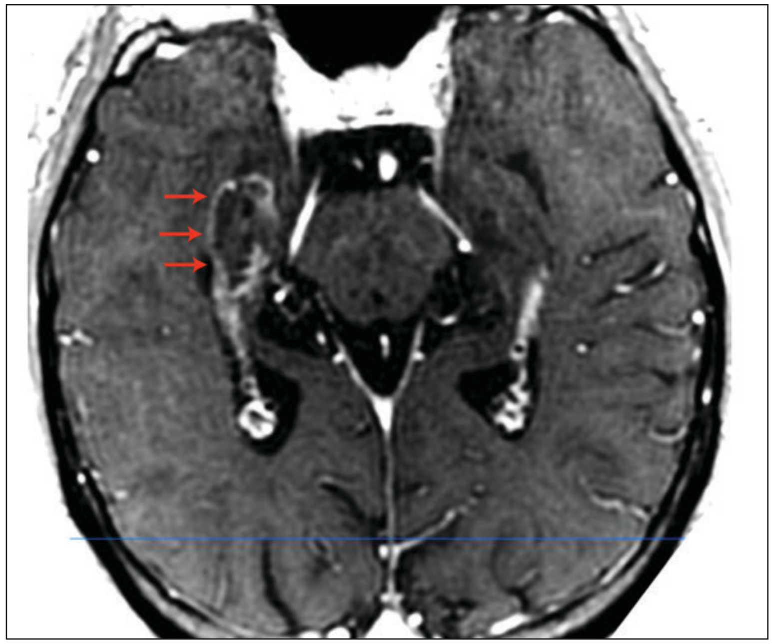

Figure 2: Postoperative MRI image demonstrating selective ablation of the hippocampus. The contrast-enhancing border of the ablated tissue is delineated with red arrows.

Cutting-edge, minimally invasive, and personalized approaches are a cornerstone of the epilepsy surgery program within the UPMC Comprehensive Epilepsy Center, the only such comprehensive program in western Pennsylvania. Individuals with recurring seizures, their families, and/or their physicians, are encouraged to contact the program for more information regarding the modern standards of diagnostic and therapeutic epilepsy care.

R. Mark Richardson, MD, PhD
Director of the Epilepsy and Movement Disorders Surgery Program at the University of Pittsburgh School of Medicine

Paralyzed Man Regains Sense of Touch

Imagine being in an accident that leaves you unable to feel any sensation in your arms and fingers. Now imagine regaining that sensation, a decade later, through a mind-controlled robotic arm that is directly connected to your brain.

That is what 28-year-old Nathan Copeland experienced after he came out of brain surgery and was connected to the Brain Computer Interface (BCI), developed by researchers at the University of Pittsburgh and UPMC. In a study published online in October 2016 in *Science Translational Medicine,* a team of experts led by Robert Gaunt, PhD, assistant professor of physical medicine and rehabilitation at Pitt, demonstrated for the first time ever in humans a technology that allows Mr. Copeland to experience the sensation of touch through a robotic arm that he controls with his brain.

"The most important result in this study is that microstimulation of sensory cortex can elicit natural sensation instead of tingling," said study co-author Andrew B. Schwartz, PhD, distinguished professor of neurobiology and chair in systems neuroscience, Pitt School of Medicine, and a member of the University of Pittsburgh Brain Institute. "This stimulation is safe, and the evoked sensations are stable over months. There is still a lot of research that needs to be carried out to better understand the stimulation patterns needed to help patients make better movements."

President Barrack Obama "shakes hand" of Nathan Copeland at White House Frontiers Conference, a national convening of leading scientists and innovators held in Pittsburgh this past October to discuss building U.S. capacity in science, technology, and innovation. *Photo courtesy of University of Pittsburgh*

Researcher Robert Gaunt prepares Nathan Copeland for sensory testing, where Nathan feels his fingers through the mind-controlled robotic arm. *Photo courtesy of University of Pittsburgh*

This is not the Pitt-UPMC team's first attempt at a BCI. Four years ago, study co-author Jennifer Collinger, PhD, assistant professor, Pitt's Department of Physical Medicine and Rehabilitation, and research scientist for the VA Pittsburgh Healthcare System, and the team demonstrated a BCI that helped Jan Scheuermann, who has quadriplegia caused by a degenerative disease. The video of Scheuermann feeding herself chocolate using the mind-controlled robotic arm was seen around the world. Before that, Tim Hemmes, paralyzed in a motorcycle accident, reached out to touch hands with his girlfriend.

But the way our arms naturally move and interact with the environment around us is due to more than just thinking and moving the right muscles. We are able to differentiate between a piece of cake and a soda can through touch, picking up the cake more gently than the can. The constant feedback we receive from the sense of touch is of paramount importance as it tells the brain where to move and by how much.

