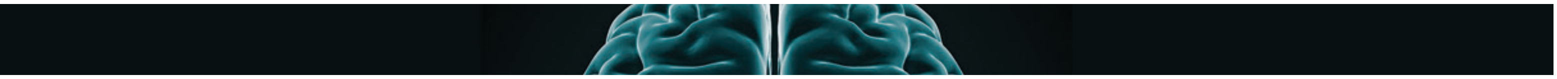
NEUROSURGERY
NEWS
WINTER 2023
DEPARTMENT OF NEUROLOGICAL SURGERY



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Disclosures: *Jorge A. González-Martínez, MD, PhD, is a consultant for Zimmer Biomet. Pascal Zinn, MD, PhD, receives grant research support from UPMC startup funds. Marco Capogrosso, PhD, has received grant research support from GTX Medicals. Robert Friedlander, MD, MA, is a consultant for NeuBase Therapeutics and DiFusion Inc., and receives grant research support from the NIH and Clear Thoughts Foundation. All other contributing authors report no relationships with proprietary entities producing health care goods or services.*

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Epilepsy Surgery for Focal Cortical Dysplasia

Jorge A. González-Martínez, MD, PhD, FAANS
Director, Epilepsy and Movement Disorders Program

In 1971, Taylor, Falconer, and Corsellis published the paper *Focal Dysplasia of the Cerebral Cortex in Epilepsy.* They discussed 10 cases of patients with epilepsy operated on by Dr. Falconer (eight cases) in the Guy's–Maudsley Hospital and King's College Hospital Neurosurgical Unit, London, and two other cases treated at other institutions. Every case was exceptionally detailed both from the clinical and surgical point of view. Schematic drawings clearly depicted the typical aspect of the cortex thickening and blurring, the image of which could only be seen preoperatively decades later after the introduction of magnetic resonance imaging (MRI) into clinical practice. They also described at microscopic examination the characteristic "disruption of the normal cortical lamination and an excess of large aberrant neurons scattered randomly through all but the first layer … the most characteristic feature, therefore, was the disorganization both of the cortical architecture and of many of its individual neurons. In seven of 10 cases, the anarchy was aggravated by the addition of malformed cells of uncertain origin with large, sometimes multiple, nuclei surrounded by an excess of opalescent pseudopodic cytoplasm."

Although some authors had already published isolated cases of the same pathology, Taylor's work is an original contribution in the sense that he correctly stressed the main features of focal cortical dysplasia (FCD) and described typical clinical features and image correlates. The impact of this publication in the field of epilepsy surgery has been paramount.

FCD represents the most common etiological entity concerning epilepsy surgical cases in children, amounting roughly to a third of all cases and a significant number of cases in the adult population. Its variegated mode of presentation and protean character from patient to patient justifies this publication aimed at pointing out the major advances in the presentation at diagnosis, indications, and results of surgery. Epilepsy surgery remains most successful for "lesional" epilepsy, and removal of the lesion, with or without adjacent tissue resection, is sufficient to permanently control the epileptic activity in some patients.

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BEST HOSPITALS
U.S.News & WORLD REPORT
NEUROLOGY & NEUROSURGERY
2022-23

Chair Letter: A Tradition of Excellence and Innovation

Innovation Is the Engine That Advances Medical Care

Robert M. Friedlander, MD, MA

In the 1960s, **Peter Jannetta, MD**, long-time chair of the University of Pittsburgh Department of Neurological Surgery, developed microvascular decompression, a novel procedure that helped alleviate chronic pain and spasms in facial muscles. In the 1980s, **L. Dade Lunsford, MD**, director of the UPMC Center for Image-Guided Brain Surgery, brought the first Gamma Knife in North America to the University of Pittsburgh, ushering in a new era of minimally invasive treatment of brain tumors and other cranial disorders. And in the last decade, **Paul Gardner, MD**, co-director of the UPMC Cranial Base Center, and his team furthered endoscopic endonasal approaches to brain tumors that were unthinkable 20 years ago.

These innovative advancements — along with our unique collaborative environment that fosters the healthy exchange of ideas and solutions — has helped establish UPMC and the University of Pittsburgh Department of Neurological Surgery as a world leader in neurosurgical care. More importantly though, these advancements and collaborations have allowed us the opportunity to offer our patients innovative means to help them return to as normal a lifestyle as possible as soon as possible.

Today, we continue our tradition of innovative research and clinical advancements. Our Alba Tull Center for Neuro Imaging and Therapeutics is embracing the new world of artificial intelligence, taking medical care treatment possibilities in an exciting new direction. Neuroprosthetics and spinal cord researcher **Marco Capogrosso, PhD**, and minimally invasive spine surgery expert **Peter Gerszten, MD**, are developing a spinal cord stimulation procedure to help restore upper extremity motor function in patients with spinal cord injuries. **Jorge A. González-Martínez, MD, PhD** — a world-renowned expert in epilepsy and functional neurosurgery — is offering patients new hope with innovative procedures to combat epilepsy and movement disorders.

Young, brilliant minds are also helping us push the boundaries of medical care.

