Traumatic Brain Injuries

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On the cover: axial image of a patient with a traumatic brain injury, created by fusing two MR data sets (T1 and T2).
Dear Colleagues

We’re all too conscious of the brain injuries that are occurring daily in war zones like Iraq and Afghanistan, but brain injuries are also being sustained on streets, playgrounds and in people’s own homes across the world to an extent that no one is able to fully measure.

In 1999, a 33-year-old man incurred trauma to his head so severe that he spent more than six years in a minimally conscious state. Through deep brain stimulation at Cleveland Clinic, he is now able to communicate with his family, chew and swallow and comb his own hair.

For the American troops serving overseas and the local people caught in the midst of a war zone, the intricacies of brain damage incurred from roadside bombs and IEDs are not yet fully understood. We also are exploring the unique qualities of these injuries and how they best should be treated.

Certainly brain injuries are a huge problem across the spectrum, whether they are sustained due to trauma, a tumor, stroke, seizures or dementia.

Daily, we strive to better understand and treat these injuries, utilizing enhanced surgical techniques like subcortical navigation, stenting intracranial atherosclerosis to prevent TIAs and stroke, investigating MS pathology with unique imaging modalities, and operating on pediatric epilepsy patients even earlier to reduce the amount of developmental delay continual seizures can cause.

At Cleveland Clinic, we believe that coming together in a group setting to pool our collective knowledge can lead to the best outcomes for our patients, the greatest improvement in our medical understanding and the best alleviation of the suffering all brain injuries cause. That is why our Neurological Institute brings together neurology, neurosurgery, neuropsychology, imaging, nursing and research to provide our patients with a complete continuum of care.

In this issue of *Pathways*, we explore a host of these topics. I hope you enjoy reading these articles. As always, I welcome your feedback.

Sincerely,

Michael T. Modic, MD, FACR
Chairman, Cleveland Clinic Neurological Institute
Primary blast injuries occur when changes in atmospheric pressure cause organs containing air (such as the lungs, bowels and inner ear) to rupture. While the effects of primary blast on the brain have been considered to be the result of ruptured air emboli in blood vessels, primary blast may cause damage to the brain via other mechanisms. For example, a blast to the abdomen may transfer kinetic energy from blast overpressure to the central nervous system via major blood vessels.

Secondary blast injuries are caused by objects set into motion by the explosion (e.g., missiles). Tertiary blast injuries are due to the whole body being set into motion by changes in air pressure and hitting objects. Quaternary, or miscellaneous, blast-related injuries include crush injuries due to collapsed objects, burns and smoke inhalation.

Traumatic brain injury (TBI) can result from any of these categories of blast injury. While physiological and other effects of secondary and tertiary blast injury may be similar to those in mechanical TBI due to falls or motor vehicle accidents, the effects of a primary blast to TBI are less known. Some similarities, such as edema and oxidative stress, however, are common to mechanical TBI and have been suggested in animal models. More than 50 percent of blast-related TBIs fall within the mild-to-moderate severity range.

Understanding War-Related Traumatic Brain Injuries

By Stephen M. Rao, PhD, and Stephen E. Jones, MD, PhD

Explosions are the leading cause of injury in the Afghanistan and Iraq wars. In a study with Marine and Navy personnel wounded in action in Iraq during a one-month period in 2003, approximately 50 percent of the injuries were due to improvised explosive devices (IEDs). In an Army medical facility, IEDs and mortar were responsible for 88 percent of the wounded.

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Department of Defense grant

The U.S. Department of Defense recently awarded Cleveland Clinic, in collaboration with the Baylor College of Medicine in Houston, a three-year grant to assess the sensitivity of computerized neurocognitive testing and advanced MRI techniques — task-activated functional MRI (fMRI) and diffusion tensor imaging (DTI) — in diagnosing the neural changes underlying blast-related TBI. The study will compare neurobehavioral and neuroimaging findings obtained from military personnel who have experienced a blast injury with those obtained from civilians who have experienced TBI from motor vehicle accidents. Controls will consist of military personnel and civilians with orthopaedic injuries.

All participants will undergo a single five-hour evaluation consisting of a two-hour MR scanning session and a three-hour comprehensive neuropsychological evaluation, including an assessment of post-traumatic stress disorder symptoms (PTSD) and the Automated Neuropsychological Assessment Metrics (ANAM), a portable computerized library of tests currently undergoing evaluation as a potential screen for TBI in the field.

Functional MRI and diffusion tensor imaging

All subjects also will undergo neuroimaging examinations consisting of fMRI and DTI. fMRI is a noninvasive method for measuring brain activity in response to cognitive, sensory and motor tasks. For this study, we will use activation tasks that assess short-term memory and inhibitory control, the two most commonly impaired cognitive processes in TBI. DTI will be used to assess the integrity of the white matter fiber tracts in the brain that interconnect gray matter regions activated by the tasks. Tiny foci of damage are more visible on DTI than conventional MR imaging. White matter, responsible for transmitting neural impulses over long distances, frequently is affected by the shearing and stretching forces associated with TBI.

Understanding the potentially unique sequelae of blast-related TBI is critical to making decisions regarding return to active duty and for designing pharmacological and neurorehabilitation interventions. If successful, results of this neuroimaging study will produce a shift in how individuals who have experienced TBI during military deployment are assessed and treated. fMRI and DTI are commonly available on most commercial MR scanners, and image analysis and interpretive procedures are becoming more automated and reliable. Although more costly than standard MR scans, the improved accuracy...
Computer models of blast-related TBI

There remain many mysteries regarding detailed mechanisms of traumatic brain injury, and researchers at Cleveland Clinic are contributing to this investigation by combining advanced computer simulations with DTI. We anticipate this marriage of two recent cutting-edge technologies to provide clues relating the pattern of injury to the mechanism of injury. First, we will relate the location of injured white matter to the direction of white matter fibers, by using DTI. Second, we will relate the direction of these fibers to the direction of the blast waves, using large-scale computer simulations called finite element models. Demonstrating a strong correlation will provide important insights about the exact mechanism of white matter injury.

Stephen M. Rao, PhD, is the Ralph and Luci Schey Chair and Director of the Schey Center for Cognitive Neuroimaging at Cleveland Clinic. His primary research areas are the application of fMRI to study motor control; temporal processing; working, episodic and semantic memory; and conceptual reasoning in healthy young and older participants, patients with multiple sclerosis, Parkinson’s disease and traumatic brain injury, and individuals in the preclinical stage of Huntington’s and Alzheimer’s diseases. He can be contacted at 216.444.7747 or raos2@ccf.org.

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Although many TBI lesions are not visible on conventional MRI, subtle changes in the white matter fiber-tracks are detectable using the recent technique of DTI. In this simulated example, a lesion involving a portion of the large midline white matter bundle called the corpus callosum, which connects the two cerebral hemispheres, causes a loss of white matter integrity that is visualized as a lack of fiber-track density.
Left: This illustration shows the effect of a blast wave propagating through the brain. In mild TBI patients, after a blast wave, multiple small foci of trauma are formed at locations most susceptible to injury. Most of these lesions are not visible using conventional MRI. However, new advanced MRI techniques such as DTI can reveal the location and pattern of these injuries. We hypothesize that this pattern is related to the underlying directions of the white matter fiber tracks. The application of a large-scale computer simulation to the blast can provide important clues regarding detailed mechanisms of brain tissue injury.

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Making the Inoperable Operable:
Subcortical Navigation for Brain Tumors

By Gene Barnett, MD, FACS

Many new surgical techniques and radiologic advancements have aided in the success for removal of brain tumors, but few have created as dramatic and as immediate results as diffusion tensor imaging (DTI) with fiber tracking. The inoperable brain tumor, historically a diagnosis for which you can give your patient little to no hope, now needs to be reconsidered for surgery.

Since the early 1990s, Cleveland Clinic has had the ability to navigate around and in the brain to localize tumors and edema with MRI, visualizing the surface features, including the deep surfaces. With newer techniques in the last five to 10 years, we have been able to apply maps of brain function to these traditional images of the brain. We could not, however, see the white matter tracts — the wiring of the brain itself — which can be distorted or involved in very unpredictable ways by brain tumors.

The development of an excellent awake craniotomy team and navigation technologies in Cleveland Clinic’s Brain Tumor and Neuro-Oncology Center has allowed us to push the envelope on what we can operate, while improving the outcome. With these navigation technologies (which function like GPS for the brain), however, it was never fully known how the nearby white matter structures were involved with the tumor. We could not operate on cases too close to vital tracts or accurately predict deficits created by surgery. The use of DTI, however, makes some of these cases operable.

For the past year, we have been working with neuroradiologists from Cleveland Clinic’s Imaging Institute to incorporate the images from DTI with fiber tracking into our navigation system.

DTI, first introduced in the mid-1980s, combines the principles of nuclear magnetic resonance (NMR) imaging with directional molecular diffusion effects in the NMR signal. Molecular diffusion refers to the random translational motion of molecules that results from the thermal energy carried by these molecules. Water is the most convenient molecule to use and is measured within a specific volume. Fiber tracking is possible due to the fact that water molecules in the brain diffuse preferentially along the white matter fiber tracks as opposed to across them. The image demonstrates the diffusion, or preferential flow, throughout the brain (see figure 1). It identifies all white matter tracks more than an inch long.
These images are then superimposed onto the high resolution MR images, which results in a combination of anatomical detail of the MRI, functional data from fMRI and the fiber tracking information of DTI. This gives a map of both tumor features and surface anatomy, as well as the inner wiring around the tumor.

Figure 3: The navigation system images help to identify which fiber tracks go around the tumor and which are involved, as well as to predict postoperative deficits. Here, the orange mass is the tumor, the purple and magenta are speech areas and the yellow is a motor area. The green line is the probe.

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Cleveland Clinic Leads Initial Investigation of Intra-cranial Atherosclerosis

By Peter Rasmussen, MD

Over the past few years, intracranial atherosclerosis (ICAD) has emerged as a leading cause of transient ischemic attack (TIA) and stroke. Large vessel atherostenosis involving the distal internal carotid artery, middle cerebral artery, vertebral artery and basilar artery frequently is the cause of hemodynamic or thromboembolic neurologic events. Initially, these lesions were thought to be the cause of stroke in only a minority of cases. As new treatments have emerged, however, these lesions are becoming recognized more and more often as a cause of stroke.

Given the intracranial location of such lesions, surgical approaches and procedures traditionally have been too challenging technically to address these problems. Extra-cranial to intra-cranial bypass likewise has been shown to be ineffective. Therefore, medical therapy has been the mainstay of treatment up until the last two years. Now, with the FDA approval of the Wingspan Stent System, an endovascular treatment is available for patients with ICAD.

As with the advent of most new techniques and treatments, initial enthusiasm gives way to rational caution as pitfalls and caveats to treatment are identified. Additionally, understanding the risk-to-benefit ratio of a new treatment needs to be compared with existing therapies. It is here where Cleveland Clinic’s Cerebrovascular Center has been focusing research efforts in order to better understand this technology and its treatment of ICAD.

Led by Cleveland Clinic, the U.S. Multi-Center Wingspan Registry is the largest data sample to date on the endovascular management of this disease. The University of Texas-Southwestern, the University of Buffalo, the Barrow Neurological Institute and the University of Wisconsin also are collaborating on this registry. More than 150 patients have been treated and enrolled, all with medically refractory symptomatic ICAD and atherostenosis greater than 50 percent of a major intracranial artery. With planned follow-up of these patients to two years, this registry has contributed greatly toward the design of the NIH-funded SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) trial. This randomized trial, which is scheduled to start enrolling patients in 2008, will compare stenting with medical therapy in 764 patients (382 in each arm) with intracranial stenosis. Patients will be followed for a mean period of about two years.

The natural history of medical therapy of ICAD was defined in the WASID (Warfarin–Aspirin Symptomatic Intracranial Disease) trial, which showed that patients with symptomatic ICAD who present with stroke and harbor an atherostenosis of greater than 70 percent have an approximately 25 percent chance of an additional stroke over the next two years. Additionally, most of this risk is accumulated early — implying that if endovascular treatment is considered, it should be offered early — within the first two weeks after a neurologic event.

The Wingspan Stent System opens blocked arteries in the brain, which improves blood flow and reduces the risk of recurrent blockage or narrowing.
Initial data evaluation suggests that the Wingspan Stent System is safe and effective. Successful treatment of patients with symptomatic ICAD occurs in greater than 90 percent of patients. Frequently this means resolution of medically refractory TIAs or recurrent strokes.

The registry and the WASID trial have made it possible to compare the two treatment arms (medical vs. endovascular) of ICAD.

