Cleveland Clinic

Neuroscience

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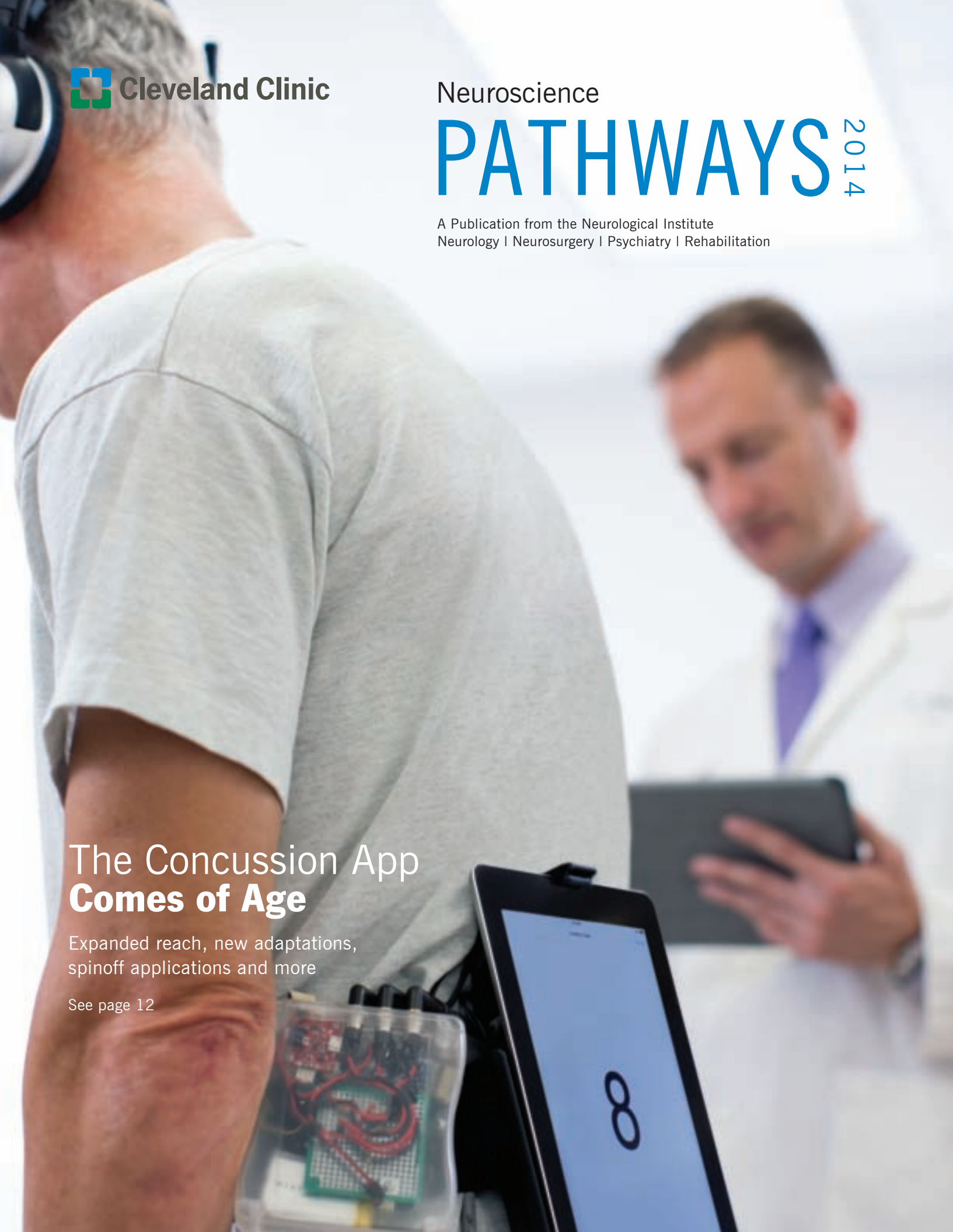

The Concussion App **Comes of Age**

Expanded reach, new adaptations, spinoff applications and more

See page 12

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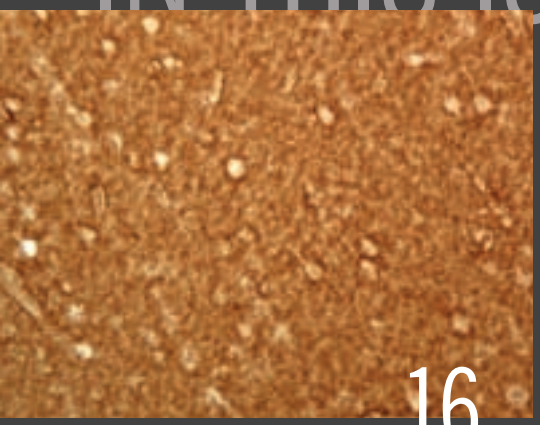

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ON THE COVER: Jay Alberts, PhD, performs motor and cognitive assessments on a patient with Parkinson disease using an adaptation of the Cleveland Clinic Concussion App. See pp. 12-15.

DEAR COLLEAGUES,

Cleveland Clinic is committed to the neurosciences at the highest level. Our goal is to transform patient care and research models for neuroscience-based diseases. Cleveland Clinic CEO and President Toby Cosgrove, MD, has declared: "The brain is the final frontier. We intend to do for the brain what we did 30 years ago for the heart."

The Neurological Institute is realizing this vision through comprehensive, coordinated, multidisciplinary efforts across four major fronts, and this issue of *Neuroscience Pathways* offers focused reports on progress in each area.

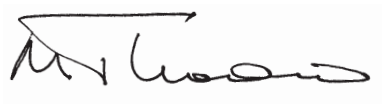
Systems and processes. The Neurological Institute has recently directed enormous energy toward ensuring that all our patients get the right care at the right place and right time from the right providers — both to enhance patient experience and to optimize healthcare value. Central to these efforts have been our robust program of care paths for over two dozen neurologic conditions (profiled on p. 44) and the strategic development of a suite of healthcare apps for a range of neurologic conditions, as discussed in our cover story (p. 12). Additional process-based care solutions are proliferating across the institute, like the successful application of the novel 6 Clicks tool in the Department of PM&R (p. 38).

Clinical trials and translational research. Research studies are at the heart of all academic centers' efforts toward biomedical progress, and examples abound here. I especially recommend checking out the article on p. 5 detailing Cleveland Clinic's launch of the Lou Ruvo Center for Brain Health Biobank. This initiative promises to make important contributions to collaborative biobanking efforts at the global level while providing rapid access to well-characterized biospecimens for the Lou Ruvo Center's expansive clinical trials program in neurodegenerative diseases.

Characterization of patients for predictive analytics. Predictive analytics are one of the goals of our institute's care path and mobile app initiatives. As more care paths are integrated into the EMR, they will produce the continuous data streams needed to enable predictive analytics, which will ultimately allow us to manage patients in a much more individualized way. The quest for predictive analytics is likewise a key objective driving our strategic "Orchard of Neurological Apps" approach to healthcare app development, as detailed in the cover story on the evolution of the Cleveland Clinic Concussion App.

Innovative therapeutic approaches. Finally, our institute's clinicians and researchers are keenly focused on pioneering and refining techniques and treatment strategies that are less invasive and more efficacious than yesterday's approaches. Take our new Minimally Invasive Cranial Base and Pituitary Surgery Program (p. 7), which is using endoscopy to perform complex skull base procedures with far less morbidity. Or consider our leading-edge application of stereoelectroencephalography to perfect the planning of surgical resection in pediatric patients with refractory epilepsy (p. 36).

Progress in meeting the challenges of brain diseases involves both standardizing care around today's best evidence and relentlessly and strategically pursuing tomorrow's breakthroughs. At the Neurological Institute, we're on both of those tasks. We're proud to share the following progress reports, and we welcome your collaboration on the work ahead.



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Circulating Astrocytic Protein S100B May Indicate Blood-Brain Barrier Disruption Due to Childhood Emotional Trauma

By Tatiana Falcone, MD

The glial cell protein S100B is a validated, reliable biomarker of blood-brain barrier (BBB) disruption and brain injury.[1] In Europe, emergency departments are using a serum test for S100B to assess the severity of head injuries.

At Cleveland Clinic's Neurological Institute, we have found evidence that S100B could be useful as a biomarker for BBB breakdown triggered by childhood trauma and abuse. If further validated, a serum test for S100B might become a clinical tool to assess the severity of emotional injury and the need for intervention.