We have recruited **Costas Hadjipanayis, MD, PhD**, a graduate of our residency program and an acclaimed NIH-funded researcher and neuro-oncology pioneer, to advance the innovative stereotactic radiosurgery work of Dr. Lunsford and the innovative personalized brain tumor treatment approaches of **Pascal Zinn, MD, PhD**, and **Kalil Abdullah, MD**. Dr. Hadjipanayis was the first to use 5-ALA (Gleolan) and perform fluorescence-guided surgery (FGS) in the United States, a game-changer in the neurosurgical field.

Michael McDowell, MD, who joined our Pediatric Division this past summer after serving his residency here, is part of a collaborative study with Carnegie Mellon University to develop a new near-infrared, noninvasive sensor capable of estimating intracranial pressure and opening up the possibility of easily and accurately evaluating an array of cranial conditions. **Georgios Zenonos, MD** — yet another graduate of our residency program — and our cranial base team are developing a novel contact endoscopy procedure that will allow for safer and more effective pituitary procedures, possibly eliminating the need for biopsies, decreasing costs and operative time, and potentially avoiding unnecessary injury to the normal pituitary gland.

The University of Pittsburgh Department of Neurological Surgery and UPMC continue to advance the frontiers of medical care, providing the best possible individualized care for our patients, which is our number one priority. It's our tradition — excellent care and innovation.

Robert M. Friedlander, MD, MA
Chair, Department of Neurological Surgery
Walter Dandy Distinguished Professor of Neurosurgery, Neurology, and Neurobiology
University of Pittsburgh School of Medicine

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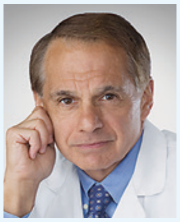
Alba Tull Center for Neuro Imaging and Therapeutics Incorporating Technology to Change Medicine

Edward Andrews, MD
Chief Resident



Joseph Maroon, MD
Heindl Scholar in Neuroscience

The Alba Tull (AT) Center for Neuro Imaging and Therapeutics provides a robust health care innovation community that clinicians and students query for team members, advice, and resources. The AT Center focuses on solutions incorporating technologies poised to change medicine, namely:

- Extended reality — augmented reality (AR), virtual reality (VR)
- Artificial intelligence (AI)
- Machine learning (ML)
- 3D printing

Given its proximity to neighboring UPMC, the AT Center provides an accessible physical space that serves as a meeting point for clinicians and health sciences personnel; it also connects undergraduate and graduate students across the University of Pittsburgh through a common virtual hub. A robust online community is supported by a dynamic online presence that includes an interactive project repository where new projects can be proposed, ongoing projects can gain new members, and interdisciplinary teams may form based on common interests. The AT Center acts as a gathering and project access point for medical innovation, as well as a switchboard to existing University of Pittsburgh innovation organizations. It also serves as a bridge to synergize and partner with neighboring institutions in the greater Pittsburgh area, aiming to create a citywide innovation community. The AT Center will catalyze medical innovation along many fronts and promises to yield technologies and devices that improve health care and medical training.

The AT Center provides solutions to unmet needs in certain key areas not addressed in the current innovation ecosystem at Pitt. The AT Center occupies a unique niche that combines all the following characteristics:

- A multidisciplinary community with an integrated physical and digital space
- An interinstitutional community
- A focus on AR, VR, AI, and ML
- A robust digital infrastructure that has embedded discussion feeds, a project repository, and users
- An ability to rapidly prototype, demo, and test a clinical solution
- Accessibility due to its physical proximity to clinicians and members of the health sciences community
- A biomedical focus

The target audience will be health sciences students, graduate sciences students (particularly computer and bioengineering), clinicians, and undergraduate students interested in health care innovation. The AT Center's focus on digital and bioengineering technologies is supported by the following key components and initiatives.

Surreality Lab: Integrated into the AT Center, the Surreality Lab focuses on medical and surgical applications of AR and VR. The AT Center and Surreality Lab forged a collaborative commercial and academic partnership among UPMC, Medivis (a New York-based mixed reality software company), and the UPMC Department of Neurosurgery to validate and mature this technology inside and outside of the operating room. There are now multiple departments at UPMC partnering with the Surreality Lab to plan projects with this technology to validate it within their respective specialties.

Healthcare AI/ML Lab: AI and ML drive technical solutions to big challenges in digital health and medicine. Increasingly, computational analyses of patient data and workflow can optimize individual treatment strategies as well as health care efficiency. These technologies are transforming and will continue to transform the landscape of health care. The Healthcare AI/ML Lab builds the infrastructure to develop and test medical AI solutions in tandem with academic and industry partnerships.

Treating Brain Tumors

Constantinos Hadjipanayis, MD, PhD

Director, Center for Image-Guided Neurosurgery and Executive Vice-Chair, Neurological Surgery

Kalil Abdullah, MD

Director, Translational Neuro-oncology

Pascal Zinn, MD, PhD

Director, Adult Neurosurgical Oncology

The UPMC Department of Neurological Surgery welcomes back **Constantinos Hadjipanayis, MD, PhD**, as the new director of the Center for Image-Guided Neurosurgery. He is taking over this important role from his long-time mentor and colleague **L. Dade Lunsford, MD**, who has successfully built a world-renowned Center over the last 35 years, treating over 18,000 patients with Gamma Knife stereotactic radiosurgery. The Center for Image-Guided Neurosurgery was the first center in North America to treat patients with the Gamma Knife. Dr. Hadjipanayis completed his neurosurgery residency at the University of Pittsburgh School of Medicine in 2006 and obtained a doctoral degree in molecular genetics and biochemistry at the University of Pittsburgh while completing his residency. Dr. Hadjipanayis returns to the department after serving as site chair of neurosurgery at Mount Sinai Beth Israel Hospital in New York City and director of neuro-oncology for the Mount Sinai Health System. He is a neurosurgeon-scientist who directs the NIH-funded Brain Tumor Nanotechnology Laboratory at UPMC Hillman Cancer Center.