Initial data evaluation suggests that the Wingspan Stent System is safe and effective. Successful treatment of patients with symptomatic ICAD occurs in greater than 90 percent of patients. Frequently this means resolution of medically refractory TIAs or recurrent strokes. This is in association with a low complication rate that compares favorably with the incidence of subsequent stroke in a comparable group of medically managed patients. Complications appear to occur in only about 5 percent of patients, putting this procedure on par with other established treatments such as the surgical or endovascular management of cerebral aneurysms.

One surprising finding of this registry was the rate of restenosis that occurs following this procedure. Long known to be of concern following coronary angioplasty and stenting, it was not known to be of such concern for intra-cranial circulation — at least until this study. Recurrent stenosis accounts for a substantial portion of subsequent neurologic events in successfully treated patients and understanding this phenomenon will enable investigation into safer treatments in the future.

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Invasive Neurophysiologic Mapping of Epileptogenicity and Eloquent Brain Function

By Dileep R. Nair, MD

Patients with medically intractable focal epilepsy may be candidates for epilepsy surgery. The evaluation needed for surgery involves a series of tests that are designed to determine, in a specific patient, the likelihood for seizure freedom after surgery, as well as the risk for surgically related morbidity. These are some of the key issues that need to be addressed when determining whether a patient is a good surgical candidate. The evaluation for epilepsy surgery typically involves an admission to an epilepsy monitoring unit, a high-resolution magnetic resonance imaging (MRI) scan, neuropsychological tests, a positron emission tomography (PET) scan, and often an ictal single photon emission computed tomography (SPECT).

Further testing is required when there is discordant data when attempting to determine the region from where the epilepsy is arising. This situation often presents itself when there is a lack of imaging finding to implicate a specific region in the brain that is giving rise to the seizures. Further testing may also be needed when the suspected region of epileptogenicity is in close association with a region of eloquent brain function. In these patients, further testing often involves invasive EEG using subdural or depth electrode recording to further delineate epileptogenicity and brain function to answer these key questions.1

Electrocorticography

Electrocorticography (ECoG) is a method of recording EEG activity directly from the cerebral cortex. Hans Berger first pioneered the use of ECoG in the 1920s when he recorded EEG from electrodes placed over the dura in patients with skull defects. The use of ECoG to define the limits of epileptogenicity has a long history, and its use in the current treatment of epilepsy has become well-established at several centers. Its role in epilepsy surgery, however, still remains controversial due to the inherent risks associated with implanting subdural and depth electrodes. One of the main issues associated with the use of invasive EEG is that it provides a microscopic view of brain activity. As a result, it potentially can help in refining regions of the active epileptic focus (see figure 1). If they are not placed accurately, however, it may provide no useful data and might even confuse the region of epileptogenicity.

In order to guide the use of ECoG, the team involved in the patient's surgical therapy must have a clear hypothesis for where the epilepsy is arising prior to implanting electrodes. The advent of newer methods of analysis such as evaluation of high frequency oscillations and other technology such as combined use of stereo-EEG and subdural grids should improve our ability to more accurately locate regions of epileptogenicity.

Mapping of eloquent brain function

Mapping the human cortex traditionally has been performed with evoked potentials and cortical stimulation. In the late 1940s, Woolsey was the first to record...
Figure 2: Central sulcus localization technique using cortical SEP mapping shows the central sulcus to be between electrodes 10 and 7. The curved black line marks central sulcus at this point. The cross hairs used during surgery on neuronavigation software confirm this localization.

Figure 3: Connectivity between anterior and posterior language areas is shown in this circle map reflecting amplitude produced by cortico-cortical evoked potentials (a technique pioneered at Cleveland Clinic).
evoked potentials from the human cortex. The primary somatosensory cortex and the adjacent motor cortex give rise to potentials of opposite polarity. When these potentials are recorded by an electrode array that is placed across the central sulcus, a phase reversal is seen between the two electrodes that sit on either side of the central sulcus (see figure 2). In cases of frontal, parietal, perioral and supplementary sensorimotor epilepsy, the location of the central sulcus is of extreme importance. In some patients, the central sulcus can be determined with reasonable confidence by MRI and stereotactic wand-guided technology. However, there are variations between patients in the course and morphology of the central sulcus. Verification with neurophysiologic methods helps the surgeon be more confident in locating the central sulcus. Cortical somatosensory evoked potential (SEP) testing can aid in this.

In the mid 1800s, Gustav Frisch and Edouard Hitzig showed that electrical stimulation to various cortical regions in a dog could elicit local motor responses. Much later, intraoperative stimulation for localization of language representation was performed by Penfield and Roberts. Since that time, cortical stimulation has become a valuable tool in localization of eloquent cortex. Since much of the testing requires the patient to be awake and cooperative, it is most successfully performed in the extraoperative arena, such as in the epilepsy monitoring unit, as opposed to intraoperative testing. In testing sensory, language or visual function, the patient reports any changes of those functions that occur as a result of stimulation. Once the areas of eloquent cortex have been mapped, the proximity to the planned regions of cortical resection can be compared so that these areas are excluded in the surgical resection.

**Future directions**

Other active areas of research at Cleveland Clinic include studying the role of high frequency oscillation in defining regions of epileptogenicity, single pulse cortical stimulation evoked cortical responses in defining connectivity between eloquent regions of the brain (see figure 3) and regions of epileptogenicity, and recording of event-related potentials to evaluate regions of language function. Cleveland Clinic also is involved in a multicenter trial to determine if direct electrical stimulation of the cortex can suppress seizures using the NeuroPace device (see figure 4). These advances in neurophysiology currently are being explored to see how they may aid in further defining the margins of epileptogenicity and mapping networks of various eloquent function in order to more accurately plan epilepsy surgery and provide a low risk for surgically related morbidity.

Dileep R. Nair, MD, is an epileptologist with Cleveland Clinic’s Epilepsy Center. His specialty interests include adult epilepsy, intra-operative monitoring, evoked potentials and cortical stimulation. He can be contacted at 216.444.2560 or naird@ccf.org.

**REFERENCE**

Early Epilepsy Surgery in Children
Offers Developmental Benefits

By Prakash Kotagal, MD, and Ingrid Tuxhorn, MD

Epilepsy in infants and children is associated with impaired cognitive development. Early referral and operation in these patients not only optimizes seizure control and psychosocial outcomes, but also enhances the children’s potential for cognitive development.

At highest risk for poor cognitive development and psychosocial outcomes are patients with early seizure onset and frequent, intractable seizures. A shorter duration of epilepsy is the one predictive factor for postoperative developmental gain, suggesting that timing of surgery — the earlier, the better — is critical to optimizing long-term cognitive outcomes.

Children with larger lesions in more than one lobe are more likely to have preoperative cognitive impairment in the retardation range; however, good seizure control is not restricted to children at higher functioning levels, and all patients have the potential for improved cognitive functioning. Nonetheless, developmental status before surgery predicts developmental function after surgery.

In a recent study of 24 infants less than 3 years old operated on at Cleveland Clinic, 17 patients became seizure free; five had greater than 90 percent seizure reduction, one had greater than 50 percent seizure reduction, and one had no change.1 Younger infants had a higher increase in developmental quotient after surgery, although all patients exhibited some postoperative improvement. Patients with epileptic spasms were younger and had a lower preoperative developmental quotient (DQ), but showed the largest increase in developmental quotient after surgery. An earlier study conducted at Bethel Epilepsy Center in Germany, and published in Epilepsia found similar results — shorter duration of epilepsy was significantly associated with a postoperative increase in developmental quotients.2

Of particular concern are infants with catastrophic epilepsy. Several studies suggest that early surgical intervention is critical in these patients to prevent secondary brain damage leading to cognitive deterioration. We now have compelling evidence that appropriate timing of surgery can restart development and may result in a higher long-term level of cognitive functioning. Most patients do not experience postoperative developmental catch-up or normalization of developmental deficits, suggesting that the window of opportunity to give these infants the best chance for recovery is quite narrow.

Postoperative development continues at a stable rate in all patients, although developmental gains tend to accumulate over a long period of time and not be apparent immediately after surgery. Catch-up development is possible, but only in children who are seizure-free after surgery.

Etiologies and syndromes that are recognized as treatable with surgery include hemispheric syndromes, cortical dysplasia, Sturge-Weber syndrome, tuberous sclerosis complex, hypothalamic hamartoma and temporal lobe epilepsy.

Presurgical evaluation for infants and children with epilepsy should be a multi-step approach that includes neurodevelopmental testing for all patients. This can be an important tool for determining the optimal time for epilepsy surgery based on the presurgical developmental baseline.

Evaluation should begin with a thorough characterization of the seizure semiology by history, parental...
documentation by home video if possible, a good quality surface interictal EEG, and structural imaging with MRI. Children with unifocal epilepsy caused by a well-defined lesion can benefit from early referral to an experienced epilepsy center where the standardized presurgical evaluation also includes surface ictal EEG, functional imaging, and language, memory and cognitive testing.

Presurgical evaluation for intractable epilepsies due to multicentric or extensive bilateral disease or remote epilepsies due to strokes may require invasive video EEG monitoring with intracranial electrodes and functional imaging to localize the epileptogenic zone and delineate it from eloquent cortex.

Infants and young children with static structural epileptic encephalopathies require the expertise of experienced and knowledgeable pediatric epilepsy centers. These syndromes may be difficult to differentiate from progressive metabolic disorders, but are not necessarily contraindications to surgery.

For the majority of infants and children with surgical epilepsy, surgery should be considered first-line treatment, not a last resort.

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Effect of age at the time of surgery on developmental outcome. An increase of the DQ after surgery was most prominent in patients having operations before 12 months of age.

Change in DQ in infants with and without epileptic spasms. Improvement in DQ was more prominent in the subgroup of infants with epileptic spasms on presentation.
Magnetoencephalography in the Clinical Environment

By John C. Mosher, PhD, and Richard C. Burgess, MD, PhD

Cleveland Clinic’s Epilepsy Center has introduced advanced magnetoencephalography (MEG) techniques in order to enhance the diagnosis and treatment of epilepsy, supplementing electroencephalography (EEG), imaging and other procedures. Located within the Epilepsy Center’s existing facilities, the new MEG Suite houses the latest in sensor technology, allowing physicians and neurophysiologists new insights into brain dynamics. A greatly expanded neurophysiology and imaging research program within the center will pursue the most promising advanced imaging and source localization methods for adaptation to the demands of clinical patient care.

In the spring of 2008, the Epilepsy Center opened a new facility to incorporate MEG analyses into our examination methods. The MEG Suite features the latest model of the Elekta Neuromag®, a MEG array built by the Finnish firm Neuromag Oy, a subsidiary of the Swedish medical company Elekta AB. The array is housed in a state-of-the-art magnetically shielded room installed by the Swiss firm Imedeo AG. Cleveland Clinic’s MEG Suite is directly adjacent to surgical suites within the Neurological Institute, and in the same hospital building as the outpatient epilepsy examination, monitoring and surgical units, providing excellent access for patients and physicians.

The MEG Suite

MEG is the magnetic equivalent of EEG, non-invasively measuring the magnetic fields just outside the scalp. Both MEG and EEG are generated by neural activity inside the brain, but each measures unique spatial patterns in their respective sensor arrays. Both modalities are direct electrophysiological measures of neural function, as compared with other techniques that measure hemodynamic activity, such as fMRI, PET and SPECT. In EEG, dozens of electrodes are affixed to the scalp, compared with MEG, where the patient simply rests his or her head inside a smooth helmet comprising hundreds of sensors. MEG also can readily measure a patient with a full EEG electrode array attached, allowing simultaneous measurements of both modalities. The patient may rest quietly in the helmet for up to an hour, while the machine silently and passively records brain patterns. Additionally, the patient may listen to a series of tones, watch a series of flickering patterns, or feel a series of finger taps that aid in the analysis of brain functions. In more advanced cognitive studies, the patient may respond to questions or stimuli by clicking a button.

Source localization is part of the process for solving the “inverse problem,” i.e., determining which neural activity generated the observed MEG or EEG data; for MEG, the mathematical models are generally better than for EEG. Used alone or in conjunction with EEG measurements, MEG enhances our ability to localize abnormal areas of the brain that produce epileptic discharges, and to more precisely define non-invasively the eloquent cortical areas of cognitive, sensory and motor functions. With its high sensor count, unique field measurements and simpler patient use, MEG therefore plays an excellent complementary role to traditional EEG monitoring in the clinical examination.