For Dr. Gaunt and the rest of the research team, that was the next step for the BCI. As they were looking for the right candidate, they developed and refined their system such that inputs from the robotic arm are transmitted through a microelectrode array implanted in the brain where the neurons that control hand movement and touch are located. The microelectrode array and its control system, which were developed by Blackrock

Microsystems, along with the robotic arm, which was built by Johns Hopkins University's Applied Physics Lab, formed all the pieces of the puzzle.

In the winter of 2004, Mr. Copeland, who lives in western Pennsylvania, was driving at night in rainy weather when he was in a car accident that snapped his neck and injured his spinal cord, leaving him with quadriplegia from the upper chest down, unable to feel or move his lower arms and legs, and needing assistance with all his daily activities. He was 18 and in his freshman year of college pursuing a degree in nanofabrication, following a high school spent in advanced science courses.

He tried to continue his studies, but health problems forced him to put his degree on hold. He kept busy by going to concerts and volunteering for the Pittsburgh Japanese Culture Society, a nonprofit that holds conventions around the Japanese cartoon art of anime, something Mr. Copeland became interested in after his accident.

Right after the accident he had enrolled himself on Pitt's registry of patients willing to participate in clinical trials. Nearly a decade later, the Pitt research team asked if he was interested in participating in the experimental study.

Dr. Tyler-Kabara

After he passed the screening tests, Nathan was wheeled into the operating room last spring. Study co-investigator and UPMC neurosurgeon **Elizabeth Tyler-Kabara, MD, PhD**, associate professor, Department of Neurological Surgery, Pitt School of Medicine, implanted four tiny microelectrode arrays each about half the size of a shirt button in Nathan's brain. Prior to the surgery, imaging techniques were used to identify the exact regions in Mr. Copeland's brain corresponding to feelings in each of his fingers and his palm.

"I can feel just about every finger — it's a really weird sensation," Mr. Copeland said about a month after surgery. "Sometimes it feels electrical and sometimes its pressure, but for the most part, I can tell most of the fingers with definite precision. It feels like my fingers are getting touched or pushed."

At this time, Mr. Copeland can feel pressure and distinguish its intensity to some extent, though he cannot identify whether a substance is hot or cold, explains Dr. Tyler-Kabara.

Michael Boninger, MD, professor of physical medicine and rehabilitation at Pitt, and senior medical director of post-acute care for the Health Services Division of UPMC, recounted how the Pitt team has achieved milestone after milestone, from a basic understanding of how the brain processes sensory and motor signals to applying it in patients.

Nathan Copeland extends the mind-controlled robotic arm. *Photo courtesy of University of Pittsburgh*

"Slowly but surely, we have been moving this research forward. Four years ago we demonstrated control of movement. Now Dr. Gaunt and his team took what we learned in our tests with Tim and Jan — for whom we have deep gratitude — and showed us how to make the robotic arm allow its user to feel through Nathan's dedicated work," said Dr. Boninger, also a co-author on the research paper.

Dr. Gaunt explained that everything about the work is meant to make use of the brain's natural, existing abilities to give people back what was lost but not forgotten.

"The ultimate goal is to create a system which moves and feels just like a natural arm would," says Dr. Gaunt. "We have a long way to go to get there, but this is a great start."

Prophylactic Antiepileptics and Seizure Incidence Following Subarachnoid Hemorrhage: A Propensity Score-Matched Analysis

by David Panczykowski, MD

The development of seizures following spontaneous subarachnoid hemorrhage (SAH) is a well-documented phenomenon, with observed rates as high as 27%. Concern over the possible consequences of a seizure in the setting of an unsecured aneurysm has led to routine prophylactic administration of antiepileptic drugs (AEDs) following SAH in many centers. Current AHA/Stroke Guidelines state that the use of anticonvulsants is reasonable, and surveys suggest that up to 84% of practitioners routinely use prophylactic AEDs following aneurysmal SAH.

This study provides substantial evidence for the discontinuation of routine administration of prophylactic AEDs in patients with spontaneous SAH.

However, more recent studies, including analysis of the Nationwide Inpatient Sample database, suggest the incidence of seizures after SAH may actually be closer to 11%. Moreover, previous studies and systematic reviews evaluating AED therapy have failed to demonstrate a clear benefit for prophylactic use of AEDs after SAH, while AEDs also have been associated with both neurologic worsening and delayed functional recovery.

Against this background, we sought to investigate whether prophylactic administration of AEDs significantly decreased the incidence of post-SAH seizures.