With the arrival of Dr. Hadjipanayis, a new, multidisciplinary brain tumor center is being designed and formed, incorporating leadership from neurosurgery, neuro-oncology, radiation oncology, and medical oncology. Based at the UPMC Hillman Cancer Center, the UPMC Hillman Brain Tumor Center initially will be co-directed by Dr. Hadjipanayis and **Jeremy Rich, MD, MHS, MBA**, who is a professor of neurology and deputy director for research at the UPMC Hillman Cancer Center, as well as leadership to be named from medical and radiation oncology.

In 2022, the Department of Neurological Surgery became an integral part of the Glioblastoma Therapeutics Network, a collaborative effort by the National Cancer Institute. This program, led at UPMC by **Kalil Abdullah, MD**, director of translational neuro-oncology, is designed to stimulate scientific and clinical teams from select institutions across the country to develop promising drugs in the laboratory and then design clinical trials that can be performed at multiple sites. As a component of this NIH-funded effort, researchers are currently evaluating new drugs that may be used to treat the most difficult brain cancer, glioblastoma. One of these drugs targets IDH-mutant gliomas, which are more common in younger adults. In addition to laboratory work, clinical trials are being planned for these new drugs.

An important multidisciplinary effort toward enhancing the workflow for complex awake brain tumor surgery at UPMC includes the addition of pre-, intra-, and postoperative neuropsychological testing by **Natalie Sherry, PsyD**, and **Luke Henry, PhD**, both neuropsychologists in the Department of Neurological Surgery. Preoperative functional imaging, including magnetoencephalography (MEG), led by **Ajay Naranjan, MD**, director of the UPMC Brain Mapping Center, as well as intraoperative high-definition fiber tracking (HDFT) by **Frank Yeh, MD**, director of the High-Definition Fiber Tractography Lab, has permitted the identification of important functional pathways in the brain to avoid during brain tumor surgery. The integration of our world class intraoperative neuromonitoring program led by **Parthasarathy Thirumala, MD**, director of the Center of Clinical Neurophysiology, **Jeffrey Balzer, PhD**, director of clinical services for the Center for Clinical Neurophysiology, and Donald Crammond, PhD, vice-chairman of the American Board of Neurophysiologic Monitoring, permits maximal safe removal of brain tumors according to **Pascal Zinn, MD, PhD**, director of adult neurosurgical oncology.

A new academic-industrial partnership is being launched by the UPMC Department of Neurological Surgery, the University of Pennsylvania, and Synaptive Medical Inc. This new initiative, titled *“diffusion MRI-guided pre-operative planning for supra-total resection of high-grade gliomas,”* will be led by **Ragini Varma, MD**, professor of radiology and neurosurgery at the University of Pennsylvania, and Dr. Hadjipanayis, in partnership with Wes Hodges, founder of Synaptive Medical Inc. It will provide an enhanced preoperative planning tool for brain tumor surgery that will facilitate extended safe resection of glioblastoma tumors that are not evident with conventional imaging. The tool will be created by integrating diffusion MRI-based methods to visualize white matter pathways in edematous and infiltrated regions of the brain into a commercial neuro planning and navigational software with Synaptive Medical Inc. that will be used by clinical partners at UPMC, University of Pennsylvania, University of Nebraska, and the Ochsner Clinic Foundation for evaluation of clinical utility and patient safety. The extended resection facilitated by the enhanced tool is expected to lead to better patient outcomes.

Contact Endoscopy: A Novel Intraoperative Tissue Differentiation Tool in Pituitary Surgery

Georgios A. Zenonos, MD
Director, Cranial Nerve Program

Paul A. Gardner, MD
Neurosurgical Director,
UPMC Center for Cranial Base Surgery

Many exciting developments are ongoing within the UPMC Center for Cranial Base Surgery. One of the latest advancements has been the use of contact endoscopy for intraoperative tissue differentiation in pituitary surgery.

Pituitary tumors often have sufficiently different consistency and color pattern to be grossly identifiable during surgery, especially with experienced surgical teams. In a subset of tumors, however, or in cases of functioning micro-adenomas, the tumor may not be readily distinguishable. Precisely identifying the tumor is of utmost importance as it not only increases our ability for complete resections (particularly in hormone-secreting tumors such as in Cushing's disease, acromegaly, or tumors that produce prolactin), but it also increases safety, avoiding inadvertent injury to the normal gland.

Contact endoscopy is a technology that exploits the differences in the microvascular architecture between tumors and the normal pituitary gland. The normal gland tissue has a well-developed microvasculature pattern, which appears similar to a lattice. By contrast, pituitary tumors have a more haphazard, disrupted, or absent pattern, which can be used to differentiate them.