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The Epilepsy Center is introducing two established clinical applications employing MEG: presurgical mapping and epilepsy diagnosis. In patients scheduled
for tumor resection or functional neurosurgery, preoperative measurements of MEG in response to specific sensory stimuli allow mapping of the eloquent cortex, necessary for surgical planning. For diagnosing epilepsy, MEG can record the activity associated with sources of abnormal discharges, providing either an alternative or a unique perspective to that of EEG and with generally greater localization accuracy (see figure 2).

The challenges of the clinical environment

MEG measurements require the world’s most sensitive magnetic detectors, and nearly all MEG arrays are housed inside of magnetically shielded rooms. Cleveland Clinic’s innovative shielded room features two new advancements: a composite shielding material and an active compensation coil system. The new shielding efficiently sandwiches thin layers of magnetically permeable metal into a more effective magnetic isolation than simpler designs employing the same amount of material. The active compensation coils augment this isolation by measuring the hospital environment and generating cancelling signals within the walls of the room. The overall isolation within the room is therefore comparable to that of a much larger and heavier room. The relatively lighter weight and lower profile of our shielded room allows MEG’s installation in the existing hospital floor plan without substantial structural modifications. Thus the MEG Suite is integral to the Epilepsy Center, located directly within the existing examination, monitoring and surgical units.

The challenges of advanced applications

In addition to the accepted presurgical mapping and epilepsy diagnosis applications, the Epilepsy Center is committed to keeping Cleveland Clinic’s neurophysiological testing methods at the forefront of available technology. We also have created a research arm to adapt the leading advanced source imaging techniques, selecting the most promising to be brought closer to patient clinical care (see figure 3). With new funding from the National Institutes of Health, the Epilepsy Center has teamed with an outstanding signal and image processing institute at a major university to test the latest in EEG and MEG spatio-temporal modeling algorithms as part of their multi-year NIH grant. A separate NIH grant collaboration with another major research hospital, anticipated to start in December of 2008, will develop new software workflows to streamline processing of clinical data, while further testing advanced MEG modeling algorithms. The technical challenges include tuning the research models to the environmental challenges of an urban hospital, demonstrating the reliability and consistency of these models, and adapting the presentations of the images to the needs of the physicians in their pursuit of high-quality patient care.

Figure 2: A spike seen simultaneously on EEG and MEG, arising from the left lateral frontal/superior temporal region.

Figure 3: In this example of the envisioned directions of advanced source modeling the Epilepsy Center is pursuing, the cortical surface presented here is the gray-white layer, automatically detected, segmented and tessellated from a subject’s MRI, then smoothed to open up the sulcal folds for easier viewing. Overlaid on this surface are simulated source distributions whose intensities are represented by shades of red. The top image is an example of a linear imaging technique that blurs the image, while the sharper image on the bottom requires advanced nonlinear techniques that we are developing for use in clinical environments.

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SUGGESTED READING


PFO and Migraine: Association and Causation

By Stewart J. Tepper, MD

There is an unequivocal and strong association between migraine with aura and patent foramen ovale (PFO). This is unexpected and, although repeatedly demonstrated, causation has not yet been established. A recent controlled study to explore the utility of closing PFOs to treat migraines was entirely negative, yet additional major randomized, controlled trials are under way.

The foramen ovale — a conduit between the right and left atrium to allow direct shunting of oxygenated maternal blood to the fetal systemic circulation, bypassing the fetal lungs — closes after birth by fibrous adhesions between the cardiac septum primum and secundum. PFOs of at least probe-patent size occur in 27.6 percent of autopsies and in 10 percent to 16 percent of echocardiographic studies; however, large PFOs with major right-to-left shunts occur in only 1.7 percent to 7.3 percent of the general population.

In the Migraine Intervention with STARFlex Technology (MIST I) trial, which included subjects with refractory migraine with aura who were prospectively investigated with transthoracic echocardiography and bubble tests, frequency of PFOs with large right-to-left shunts was 38 percent.

The question is whether this association implies that PFO causes migraine and, if so, what the mechanism is by which PFO could provoke migraine with aura. Migraine is an inherited neurologic disease in which a hyperactive central generator fires due to variable triggers. Aura, which precedes migraine in about one-fifth of patients, is a cortical spreading activation of neurons with initial hyperemia, and subsequent post-ictal neuronal depression and oligemia.

Shunting may provide a conduit for provocation of migraine via a PFO. That is, under normal circumstances, without shunting, the lungs degrade serotonin, nitric oxide, kinins, calcitonin gene-related peptide and other pro-inflammatory or vasoactive chemicals, preventing chemical access to the genetically susceptible brain. In the presence of a significant shunt, and in the absence of the pulmonary filter, these chemicals might precipitate migraine with aura. Another hypothesis suggests paradoxical emboli might impact cortex, inducing aura. These same emboli also could terminate in vessels, causing infarction and thereby connecting PFO, migraine with aura, and stroke.

There also is an association of migraine with aura with Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu) disease. This is additional evidence that shunts could cause migraine, through pulmonary arteriovenous malformations.

The strong association of PFO and migraine with aura led to numerous case-controlled or uncontrolled reports of percutaneous angiographic PFO closures curing or dramatically reducing migraines with aura. Most PFO closures were for reasons other than migraine, such as recurrent stroke, scuba diver decompression illness or refractory hypoxemia syndromes from large shunts.

Because of these reports, the MIST I trial was undertaken in the United Kingdom. MIST I was the first and, to date, the only prospective, randomized, controlled trial testing whether PFO closure could improve migraine with aura. The study examined patients with refractory migraine with aura (refractory to at least two preventive medications) and prospectively obtained transthoracic echocardiograms to document shunts and presumed PFOs.

Subjects with major right-to-left shunts were given general anesthesia and half had their groins punctured without being catheterized (sham control). The other half was catheterized and closed (active group). Both groups were placed on aspirin and clopidogrel for three months. Data were then collected on migraines for the next three months.

The primary endpoint for MIST I was complete resolution of migraine. Secondary endpoints included migraine reduction and impact. Final results were negative, for both primary and secondary endpoints. There was also a relatively high rate of adverse events in MIST I in the active arm (6.8 percent), including tamponade and atrial fibrillation, as well as episodes of significant bleeding in the sham arm from the anti-platelet drugs.

The strong association of PFO and migraine with aura led to numerous case-controlled or uncontrolled reports of percutaneous angiographic PFO closures curing or dramatically reducing migraines with aura.

Given this negative study, the question now is whether the association of PFO and migraine is just that, and not causation, or whether methodologic problems bedeviled the study. The legacy of MIST I is that it has proven possible to do a surgical sham-controlled study on the utility of PFO closure for migraine and, although a negative study, lessons learned can help shape future studies.

MIST II was one of three randomized, controlled trials approved by the FDA to further study effects of closure on migraine. All three studies used endpoints of reduction in migraine rather than complete elimination. In all three, the FDA negotiated extremely difficult inclusion and exclusion criteria and insisted that the sham arm include cardiac catheterization for all, with randomization on the table after a PFO with significant shunt was confirmed angiographically.

The difficulty of the inclusion and exclusion criteria, with the prospect of cardiac catheterization and a 1:1 randomization for actual closure, and the need for both groups to receive anti-platelet therapy for three months, made recruitment for MIST II almost impossible. The FDA required that MIST II be powered for a safety outcome, rather than efficacy, so more than 500 subjects were required.

More than 30,000 hits occurred on the MIST II website, more than 1,400 patients were screened and 376 of those patients were referred to active MIST II centers. Dropout through the screening phases was extremely high, with only a handful of patients randomized. The math suggested that the study would be impossible to complete; it was discontinued early in 2008.

That leaves two trials remaining, both with cardiac catheterization in the sham arm, and both powered for safety. Cleveland Clinic participated in MIST II under the guidance of cardiologist Dr. E. Murat Tuzcu. The Center for Headache and Pain currently is negotiating joining several other PFO clinical trials. The hope is that these studies will be successful in recruiting patients to resolve the issues of association, causation and treatment with respect to PFO, shunting and migraine.

Stewart Tepper, MD, is Director of Research at Cleveland Clinic’s Center for Headache and Pain. He served as the national neurological principal investigator for the MIST II trial on PFO closure for migraine with aura. He can be contacted at 216.636.5549 or teppers@ccf.org.

REFERENCES

SUGGESTED READING
Improved Understanding and Management of Multiple Sclerosis through Magnetic Resonance Imaging

By Elizabeth Fisher, PhD

Management of multiple sclerosis (MS) is a difficult challenge, not only because available treatments are only partially effective, but also because of the wide variability in symptoms and rates of disease progression across patients. Our limited understanding of MS pathogenesis and the lack of available tools for monitoring the disease further complicate the problem. Magnetic resonance imaging (MRI) is our most sensitive and objective tool. However, the usefulness of MRI is limited due to the nonspecific nature of MRI abnormalities and the lack of correlation between lesion volumes and MS progression as defined by clinical measures.

Matching disease severity to imaging measures

At Cleveland Clinic, the departments of Biomedical Engineering and Neurosciences within the Lerner Research Institute have been working with the Mellen Center for Multiple Sclerosis Treatment and Research to find combinations of MR imaging measures that correlate better with disease severity and clinical symptoms, as well as to help us to better understand the pathogenesis of MS.

T2-weighted MRI, one of the common imaging techniques used in MS, is very sensitive to MS pathology; however, it is not specific and does not provide information about the severity of the underlying lesions. Any type of focal changes in water content will result in an apparent “lesion,” just based on the physical principles of MRI. Therefore, although very few lesions are missed with conventional MRI, it is difficult to correlate images with clinical symptoms and impossible to tell which lesions have no or only mild tissue damage and may still be capable of repair, and which lesions have severe tissue destruction with no chance of resolving.

Within the last 10 to 15 years, research groups have been trying to come up with new ways of acquiring magnetic resonance images that are more specific and could aid in understanding the pathogenesis of the disease. For example, hypointensities on T1-weighted MRIs have been found to directly correlate with the degree of axonal loss. T1 hypointensities also have been found to have a stronger correlation with disability and association with the chronic stage of lesion development. Magnetization transfer ratio (MTR), which is calculated from two MRIs acquired with and without a special magnetization transfer pulse, has been shown to be decreased in MS lesions as well as in normal-appearing brain tissue in MS patients. It also has been shown to be correlated with demyelination and axonal loss and increased disability. Unfortunately, correlations of individual measures of T1 hypointensities and decreased MTR with disease progression have been weaker than expected.

Combining T2-weighted, T1-weighted and MTR images

We have been studying new ways of analyzing and combining information from T2-weighted, T1-weighted and MTR images in an attempt to better understand the disease process and usefulness of MRI. We recently finished a study in which we correlated MRI characteristics with underlying pathology in cadaver brains from patients with MS. We looked at 110 different regions from 10 MS patients with T2-weighted, T1-weighted and MTR images acquired post-mortem, just prior to autopsy. The regions were selected based on imaging characteristics and then blindly examined histopathologically for myelin status, lesion activity, serum protein distribution, axonal area and axonal loss.

We found that regions that were only abnormal on T2-weighted images were more likely to correspond to less severe tissue damage. In fact, 45 percent of these regions were found to be normally myelinated. In contrast, regions that were T2 hyperintense, T1 hypointense and had low MTR were more likely to represent chronic inactive lesions with fewer and more swollen axons consistent with irreversible damage. Axonal swelling was a major distinguishing feature between the two types of lesions we studied (see figure). Since axonal swelling precedes axonal degeneration, we hope that refinement of MRI analysis may provide a means of understanding progression of the disease as well as more accurately identifying lesions with a possibility for repair.

We currently are conducting a longitudinal study of about 100 MS patients and healthy controls over an extended period of time with MRI and annual neurologic exams to
try to establish better markers of disease progression. Our specific aims are to determine the degree to which MRI markers relate to the irreversible loss of tissue measured by brain atrophy. Changes in the MRI characteristics within individual lesions may provide valuable information, but we also are interested in changes that occur outside of the lesions in the normal appearing white matter and especially in the gray matter.

In addition to giving neurologists better tools to manage their patients, we hope to aid in future advancements in the treatment of the disease. The development of new therapies for MS is now focused on attempts to halt neurodegeneration and axonal loss, or so-called neuroprotective therapies. The current level of specificity with MRI makes it very difficult to evaluate the neuroprotective effects of new treatments. In addition, with MS being more aggressive in some patients and more benign in others, we currently cannot reliably tell, even with MRI, which patients should be aggressively treated and which should not. Our goal is to create tools, using quantitative MRI analysis, that can help neurologists make better clinical decisions and understand the pathogenesis of the disease.