Childhood Trauma Affects Adult Health

Severe trauma during childhood has been linked to long-term mental health and social problems. The large, longitudinal Adverse Childhood Experiences study drew on questionnaires completed by more than 17,000 adult HMO patients to seek links between childhood trauma and adult health. Reports from the study found that early traumatic life events — including childhood abuse (emotional, physical and sexual) and exposure to substance abuse, mental illness, domestic violence and other adverse experiences — were strongly associated with suicidality, alcoholism, depressive disorders, illicit drug use and chronic medical diseases in adulthood.[2-5]

Similarly, children exposed to trauma in the first eight years of life have been shown to have a higher risk of developing mood disorders, psychotic disorders and post-traumatic stress disorder (PTSD) compared with children not exposed to trauma.[6,7] Numerous studies have found associations between childhood maltreatment and other forms of trauma and subsequent alterations in brain development, particularly of the hippocampus and frontal cortex.[8,9]

Emotional trauma appears to be linked to neurobiological consequences (Figure), although the pathophysiologic mechanisms are not fully understood. Studies show that stress can activate an inflammatory response and impair BBB function. We and others[10,11] have hypothesized that severe emotional trauma sets off a peripheral inflammatory response, leading to cytokine production, glial cell activation and BBB breakdown. These changes could potentially alter brain structure, cognition and behavior.

S100B: The 'CRP of the Brain'

As a potential biomarker of CNS injury, S100B has been described as "the CRP (C-reactive protein) of the brain."[12] It is an astrocytic protein that can leak into the blood circulation when the BBB is breached. Elevated serum levels of S100B are not specific but have been associated with schizophrenia, bipolar disorder, depression, Alzheimer disease and epilepsy (in addition to traumatic brain injury).

Our group first examined S100B as a potential biomarker of BBB function in suicidal adolescents with major depressive disorder and acute psychosis.[13] A subscale of the Brief Psychiatric Rating Scale for Children (BPRS-C) quantified suicidality. Mean S100B values were as follows:

- 0.152 ± 0.020 ng/mL in children with low suicidality (BPRS-C subscores 1 to 4)
- 0.354 ± 0.044 ng/mL in children with high suicidality (BPRS-C subscores 5 to 7)

Compared with healthy controls, suicidal adolescents had significantly higher serum S100B levels ($P < .05$), independent of psychiatric diagnosis.

Can Emotional Trauma Alter the BBB?

Recently, we used serum S100B as a biomarker to investigate whether childhood emotional trauma can alter the BBB.[14] Our study population included 88 psychiatric inpatients ages 12 to 18 (64 with psychosis and 24 with mood disorders) and 20 healthy adolescent controls. A detailed psychiatric history and the Life Events Checklist (LEC) documented risk factors for childhood trauma, characterized as three types:

- Early-onset (age < 8 years)
- Chronic (persisting for > 6 months)
- Severe (LEC score > 20)

The LEC assesses exposure to sexual abuse or other unwanted sexual experience, natural disasters, emotional neglect, death in family, fire, explosion, serious accident, toxic substance, physical assault, assault with a weapon, combat, captivity, life-threatening illness, severe human suffering, violent death and serious injury.

We also collected blood samples for S100B analysis. The inpatients with childhood trauma showed increased S100B blood levels, independent of psychiatric diagnosis, compared with controls and inpatients with no trauma history. Among the 30 inpatients without childhood trauma, the mean LEC score was 3.6 and mean S100B level was 0.150 ng/mL. The 58 adolescents who experienced childhood trauma had a mean LEC score of 11.71 ($P < .0001$) and mean S100B level of 0.320 ng/mL ($P = .001$).

All trauma types — early, chronic and severe — were associated with increased S100B levels. Mean S100B levels showed a graded effect:

- One type, ≈ 0.2 ng/mL
- Two types, > 0.3 ng/mL
- Three types, ≈ 0.5 ng/mL

The healthy controls and inpatients without trauma exposure had mean S100B levels < 0.2 ng/mL. We concluded that a history of

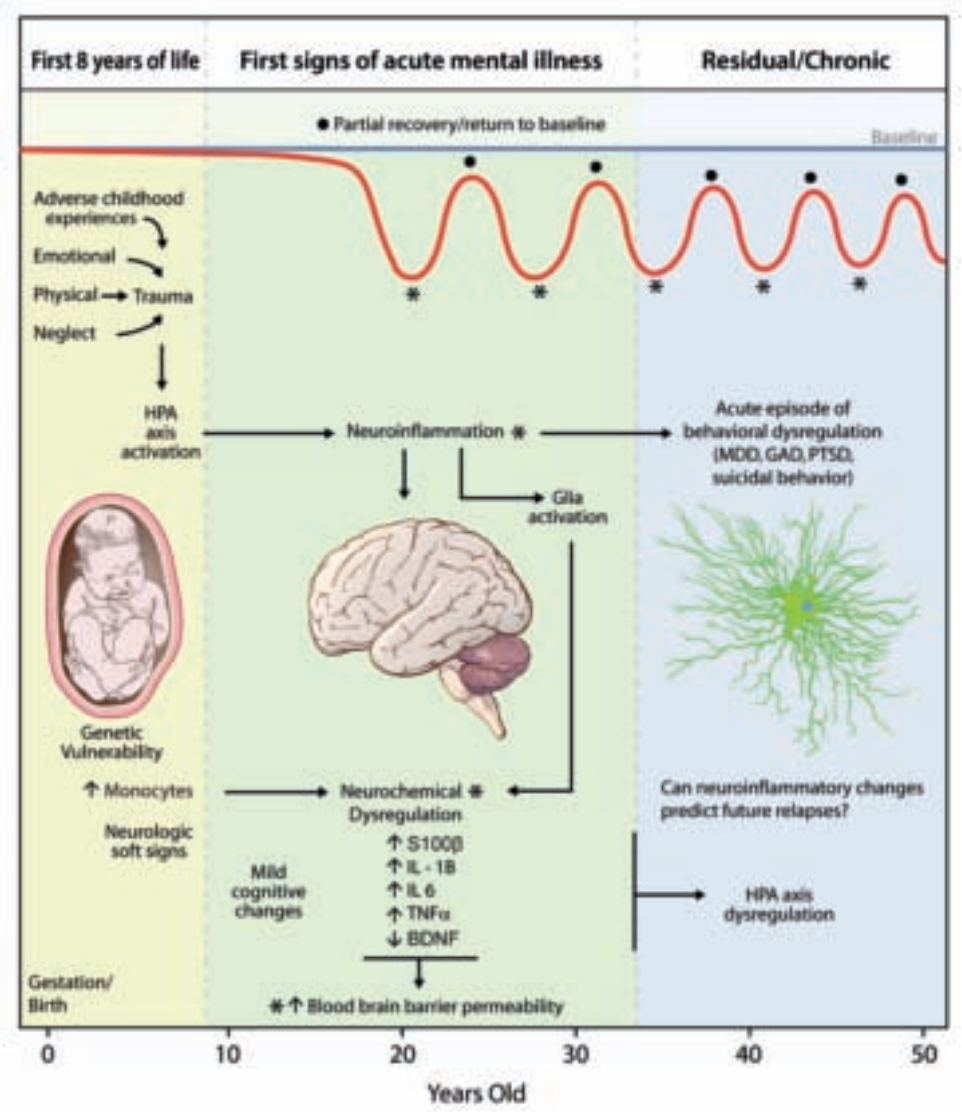

Figure. *Schematic showing emotional trauma as a trigger for mental illness. During the first eight years of life, the impact of emotional trauma can trigger hypothalamic-pituitary-adrenal (HPA) axis dysregulation and increased inflammatory response (elevated monocytes). Monocytes can cross the blood-brain barrier (BBB). A more recent hypothesis suggests brain injury is caused by BBB disruption, leading to an influx of monocytes into the CNS. Activated monocytes can trigger neuroinflammation in glial cells and perpetuate cytokine and S100B production. Each traumatic episode triggers the inflammatory response and alters the BBB. When traumatic episodes occur early in life, they can alter brain development. Patients begin experiencing cognitive dysfunction, emotional lability and memory problems, probably related to increased BBB permeability.*

Our study, along with others, suggests that emotional trauma can cause long-term changes to the brain, possibly by way of an inflammatory response.

childhood emotional trauma may be associated with BBB impairment in adolescent psychiatric patients.