In the Enhanced Contact Endoscopy (ECE) in Pituitary Adenoma Surgery study performed at UPMC, specially designed contact endoscopes were used to evaluate both tumor tissue (Figure 1) and normal tissue (Figure 2) within the pituitary. The findings were then confirmed with a biopsy and a formal impression by experienced neuropathologists. The surgeons' impression from contact endoscopy correlated very well with the pathologists' impression, proving the value and the validity of the intraoperative findings.

The aforementioned study is important as it adds a powerful tool to the armamentarium of the skull base surgeon, allowing safer and more effective pituitary surgery. This technology allows real-time feedback to the surgeon in tissue that cannot be immediately classified as normal or abnormal.

This early feedback is critical as it potentially obviates the need for a biopsy, decreasing costs and operative time, but also avoiding unnecessary injury to the normal pituitary gland. Contact endoscopy technology may prove even more useful in centers where a neuropathologist is not immediately available and will help less experienced surgeons identify and preserve the gland.

The UPMC Center for Cranial Base Surgery is directed by **Paul Gardner, MD**, and **Georgios Zenonos, MD**, in the Department of Neurological Surgery, and **Carl Snyderman, MD, MBA**, **Eric Wang, MD**, and **Andrew McCall, MD**, in the Department of Otolaryngology.

*The authors would like to acknowledge the contributions of **Benita Valappil, MPH**, Clinical Research Manager, Cranial Base Surgery, in the completion of this article.*

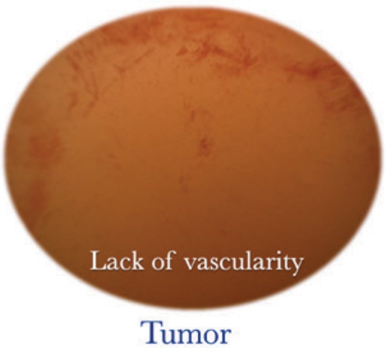


Figure 1.

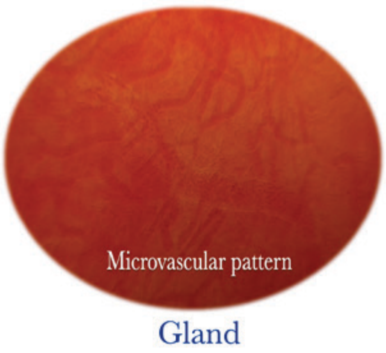


Figure 2.

Epilepsy Surgery

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Nevertheless, in a significant number of patients, the removal of a dysplastic lesion is not sufficient to arrest the occurrence of debilitating recurrent seizures. MRI anatomic and signal abnormalities have been described in FCD, but despite significant MRI abnormalities in most cases of FCD, up to 25% of patients with "normal" MRIs had histopathologic changes in focal lesions. Consequently, a sizable number of patients with FCD do not achieve a good outcome even after the apparently complete resection of the hypothetical epileptogenic zone (EZ) lesion (defined by electroencephalographic and metabolic images). These results suggest that current imaging (and evaluation) techniques may not accurately map the extent of dysplastic and epileptogenic regions in FCD and stress the fact that image-based surgery in MRI-visible FCDs will result in suboptimal seizure outcome. The exception for this statement is the Taylor-type FCD, where the complete removal of the MRI-visible dysplastic lesion is associated with permanent seizure control.

General concepts in epilepsy surgery in the "FCD scenario"

The main goal and basic principle of curative epilepsy surgery is the arrest of the epileptic activity by the complete resection (or complete disconnection) of the cortical areas responsible for the primary organization of the EZ. As the EZ can eventually coincide with functional cortical areas (eloquent cortex), preservation of these fundamental brain functions is another goal of any curative surgical resection in patients with medically refractory epilepsy. The principle can be generally applied and disregard the epilepsy syndrome etiology. Medically intractable epilepsies caused by suspected or confirmed FCD are not exceptions.

As successful FCD-related epilepsy surgery relies on accurate preoperative localization of the EZ, the appropriate presurgical evaluation is fundamental to obtain the widest and most accurate