Elizabeth Fisher, PhD, is an associate staff member in the Department of Biomedical Engineering with a joint appointment in the Mellen Center for Multiple Sclerosis Treatment and Research and an assistant professor of molecular medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. She has been researching MRI in MS at Cleveland Clinic since 1995. She can be contacted at 216.445.3317 or fishere@ccf.org.

This study was supported by a National Institute of Neurological Disorders and Stroke Program Project Grant, PO1 NS38667.

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Zebras**: The Perfect Model**

By Wendy Macklin, PhD

When investigating new drug treatments for multiple sclerosis, the use of fish embryos may not be the first place one would think to start. Yet zebrafish are a fantastic vertebrate model for understanding the basic mechanisms of human disease. Zebrafish models are quick studies, allowing for enhanced imaging and careful observation of drug responses, treatment effects on behavior and the under- and over-expression of genes.

Utilizing a living zebrafish model at Cleveland Clinic, we have been able to identify a set of small molecules that increase myelination. We will test these compounds in future rodent studies, with the intent to identify pre-clinical therapeutics for remyelination in multiple sclerosis.

**The benefits of zebrafish**

Zebrafish develop rapidly, going from a fertilized egg to an immature fish in six days. Fertilized fish eggs are transparent and develop outside the mother, making the imaging of their development straightforward and informative. Their nervous system has well-defined cells that we know a great deal about physiologically, morphologically and anatomically. Drug treatment is simple: drugs are added to the fish water. This works effectively in the brain, since the blood-brain barrier is minimal until five days post-fertilization.

**Making fish glow**

A number of years ago, investigators cloned the green fluorescent protein that makes jellyfish fluoresce. This protein has been modified to make red fluorescent protein, as well as a variety of other colors, which make living cells fluoresce, providing a useful tool in imaging.1 Real-time imaging of migration, division and differentiation of fluorescent color-tagged cells in living fish can be done for up to 24 hours, which in early stages of development defines major changes in brain development. Drugs that modify that behavior, therefore, can be identified.

Chimeric fish can be generated by transplanting cells from a mutant fish into a normal fish, often using color-tagged transgenic cells, so one can analyze the behavior of the host cells (green) or the transplanted cells (red).

Relatively simple behavioral tests in zebrafish can provide important information on brain function.2 Swimming behavior can be quantified, allowing us to analyze changes resulting from mutation or drug treatment. Even aggression, depression, drug abuse and other behavioral traits are being modeled and studied in fish.3 Some studies focusing on adult neurologic pathologies are having striking results. Several neurodegenerative diseases such as Parkinson’s disease or Alzheimer’s disease are being modeled in zebrafish.4,5

**Genetic analysis**

The zebrafish genome has been sequenced, and the conservation of genetic information across the species is remarkable. Thus, information on genes and cellular behavior identified in zebrafish is generally highly correlated with comparable cells in humans. Many new genetic tools are becoming available that allow investigators to selectively over- or under-express genes in zebrafish. Genes can be over-expressed by injecting mRNA into fertilized eggs or under-expressed by injecting short oligonucleotides, called morpholinos, which prevent mRNAs from making protein.

Zebrafish have been used for genetic screens for a number of years. They are easy to mutagenize, and relatively easy screens can be developed to identify genes of interest. For example, myelination has been targeted by several groups as an important neurologic developmental process with relevance to multiple sclerosis. A simple genetic screen in zebrafish identified more than 12 genes, at least seven of which were unexpected novel genes.6,7 Identifying the role of these genes in brain development may provide insight into certain forms of mental retardation, such as the genetic leukodystrophies. In addition, they may prove important for remyelination in the adult, which would be valuable for potential therapies in multiple sclerosis, in which myelin is destroyed.

**Enhancing myelination**

Our laboratory developed a green fluorescent protein transgenic zebrafish that selectively expresses green
fluorescent protein in oligodendrocytes, the myelinating cell of the central nervous system. We use these fish to image myelination in vivo, to screen for genetic mutants in myelination and to screen for drugs that enhance myelination, which might be therapeutic for multiple sclerosis or other demyelinating diseases. We developed an imaging analysis protocol that we use to screen small molecule libraries for drugs that increase myelination. We screen small molecule libraries for compounds that enhance myelination in zebrafish, imaging live green fluorescent protein-tagged fish 48 hours after exposure to compounds. This has allowed us to identify the set of small molecules that increase myelination in living fish. We hope to translate to rodent studies and eventually to the development of therapeutics for remyelination in multiple sclerosis patients.

Wendy Macklin, PhD, is a researcher in the Cleveland Clinic Lerner Research Institute’s Department of Neurosciences. Her research focus is on molecular control of oligodendrocyte differentiation during brain development. She can be contacted at 216.445.2680 or mackliw@ccf.org.

Example of a wild type female zebrafish, five months old (top). A transgenic zebrafish (middle), in which myelin-forming cells express green fluorescent protein. At this stage (three days post-fertilization), cells in the spinal cord are actively differentiating and producing myelin in the spinal cord (green) and retina. At higher magnification (bottom), both the cell bodies and myelin-forming processes are fluorescent. (Scale bar in lower two is 100 µm.)

REFERENCES


Pathway-specific Imaging in MS Patients

By Micheal D. Phillips, MD, and Mark Lowe, PhD

Multiple sclerosis (MS) has been extensively studied using magnetic resonance imaging (MRI). The majority of studies have focused on whole brain analysis of disease burden or assessments of whole brain atrophy. These methods typically demonstrate only modest correlation with patient disability. One of the potential reasons for this disconnect is that imaging measurements evaluate the brain globally, whereas assessments of clinical disability are pathway specific. In research funded by the National Multiple Sclerosis Society, investigators at Cleveland Clinic’s Neurological Institute and Imaging Institute have focused on several new imaging approaches to evaluate multiple sclerosis that are pathway specific. These studies have used two new MR imaging techniques for assessing neuronal pathways.

Blood oxygen level dependent functional connectivity

The first technique is called functional connectivity and measures the degree of functional connection between brain regions using blood oxygen level dependent (BOLD) functional MRI techniques to measure low frequency fluctuations in blood flow. These fluctuations are strongly correlated in brain regions that make up functional networks. In early work in multiple sclerosis completed here, we have demonstrated that motor functional networks were disconnected (see figure 1) in multiple sclerosis.1

DTI

The second MR technique to assess integrity of neural pathways and functional networks is called diffusion tensor imaging (DTI). This methodology measures the movement of water within the brain and is sensitive to small changes in white matter integrity. DTI can be analyzed to identify specific white matter pathways using fiber tracking techniques. We use this methodology to demonstrate pathway-specific damage in the white matter fibers connecting the bilateral supplementary motor areas (see figure 2). The extent of damage measured by diffusion tensor imaging correlated strongly with pathway specific motor function.2

Traditional approaches to DTI have been limited in their application in MS. Typically, fiber tracking DTI methods will not allow for tracking through multiple sclerosis lesions, which limits this technique in its analysis of white matter integrity. Recent advances in diffusion imaging have allowed for a new approach to tracking white matter pathways. This technique has been implemented at Cleveland Clinic. It allows for fiber tracking through multiple sclerosis lesions (see figure 3). Recently, we utilized probabilistic fiber tracking and functional connectivity to analyze the motor pathway connecting the two primary motor cortices.3 This study demonstrated that the degree of functional activity between the brain regions was directly correlated with the degree of pathway integrity measured by diffusion imaging. In other words, the pathway damage caused by MS lesions, as measured by DTI, produced decreased functional connection between the brain regions joined by the pathways. This is the first demonstration of a direct correlation between pathway integrity and functional connectivity demonstrated by MRI. These findings strongly suggest that partial

Figure 1: Functional connectivity results in normal (left) and multiple sclerosis (right) patients. Functional connectivity using a seed region (yellow oval) in the left primary motor region demonstrates connection throughout the motor system in normal subjects. No contralateral connectivity is demonstrated in the MS patient.
connectivity can be used as a noninvasive measure of pathway and network function.

Both DTI and functional connectivity are collected across the whole brain, allowing for potential interrogation of multiple functional pathways. The pathway-specific nature of these techniques demonstrates a greater correlation with clinical disability than conventional methods. These approaches are promising as potential sensitive tools to assess disease progression and the efficacy of therapeutic interventions in multiple sclerosis. Although MS was the focus of the initial studies in this case, both functional connectivity and DTI have great potential for investigating a wide variety of neurologic diseases. These techniques allow us to directly interrogate white matter integrity and the function of individual neuronal networks across the entire brain. The goal would be to develop a noninvasive imaging evaluation of multiple functional networks throughout the brain, which can be performed in a single imaging examination lasting less than one hour.

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REFERENCES


Deep Brain Stimulation for the Treatment of Severe Traumatic Brain Injury

By Ali R. Rezai, MD, and Cynthia Kubu, PhD

Traumatic brain injury (TBI) is among the most common neurological disorders afflicting Americans. There are 1.5 million new cases of TBI each year in the United States. Most cases of TBI are mild. However, approximately 30 percent of patients who suffer a traumatic brain injury have a moderate to severe brain injury. There are few therapeutic options for this severe TBI group beyond spontaneous recovery and physical therapy. The Centers for Disease Control estimate that at least 5.3 million Americans currently have a long-term or lifelong need for help to perform activities of daily living as a result of a TBI.1,2

Minimally conscious state

A subset of the severe TBI group fall in the category of minimally conscious state (MCS). This condition is characterized by a disorder of arousal that is separate from a vegetative state. MCS patients demonstrate intermittent, yet clearly discernable, behavioral evidence of environmental awareness. Overall, MCS patients are highly disabled and have significant limitations with respect to arousal, sustained attention, communication, interactions, responsiveness, self care and functional independence. MCS patients have widespread injury resulting in a global reduction in neuronal activity and cerebral connectivity.

It is estimated that approximately 300,000 Americans are in an MCS. Significant recovery from MCS after 12 months from injury is not uncommon. Consequently, for the most part, these patients are cared for in nursing homes or other chronic care facilities with little if any therapeutic intervention.

DBS for minimally conscious state

Our collaborative group of investigators from Cleveland Clinic, Cornell Weil Medical College and the JFK Johnson Rehabilitation Hospital recently reported on the beneficial effects of bilateral deep brain stimulation (DBS) of the intralaminar nuclei of the thalamus in a severe traumatic-brain-injured MCS patient.3 This clinical trial is the result of more than a decade of research efforts from this group, including primate research, brain imaging and the classification of severe TBI patients using the coma recovery scale (CRS) and high resolution structural and functional brain imaging. The group consists of expert neurologists (principal investigator: Dr. Nicholas Schiff, Cornell Weil Medical College), neurosurgeons (principal investigator: Dr. Ali Rezai, Cleveland Clinic), neuropsychologists (principal investigator: Dr. Joseph Giacino, JFK), neuroscientists, physical medicine and rehabilitation specialists, and ethicists.

This was an FDA IDE and multi-institutional IRB-approved trial. Ethical oversight and independent data monitoring and safety boards were employed in this prospective, double-blind, cross-over study. Using a single-subject, multiple-baseline approach, we investigated the effects of DBS in the patient, who was in an MCS for six years following a TBI. The patient, although unable to communicate, had an intact, large-scale, bihemispheric cerebral language network based on structural and functional brain imaging, suggesting that the potential for recovery was present. The patient was evaluated prior to DBS surgery using the Coma Recovery Scale-Revised (CRS-R), a measure of neurobehavioral function, and three secondary outcome measures — object naming, purposeful upper limb movement and oral feeding. Prior to the surgery and continuing throughout the study, the patient participated in a comprehensive inpatient rehabilitation program, including physical, occupational, speech and recreational therapy.

The patient subsequently underwent bilateral deep brain stimulation (DBS) implants in the anterior intralaminar thalamic nucleus (ILN). The study employed a six-month, double-blind, cross-over DBS ON vs. DBS OFF design. The outcomes demonstrated significant improvement in overall functioning, improved CRS-R arousal scores, increased functional object use and intelligible verbalization, ability to complete functional limb movement sequences, and ability to chew and swallow food with DBS ON. The patient demonstrated an improved ability to communicate and more active participation in his own care and interaction with family.

The ILN neurons are known to have strong interconnections with the brainstem arousal systems, the basal ganglia and the frontal lobe regions involved in sustained attention, vigilance, working memory and cognition. One possible mechanism of action is that the ILN DBS is activating these regions.

Our experience with a patient in a chronic minimally conscious state suggests that DBS can promote significant functional recovery. This is an ongoing clinical trial evaluating the benefits of ILN DBS for MCS patients. Patient selection and close follow-up is critical for this study. Additional patients are being recruited to participate in this study.