Inflammatory Response May Be Damage Mechanism

This study, along with others, suggests that emotional trauma can cause long-term changes to the brain, possibly by way of an inflammatory response. The next step may be to use neuroimaging to compare levels of inflammatory markers with structural changes in the hippocampus or frontal lobe.

Of course, the most exciting potentiality would be to change the trajectory of a brain trauma so that intervention with medication or psychotherapy could prevent depression, psychosis or PTSD from developing.

ACKNOWLEDGMENTS

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KEY POINTS

- An investigative team including Cleveland Clinic researchers is studying the protein S100B as a biomarker for blood-brain barrier disruption related to childhood emotional trauma.
- Blood levels of S100B are increased in adolescents exposed to emotional trauma as children, whether exposure was chronic, severe or early (before age 8).
- Mean S100B levels show a graded effect; adolescents exposed to two or three of the three trauma types (chronic, severe or early) have higher S100B levels than those with less trauma exposure.

New Biorepository Aims to Speed Access to Well-Characterized Biospecimens — and Accelerate Brain Health Research

By James B. Leverenz, MD, and Lynn M. Bekris, PhD

With stark increases in the prevalence of Alzheimer disease (AD) and other age-associated neurodegenerative disorders projected over the coming decades, more tools than ever are needed to accelerate research to combat these devastating conditions. Cleveland Clinic has augmented its efforts in this area by establishing a biorepository, the Lou Ruvo Center for Brain Health Biobank (CBH Biobank), earlier this year. By adding a major biorepository to the neurodegenerative research community, our efforts will make more critical biospecimens available for the collaborative work needed to turn the tide on aging-associated brain diseases.

Biobanking Well Underway

The CBH Biobank is housed in Cleveland Clinic's Genomic Medicine Institute and is supplied with biospecimens from the recruitment efforts of clinicians across the Neurological Institute. The specimens include biofluids (blood plasma and serum, urine, saliva, cerebrospinal fluid) as well as tissue samples (skin biopsies from live subjects and, eventually, brain tissue at autopsy). Ready access to such specimens is critical for translating basic science findings into better understanding of brain diseases and the development of biomarkers for use in diagnosis and treatment.

Specimen collection has begun in earnest and includes samples from patients diagnosed with neurological disorders and their family members as well as from healthy, cognitively normal individuals who want to support research on neurodegenerative disease.

All About Characterization

Sample collection is accompanied by highly detailed characterization of the donor's demographics, medical history, and clinical signs and symptoms. The result is a capacity to later match specimens to highly specific requests from investigators (e.g., plasma samples from AD patients under age 70 without a history of stroke).

Once collected, specimens are processed (Figure) by CBH Biobank staff in the following ways:

- Donors' de-identified clinical information is entered in a large database and linked to individual specimens for future referencing by researchers
- Whole blood is collected and processed into plasma and serum as well as other components such as DNA, RNA, proteins or cells such as leukocytes or lymphoblasts
- Cerebrospinal fluid is collected, aliquoted and placed in long-term storage
- Fibroblasts from skin biopsies can be grown into induced pluripotent stem cells and ultimately into neuronal cells or other cell types that can be used for research purposes
- Specimens are placed in long-term storage for later rapid access by investigators as needed

A Boon to Biomarker Research

Rapidity of access to well-characterized specimens is a key impetus and benefit, as the CBH Biobank will greatly accelerate the speed at which investigators can obtain materials for use and proceed with their studies. It also can bolster their prospects for attracting research funding.

The research that stands to benefit most includes work to identify new biomarkers, which loom particularly large in neurodegenerative disease, where symptom response to treatment often lags. For instance, whereas it can take months to years to detect a treatment response in an AD treatment trial, a biomarker could potentially reveal a treatment response within weeks to months, expediting the search for new therapies. As biomarkers become central components of more and more clinical trials, their importance will only grow.

The ability to store biospecimens indefinitely provides further benefit, as having readily available specimens has repeatedly proven useful in exploring new ideas.

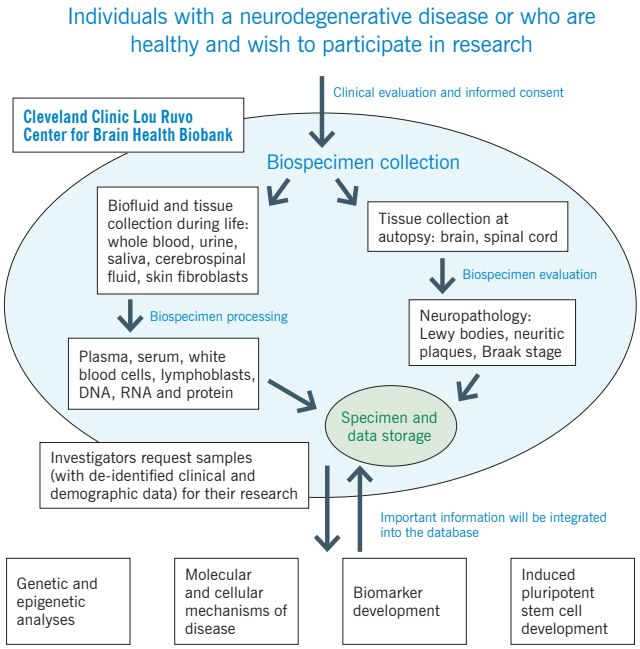
Drs. Bekris (left) and Leverenz examine a CBH Biobank specimen.

A Neurodegenerative Focus — and More

While the CBH Biobank will store specimens relating to virtually any disease of the nervous system, primary initial areas of focus include the following:

- AD, for which the Lou Ruvo Center operates one of the nation's largest clinical trial programs, which stands to benefit substantially from increased biospecimen access
- Parkinson disease, for which our efforts include work with Cleveland Clinic's Center for Neurological Restoration and the Michael J. Fox Foundation to discover new biomarkers and better understand the importance of genetics in this movement disorder

Figure. *Schematic of the CBH Biobank's operating process.*



› Normal aging, for which we are undertaking active community outreach in the perpetual challenge to recruit a steady supply of healthy volunteers to advance brain health research

Additional priorities include amyotrophic lateral sclerosis, frontotemporal dementia and normal pressure hydrocephalus. Moreover, we are actively exploring opportunities to study biomarkers for other neurological disorders, such as traumatic brain injury, underscoring the CBH Biobank's utility beyond neurodegenerative conditions.

We also intend to build on Cleveland Clinic's long-standing leadership in neuroinflammation research — much of it coming out of our Mellen Center for Multiple Sclerosis Treatment and Research — by facilitating swifter translation of key basic science findings to biomarker research. Work to that effect is now underway through recent Alzheimer's Association grants to study neuroinflammatory markers in blood and spinal fluid.

It Takes a Village

The CBH Biobank stands to yield benefits beyond Cleveland Clinic's neurological research enterprise or even the community of fellow investigators in our region. As more and more genetic studies require large sample sizes well beyond the capacity of any single center, multicenter collaboration is increasingly the rule — and the more contributors, the better. The addition of Cleveland Clinic's CBH Biobank to the community of major brain disease biorepositories will make more specimens available for pooling and sharing, further accelerating the quest for breakthrough advances.

We currently have collaborations in place for sharing materials with the Parkinson disease biorepository at the University of Washington, which one of us (J.B.L.) helped establish. We will be leveraging that experience to forge additional collaborations for specimen pooling with other neurodegenerative disease biorepositories around the nation and the world. We believe several factors make the CBH Biobank an especially compelling partner for such collaborations:

› The large and highly diverse population managed across Cleveland Clinic's integrated health system, which includes patients from around the world
› The Lou Ruvo Center's multisite clinical trial program in three diverse U.S. regions (Cleveland; Las Vegas; and Weston, Florida), providing superior representation of the U.S. population as a whole
› Cleveland Clinic's well-established leadership in neuroinflammation research

Cleveland Clinic is excited to be an active part of biobanking efforts in neurodegenerative and aging-related brain disease. We look forward to opportunities to collaborate with colleagues running similar efforts elsewhere.

Dr. Leverenz is Director of the Cleveland Lou Ruvo Center for Brain Health and Director of the CBH Biobank. He holds the Dr. Joseph Hahn Endowed Chair of the Neurological Institute. He can be reached at leverej@ccf.org or 216.636.4044.

Dr. Bekris is an investigator in Cleveland Clinic's Genomic Medicine Institute and Associate Director of the CBH Biobank. She can be reached at bekrisl@ccf.org or 216.444.0111.

KEY POINTS

••• Cleveland Clinic has established the Lou Ruvo Center for Brain Health Biobank (CBH Biobank) to make well-characterized biospecimens rapidly available for use in research on neurodegenerative and aging-associated brain diseases.