To evaluate this, we retrospectively analyzed a prospectively collected database of SAH patients admitted to UPMC Presbyterian between 2005 and 2010. Between 2005 and 2007, all patients received prophylactic AEDs upon admission. After 2007, no patients received prophylactic AEDs or they had AEDs immediately discontinued if initiated at an outside hospital. The results of prior trials have been confounded by who was selected for AED treatment. To solve these shortcomings and reduce selection bias, we implemented propensity-matched analysis of the risk for seizure development in relation to prophylactic AED treatment using covariates (Hunt-Hess grade, SAH burden, intraventricular hemorrhage, intraparenchymal hemorrhage, hydrocephalus, craniotomy, and aneurysmal etiology). The covariates used in propensity score generation included clinical characteristics (admission Hunt-Hess score, cisternal SAH thickness, intraventricular hemorrhage, and intraparenchymal hemorrhage), procedural characteristics (aneurysm occlusion modality, craniotomy for hemorrhage evacuation), and monitoring characteristics (use of EEG monitoring).

In total, 353 patients were admitted with a diagnosis of SAH. Of these patients, 57% did not receive AEDs upon admission — to date the largest reported sample not treated with prophylactic AEDs. Overall, 10% of patients suffered clinical and/or electrographic seizures, most frequently occurring within 24 hours of ictus (47%), an incidence consistent with other recent trials. Clinical characteristics significantly associated with seizures were poor neurologic grade on admission, cisternal SAH burden, and intraventricular hemorrhage. Notably, aneurysm treatment modality (craniotomy and clip occlusion vs. coil embolization) was not significantly associated with risk of seizure.

Propensity score-matched analyses revealed that prophylactic AED treatment did not significantly impact the incidence of seizure following SAH (p=0.49), providing the most robust support to date for discontinuing the routine, prophylactic administration of AED. Furthermore, adjusted analyses for secondary outcome measures suggested prophylactic AED treatment was significantly associated with cerebral vasospasm (OR1.21, 95%CI 1.05-1.40); however, 12-month functional outcome was not. Continued justification for prophylactic AEDs administration has focused on the unsubstantiated risk of seizures contributing to aneurysmal re-rupture. Importantly, in this current study neither the incidence of acute seizure nor the occurrences of aneurysm re-rupture significantly differed between AED treatment cohorts (p=0.26).

In this sample of patients suffering from SAH, the overall risk of seizure during the acute hospitalization period was low. Propensity score-matched analysis suggests that prophylactic AEDs do not significantly reduce the risk of seizure occurrence following SAH. After controlling for markers of SAH severity, patients receiving prophylactic AED therapy did display an increased risk of cerebral vasospasm. This study provides substantial evidence for the discontinuation of routine administration of prophylactic AEDs in patients with spontaneous SAH.

The full manuscript has been published in the journal *Stroke* (2016 Jul; 47(7): 1754-60. PMID: 27301932) and was awarded runner-up at the 2014 University of Pittsburgh Department of Neurological Surgery Stuart Rowe Research Day.

Matthew Pease, MD, Yin Zhao, BS, Gregory Weiner, MD, William Ares, MD, Elizabeth Crago, RN, PhD, Brian Jankowitz, MD, and Andrew Ducruet, MD, contributed to this article.

News & Notes

Tyler-Kabara, Okonkwo Prominent Participants at White House Frontiers Conference

David O. Okonkwo, MD, PhD, and **Elizabeth Tyler-Kabara, MD, PhD**, were each prominent participants in the first-of-its-kind White House Frontiers Conference, a national convening of hundreds of leading scientists, innovators, and industry officials designed to explore the future of scientific innovation, held in Pittsburgh, on October 13.

Hosted by the White House, the University of Pittsburgh, and Carnegie Mellon University, discussions at the conference focused on building U.S. capacity in science, technology, and innovation, and the new technologies, challenges, and goals that will continue to shape the 21st century and beyond.

Dr. Okonkwo participated in a panel discussion, "Building Science Capacity for the Future of Health," while Dr. Tyler-Kabara was involved with an exhibit that piqued President Barack Obama's interest, showcasing how scientists can help spinal cord-injured patients regain movement and touch in their arms and hands. *(See related article on pages 4-5.)*

Richardson to Lead BRAIN Initiative

R. Mark Richardson, MD, PhD, will lead a multidisciplinary team of experts from the University of Pittsburgh, Carnegie Mellon University, and Johns Hopkins University in a major research project designed to gather a deeper understanding of how speech is controlled in the brain.

The project, recently funded by a $3.3 million grant from the National Institutes of Health (NIH), is part of the NIH's BRAIN Initiative launched by President Obama in 2013 as a large-scale effort to understand the brain and apply the knowledge to treating a variety of brain disorders, including Alzheimer's, schizophrenia, autism, and traumatic brain injury, among others.