In addition to the ongoing MCS DBS study described above, we are investigating the utility of DBS for treatment of higher functioning severe TBI patients in a new clinical study.

The outcomes demonstrated significant improvement in overall functioning, improved CRS-R arousal scores, increased functional object use and intelligible verbalization, ability to complete functional limbic movement sequences, and ability to chew and swallow food with DBS ON.

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REFERENCES


Deep Brain Stimulation for the Treatment of Severe Obsessive-Compulsive Disorder

By Ali R. Rezai, MD, Donald Malone Jr., MD, and Cynthia Kubu, PhD

Obsessive-compulsive disorder (OCD) affects 2 percent to 3 percent of the U.S. population. Despite advances in medication and behavior therapy, at least 10 percent of patients have refractory and disabling OCD. In its most severe and treatment-resistant form, OCD results in marked suffering and impairment in self-care, education, work and social life. Those most severely affected fail to obtain adequate relief despite years of conventional behavioral and drug therapies. For this group of severely disabled patients, the approach of deep brain stimulation (DBS) may provide help and relief.

DBS background

In the past two decades, DBS has become an increasingly utilized approach for the treatment of severe and medically intractable movement disorders with more than 40,000 implants worldwide. DBS technology is reversible and adjustable and has a demonstrated safe and efficacious track record for treatment of movement disorders.

Since 1998, teams of psychiatrists and neurosurgeons in Europe and the United States have investigated DBS of the ventral anterior limb of the internal capsule and adjacent ventral striatum (VC/VS) for severe and highly treatment-resistant OCD. The VC/VS target selection initially was based on anterior capsulotomy, a technique introduced by Talairach and later refined by Leksell. Deep brain stimulation of this region was initiated by the Leuven/Antwerp group in Belgium with patient implant beginning in the late 1990s. Subsequently, DBS technology was applied in a multidisciplinary, prospective clinical trial in the United States with Butler Hospital/Brown Medical School, Cleveland Clinic and the University of Florida, Gainesville.

Patients and methods

A dedicated, multidisciplinary team of neurosurgeons, psychiatrists, neuropsychologists, neurologists and ethicists from the University of Leuven, Belgium, Butler Hospital/Brown University, Cleveland Clinic and the University of Florida, Gainesville, participated in this study. The study was conducted with IRB and FDA IDE approval, as well as an independent monitoring committee from the U.S. institutions and corresponding organizations and boards in Belgium.

Twenty-six patients with severe, disabling and treatment-refractory OCD were included in the study. All patients had disease duration of at least five years and were treatment refractory with a Yale-Brown Obsessive Compulsive Scale (YBOCS) score ≥28. Refractoriness was defined as failure to respond to at least two adequate trials (> three months, with doses at or, if tolerated, beyond the FDA maximum recommended dose) of serotonin reuptake inhibitors (SRIs), and failure to respond to at least one trial combining an SRI with additional medications (including a neuroleptic and a benzodiazepine). In addition, all patients were required to have had behavior therapy, defined as a minimum of 20 sessions of therapist-guided exposure and response prevention. Exclusion criteria included history of a current or past psychotic disorder, active substance abuse or general surgical contraindications.

Patients underwent implantation of bilateral DBS leads in the ventral portion of the anterior limb of the internal capsule and ventral striatum (VC/VS) using stereotactic technique and high resolution MRI targeting. The programming of the DBS was performed by the psychiatrists in the outpatient setting. Patients underwent close clinical monitoring each month and had outcome assessment measures monthly.

Outcome assessment consisted of YBOCS, GAF, HAM-D, HAM-A and MOS-36 standardized scales, which are used in the various pharmaceutical trials. Neuropsychological measures were done at six months and one year. The primary outcome measure was the YBOCS. Scores were analyzed as a continuous outcome with repeated measures analysis. OCD severity also was assessed categorically, as the number of patients at each rating point was assigned to one of three categories:

- a) those with a less than 25 percent YBOCS decrease from pre-implantation baseline;
- b) those with at least a 25 percent, but less than a 35 percent, reduction in OCD severity; and
- c) those with at least a 35 percent decrease.

Functional outcomes were assessed using the Global Assessment of Functioning (GAF), occupational and

By Ali R. Rezai, MD, Donald Malone Jr., MD, and Cynthia Kubu, PhD
social functioning and capacity for independent living (including ADLs), and social engagement.

Outcomes

Patients enrolled in the study had illness duration ranging from 8 to 41 years (22 ± 1.5 years) with an average YBOCS OCD severity at presurgical baseline of 34.0 ± 0.5. All patients scored at least 30, which classifies these patients as the most severe and disabled OCD patients. Seventeen of 26 patients had at least 24 months of follow-up, and 12 had reached 36 months (see the figure).

Mean YBOCS scores decreased after DBS, reaching 20.9 ± 2.4 at 36 months (p=0.002). This degree of improvement was apparent by the third month of active stimulation, when the mean YBOCS had declined to 21.0 ± 1.8. In looking at YBOCS outcomes categorically, the percentage of patients meeting the full response criterion (≥ 35 percent YBOCS decrease) increased from 28 percent at one month to 61 percent at last follow-up. GAF scores improved significantly, with the presurgical baseline mean GAF of 34.8 ± 1.1 improving to 59.0 ± 3.3 at last follow-up (p=0.006). In addition, work, school and ability for independent living and social engagement were improved.

Surgical complications included two patients with small intracerebral hemorrhages after lead insertion. One hemorrhage was asymptomatic and the other resulted in transient apathy. There were no permanent neurological deficits. One patient had an isolated seizure after lead implant with no further issues, and another patient developed a superficial wound infection, which was successfully treated with antibiotics.

These data show that DBS is a safe and effective therapy with long-term follow-up for patients suffering from severe and medically intractable OCD. The improvements noted in this study were progressive and long lasting, with no associated permanent adverse side-effects. These results are particularly promising given the severity and refractoriness of this population. Close collaboration between a multidisciplinary group of specialists (neurosurgeons, psychiatrists and psychologists) is necessary to carry out these studies with regard to patient selection, surgical procedure and long-term maintenance and adjustment of the DBS systems.

The promising outcome of this initial open-label study has resulted in a new prospective, randomized and blinded cross-over study with Ben Greenberg, MD, (Butler Hospital) serving as the principal investigator. The study is funded by the National Institute of Mental Health, and study sites include Butler Hospital/Brown University (PI: Ben Greenberg, MD), Cleveland Clinic, Massachusetts General Hospital and the University of Florida. It will compare active stimulation to a sham stimulation group. All 30 patients will eventually receive treatment.

SUGGESTED READING


There are two manifestations of CRPS. Type I was formerly known as reflex sympathetic dystrophy, a term we no longer use. Patients in this group typically have a nerve injury that cannot be immediately identified. Type II, formerly known as causalgia, includes patients in whom a distinct injury to a nerve has occurred.

Often, CRPS develops without a clear reason. Typically, a patient will have an injury such as hitting his or her foot, and the area becomes hot, red, swollen and very painful. Most often the hands or feet are affected, but the pain can spread to include an entire arm or leg. It can also spread from one limb to another and from one side to the opposite. Although the natural evolution is toward improvement and some patients experience spontaneous remission of symptoms, this can take years and some patients are never again free of unrelenting pain.

Sympathetic nervous system involvement

Cleveland Clinic’s Neuromuscular Center has conducted research on this condition and has come to view CRPS as a generalized widespread problem, not an aberrant local manifestation. We believe that it is linked to a defect in the autonomic nervous system, particularly the sympathetic branch. Many CRPS patients report symptoms that point to an overactive sympathetic nervous system, such as increases in their heart rate, breathing, sweating and pupil dilation. Swelling, excessive sweating, extreme sensitivity to typically nonpainful stimuli (e.g., touching the skin) and vasomotor changes, such as variations in skin color and temperature, also have been reported — further indicators of overactivity in the sympathetic branch.

We currently are in the process of testing patients with CRPS to quantify these variables, especially in areas of their body that are far away from the injury. This work is hoped to demonstrate that there is a widespread dysfunction of the autonomic nervous system in patients with CRPS, which would raise the broader question of whether there is an autonomic predisposition to develop CRPS in certain patients and which could shed light on certain types of pain that are mediated by the autonomic nerve system.

CRPS research projects

Previously, we conducted research published in *Annals of Neurology* showing that an autonomic dysfunction exists in the sweat glands of CRPS patients. This novel study used the technology of the Quantitative Sudomotor Axon Reflex Test (QSART) that tests the post-ganglionic sudomotor (sweat) system and demonstrated that patients with CRPS type I developed a sweat response to a substance, phenylephrine, that activates sympathetic alpha receptors. Phenylephrine, on the other hand, did not produce any significant sweat response in normal controls or the unaffected limb of CRPS patients. This finding raised the question of the development of sympathetic adrenergic sweating in CRPS, as opposed to sympathetic cholinergic sweating in normal physiological conditions. It also confirmed the presence of a supersensitivity of the sweat alpha receptors in CRPS, which also was demonstrated by others at the level of the skin blood vessels.

More recently, some of our additional findings published in *Neurology* demonstrated a loss of unmyelinated somatic and autonomic small nerve fibers in the epidermis and around sweat glands in the affected limbs of patients with CRPS type I, a finding that was also separately reported by another group at the Massachusetts General Hospital (Harvard Medical School). This is the first time an objective direct finding of a nerve abnormality is reported in CRPS type I. Another important observation we made is that nerve degeneration at the site of CRPS symptoms and signs can be caused by an injury that occurred far from the affected area, such as a stroke in the brain. This finding gave more weight to our hypothesis that CRPS is a systemic disorder rather than just a localized phenomenon.

Cleveland Clinic’s CRPS research recently received a two-year grant from the Bakken Heart-Brain Institute to further explore the role of the autonomic nervous system.
This novel study used the technology of the Quantitative Sudomotor Axon Reflex Test (QSART) that tests the post-ganglionic sudomotor (sweat) system and demonstrated that patients with CRPS type I developed a sweat response to a substance, phenylephrine, that activates sympathetic alpha receptors. Phenylephrine, on the other hand, did not produce any significant sweat response in normal controls or the unaffected limb of CRPS patients.

in patients with CRPS type I. The research project, which will be conducted jointly with the CRPS program at University Hospitals of Cleveland — Case Western Reserve University, is aimed to confirm that sympathetic overactivity in patients is due to supersensitivity in alpha receptors at the level of the sweat glands and that CRPS is a systemic disorder of the autonomic nervous system. It is suspected that CRPS causes (or is caused by) a central nervous stem disorder at the level of the dorsal horns of the spinal cord or even in the brain itself. Future research should be aimed at confirming such a link, which would open the door to finding ways to manage these pathological changes, allowing us to offer a greater range of treatment.

Clinical management of CRPS
At Cleveland Clinic, CRPS is managed utilizing a multidisciplinary approach that includes neurological and pain management evaluations. Patients are typically first seen by a neurologist, tested and diagnosed, then referred to a pain management specialist for exploration of pain management procedures. The use of antiepileptic drugs and conventional pain and symptomatic management, such as non-steroidal anti-inflammatory drugs, antidepressants, corticosteroids, opioids and topical analgesics, along with physical therapy and occupational therapy, is the first line of treatment for CRPS. For refractory cases, sympathetic nerve blocks and spinal cord stimulation are used. Exploration of music therapy, peripheral nerve and deep brain stimulation for CRPS treatment is under way.

Kamal R. Chémali, MD, is a neurologist with Cleveland Clinic’s Neuromuscular Center and the Arts & Medicine Institute. His specialty interests include electromyography, small fiber neuropathies, complex regional pain syndrome, autonomic nervous system diseases and testing, and pupillometry. Dr. Chémali is also a musician interested in music therapy, and music and the brain research. He can be contacted at 216.444.5554 or chemalk@ccf.org.

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In this case, the pregnancy progressed without issue and the baby was born by elective Cesarean section slightly prematurely, when lung maturity was reached, due to progressive hydrocephalus. There were no difficulties or resuscitation required at delivery, with Apgar scores of 9 at one minute and five minutes.

At birth, the baby's head circumference was significantly above the 98th percentile, with splaying of the sutures and a "sunset sign" indicative of raised intracranial pressure. There was also adduction and flexion contractures of the thumbs as had been seen on fetal MRI, raising the suspicion for X-linked aqueductal stenosis due to the L1CAM mutation. A head ultrasound on day one of life confirmed aqueductal stenosis, severe hydrocephalus and thinning of the cortical mantle. Subsequent genetic testing was positive for the L1CAM mutation. The baby remained hemodynamically stable and underwent the placement of a right occipital ventriculoperitoneal shunt with micro-Medos valve at one week of life.