••• Alzheimer disease, Parkinson disease, normal aging and neuroinflammation are among priority focus areas of the CBH Biobank's collection and storage efforts, which aim to promote identification of novel biomarkers.

••• The CBH Biobank promises to make important contributions to collaborative biobanking efforts in view of its large and diverse underlying patient population and Cleveland Clinic's neuroinflammation research expertise.

Yesterday's Tag Team Is Today's Dance: The Case for Minimally Invasive Endoscopic Cranial Base Surgery

By Pablo Recinos, MD, and Raj Sindwani, MD

Minimally invasive endoscopic cranial base surgery is now a reality at Cleveland Clinic, with the recent establishment of our multidisciplinary Minimally Invasive Cranial Base and Pituitary Surgery Program. By accessing the brain and pituitary gland endoscopically through the nasal passages, our surgeons now can effectively perform complex procedures with far less morbidity.

Beyond Craniotomy: Endoscopy Curbs Morbidity

The cranial base contains a large number of critical structures (e.g., cranial nerves, carotid arteries, basilar artery) in a small area. The proximity of these structures means that tumors involving the cranial base are among the most difficult tumors to access. A basic tenet of skull base surgery has been to create bony corridors in order to gain access to the target region and thereby minimize disruption of the overlying brain. Traditional approaches to the cranial base have involved large external incisions and craniotomies. More recently, endoscopic approaches via the nasal corridor have been used to access the cranial base (Figure 1, next page), further minimizing the morbidity associated with these surgeries.

From a Tag Team to a Dance

Use of the endoscope in cranial base applications began with removal of pituitary tumors. Until recently, standard pituitary approaches were typically performed by an otolaryngologist using a sublabial or transnasal approach. Once the sella turcica (the region where the pituitary gland sits) was exposed, a metal retractor would be inserted. A neurosurgeon would then introduce the operating microscope and perform the tumor resection, after which the otolaryngologist would close the remaining defect. Visualization in these approaches was limited to the narrow corridor provided by the metal retractor, since the light source (the microscope) was outside the nose.

Recent years have seen increasing use of the endoscope instead of the operating microscope in pituitary surgery. With the tip of the endoscope serving as the light source, visualization of significantly larger areas has become possible, including the ability to look around previously unviewable corners.

An important distinction of endoscopic surgery is that it requires the otolaryngologic surgeon and the neurosurgeon to work simultaneously, as opposed to the sequential "tag team" approach used in traditional endonasal surgery. This "two surgeons, four hands" simultaneous approach allows us to tackle a wide array of complex cranial base conditions, but its success requires a shared philosophy and understanding between the two surgeons. We like to call this partnership "the dance," as the two surgeons must perform their respective roles without stepping on each other's toes.

Concurrent Advances in Imaging and Tissue Reconstruction

Together with successful integration of the endoscope in pituitary surgery, advances in imaging technology and reconstructive techniques have expanded endoscopic techniques to significantly more complex cranial base locations. Specifically, high-resolution MRI and CT are used for intraoperative neuronavigation, which allows precise intraoperative localization similar to the way that GPS technology provides precise location information to a driver navigating a city. With the information from neuronavigation, more precise routes can be made to the target area, and critical structures are more easily identified and avoided. The result is a safer surgery.

Additionally, experience from open cranial base surgery has made clear that repair of large defects is critical to minimizing complications from the surgery. The use of vascularized tissue for repair has been the gold standard in cranial base surgery. Advances in reconstructive techniques using intranasal vascularized flaps have made repair of large cranial base defects possible even while the surgical team works through a purely endonasal corridor (Figure 2, p. 9).

Applications and Advantages

Endoscopic approaches are now used to treat a wide array of pathologies, such as chordomas, chondrosarcomas, craniopharyngiomas, meningiomas, schwannomas and sinonasal cancers.

Endoscopic approaches offer a number of significant advantages over traditional open approaches for these problems. These include:

- Avoidance of skin incisions, large craniotomies and, importantly, brain retraction
- Less postoperative pain, no scars, fewer days in the hospital and an easier recovery for the patient
- Advantages to the healthcare system, including use of fewer resources, shorter or no ICU stays, and shorter hospital stays

The Multidisciplinary Imperative

Establishment of Cleveland Clinic's Minimally Invasive Cranial Base and Pituitary Surgery Program has been a highly multidisciplinary undertaking. In addition to our subspecialty-trained skull base neurosurgeons and rhinologists, the program draws on the essential expertise of pituitary endocrinologists, neuro-ophthalmologists, neuroradiologists, neuro-oncologists and radiation oncologists. The aim has been to align this expertise in a single program to provide a streamlined experience for patients with a range of cranial base pathologies.

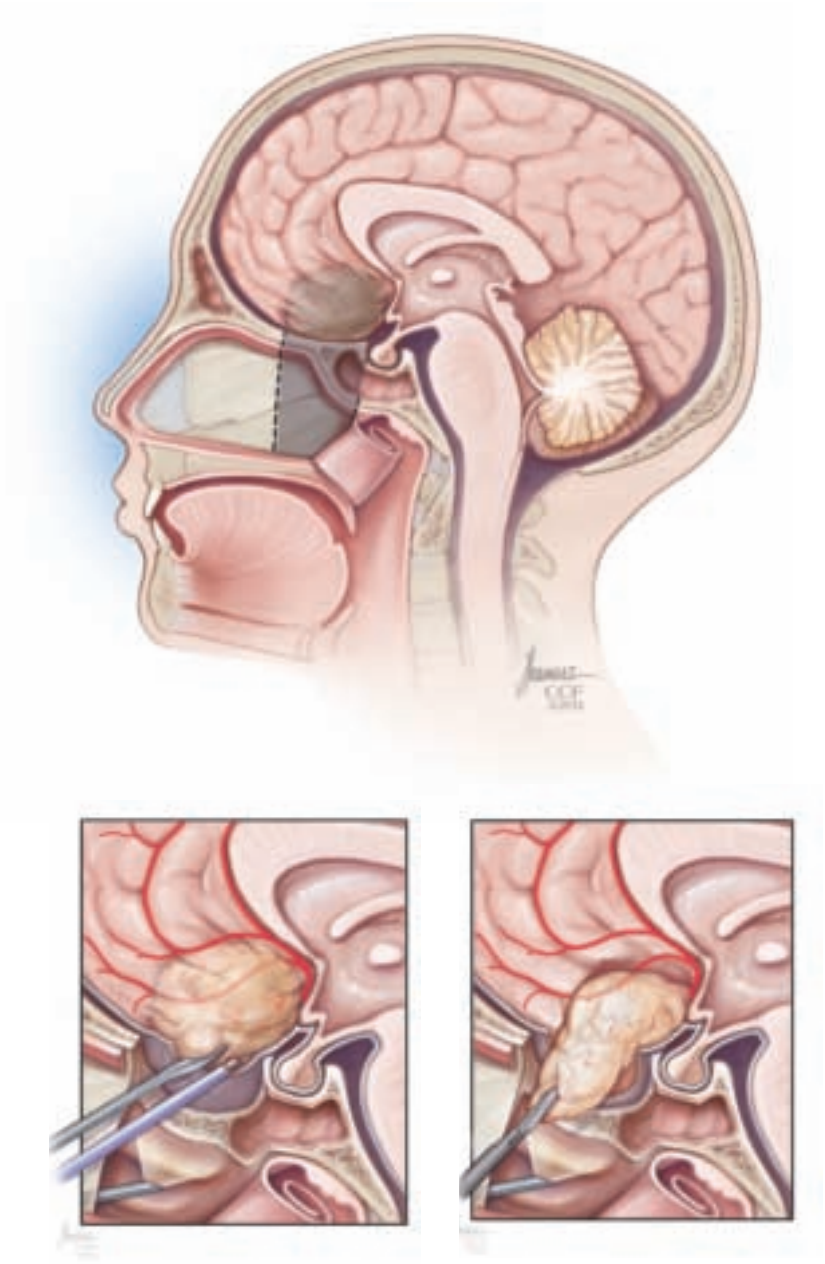
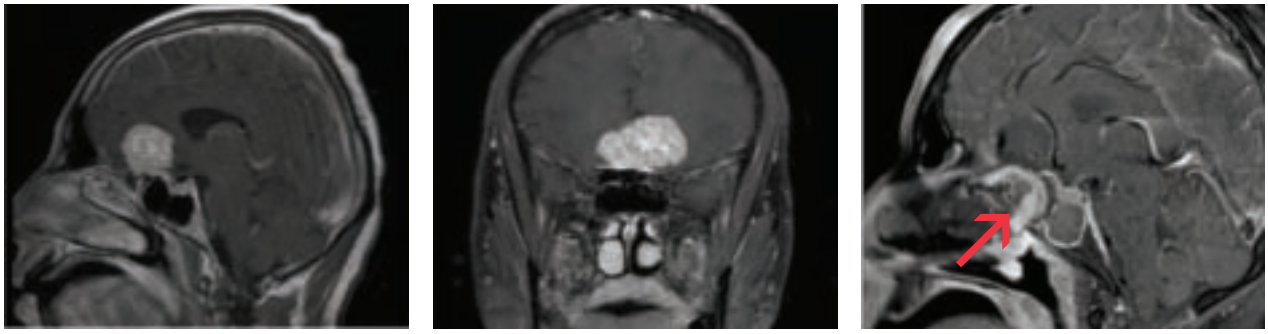