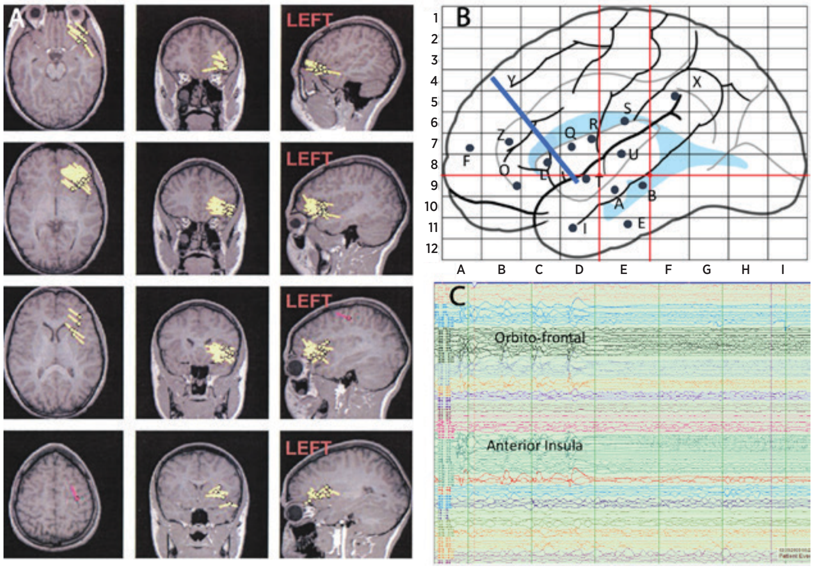

Figure 1. Presurgical evaluation in "FCD scenario." **A.** MEG scan in a patient with nonlesional medically refractory focal epilepsy showing the presence of MEG dipoles in cluster, located in the left anterior perisylvian/insula areas. **B.** SEEG exploration from the same patient, demonstrating an anterior perisylvian SEEG exploration with orthogonal (dots) and oblique (lines) electrodes targeting the pre-implantation hypothesis, which includes the frontal/temporal/insula and parietal areas. **C.** Interictal and ictal SEEG recordings demonstrating the presence of epileptiform interictal activity in the orbito-frontal and anterior insula areas, transitioning to ictal patterns, with low amplitude and high frequency recordings located in similar cortical areas. The transition between the interictal and ictal recordings was characterized by the emerging of the ictal semiology (autonomic symptoms of tachycardia and nausea).

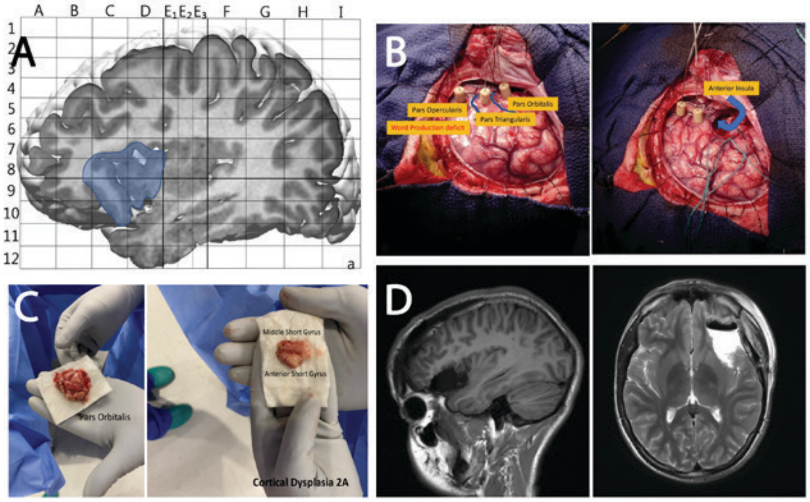

Figure 2. Surgical strategy in nonlesional medically intractable focal epilepsy in FCD scenario (patient illustrated in Figure 1). **A.** Demarcation of the resection areas in stereotaxic space. The blue shadow illustrates the anterior insula and posterior orbito-frontal areas as defined by the SEEG exploration. **B.** Intraoperative pictures demonstrating the anatomical exposure of the frontal opercular area during adjuvant ECOG recordings with depth electrodes. The functional mapping performed during the SEEG evaluation demonstrated the presence of word production deficits in pars-opercularis. Initially, the pars-orbitalis was resected, exposing the anterior face of the insula, which was resected through the open surgical corridor created by the frontal resection. **C.** Demonstrates the resected portions of the pars-orbitalis (left) and anterior insula (right). Surgical pathology from the respective specimens reviewed FCD IIA in the anterior insula specimen and no pathological findings in orbito-frontal segment. **D.** Demonstrates the postoperative MRI (sagittal T1 and axial T2), showing the resection cavities in the anterior insula and posterior orbito-frontal areas. Patient had an optimal outcome (Engel IA) with no neurological deficit.

spectrum of information from clinical, anatomical, neurophysiological, and neuropsychological aspects, with the primordial goal of performing an individualized and safe resection. The noninvasive methods of seizure localization and lateralization — scalp electroencephalogram, magnetoencephalography (MEG), positron emission tomography (PET), ictal single photon emission computed tomography (SPECT), functional MRI, and diffusion tensor imaging — are complementary, and results are interpreted in conjunction and never in isolation in the attempt to compose a hypothesis of the anatomical location of the EZ. If the anatomical hypothesis is precisely delineated, there is no need for further studies and surgery may be carried on accordingly. This is pertinent to "lesional epilepsies," where FCD II lesions are located in cortical areas that correspond to the localization hypothesis. In this scenario, the complete treatment of the EZ, which overlaps the lesion, is associated with a high degree of success. In general, extra-operative invasive monitoring is not required and intraoperative monitoring, such as electrocorticography (ECOG), may be applied as an adjuvant method to guide the resection. Nevertheless, when the noninvasive data is insufficient to define the EZ, extra-operative invasive monitoring may be indicated (Figure 1).

Regarding the different methods of extra-operative invasive monitoring, indications of subdural grid recording (SDG) and stereoelectroencephalography (SEEG) most often do not overlap. The two-dimensional versus tri-dimensional brain sampling dictates a quite different strategy for phase I goals, as well as for data analysis. The "presurgical" attribute bears distinct meaning for SDG, which in most cases immediately leads to surgical resection to take advantage of the craniotomy, whereas SEEG evaluation leaves a period between removal of the electrodes and operation, so that an eventual contraindication for surgery can still be decided.

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Frontiers in Neurosurgery and Neuromodulation:
Innovation and Leadership in Epilepsy, Movement Disorders, and Spasticity

March 16-17, 2023
Wyndham Pittsburgh University Center
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Join us for this two-day symposium under the direction of world-renowned leaders in the care and treatment of epilepsy and movement disorders, **Jorge A. González-Martínez, MD, PhD, Houman Homayoun, MD,** and **Marco Capogrosso, PhD**.