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Images provided by Janet Reid, MD, Head of Cleveland Clinic’s Section of Pediatric Radiology.
L1CAM GENE VARIATIONS
AT A GLANCE

X-linked hydrocephalus due to aqueductal stenosis is just one of the phenotypic expressions of mutations in the L1CAM gene. Others include MASA syndrome (mental retardation, aphasia, shuffling gait and adducted thumbs), spastic paraparesis type I and X-linked agenesis of the corpus callosum. There is, however, a variation in disease expression and severity both intra- and interfamilially. The gene product is the L1 protein, which is a part of the neuronal cell adhesion molecule family and is important in nervous system development and function. Some series have estimated that mutations of the L1CAM gene may account for up to 25 percent of isolated cases of congenital hydrocephalus in males. Additionally, if there are any of the other features to suggest a L1CAM spectrum disorder, such as adducted thumbs, mental retardation or spasticity, the detection rate may be as high as 90 percent.

A. Sagittal true FISP (Fast Imaging with Steady State Precession) reveals adducted, or clasped, thumbs (circle) and normal fourth ventricle (arrow), suggesting obstruction at the aqueduct of Sylvius.

B. Axial view shows severe, dilated ventricles and thin, compressed brain cortex.

C. Image of male scrotum confirms gender (arrow).
Neonatal Brain Monitoring with aEEG

By Manikum Moodley, MBChB, and Vladimir Burdjalov, MD

Monitoring neonatal cardiac function, respiratory function and thermoregulation has been standard practice in the routine care of any newborn infant admitted to a neonatal intensive care unit for many years. Only recently, however, have the benefits of monitoring brain function in the overall care of the newborn become well known.

The ideal technique for monitoring neonatal brain function should be one that is noninvasive, user friendly, easily available at the bedside and one that can be applied for prolonged periods, allowing continuous assessment of cerebral nervous system integrity and function during intensive care periods. Amplitude-integrated EEG (aEEG) provided by a cerebral function monitor (CFM) is a unique technology available for this purpose.

Recently, aEEG has gained widespread popularity as an alternative to conventional continuous EEG monitoring in neonates. aEEG overcomes most of the problems of conventional EEG, which requires more complex and sophisticated equipment, is not easily accessible, is difficult to interpret at the bedside by neonatologists and nurse practitioners (it requires highly trained individuals to interpret the recording), and is technically difficult to use as a long-term monitoring device. In contrast, aEEG is relatively easy to apply, interpret and use on a long-term basis.

Two of the major advantages of CFM are its simplicity and the possibility of quick online analysis of overall brain function using pattern recognition. Initially developed by Maynard and Prior in the early 1970s, this technology was later adapted for neonatal use by Hellstrom-Weston and Svenningsen in the 1980s.

aEEG technique

Usually, aEEG signal is obtained from one or two channels, from a pair of bi-parietal electrodes corresponding to P3 and P4 according to the international EEG 10–20 classification. These channels integrate electrical activity in the underlying brain regions that receive the bulk of cerebral blood flow. The use of two channels may be valuable in patients with unilateral lesions. The signal then is amplified and passed through a band filter, which strongly attenuates activity below 2 Hz and above 15 Hz in order to minimize artifacts. Additional processing includes semilogarithmic amplitude compression, rectification and time compression. Amplitude-integrated signal is digitally recorded on a semilogarithmic scale at the standard speed of 6 cm/h (or at a customized speed) and finally displayed on a monitor.

The bandwidth of the aEEG trace reflects variations in minimum and maximum EEG amplitude. A semilogarithmic scale permits changes in background activity of very low amplitude (0.5 mV) to be enhanced. The aEEG display is time-compressed, which allows a recording of long-term trends in cerebral activity. In addition, the electrode impedance is continuously recorded. The new CFM monitors currently available show the aEEG and the original, simultaneously recorded raw EEG (see figure 1).

Clinical use of aEEG in NICU

Multiple studies have shown that a CFM monitor can be used efficiently in a variety of ways in the assessment of neonatal cerebral development and injury in the NICU setting.

Overall there appears to be a good correlation between aEEG and EEG background pattern in the sick full-term infant. Currently, CFM is being used in increasing numbers in many neonatal centers for:

- Evaluation of cerebral injury and recovery after hypoxic-ischemic insult
- Detection of seizure activity and effect of anticonvulsant medications
- Long-term, continuous monitoring of cerebral electrical activity

Evaluation of cerebral injury and recovery after hypoxic-ischemic insult. With hypoxic-ischemic insult (HIE), the infant’s aEEG patterns reveal a certain sequence of events with progressive injury: loss of cycling, broadening of the bandwidth and the baseline depression of the recording, seizures and burst-suppression appearance with decreased overall electrical activity and spikes (see figure 2).

The pattern of recovery in aEEG tracings has been shown to be an accurate predictor of outcome in asphyxiated infants between 3 and 48 hours of postnatal age and has a prognostic accuracy of 80 percent to 85 percent for neurological outcome if evaluated within the first few
hours following perinatal asphyxia. At this early age, aEEG recording is also the most suitable method for identifying infants eligible for neuroprotective treatment following asphyxia (e.g., hypothermia).

Detection of seizure activity and effect of anticonvulsant medications. Epileptic seizure activity, often without clinical signs, is very common in sick neonates, especially after hypoxic-ischemic insult, and also in premature infants. Long-term, continuously recorded aEEG may detect this subclinical seizure activity that otherwise could pass unrecognized. Seizures most often show a sudden, rapid rise in both the lower and upper margins of the aEEG trace. A status epilepticus usually looks like a “saw tooth” pattern, but a continuously raised background pattern can also sometimes be seen (see figure 3).

Correct interpretation is enhanced significantly when a simultaneous raw EEG is available. However, owing to the nature of the limited number of channels recorded and the compression of the recording, very brief seizures (less than 30 to 60 seconds) and focal seizures may be missed.

Long-term, continuous monitoring of cerebral electrical activity. Increasingly, aEEG is being used in many NICUs for long-term, continuous monitoring of cerebral electrical activity. Several case reports have demonstrated that aEEG shows serious deterioration of brain function related to such conditions as meningitis, acidosis, metabolic disease, hypoglycaemia and pneumothorax. aEEG can also be useful in monitoring cerebral activity during extracorporeal membrane oxygenation (ECMO), a not uncommon procedure in very sick neonates.

aEEG monitoring has proven to be a good clinical tool in sick neonates of all ages and is now increasingly used in NICUs around the world. It can play an important role in our understanding of the factors that influence normal neonatal cerebral development, and affect the severity of brain injury and the possibility of recovery from that injury. It is important to note that aEEG monitoring does not replace standard EEG, but should be used as a complement to EEG in high-risk infants. aEEG technology is easily learned by neonatologists and nurses, but support from neurophysiologists improves accuracy of evaluations.

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**THE IMPORTANCE OF NEONATAL BRAIN MONITORING**

The neonatal population, in particular the very low birth-weight infant, is at increased risk for complications that may result in significant neurologic injury, including intraventricular hemorrhage, periventricular hemorrhagic infarction, periventricular leukomalacia, hypoxic-ischemic cerebral injury, seizures and meningitis. These complications are well known to lead to global developmental delay and cerebral palsy, thus highlighting the need for improved monitoring of brain function during this vulnerable period.

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Anxiety and Heart Disease

By Leo Pozuelo, MD, FACP, and Jianping Zhang, MD, PhD

Much attention has been paid to the connection between depression and coronary heart disease, both in the research community and in the general population. Depression is linked to increased risks of developing coronary heart disease (CHD) among initially healthy people, as well as conferring increased morbidity and mortality in cardiac patients who subsequently get depressed.

In one of our prospective cohort studies, we found that increasing depressive symptoms over time in an elderly sample was associated with 57 percent higher risks of mortality. Compared with people who were stable, those with increased depressive symptoms died almost four years earlier.¹

In contrast, anxiety — another prevalent condition in the population — has been less studied regarding its relationship with heart disease. The prevalence of anxiety disorders in the population is about 15 percent to 20 percent. Anxiety can present in many different forms. There are several clinical subtypes of anxiety disorders, including panic disorder, social anxiety disorder, generalized anxiety disorder, simple phobia, obsessive-compulsive disorder and post-traumatic stress disorder. Anxiety may be a normal reaction to a stressful situation. From the evolutionary perspective, anxiety is a built-in alarm system to respond to potential dangers in the environment, which has benefited the human species for thousands of years. The “fight or flight” response, coupled with activation of the sympathetic nervous system and hypothalamus-pituitary-adrenal system, allows an individual to get ready for the potential threat.

However, in modern society, anxiety and the ancient “fight or flight” response may be more maladaptive and likely to be a “false alarm,” because in many situations an individual needs a calm and rational approach to cope with stress. Therefore, people with chronically elevated anxiety, or an extremely high level of anxiety, may overdrive their physiological system and put themselves at risk of developing health problems. In fact, research has shown that anxiety can lead to decreased vagal tone (i.e., heart rate variability), increased blood cortisol levels and elevated resting blood pressure and heart rate, all of which can increase the risk of developing heart disease.

Several longitudinal studies have shown that anxiety can be predictive of new onset of CHD. In the Normative Aging Study, a large prospective study conducted in the Boston area, higher levels of worry (an important component of anxiety) was predictive of increased risks of both myocardial infarction (MI) and fatal CHD in male subjects at 20-year follow-up.² Men reporting highest levels of worry had adjusted relative risks of MI more than doubled (RR = 2.41) compared with those with lowest levels of worry. Despite these findings, we still tend to tell our patients (perhaps erroneously) that panic attacks won’t kill them, to not worry, “your heart is fine.” This especially plays out in the emergency room, where the chest pain patient is ruled out for myocardial damage, and panic and anxiety is strongly suspected as the culprit of the chest pain symptoms.

A very recent study supported the notion that panic attacks may be an independent risk factor for cardiovascular morbidity and mortality. In the Women’s Health Initiative Study, a six-month history of full-blown panic attacks was associated with three- to four-fold increase in risks of CHD or stroke.³

Anxiety also is relevant in clinical care for patients with heart disease. Up to 10 percent of patients after MI suffer from post-traumatic stress disorder, which further interferes with treatment compliance and leads to poor outcomes.⁴ Many patients also have high anxiety in anticipation of coronary artery bypass grafting surgery (CABG). A recent study showed that pre-operative anxiety was associated with higher post-CABG mortality, whereas pre-operative depression was not.⁵ However, research in this area is still in its early stages, and the relationship between anxiety and CHD as well as mortality may be more complicated than we expected.

Recently, we found in a prospective cohort study that there were interesting gender differences in linking anxiety to long-term mortality in a group of community-dwelling elderly.⁶ These results were presented at the 2008 American Psychosomatic Society annual meeting in Baltimore. Increasing anxiety symptoms over time was associated with 42 percent higher risks of all-cause mortality at the 15-year follow-up in men, but not in women. In contrast,
higher anxiety levels at baseline were actually associated with lower mortality in women, but not in men. A potential explanation is that men and women deal with anxiety differently, and that moderately higher anxiety in women may motivate them to seek more healthcare, which may result in early diagnosis and intervention for certain illnesses, which, in turn, leads to lower mortality. More research is needed to replicate the finding and elucidate the potential mechanisms.

The relationship between depression and heart disease is well established. It now appears that anxiety is also an important factor in the management of cardiac patients. We need to screen for these disorders more effectively, continue to study the links that tie anxiety to cardiac disease, and develop effective treatment strategies that can improve the quality of life of the anxious and depressed cardiac patient, as well as improve outcomes.

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Polysomnography: Not Just for Sleep Labs Anymore

By Nancy Foldvary-Schaefer, DO

Polysomnography (PSG) performed under the direct supervision of a trained technologist in the sleep laboratory has long been considered the gold standard for the diagnosis of sleep apnea and a host of other sleep disorders. However, with the recent CMS approval of home sleep testing for continuous positive airway pressure (CPAP) coverage and growing awareness of the adverse impact of untreated sleep apnea on perioperative morbidity and mortality, PSG increasingly will be performed in the home and other settings, including the hospital room.