Figure 1. *Illustration of an endoscopic endonasal resection of a planum sphenoidale meningioma.* ***(Top)*** *Sagittal view demonstrating the relationship among the tumor, the cranial base, the nose and the frontal lobes that have been displaced by the tumor. Accessing the tumor requires removal of the bone from the anterior cranial base (darkened corridor) and elevation of a vascularized flap of tissue from the nasal mucosa for subsequent reconstruction.* ***(Bottom left)*** *By accessing the tumor through a nasal corridor and initially removing the portion at the cranial base, the surgeons are able to remove the arteries that feed the tumor first, making tumor debulking safer and minimizing blood loss.* ***(Bottom right)*** *With the tumor adequately debulked, the lining of the tumor is removed without disrupting the surrounding brain and while preserving the anterior cerebral arteries, reducing patient morbidity.*

Figure 2. *(Left and middle) T1-weighted MRIs showing a large anterior skull base meningioma that our surgical team resected completely via an endoscopic approach. Reconstruction of the large cranial base defect was performed with a pedicled nasoseptal flap. (Right) Postoperative MRI showing complete removal of the tumor and the presence of the nasoseptal flap (arrow).*



This specialized clinical know-how is complemented by a leading-edge operating theater equipped with the most advanced equipment. In addition to the neuronavigation system, the program's OR includes endoscopic ultrasound devices, specialty microdebriders and drills, and a large array of newly designed sinus and skull base instruments adapted for complex endoscopic cranial base and pituitary procedures.

Although not all cranial base conditions can or should be treated endoscopically, our experience is revealing that expertise in endoscopic approaches is an essential component of truly comprehensive care for cranial base problems.

Dr. Recinos is Section Head of Skull Base Surgery in the Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center in Cleveland Clinic's Neurological Institute. He is also Co-Director of the Minimally Invasive Cranial Base and Pituitary Surgery Program. He can be reached at recinop@ccf.org or 216.445.2901.

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KEY POINTS

- Cleveland Clinic recently established a Minimally Invasive Cranial Base and Pituitary Surgery Program to facilitate endoscopic approaches to complex cranial base conditions. These approaches rely on simultaneous, highly coordinated operative work by a neurosurgeon and an otolaryngologic surgeon.
- Advantages of endoscopic approaches over traditional open surgery for cranial base tumors and related pathologies include avoidance of skin incisions, large craniotomies and brain retraction, as well as less postoperative pain, easier recovery, and shorter hospital and ICU stays.
- In addition to recent advances in endoscopic technology, intraoperative neuronavigation capabilities and advances in reconstructive techniques using intranasal vascularized flaps have made these minimally invasive approaches to cranial base surgery a reality.

Even in a High-Acuity Neurological ICU, Quality Initiatives Can Drive Down Hospital-Acquired Infections

By Edward M. Manno, MD, FCCM, FAHA, FAAN, FANA

No one disputes that high patient acuity raises the risk of hospital-acquired infections, but that reality doesn't lessen the stakes or gravity of such an infection when it develops in an individual patient.

With that mindset, the staff of Cleveland Clinic's Neurological Intensive Care Unit (Neuro ICU) recently undertook initiatives to reduce the unit's hospital-acquired infection rates — despite caring for patients from a neurological referral base that University HealthSystem Consortium (UHC) data show to be the sickest in the country. This article profiles those efforts and shares results in achieving infection rate improvements in the face of high acuity.

The Neuro ICU at a Glance

Cleveland Clinic's Neuro ICU is a 21-bed critical care unit staffed by nurse practitioners, critical care fellows, and neurology and neurosurgery residents who provide continual hands-on treatment of patients with acute neurologic injury. This team is managed and supervised by eight neurocritical care physicians who staff the Neuro ICU on a 24/7 basis. The unit has achieved the lowest odds-adjusted mortality in the nation, according to UHC data.

Hospital-Acquired Infections: The Nature of the Challenge

The acuity of our Neuro ICU population requires multiple invasive procedures, which put patients at risk for developing hospital-acquired infections. Some 1.7 million hospital-acquired infections develop each year in the U.S., accounting for nearly 100,000 deaths annually, according to Centers for Disease Control and Prevention estimates. In the ICU setting, the most commonly acquired infections are catheter-acquired urinary tract infections (CAUTIs), central line-associated bloodstream infections (CLABSIs) and ventilator-associated pneumonias.

Due to the acuity of our patients, the Neuro ICU's hospital-acquired infection rates were initially above national averages. The unit's staff decided to undertake an aggressive effort to improve these rates through a multidisciplinary approach involving physicians, nurses and all auxiliary personnel involved in the Neuro ICU.

Our first step was to develop teams — dubbed "tackle teams" — to address each of the three major types of acquired infections. Each team consisted of a staff physician, a nurse practitioner or fellow, nurses, and nursing leadership; one or more team members were present around the clock to address issues relevant to the team's designated infection type. The teams identified sources of past problems in the unit's population and developed an action plan for the education of staff regarding these sources and best practices for avoiding them in the future.

CLABSIs: New Practices and Results

The CLABSI team determined that most of our CLABSIs were occurring nine to 12 days after placement of the central line. We instituted a policy that all central lines are to be placed under maximal sterile barrier precautions and changed if still required after one week of use. Femoral access is permitted only in emergency situations and is changed to a less infection-prone site as soon as the patient is stable. Dressing sites are inspected daily by both nurses and physicians, and dressings are now changed at least weekly — and more often as indicated based on these inspections. To avoid unnecessary placement of central lines, the nursing staff obtained a "vein finder" machine that helps identify peripheral veins.

These measures were associated with a dramatic decrease in the incidence of CLABSIs in our Neuro ICU throughout 2013, including no new CLABSIs at all in the second half of the year (Figure 1).

CAUTIs: New Practices and Results

The prospect of reducing our CAUTI rate was particularly challenging because most of our patients are significantly debilitated and require long-term Foley catheter placement. Curbing these infections depended entirely on developing a culture change around how we address this issue.

The nursing staff was re-educated on both the timing and placement of Foley catheters, with catheters being removed as soon as feasible. Other nursing measures included reducing redundant loops and ensuring that there is no backflow of urine into the bladder when patients are transferred for a study or procedure.

The unit's physicians decided as a group on their definition and culturing protocol for Neuro ICU patients who develop a fever. The protocol specifies that a urine analysis is to be sent first if a urinary tract infection is suspected. Urine cultures are to be ordered only by attending staff and only if the urine analysis is positive and clinical suspicion remains high.

As detailed in Figure 2, the above measures were associated with a reduction in CAUTI incidence throughout 2013 similar to that observed for CLABSIs.

Next Steps and Lessons Learned

We have started similar initiatives in 2014 to reduce ventilator-associated pneumonia rates and hope to achieve similar successes.

Many of our infection prevention measures are being adapted by intensive care units throughout the Cleveland Clinic enterprise.