A Research Initiative to Tackle Diseases of the Sensory-Motor Circuits of the Spinal Cord Using Spinal Cord Stimulation

Marco Capogrosso, PhD
Director, Spinal Cord Stimulation Laboratory

Peter Gerszten, MD, MPH
Director, Percutaneous Spine Service

Spinal cord stimulation (SCS) has been an approved therapy for the treatment of refractory pain since the 1970s.[1] SCS entails the permanent implantation of a multicontact electrode into the epidural space of the spinal cord, commonly at the thoracic level. Because of the relatively low risk of the surgical procedure (no opening of the dura mater), SCS was rapidly employed in off-label investigational studies exploring its effects on motor control in humans.[3–6] These studies followed anecdotal reports on motor improvements in patients who received an implant to treat pain but who had some form of unrelated paralysis. These pioneering reports suggested that SCS can enable voluntary limb movements in a variety of motor disorders ranging from multiple sclerosis to spinal cord injury.[2,5,6] Involuntary and reflex motor activity were performed before and during SCS. At the end of the test period, eight patients showed a significant improvement in their motor performance. The EMG analysis confirmed the clinical data. SCS was followed by a reduction or disappearance of synergic coactivation with better agonist-antagonist coordination, a decrease of clonus both in duration and spreading, and better endurance. The effect on motor control did not increase with time after the first month of SCS but was long lasting (mean follow-up: 2 years). More specifically, individuals with chronic clinically complete spinal cord injury (SCI) regained the ability to produce single-joint voluntary movements of previously paralyzed leg joints with SCS.[4,7,8] Disappointingly, these earlier studies did not generate momentum and remained largely proof-of-principles with no impact on clinical guidelines. The reasons for these failures include a lack of understanding of the mechanisms, and significant variation in the chosen implant locations across studies, which contributed to less-than-optimal clinical outcomes.[2] Additionally, SCS was not systematically tested in conjunction with intense physical therapy training, which greatly increases effect size.[8–11]

Thanks to the work of multiple laboratories, including the Spinal Cord Stimulation Laboratory, under the direction of **Marco Capogrosso, PhD**, and part of the University of Pittsburgh Rehabilitation and Neural Engineering Laboratory, it is now widely accepted that SCS primarily targets primary sensory afferents in the dorsal columns and the dorsal roots.[12–16] These fibers form excitatory connections to spinal motoneurons and other spinal interneurons, thus substantially increasing, or even driving, excitation in the cord, which is normally reduced by lack of descending drive after events such as SCI. This understanding has led

Figure 1. Graphic representation of spinal leads located in the cervical epidural space to treat upper limb paralysis and implantable stimulator located near the left hip.

to standardization of implant locations: effect sizes were largest[2] when implants were located in the epidural space surrounding the spinal regions hosting the motor pools of relevant muscles, i.e., the lumbosacral enlargement for leg movements and the cervical enlargement for the upper limb (Figure 1).[2,7–9,11,13,17] In the 2000s, a new wave of studies leveraged these developments, combining optimal SCS placement with physical training, which led to unprecedented, consistent effects in people with SCI.[8,9,11,18] Namely, there was a recovery of voluntary movements of previously paralyzed limbs and even overground locomotion in patients with full motor paralysis.

While research in SCI has continued, neurostimulation expert Dr. Capogrosso, together with neurosurgeons **Robert Friedlander, MD**, and **Peter Gerszten, MD**, wondered whether SCS should not only be seen as a therapy for SCI alone, but more generally as an intervention to tackle dysfunction of the corticospinal tract-motoneuron-sensory afferent circuit in the spinal cord, the building block of movement.[19,20] We began a program to expand the potential application of SCS moving in two distinct directions: 1) diseases of the cortico-motoneuronal system and 2) diseases of the afferent-motoneuron circuit. They have subsequently started two parallel clinical trials: the first is to explore the effects and mechanisms of SCS for the recovery of upper limb motor control after stroke (NCT04512690, Cortico-Spinal Tract to Motoneuron Dysfunction[20]) and the second trial is exploring the effects and mechanisms of SCS for the treatment of motor deficits in patients with spinal muscular atrophy, a genetic disease of the Ia-motoneuron system[21] (NCT05430113). These works are currently supported by a grant from the NIH (UG3NS123135-01A1, stroke) and an industrial research grant (SMA).

The group recently reported the preliminary findings of their stroke trial demonstrating that SCS improved strength, dexterity, and motor control in the first two participants suffering from moderate and severe chronic stroke.[22] While they continue to collect data on preliminary safety and efficacy in both trials, they are simultaneously conducting a battery of imaging and electrophysiology tests in order to study the mechanisms of SCS outside the application of SCI. Dr. Capogrosso, Dr. Friedlander, and Dr. Gerszten hope to be able to show that SCS is a disease-modifying intervention for dysfunctions of the spinal sensorimotor units and, therefore, could be applied to a variety of disorders of this simple but critical neural unit in motor control. Hopefully, this research program will contribute to the global efforts to defeat paralysis in all its forms.