Sleep apnea is highly prevalent, affecting an estimated 4 percent of men and 2 percent of women.1 The American Academy of Sleep Medicine estimates that nearly 90 percent of people with sleep apnea are not yet diagnosed. The prevalence in hospitalized patients is likely to be higher due to the presence of co-morbid medical conditions such as obesity, heart failure, coronary artery disease and chronic obstructive pulmonary disease. A retrospective study of 318 patients admitted for elective surgery (general surgery, orthopaedics, urology, plastic surgery, ophthalmology or neurosurgery) found that more than 1 in 5 patients were at risk for sleep apnea.2 Gastric bypass has received the most attention in this regard, due to both the high co-morbidity between obesity and sleep apnea and the recent popularity of the procedure. Obstructive sleep apnea has been observed in 55 percent to 77 percent of adolescents and adults undergoing this type of surgery.3,4

Despite its prevalence, routine assessment of sleep apnea is not part of surgical planning. Yet, surgery patients with undiagnosed sleep apnea are at risk for respiratory complications after general anesthesia. Anesthetics, opiates and sedative agents depress the central nervous system, leading to a decrease in pharyngeal muscle tone and suppression of the respiratory drive. Normal muscle atonia during rapid eye movement (REM) sleep promotes respiratory complications in the postoperative period. Compounding this problem is the technical difficulty of managing an occluded airway, especially during a crisis. In a study performed at Cleveland Clinic involving cardiac surgery patients, mediastinitis and postoperative encephalopathy were significantly more common among those with obstructive sleep apnea than those without.5 Although no differences were noted in rate of reintubation and total tube time, patients with sleep apnea had longer ICU stays after cardiac surgery.

Awareness of the dangers of undiagnosed sleep apnea is on the rise. Recently, the American Society of Anesthesiologists issued a practice guideline highlighting the need for a more aggressive preoperative, intraoperative and postoperative intervention for surgery patients with sleep apnea.4 The success of perioperative management hinges on accurate preoperative patient assessment. Although ICU monitoring may recognize unanticipated complications, it is neither cost effective nor practically feasible to admit every sleep apnea suspect to the ICU following surgery.

While diagnostic sleep testing traditionally is conducted in the sleep laboratory, pre-operative assessment of the hospitalized patient often is done in the hospital or as an outpatient immediately before the planned procedure. There are other reasons that warrant the use of PSG in the hospital for at-risk surgery patients. It is estimated that more than half of the hospitals in the United States do not have sleep laboratories.7 For others, while sleep laboratory access is improving, schedules remain busy, which might delay or complicate a timely pre-surgical assessment.

To address some of these issues, sleep researchers at Cleveland Clinic and Johns Hopkins Medical Center are conducting a trial using the Crystal 20-H PSG telemetry monitor (Cleveland Medical Devices, Inc., Cleveland, Ohio), developed with a wireless data transmission protocol dedicated to the hospital environment. The sleep technologist monitors the study in real time as data are transmitted from the patient’s room to the sleep laboratory. The study will compare perioperative morbidity and mortality in cardiovascular surgery patients with and without sleep apnea and test the data transmission features of the device.

Ambulatory PSG is the next chapter of the rapidly evolving field of sleep medicine. While this will change the way sleep laboratories traditionally have operated and raises a number of unanswered questions, the shift undoubtedly will extend the reach of sleep diagnostic testing to new, at-risk patient populations.

By Nancy Foldvary-Schaefer, DO
While diagnostic sleep testing traditionally is conducted in the sleep laboratory, pre-operative assessment of the hospitalized patient often is done in the hospital or as an outpatient immediately before the planned procedure.

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Innovation: Making the Commitment, Managing the Conflict in the Neurological Institute

By Edward Benzel, MD, Shuvo Roy, PhD, Lars Gilbertson, PhD, Richard Schlenk, MD, and Paul Ford, PhD

We in Cleveland Clinic’s Neurological Institute and our collaborators in the Lerner Research Institute have come to view innovation not as an option, but as an obligation, as part of our duty as medical specialists. That adds innovation to the traditional academic model of clinical research, education and patient care, and brings new challenges with it.

Those challenges include finding ways to create and maintain the culture of innovation, and to manage the conflicts associated with it. To help us accomplish those goals, we have established the Neurological Institute Community of Collaborative Innovation (NICCI), a multidisciplinary group of physicians, scientists and bioethicists from the Neurological Institute, the Lerner Research Institute and the Department of Bioethics.

NICCI’s greatest challenge is to take down the barriers to innovation, encouraging collaboration so that one idea can beget more and the best can be taken through the development process for dispersion of the innovation, which often includes commercialization. Those ideas include not only innovations in treatment technology, such as OrthoMEMS’ OrthoChip spine sensor, but also those in education, such as the ACGME Learning Portfolio (ALP) medical educational software.

Conflict in innovation

Innovation also begets potential conflicts of interest. The forces that drive innovators are powerful and can blind them to negative results or inappropriate influences. But conflicts, which will always exist, are no reason to abandon innovation. Rather, they must be managed, and even though the guidelines we develop to do so are constantly evolving, conflicts can be managed effectively and ethically if one principle guides them — doing what is best for patients.

American medicine’s focus on conflict of interest and concepts of what constitutes it are changing rapidly. Only a few years ago, accepting some pharmaceutical or device company-sponsored gifts were considered routine. Now, even token gifts such as pens and pads with company logos can be considered unacceptable. Those changing concepts have prompted us to examine our potential conflicts of interest with vigor and to develop ways to manage them.

Some of these conflicts are commonly recognized and managed similarly by many institutions, including disclosure of financial interest in publications, and at medical meetings, rules on the conduct of clinical trials and financial benefit from the sale of devices to patients we treat, and institutional rules on allocation of profits to inventors.

Cleveland Clinic policies

Cleveland Clinic, however, has taken an even stricter approach than many to managing conflicts of interest. In articles we or our collaborators submit for publication in peer-reviewed journals — including even those who did research with us here but are no longer at the institution — we include a lengthy disclosure describing how the authors and Cleveland Clinic might benefit from the results of this study in the future.

According to Cleveland Clinic policy, anyone who has a vested interest in a product or anyone who exerts influence over those with a vested interest in a product may not directly participate in a clinical trial of the product. Once a device is ready to be used in patients, we may then participate in the surgery, with the patient’s informed consent, but we may not benefit financially from the sale of the device to that patient or any patient who receives the device at Cleveland Clinic.

Through NICCI, we also are developing strategies to manage other conflicts of interest that are not so commonly recognized or are not managed in any standard way. We recognize, for example, that intellectual property concerns can hinder the exchange of scientific informa-
EMBRACING INNOVATION CHALLENGES: ORTHOMEMS

To move innovations forward, Edward C. Benzel, MD, and Shuvo Roy, PhD, along with two other colleagues, took an unusual step — founding a for-profit company, OrthoMEMS, to develop and commercialize spine surgery devices based on MEMS technology. One such device is the OrthoChip, a sensing and telemetry device that measures, among many other variables, intradiscal pressure. In the intradiscal application, the OrthoChip is implanted into the disc using a minimally invasive delivery tool. Intradiscal pressure information subsequently is transmitted from the implanted sensor to an external reader unit via wireless telemetry. Such technology is potentially ‘game-changing’ in nature. It could lead to the ability to accurately establish indications for fusion or artificial disc surgery; to determine whether or not bone healing is transpiring properly; and even to change the way we practice spine and musculoskeletal medicine.

Prior to the launch of the company, the inventors were following a more established model for an academic medical center: filing invention disclosures with Cleveland Clinic Innovations (CCI), the hospital’s technology commercialization arm, as their research collaboration began to accumulate intellectual property. CCI then attempted to license the property to large medical device companies, but was unsuccessful. To move the projects toward patient care, a capable CEO with extensive experience in venture capital and medical device industry was identified and OrthoMEMS was formed.

The company has proved to be an innovation incubator that larger device companies could seldom mimic. So far, OrthoMEMS has submitted more than 40 invention disclosures to CCI, many of which have been patented and are now the basis for products under development. In addition to Cleveland Clinic, a few other academic medical institutions are taking this approach to innovation and commercialization, and the numbers are growing.

The very structure of OrthoMEMS is designed to manage potential conflict between financial interest and invention. Drs. Benzel and Roy are two of the four founders, but not officers, of the company and play no role in the company’s business side. Distribution of income to Cleveland Clinic from the company follows clear-cut policies. No monies are distributed until all of Cleveland Clinic’s expenses have been paid and, after that, 60 percent of the net income to Cleveland Clinic stays with Cleveland Clinic, while the remaining 40 percent is distributed among the inventors, should any of the products become commercially successful.
tion because, once a patentable idea is disclosed, the originators have a year to secure U.S. patent rights and international rights are lost.

An even thornier problem in innovation is the dissemination of negative results, which researchers may be reluctant to do and journals to publish. But not doing so can waste resources, including experimental animals, and even harm patients when other groups attempt research protocols and fail. Innovation may even pose risks to professional advancement, since the traditional metric for promotion is publications and grants, not patent submissions or software development, and work on innovations can also rob our time from other forms of professional development and patient care. The NICCI continues to explore ways to offset these professional risks and to properly acknowledge and reward good faith efforts in attempts to innovate.

Finally, we are working toward creating an environment of careful deliberation and multidisciplinary collaboration in safeguarding patients in our obligations to provide access to reasonable innovations and to protect them from undue risk. Creating a rich environment of innovation that values transparency and communication between innovators promises to maximize both progress and protection for patients.

Our strategies are evolving continuously, but we believe the key to successfully managing them is a sustained effort to tackle those questions while also fostering our culture of innovation.

According to Cleveland Clinic policy, anyone who has a vested interest in a product or anyone who exerts control over them may not directly participate in a clinical trial of the product.

Edward C. Benzel, MD, is Chairman of Neurosurgery, Director of Cleveland Clinic’s Center for Spine Health, and a founder of OrthoMEMS. He can be contacted at 216.445.5514 or benzele@ccf.org.

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2008-2009 CONTINUING MEDICAL EDUCATION

All physicians are cordially invited to attend the following Cleveland Clinic Neurological Institute CME symposia and ongoing programs:

September 26-27, 2008
Optimizing Function through Spasticity Management: Midwest Spasticity Conference 2008
COURSE DIRECTORS: Francois Bethoux, MD, and Mark Luciano, MD, PhD
Bertram Inn and Conference Center
Aurora, Ohio

October 20-22, 2008
Gamma Knife Perfexion — Update Training
COURSE DIRECTOR: Gene Barnett, MD
Cleveland Clinic Gamma Knife Center
Cleveland, Ohio

October 30-31, 2008
Neuroimaging in Traumatic Brain Injury
COURSE DIRECTORS: Stephen Rao, PhD, Harvey Lenin, PhD, and Micheal Phillips, MD
InterContinental Hotel and Bank of America Conference Center
Cleveland, Ohio

November 5-7, 2008
11th Annual Neuroscience Nursing Symposium
COURSE DIRECTOR: Kimberly Hunter
Hilton Garden Inn Hotel, Downtown Cleveland
Cleveland, Ohio

November 6-8, 2008
Neuro-Oncology: Current Concepts in conjunction with Mexican Neurosurgery, Neuro-Oncology, and Radiosurgery Societies
COURSE DIRECTOR: Gene Barnett, MD
Fiesta Americana Grand Los Cabos
Los Cabos, Mexico

November 21, 2008
3rd Annual Post Traumatic Stress Disorder Symposium
COURSE DIRECTORS: Joseph Janesz, PhD, and Bridget Dwyer, MA, PC
InterContinental Hotel and Bank of America Conference Center
Cleveland, Ohio

December 1-5, 2008
Gamma Knife Perfexion Training
COURSE DIRECTOR: Gene Barnett, MD
Cleveland Clinic Gamma Knife Center
Cleveland, Ohio

December 4-7, 2008
North American Neuromodulation Society 12th Annual Meeting
SCIENTIFIC PROGRAM DIRECTOR: Ali R. Rezai, MD
Mandalay Bay Resort and Casino
Las Vegas, Nev.

February 9-11, 2009
Case Studies in Epilepsy Surgery
COURSE DIRECTORS: William Bingaman, MD, and Imad Najm, MD
The Silvertree Hotel
Snowmass Village, Colo.

February 20-22, 2009
3rd Annual International Symposium on Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery
COURSE DIRECTORS: Lilyana Angelov, MD, Gene Barnett, MD, Edward Benzel, MD, Sam Chao, MD, and John Suh, MD
The Grand Floridian Resort and Spa
Lake Buena Vista, Fla.