Figure 1. *Incidence of CLABSIs (per 1,000 patient days of central venous catheter use) in the Neuro ICU by month throughout 2013.*

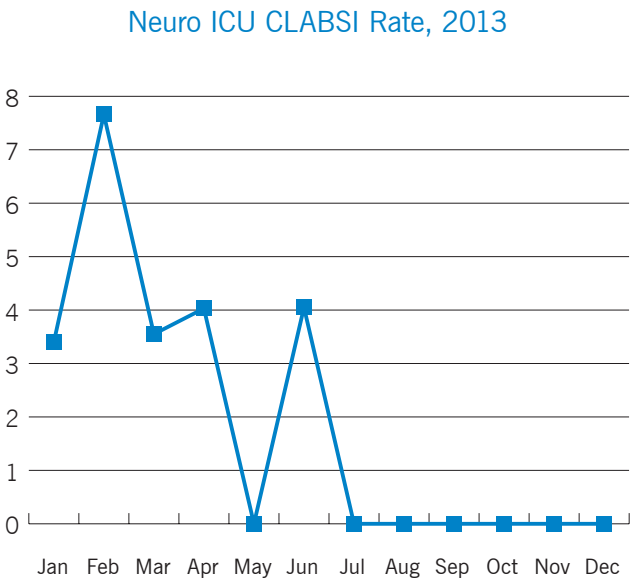
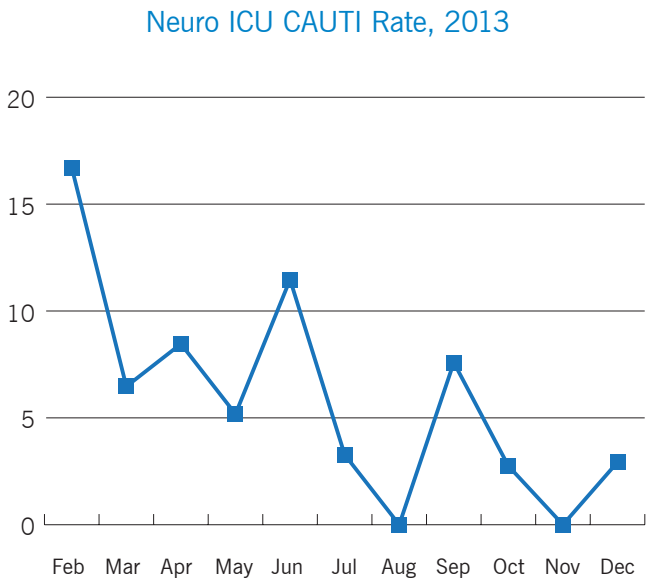


Figure 2. *Incidence of CAUTIs (per 1,000 patient days of Foley catheter use) in the Neuro ICU by month throughout 2013.*



The above initiatives reflect a complete team approach to hospital-acquired infections that complicate and worsen the outcomes of too many patients both locally and across the country. Close attention to the details that lead to these infections and collaborative planning to combat these specific problems have led to a safer environment for our patients.

Our results have not gone unnoticed, and many of our measures are being adapted by intensive care units throughout the Cleveland Clinic enterprise. We also hope to apply our tackle-team model across the entire Cleveland Clinic health system.

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KEY POINTS

- To reduce rates of hospital-acquired infections in Cleveland Clinic's high-acuity Neurological ICU, the unit's staff developed multidisciplinary "tackle teams" for specific infection types to identify infection sources and develop aggressive action plans to avert infections from those sources.
- The teams' efforts were associated with dramatic and enduring reductions in both CLABSIs and CAUTIs in the Neurological ICU throughout 2013. Most notably, no new CLABSIs developed on the unit in the last six months of the year.

COVER STORY

The Concussion App Comes of Age: Expanded Reach, New Adaptations, Spinoff Applications and More

By Jay Alberts, PhD

When it comes to healthcare apps developed for the iPad®, peer-reviewed publication of validation studies is essential. Yet it simply doesn't give an app the reach and opportunity to touch the public imagination that come with being highlighted in Apple's "What will your verse be?" iPad campaign (apple.com/your-verse/concussion-game-plan/) — the ultimate third-party endorsement of the approach behind an app.

We are honored that the Cleveland Clinic Concussion (C3) App achieved both of these distinctions this year. Together they provide further support for a broad, coordinated "Orchard of Neurological Apps" strategy now underway across Cleveland Clinic's Neurological Institute to adapt the C3 App's functionalities for new and enhanced clinical applications to other neurological diseases. This article summarizes this and other recent developments in the C3 App's evolution and the implications for concussion management.

C3 App: A Quick History

The C3 App, which has been profiled in past issues of this publication, utilizes the iPad's gyroscope and accelerometer to collect biomechanical data that are used to objectively quantify postural stability while an individual performs balance tests with the iPad secured at the waist. The C3 App also assesses cognitive function through tasks performed with a stylus on the iPad screen.

Originally developed for concussion assessment in athletes, the app is used for baseline testing and then deployed by athletic trainers, physicians and physical therapists for assessment across the injury spectrum, from injury to return-to-play/return-to-school decisions. The use of a common set of assessment information results in better handoffs between caregivers across disciplines.

In recent months, Cleveland Clinic Concussion Center researchers have published studies validating the C3 App's ability to quantify postural stability as precisely and accurately as gold-standard measures do.[1,2]

Use of the C3 App by high schools and colleges for students playing contact sports has grown substantially since its debut in the 2011-2012 school year (see Table). Use has extended beyond Northeast Ohio to include teams at various universities around the nation, including Texas A&M University, University of Kansas, Colgate University, University of Texas, Harvard University and others.

Table. Use of the C3 App Among Student Athletes Over Time

	2011-2012	2012-2013	2013-2014
Baseline assessments	120	4,921	12,033
Post-injury assessments	35	1,105	1,755

Tale of Two Schools: Raising the Bar While Leveling the Playing Field

The Concussion Center has a particular interest in making the C3 App available to high school athletes in communities that may lack, or have barriers to accessing, providers with experience in managing concussion and the complex return-to-school and return-to-play decisions concussed athletes face.

To that end, we have made the C3 App available, along with portions of the Cleveland Clinic Concussion Care Path, for use in athletes at high schools in the rural town of Rock Valley, Iowa, as well as in inner-city Los Angeles. Although these two student populations differ widely in demographic and socioeconomic status, they face a similar challenge: access. Both groups lack access to providers with specialized concussion experience. Our hope is that the C3 App and the care path (designed to reduce inappropriate and costly variations from evidence-based care) will do the following:

- Improve continuity of concussion care in these communities
- Improve handoffs between providers
- Help educate local providers
- Offer local providers an objective, quantitative and systematic approach for improving patient outcomes

LEFT: Dr. Alberts and doctoral student Sarah Ozinga perform motor and cognitive assessments on a patient with Parkinson disease using an adaptation of the Cleveland Clinic Concussion (C3) App.

We believe sharing these tools to measure outcomes and guide care processes delivers value far beyond what stand-alone consulting can offer, although Cleveland Clinic concussion specialists are available to providers in these communities for consultation as needed.

Further Dissemination — and the Promise of Predictive Modeling

Meanwhile, the Concussion Center is pursuing funding for a project to deploy the C3 App and Concussion Care Path to at least 10 more hospital affiliates around the country to study how these tools' standardized management approach can impact concussion care beyond Cleveland Clinic in terms of objective clinical, quality-of-life and financial outcomes. The resulting demographic and outcomes data should enable us to develop injury prevention models (based on sport, gender, age and other variables) as well as predictive recovery curves.

Figure. *A patient with Parkinson disease undergoes dual-task assessment via a modified version of the C3 App. The patient is using a handheld switch to signal responses to a cognitive challenge presented through headphones while the app simultaneously monitors his postural stability.*

Our ability to transfer these tools to remote settings stems from the fact that the C3 App is integrated into the Concussion Care Path without being reliant on or requiring integration into an institution's given electronic medical record (EMR) system. This is helpful since most caregivers on the playing field do not have access to an EMR system. This independence from the EMR also helped pave the way for the C3 App's recent addition to Apple's business-to-business (B2B) app store to enable its use by interested healthcare organizations.

App Refinements Continue

The third version of the C3 App was released in August, with refinements that improve the user interface and in-app data visualization capabilities.

A key addition is a new "incident report" workflow module that essentially bookends the injury by documenting the timing and essentials of the injury (major symptoms and signs, plus demographics) as well as when the athlete begins the return-to-play process. While these may seem like basic data points, they are not easily collectible via many EMR systems, so integrating their capture into the app itself ensures their systematic collection to allow better understanding of injury severity and how it impacts care, recovery and utilization of services (and thus costs) across large populations. This will prove invaluable to future efforts to develop predictive analytics around return to play and similar issues.

Another refinement is the recent release of a version of the app for the iPhone and iPod Touch, currently in beta testing.