The research team will study patients with Parkinson's disease while they undergo deep brain stimulation (DBS) surgery.

Okonkwo to Lead Clinical Efforts in Pitt-Led Department of Defense-Funded Trauma Network

David O. Okonkwo, MD, PhD, will coordinate clinical efforts in a multimillion dollar research project intended to help improve trauma care for both civilians and military personnel.

The project — which could involve up to $90 million in funding over 10 years — launched this past October with an initiative to create a nationwide network of trauma systems and centers capable of conducting detailed research to improve military trauma care. The Linking Investigations in Trauma and Emergency Services (LITES) Network will include extensive data collection to obtain and link information that covers pre-hospital care through recovery after discharge on potentially thousands of trauma cases across the country.

The LITES Network is expected to provide epidemiological data on moderate and severe injuries in the U.S. and identify any regional variations in the types of injuries and the way they're managed.

Peter J. Jannetta Symposium Set for April 8

The Department of Neurological Surgery, the University of Pittsburgh School of Medicine, and UPMC will host the inaugural Peter J. Jannetta Symposium, April 8, honoring the late neurosurgical icon and highlighting the history and future of innovations in the field of neurological surgery. Events will take place at the Hotel Monaco in downtown Pittsburgh. CME credit will be available. **For program information, please call Diann Bruni at 412-647-6358 or visit neurosurgery.pitt.edu/jannetta-symposium.**

Congratulations

Joseph Maroon, MD, was named to the medical advisory panel of the Chuck Noll Foundation for Brain Injury Research. The Foundation — honoring the late, legendary Pittsburgh Steelers head coach who challenged physicians to develop an objective analysis of head injuries — was launched in November with a $1 million donation from the Steelers and will help fund research deemed most promising in the area of sports-related concussions and related conditions.

Nitin Agarwal, MD, PGY-3 resident, is co-editor of the newly released book, *The Evolution of Health Literacy: Empowering Patients Through Improved Education,* published by Nova Science Publishers. The book deals with advocating for improved medical resources for patients and advancing the field of patient education.

The **UPMC Presbyterian Gamma Knife team** received the UPMC Achievement in Excellence Award, given quarterly to a UPMC team that demonstrates excellence in patient care. The Gamma Knife staff received the award for their outstanding work this past summer following a flood in the Gamma Knife unit. With water damage to most of the unit from a burst pipe, the staff was forced to work off-site and for long hours. They never lost sight of ensuring top quality care for all their patients. They came together as a team in a very difficult situation.

UPMC LIFE CHANGING MEDICINE

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Neuroendovascular Surgery Fellowship Receives Accreditation From the Committee on Advanced Subspecialty Training

by Benjamin Zussman, MD, and Gregory Weiner, MD

Under the leadership of fellowship director Brian Jankowitz, MD, the UPMC neuroendovascular surgery fellowship obtained accreditation from the Society of Neurological Surgeons' Committee on Advanced Subspecialty Training (CAST) in June 2016. The committee is responsible for the accreditation of subspecialty training fellowships and for subspecialty certification of fellows in neurosurgery. With this accreditation, the UPMC fellowship joins an elite handful of nationally respected training programs that use minimally invasive catheter-based technologies, radiological imaging, and clinical expertise to diagnose and treat neurovascular diseases.

The fellowship was established in July 2007 and has blossomed into one of the busiest clinical and academically productive training programs in the U.S., performing more than 2,200 neuroendovascular cases annually and publishing multiple peer-reviewed research articles. Faculty members include Brian Jankowitz, MD, and Bradley Gross, MD, from the Department of Neurological Surgery, and Tudor Jovin, MD, and Ashutosh Jadhav, MD, PhD, from the Department of Neurology. Clinical worksites include UPMC Presbyterian, UPMC Shadyside, UPMC Mercy, and the Children's Hospital of Pittsburgh of UPMC.

The fellowship aims to provide world-class, comprehensive subspecialty training in neuroendovascular surgery, and trainees develop clinical competence in caring for patients with a broad spectrum of pathologies, including aneurysms, stroke, atherosclerosis, subarachnoid hemorrhage, trauma, intracranial hemorrhage, arteriovenous malformations and fistulas, tumors, vasospasm, vasculitis, venous thrombosis, and others. They learn to perform diverse catheter-based procedures, including diagnostic cerebral and spinal angiography, intra- and extracranial stenting, aneurysm coiling and flow diversion, embolization of arteriovenous malformations, fistulas and tumors, thrombectomy, vasospasm treatment, balloon test occlusion, venous sinus sampling, and others.

Because neurovascular disease is increasingly treated with neuroendovascular therapies, the presence of a robust neuroendovascular program is critical to providing superlative patient care in the current era and growing the field's leaders for the future.

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