June 19-21, 2009
Epileptology: Comprehensive Review and Practical Exercises
COURSE DIRECTORS: Andreas Alexopoulos, MD, Deepak Lachhwani, MD, and Imad Najm, MD
InterContinental Hotel and Bank of America Conference Center
Cleveland, Ohio

June 22-24, 2009
18th International Cleveland Clinic Epilepsy Symposium: Epilepsy Surgery — Improving Outcomes
COURSE DIRECTORS: Imad Najm, MD and William Bingaman, MD
InterContinental Hotel and Bank of America Conference Center
Cleveland, Ohio

For more information, please visit clevelandclinic.org/neuroscience/CME.
Neurological Institute Select Clinical Trials

The Neurological Institute prioritizes offering new research developments and clinical therapeutic trials to patients with neurological problems. We have more than 175 clinical research trials currently under way, with supported funding of more than $13 million. For more information on all of our clinical trials, please call our Neurological Institute Research and Development office at 216.444.3507.

BRAIN TUMOR AND NEO-ONCOLOGY CENTER

**Phase II Trial of Ritonavir/Lopinavir in Patients with Progressive or Recurrent High-Grade Gliomas**

Purpose of the study is to evaluate the safety and efficacy of Ritonavir/Lopinavir in this patient population.

**Principal Investigator**
David Peereboom, MD

**Contact**
Carol Patton, RN, 216.445.1067

**A Phase II, Multicenter, Exploratory Study Evaluating the Treatment Effect of Surgery Plus GLIADEL Wafer in Patients with Metastatic Brain Cancer**

The primary objective is to evaluate the effect of the surgical intervention and insertion of GLIADEL wafers on the neurocognitive functioning in patients with metastatic brain cancer.

**Principal Investigator**
Michael Vogelbaum, MD, PhD

**Contact**
Cathy Brewer, RN, 216.444.7937

**Clinical Study to Assess Entry of Chemotherapeutic Agents into Brain Metastases in Women with Breast Cancer**

The purpose of the study is to determine the concentration of certain chemotherapeutic drugs in brain metastases from breast cancer.

**Principal Investigator**
David Peereboom, MD

**Contact**
Cathy Brewer, RN, 216.444.7937

CEREBROVASCULAR CENTER

**Carotid Occlusion Study (COSS)**

Study seeking to determine if medical management alone or medical management with added surgery (EC/IC bypass) prevents stroke at two years in patients with symptomatic carotid occlusion and increased oxygen extraction fraction ratio as measured by PET scan.

**Principal Investigator**
Peter A. Rasmussen, MD

**Contact**
Doreen Andrews-Hinders BS, RN, CCRP, 216.445.9243

**Interventional Management of Stroke Trial – (IMS-III)**

A phase III, randomized, multicenter, open label, 900-subject clinical trial that will examine whether a combined intravenous (IV) and intra-arterial (IA) approach to recanalization is superior to standard IV rt-PA (Activase®) alone when initiated within three hours of acute ischemic stroke onset.

**Principal Investigator**
Rishi Gupta, MD

**Contact**
Rebecca Forkapa, RN, 216.445.4488
or Lori Sroznicki, CCRC, 216.445.2641

**The Evaluation of Patients with Acute Hypertension and Intracerebral Hemorrhage with Intravenous Clevidipine Treatment (ACCELERATE)**

To evaluate the efficacy and safety of an intravenous infusion of clevidipine for the treatment of acute hypertension (systolic blood pressure > 160 mmHg) in patients with intracerebral hemorrhage (ICH).

**Principal Investigator**
Gwendolyn Lynch, MD

**Contact**
Rebecca Forkapa, RN, 216.445.4488,
or Lori Sroznicki, CCRC, 216.445.2641

EPILEPSY CENTER

**Responsive Neurostimulator System Pivotal Clinical Investigation**

A double-blinded, multicenter trial to assess the safety and efficacy of the NeuroPace Responsive Neurostimulator System (RNS) for the treatment of seizures that are not adequately controlled by medications.

**Principal Investigator**
Dileep Nair, MD

**Contact**
Diane Davies, 216.444.0173

**A Double-Blind, Placebo-Controlled, Parallel-Group Study of Rufinamide Given as Adjunctive Therapy in Patients with Refractory Partial Seizures**

To evaluate the effect of rufinamide on total partial seizure frequency in adolescent and adult patients (between 12 and 80 years old, inclusive) with refractory partial onset seizures maintained on a maximum of three stable antiepileptic medications.

**Principal Investigator**
Ajay Gupta, MD

**Contact**
Diane Davies, 216.444.0173

**A Multicenter, Double-blind, Historical Control, Randomized Conversion to Monotherapy Study with Keppra XR for Treatment of Partial Onset Seizures**

Study to assess the safety and efficacy of Keppra XR as a long-term anti-epileptic monotherapy. This study will also determine if once daily dosing of Keppra XR is able to help in the treatment of partial onset seizures.

**Principal Investigator**
Nancy Foldvary-Schaefer, DO

**Contact**
Jocelyn Riley, 216.444.8638

CENTER FOR HEADACHE AND PAIN

**A Randomized, Double-blind, Placebo-controlled, Parallel-Group, Phase III Study of MAP0004 in Adult Migraineurs for a Single Migraine Followed by Open-label Extensions to 26/52 Weeks**

Study to determine the safety and efficacy of inhaled DHE for treatment of acute migraine.

**Principal Investigator**
Roderick C. Spears, MD

**Contact**
Mary R. Horvat, 216.445.1947

**A Randomized, Double-blind, Double-dummy, Placebo-controlled, Crossover Study to Evaluate the Efficacy of TREXIMA™ (Sumatriptan + Naproxen Sodium) Versus Butalbital-containing Medications (BCM) for the Acute Treatment of Migraine**

Compared the efficacy of the study drug dose (Trexima) compared with BCM when administered during the moderate to severe pain phase of the migraine.

**Principal Investigator**
Mark Stillman, MD

**Contact**
Mary R. Horvat, 216.445.1947

MELLEN CENTER FOR MULTIPLE SCLEROSIS TREATMENT AND RESEARCH

**CONFIRM**

A multicenter, phase III trial comparing fumarate (BG00012) with Copaxone® and placebo in patients with relapsing-remitting multiple sclerosis.

**Principal Investigator**
Robert Fox, MD

**Contact**
Cynthia Schwanger, 216.445.5788
BRAVO
A multicenter, phase III study comparing laquinimod with Avonex® and placebo in patients with relapsing-remitting multiple sclerosis.

PRINCIPAL INVESTIGATOR
Jeffrey Cohen, MD

CONTACT
Cynthia Schwanger, 216.445.5788

CARE-MS II
A multicenter, phase III study comparing two doses of alemtuzumab (CAMPATH-1h) with Rebif® in patients with relapsing-remitting multiple sclerosis.

PRINCIPAL INVESTIGATOR
Jeffrey Cohen, MD

CONTACT
Vinette Zinkand, 216.444.4817

COMBI-RX
A multicenter study comparing combined Avonex® and Copaxone® with either agent alone in patients with relapsing-remitting multiple sclerosis.

PRINCIPAL INVESTIGATOR
Lael Stone, MD

CONTACT
Vinette Zinkand, 216.444.4817

Atacicept Frequent MRI Study in RMS
A multicenter, phase II study assessing the safety and efficacy of three doses of Atacicept monotherapy in patients with relapsing-remitting multiple sclerosis.

PRINCIPAL INVESTIGATOR
Alexander Rae-Grant, MD

CONTACT
Vinette Zinkand, 216.444.4817

CENTER FOR NEUROLOGICAL RESTORATION

DBS for Obsessive-Compulsive Disorder
Stimulation of the internal capsule for acute management of obsessive-compulsive disorder.

PRINCIPAL INVESTIGATOR
A. David Rothner, MD

CONTACT
Diane Davies, 216.444.0173

DBS for the Minimally Conscious State
Using deep brain stimulation to the intralaminar nuclei for treatment of the minimally conscious state, which may improve the consciousness and responsiveness after severe brain injury.

PRINCIPAL INVESTIGATOR
Ali Rezai, MD

CONTACT
Jenna Stump, 216.444.2673

CENTRAL FOR PEDIATRIC NEUROLOGY AND NEUROSURGERY

A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy, and to Determine the Pharmacokinetics of Two Doses of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Pseudobulbar Affect in Patients with ALS and MS
This study will test the ability of two different doses of AVP-923 to effectively treat pseudobulbar affect in patients with amyotrophic lateral sclerosis or multiple sclerosis.

PRINCIPAL INVESTIGATOR
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SCHUY CENTER FOR COGNITIVE NEUROIMAGING

Cognitive and Functional Brain Changes in Preclinical Huntington’s Disease
Study to examine the sensitivity of fMRI in identifying neural dysfunction in preclinical Huntington’s Disease (HD) participants and to determine the association between DNA-based estimations of disease onset and indices of brain dysfunction over time.

PRINCIPAL INVESTIGATOR
Stephen M. Rao, PhD

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SLEEP DISORDERS CENTER

Portable Monitoring in the Diagnosis and Management of Obstructive Sleep Apnea (OSA)
The “gold standard” for OSA testing and CPAP treatment has been based on overnight tests performed in a sleep laboratory. This study looks at whether OSA testing and CPAP treatment can be based on simpler testing performed in the home.

PRINCIPAL INVESTIGATOR
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DEPARTMENT OF PSYCHIATRY AND PSYCHOLOGY

Mood Disorders Psychopharmacology Unit (MDPU)
Long-term, observational, multicenter patient outcome registry created to collect data from patient care in the Mood Disorders Psychopharmacology Unit for the scientific study of the causes, treatments and illness course for primary mood disorders.

PRINCIPAL INVESTIGATOR
David Muzina, MD

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Elisa Colangelo, 216.445.7168

Bipolar Disorder in Pregnancy and Postpartum Period: Predictors of Morbidity
Prospective study to delineate the clinical, psychosocial and pharmacologic predictors of BPD recurrence during pregnancy.

PRINCIPAL INVESTIGATOR
Adele Viguera, MD

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Neurophysiology of Bipolar Depression
Study to determine functional and neurochemical changes in the ALN of patients with bipolar depression.

PRINCIPAL INVESTIGATOR
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P-15 Bone Putty in Anterior Cervical Fusion with Instrumentation Investigational Plan
An assessment of effectiveness of P-15 bone putty in cervical fusion surgical procedures.

PRINCIPAL INVESTIGATOR
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Cleveland Clinic’s Neurological Institute is a multidisciplinary team of specialists offering innovative technology for diagnosis and treatment of all neurological conditions affecting adult and pediatric patients. Because of our clinical expertise, academic achievement and innovative research, the Neurological Institute has earned an international reputation for excellence.

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The Neurological Institute is one of 26 institutes at Cleveland Clinic that group multiple specialties together to provide collaborative, patient-centered care. The institute is a leader in treating the most complex neurological disorders, advancing innovations such as deep brain stimulation, epilepsy surgery, stereotactic spine radiosurgery and blood-brain barrier disruption. Annually, our staff of more than 200 specialists serves 140,000 patients and performs 6,000 surgeries. Cleveland Clinic is a nonprofit multispecialty academic medical center, consistently ranked among the top hospitals in America by U.S. News & World Report. Founded in 1921, it is dedicated to providing quality specialized care and includes an outpatient clinic, a hospital with more than 1,000 staffed beds, an education institute and a research institute.

OUTCOMES DATA AVAILABLE

The latest outcomes data from Cleveland Clinic’s Neurological Institute are now available. Charts, graphs and tables illustrate the scope and volume of procedures performed in our institute each year. To view the outcomes books for the Neurological Institute and many other Cleveland Clinic institutes, visit clevelandclinic.org/quality/outcomes.

Cleveland Clinic’s neurology and neurosurgery programs were ranked sixth in the nation, according to U.S. News & World Report’s annual best hospitals survey.
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HOW TO REFER

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This fall, Cleveland Clinic is introducing the future of healthcare with the opening of the Sydell and Arnold Miller Family Pavilion and the Glickman Tower.

These buildings, which represent the largest construction and philanthropy project in Cleveland Clinic history, embody the pioneering spirit and commitment to quality that define Cleveland Clinic. These structures are a tangible expression of institutes, our new model of care that organizes patient services by organ and disease.

At 1 million square feet, the Miller Family Pavilion is the country's largest single-use facility for heart and vascular care. The 12-story Glickman Tower, new home to the Glickman Urological & Kidney Institute, is the tallest building on Cleveland Clinic's main campus. Both will help us improve patient experience by increasing our capacity and by consolidating services, so patients can stay in one location for their care.

With 278 private patient rooms, more than 90 ICU beds and a combined total of nearly 200 exam rooms and more than 90 procedure rooms, patients will have faster access to Cleveland Clinic cardiac and urological services.

For details, including a virtual tour, please visit meetthebuildings.com.