From Playing Field to Battlefield

More dramatic C3 App refinements are now underway thanks to a Department of Defense grant we've received to adapt the app for assessing mild traumatic brain injury (mTBI) in military personnel. This work aims to determine military-based norms in the motor and cognitive functions measured by the app, under the assumption that these norms differ from those among student athletes, given the stress, unpredictable sleep and other factors that military personnel are subject to.

These norms will be developed over six to nine months of study among 300 troops at Marine Corps Base Camp Lejeune in North Carolina. We will then adapt the C3 App for military use, making additions and deletions as needed and leaving behind the technology for use in assessing Marines with mTBI who come through for training.

Taking Testing to the Dual-Task Level

The military studies will also include testing of dual-task paradigms (such as balance plus cognitive tasks) to reflect the reality that military personnel increasingly need to perform demanding cognitive tasks (e.g., visually monitoring data displays or interpreting radio transmissions) while performing taxing physical activities. In these studies, the iPad will monitor subjects' postural stability and other motor/functional measures while subjects use handheld switches to indicate responses to a cognitive task presented visually or via headphones.

We are developing the same type of dual-task testing to monitor and assess deep brain stimulation (DBS) in patients with Parkinson disease (PD) (Figure). This work is prompted by the fact that stimulation in the subthalamic nucleus may compromise the patient's cognitive function. We are aiming to monitor cognitive function and postural stability in patients during DBS to enable adjustment of stimulation parameters to maintain improvements in stability and gait without hindering cognitive function.

Rather than creating one-off healthcare apps resulting in multiple fragmented approaches to care, our aim is to look at mobile apps as modules to be applied across common functional domains for various conditions.

The Orchard vs. the Trees

These efforts to expand and adapt the C3 App's capabilities to assess additional conditions are consistent with the Neurological Institute's emerging Orchard of Neurological Apps initiative to leverage digital health technology and common data elements across a range of neurologic conditions.

Rather than using new digital health technologies to create one-off apps, which results in multiple fragmented approaches to care, our aim is to look at mobile apps as modules to be applied across common functional domains for various conditions (think orchard vs. individual trees). This approach lends itself to pooling of data, when appropriate, to enable aggregation of large data sets to make possible powerful predictive analytics around elements of cognitive and motor functioning.

The Example of Balance

Balance is a prime example. Our aforementioned study validating the C3 App's ability to quantify postural stability in older adults[2] was an essential step toward translating the app's balance component — which we call the Cleveland Clinic Balance App — for use in populations such as patients with PD, stroke, multiple sclerosis and mTBI.

Another highly promising application of the Balance App is for falls prediction and prevention. Patient falls remain a stubbornly common and costly adverse event, and traditional fall-risk questionnaires are notoriously subjective, largely ineffective and lacking in precision. To address this challenge, we are conducting a pilot study in which Cleveland Clinic nurses will use the Balance App to quickly assess hospitalized patients' postural stability to predict risk for falls and eventually guide prevention interventions accordingly. We will compare fall rates and associated costs between inpatients screened with the Balance App and those screened with traditional questionnaires.

We are working with a collaborator at a nursing home in western Pennsylvania to conduct a similar pilot study in the dependent care setting.

From Electronic Notebooks to Data Collection Systems

Examples of similar spinoffs and adaptations of the C3 App apply to Cleveland Clinic's emerging technology-enabled approaches to PD, multiple sclerosis and other conditions. Our goal is to strategically use complementary healthcare apps to transform mobile devices from expensive electronic notebooks into scalable data collection systems. Predictive analytics will follow, which promise to bring improved outcomes, reduced cost and increased value.

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KEY POINTS

- Use of the Cleveland Clinic Concussion App (C3) to guide concussion management in student athletes continues to grow. A study is planned to assess the app's use by 10 or more hospitals around the country with a goal of yielding injury prevention models and predictive recovery curves.
- Under a Department of Defense grant, we are determining motor and cognitive norms among military personnel to adapt the C3 App for use in managing mild traumatic brain injury in military personnel and to assess the app's use in dual-task functional testing.
- Modules of the C3 App are being adapted and applied to functional assessment in additional patient populations in a broad Neurological Institute effort to leverage common data elements to enable powerful predictive analytics for improved healthcare value.

Uncovering Molecular Mechanisms of Epilepsy Progression: Looking Beyond the Lesion to Growth-Associated Protein 43

By Zhong Ying, MD, PhD, and Imad Najm, MD

THIS ARTICLE is excerpted from the authors' article in the July 2014 *Annals of Clinical and Translational Neurology*, which is copyrighted by the authors: Ying Z, Najm I, Nemes A, Pinheiro-Martins AP, Alexopoulos A, Gonzalez-Martinez J, Bingaman W. Growth-associated protein 43 and progressive epilepsy in cortical dysplasia. *Ann Clin Transl Neurol.* 2014;1(7):453-461.

Focal cortical dysplasias (FCDs) are the most common pathologic substrates in both adults and children with pharmacoresistant focal neocortical epilepsy. Postoperative seizure outcome has been less successful in patients with FCDs as compared with patients who have mesial temporal lobe epilepsy due to hippocampal sclerosis (mTLE/HS). Previous studies suggest that the most important predictor of success following epilepsy surgery is complete resection of the epileptic focus. There has been increasing awareness, however, that epileptogenicity in FCDs encompasses a more complex network extending beyond the lesion. Moreover, epilepsy associated with FCDs is a progressive disease with compelling evidence of seizure worsening over time, change of EEG patterns and improved outcomes with early surgical resection.

Focusing on GAP-43

At Cleveland Clinic's Epilepsy Center, we aim to discover the molecular mechanisms that underlie epilepsy progression in FCD. Our translational research has focused on growth-associated protein 43 (GAP-43) as a potential substrate contributing to epileptogenic networks and the progression of epileptogenesis.

GAP-43 has been known as a marker for axonal growth and synaptic plasticity and is maximally expressed during brain development. Once growing axons reach their targets and synaptogenesis is established, GAP-43 levels rapidly decline. Re-expression of GAP-43 in human adult brain occurs during axonal sprouting following stroke, mossy fiber sprouting in sclerotic hippocampi, and axonal regeneration in multiple sclerosis and post-traumatic brain injury lesions.

GAP-43 and Epileptogenicity

We investigated GAP-43 levels using western blot analysis in electrophysiologically defined epileptic vs. nonepileptic brain samples from three patients with FCD-associated intractable epilepsy (using extraoperative recordings from subdural grid electrodes or stereotactically implanted depth electrodes/SEEG). As shown in Figure 1, the epileptic brain samples from all three patients (pathology-confirmed FCD type II lesions) exhibited clear within-patient increases of GAP-43 relative to each patient's corresponding nonepileptic area. The optical densities of GAP-43 bands demonstrated that, in each patient, the epileptic area clearly showed higher gray values compared with the nonepileptic cortex. These findings show that GAP-43 is differentially upregulated in FCD epileptic cortex compared with adjacent nonepileptic cortex within the same patient, indicating that GAP-43 expression may contribute to (and be a potential biomarker of) epileptogenic mechanisms.

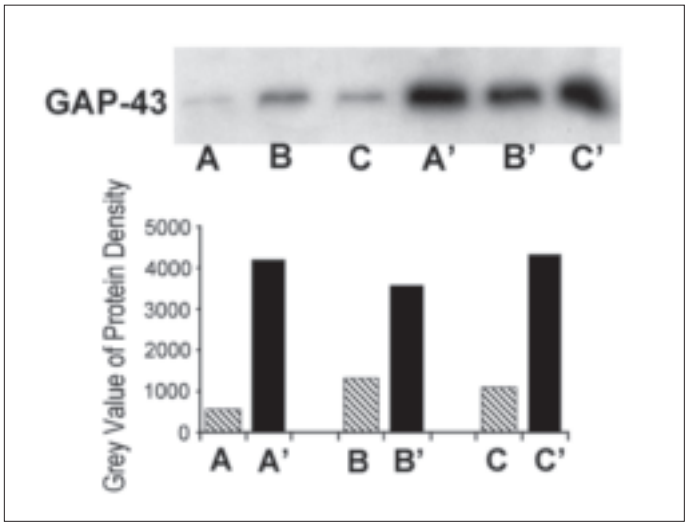

Figure 1. *Western blot analyses of GAP-43 in three patients. Each patient had samples taken from subdural grid-characterized epileptic areas (lanes A´, B´ and C´) and nonepileptic areas (lanes A, B and C). (A and A´ are from the first patient, B and B´ from the second patient, etc.) Note the greater GAP-43 levels in the epileptic areas relative to the nonepileptic areas in all three patients.*

Increased GAP-43 Expression at the Cellular Level

GAP-43 is synthesized in the neuronal cell body as a soluble protein that is quickly bound to the membranes, packaged on vesicles and transported in the rapid phase of transport down axonal processes; therefore, GAP-43 accumulates in the somata.