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Noninvasive Measurement of Intracranial Pressure Using Near-infrared Light

Michael M. McDowell, MD
Assistant Professor

Elevated intracranial pressure is a major problem in many conditions and often requires surgical intervention. Unfortunately, the most accurate ways to measure elevated intracranial pressure are invasive. The placement of an external ventricular drain or other monitoring device puts the patient at risk of infection, hemorrhage, and brain injury (Figure 1). Investigators at Carnegie Mellon University, under the leadership of Jana Kainerstorfer, PhD, have developed a noninvasive sensor capable of estimating intracranial pressure using two related forms of optical imaging called near-infrared spectroscopy (NIRS) and diffuse correlation spectroscopy (DCS) (Figure 2). This was tested with impressive results in a nonhuman primate model.[1,2] Based on these encouraging results, an observational clinical trial was developed at UPMC Children's Hospital of Pittsburgh and supervised by **Michael McDowell, MD**. The preliminary results of this clinical trial were reported at the 2021 AANS/CNS Joint Section of Pediatric Neurological Surgery, where Dr. McDowell was awarded the 2021 Hydrocephalus Association Award.

Figure 1. Large left-sided catheter tract hemorrhage secondary to external ventricular drain placement.

Patients who received external ventricular drains or other intracranial pressure monitors for clinical purposes were enrolled. The pressure readings and intracranial pressure waveforms from standard devices were compared to the noninvasive device for up to six hours per day up to seven days. To date, more than 30 patients have been enrolled and over 2 million measurements collected in patients ranging from under 1 year of age to young adulthood. Intracranial pressure estimation was performed by using a machine learning algorithm to analyze some of the waveform data collected. The algorithm found features of the waveform that correlated with intracranial pressure. Three representative cases with normal, moderate, and high intracranial pressure are displayed in Figure 3. It was found that there was a strong correlation between estimated and measured intracranial pressure ($r^2 = 0.94$) in all three cases. Further, it was found that 95% of the noninvasive sensor's estimated measurements were within 3.3 mmHg of the pressure calculated by the invasive device.

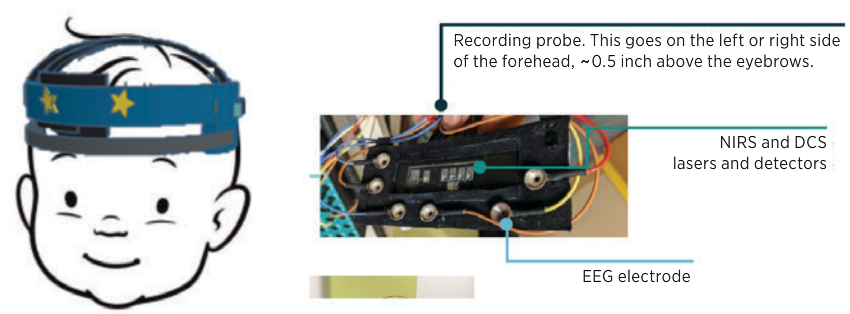

Figure 2. Illustrated example of the NIRS device secured to right forehead (left), with breakdown of components of device (right).

The ability to measure intracranial pressure noninvasively would be a paradigm shift in the management of intracranial pressure. Not only would it allow for the safe, rapid screening of patients where it is not clear if elevated pressure is present, but it also opens up the opportunity to explore new conditions that may benefit from intracranial pressure measurement.

Concussion, for example, likely has some mild component of intracranial pressure elevation or loss of regulation but typically is not severe enough to justify subjecting patients to the risks of invasive intracranial pressure monitoring. Being able to noninvasively detect these issues would potentially allow for improved treatment of patients with concussions and guide return-to-play decisions in the case of sports-related concussion. Ultimately, noninvasive intracranial pressure measurements have the potential to become the next "vital sign." The full results of this pilot study will be available in an upcoming edition of the *Journal of Neurosurgery*.

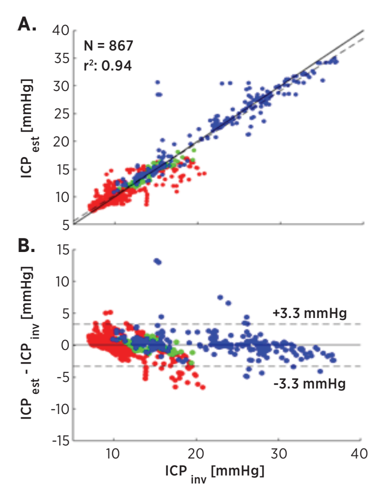

Figure 3. Demonstration of three color-coded patients with low, moderate, and high mean intracranial pressure. A strong correlation between estimated intracranial pressure (y axis) and pressure derived via invasive monitoring is seen in Figure 3A. The discrepancy between estimated and measured intracranial pressure was within 3.3 mmHg for 95% of all samples, as seen in Figure 3B.

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News & Notes

Fridays With Friedlander

In the spring of 2020, the department inaugurated the *Fridays With Friedlander* webcast, hosted by department Chair **Robert Friedlander, MD, MA**. This weekly webcast presents updates on topical neurological surgery issues and features department faculty, residents, alumni, and prominent figures in medicine presenting updates on topical neurological surgery issues — followed by an interactive Q&A session. The webcasts are streamed live via Microsoft Teams. Links to past episodes can be found at **neurosurgery.pitt.edu/fridays-with-friedlander**.

To Identify a Voice, Brains Rely on Sight

In a recent study published in the *Journal of Neurophysiology,* researchers suggest that voice and face recognition are linked even more intimately than previously thought, offering an intriguing possibility that visual and auditory information relevant to identifying someone feeds into a common brain center, allowing for more robust, well-rounded recognition by integrating separate modes of sensation.

"From behavioral research, we know that people can identify a familiar voice faster and more accurately when they can associate it with the speaker's face, but we never had a good explanation of why that happens," said senior author **Taylor Abel, MD**, associate professor of neurological surgery at the University of Pittsburgh School of Medicine. "In the visual cortex, specifically in the part that typically processes faces, we also see electrical activity in response to famous people's voices, highlighting how deeply the two systems are interlinked."

Machine Learning Model to Help Traumatic Brain Injury Patients

A prognostic model developed by University of Pittsburgh School of Medicine data scientists and UPMC neurotrauma surgeons is the first to use automated brain scans and machine learning to inform outcomes in patients with severe traumatic brain injuries (TBI). "Every day, in hospitals across the United States, care is withdrawn from patients who would have otherwise returned to independent living," said co-senior author **David Okonkwo, MD, PhD**. "The majority of people who survive a critical period in an acute care setting make a meaningful recovery — which further underscores the need to identify patients who are more likely to recover."

Sameer Agnihotri, PhD, Awarded Prestigious Research Grant

A University of Pittsburgh expert in aggressive brain tumors is one of five scientists awarded a prestigious 2022 Distinguished Scientist Award from the Sontag Foundation. **Sameer Agnihotri, PhD**, director, University of Pittsburgh Brain Tumor Biology and Therapy Lab, was recognized for his research on pediatric brain tumors. Dr. Agnihotri's research revealed that a mutation in proteins that provide structural support to the DNA makes diffuse midline gliomas and diffuse intrinsic pontine gliomas cells particularly vulnerable to depletion of methionine, an amino acid building block essential for making up proteins.

The Sontag Distinguished Scientist Award provides $600,000 in funding over four years to outstanding scientists whose pioneering research has the potential to make significant impact in the field of brain cancer.

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About Us

The Department of Neurological Surgery at the University of Pittsburgh was founded 80 years ago with a strong commitment to patient care, education, and research. Today, the department is the largest neurosurgical academic provider in the United States, performing more than 11,000 procedures a year.

Annually, the department has been highly ranked in total research funding, a direct result of the success and quality of our research and development. In the 2022 fiscal year, our faculty and residents were involved in almost 200 research projects having a total annual budget award of more than $13 million, an increase of 30% over the prior year.

Our physicians are pioneers in their field, developing new techniques and tools in brain, spine, and peripheral nerve care. Within our department, a number of minimally invasive treatments have been pioneered and refined, offering new hope to patients with complex neurosurgical disorders.

Our mission is to deliver the best possible care, to train the next generation of neurosurgical leaders, and to advance our field through innovative and high impact research.

Patients with complex disorders are seen and evaluated by our multidisciplinary subspecialists, and their cases discussed in one of our many multidisciplinary conferences. One of our strengths is the broad spectrum of available technical approaches for the treatment of both common as well as unusual and complex disease entities. With an unparalleled technical spectrum of abilities, we tailor treatment to individual patient needs, always seeking to do our utmost.

For example, intracranial aneurysms are evaluated by microvascular as well as endovascular neurosurgeons in multidisciplinary conferences, providing the patient both with options and the combined expertise of different therapeutic approaches. Brain and spinal cord tumors are evaluated and treated using a broad variety of techniques including endoscopically approached, microsurgery, as well as radiosurgery. Complex spinal disorders are treated by highly experienced neurosurgeons providing a broad spectrum of minimally invasive techniques and modern instrumentation. This kind of work is possible because we have close collaborative efforts with many leading subspecialists from a myriad of different departments.

Our department is fortunate to house a significant number of talented individuals who continuously move our field forward. Being a clinical department, our overriding goals are to develop novel approaches for the treatment of a broad spectrum of devastating diseases. Given the limited regenerative abilities of the brain and spinal cord following injury, our goal is to develop therapies that both reduce the impact of initial damaging events and enhance endogenous abilities for neurologic recovery.

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A $24 billion health care provider and insurer, Pittsburgh-based UPMC is inventing new models of patient-centered, cost-effective, accountable care. The largest nongovernmental employer in Pennsylvania, UPMC integrates 92,000 employees, 40 hospitals, 800 doctors' offices and outpatient sites, and a more than 4 million-member Insurance Services Division, the largest medical insurer in western Pennsylvania. In the most recent fiscal year, UPMC contributed $1.7 billion in benefits to its communities, including more care to the region's most vulnerable citizens than any other health care institution, and paid more than $900 million in federal, state, and local taxes. Working in close collaboration with the University of Pittsburgh Schools of the Health Sciences, UPMC shares its clinical, managerial, and technological skills worldwide through its innovation and commercialization arm, UPMC Enterprises, and through UPMC International. *U.S. News & World Report* consistently ranks UPMC Presbyterian Shadyside among the nation's best hospitals in many specialties and ranks UPMC Children's Hospital of Pittsburgh on its Honor Roll of America's Best Children's Hospitals. For more information, go to UPMC.com.