We studied GAP-43-stained elements around cell surface (rim) structures and intercellular tubular punctate structures. The features of GAP-43 immunohistochemistry in normal and dysplastic cortex are shown in Figure 2. The normal-appearing cortex is defined by well-preserved columnar organization and horizontal lamination

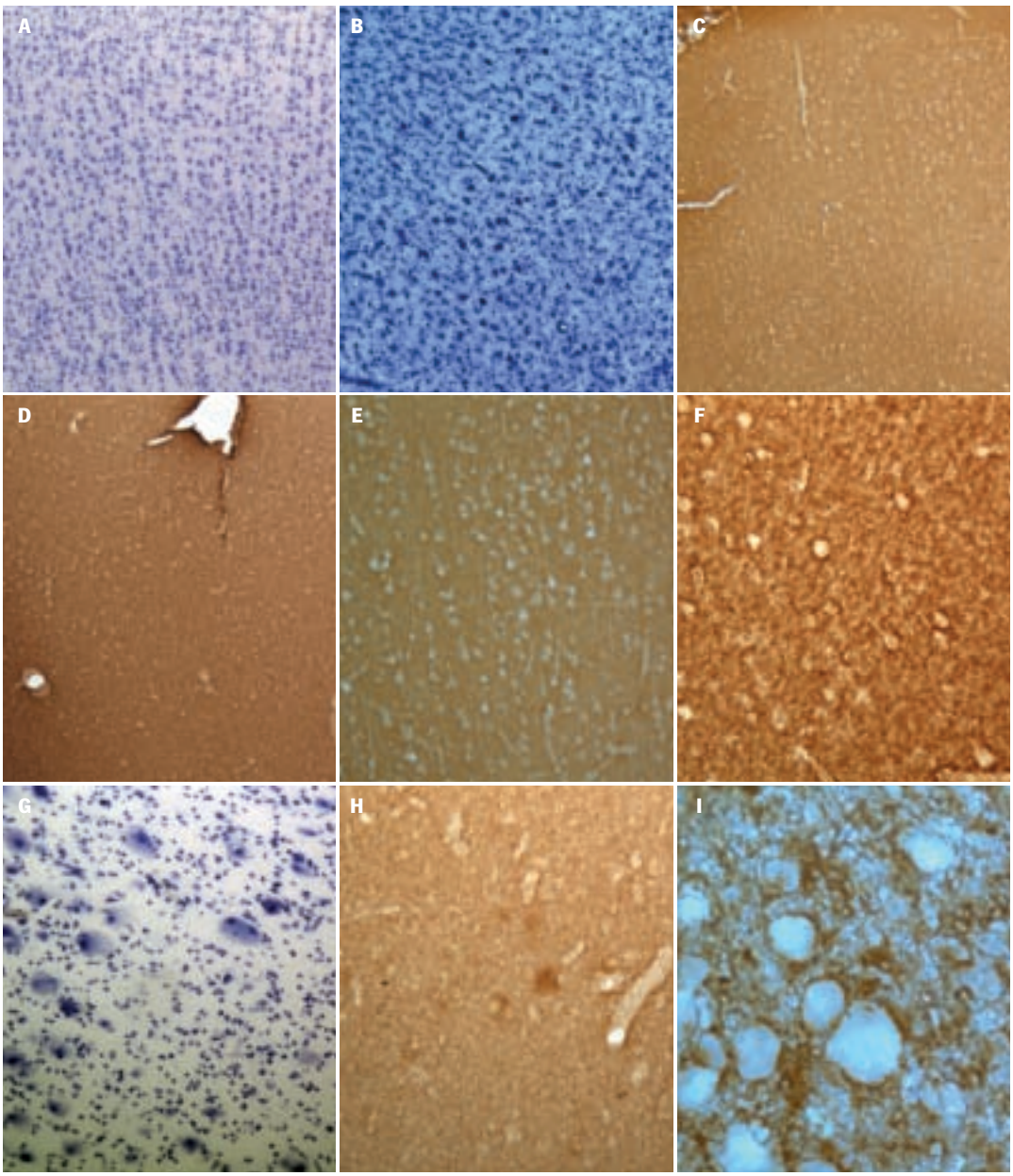

Figure 2. *Photomicrographs of cresyl echt violet (CV) and GAP-43 immunohistochemistry (IHC) staining from normal-appearing cortex (panels A, C and E) and dysplastic cortex (panels B, D, F, G, H and I).* ***Normal-appearing cortex:*** *A CV-stained section* ***(A)*** *shows well-laminated cortical pyramidal cells with dendrites appropriately positioned toward the pial surface. The adjacent section with GAP-43 IHC* ***(C)*** *shows only background staining. At higher magnification* ***(E)****, no specific GAP-43 immunostaining is seen in cell bodies or intercellular space.* ***Dysplastic cortex:*** *A CV-stained section* ***(B)*** *shows that the vertical and horizontal laminations are disrupted and dysmorphic cells are darkly stained. In this area, GAP-43* ***(D)*** *shows increased immunoreactivity. Higher magnification* ***(F)*** *reveals GAP-43 staining of the cell surface in a rim pattern as well as stained punctate clumps or tubular structures. Those GAP-43-stained patterns in dysplastic cortex are illustrated at higher magnification* ***(I)****. The balloon cells appear as strikingly large opalescent cytoplasm with eccentric nuclei* ***(G)****. Some of these balloon cells are faintly stained with GAP-43 in the cytoplasm* ***(H)****.*

Assuming that GAP-43 expression is a biological correlate of disease progression/epileptogenesis, it is possible that early timing of resection of FCD type II lesions may halt epileptogenesis.

with no dysmorphic neurons. In normal-appearing neocortex, there was an absence of GAP-43 immunoreactivity in the neuronal somata and cell surface as well as a lack of punctate tubular elements; GAP-43 immunohistochemistry showed homogeneous, nonspecific background staining. In the dysplastic cortex, GAP-43 immunoreactivity was seen within the neuronal cell surface, resulting in a rim staining appearance, and was also present between neurons, giving the appearance of punctate tubular structures. This punctate tubular staining can have an intensely "clumped" appearance at higher magnification. Neuronal somata were negative for GAP-43 immunoreactivity.

GAP-43 and Epilepsy Duration

We also performed semiquantitative analyses of GAP-43 immunohistochemistry labeling by grading the percentage of cells with GAP-43-stained rim appearance and the intensity of GAP-43-stained punctate tubular structures. The final GAP-43 grading score for each brain specimen was obtained by adding scores of both rim and tubular staining. We studied GAP-43 immunohistochemistry in samples from three groups of patients:

- 12 non-temporal lobe specimens from patients with pathologically verified FCD type II (IIA or IIB)
- 9 non-temporal lobe specimens from patients with FCD type IA
- 20 histologically normal neocortical temporal lobe specimens from patients with mTLE/HS (used as an "epilepsy" control group)

As illustrated in Figure 3, higher GAP-43 immunoreactivity scores showed a significant correlation with longer epilepsy duration only in patients with FCD type IIA/B pathology ($P < .0001$; ordinal logistic regression). Despite the absence of a significant difference in epilepsy duration between FCD IIA/B and FCD IA groups, GAP-43 scores in patients with FCD IA were not correlated with epilepsy duration (Figure 3B), although it should be noted that the FCD IA group had a small sample size. Similarly, GAP-43 scores did not correlate with duration of epilepsy in the mTLE/HS group even though these patients had longer epilepsy duration (Figure 3C).

Among many plausible epileptogenic mechanisms, our hypothesis is that dysplastic neurons in FCD type II retain their ability to continue upregulating GAP-43 expression, which may associate with synaptogenesis and the presence of positive feedback interplay between intrinsic epileptic discharges.

The mechanisms for increased expression of GAP-43 are likely multifactorial, including such factors as an intrinsic program-driven increase of GAP-43 mRNA in dysmorphic neurons (but not in normal pyramidal cells). In addition, the increase of GAP-43 could be modulated by NMDA receptor activation. Our studies have demonstrated upregulation of the NMDA receptor complex in dysplastic neurons. Together, the upregulation of NMDA subunits could provide a molecular-functional underpinning for seizure-dependent (and time-dependent) selective GAP-43 expression in FCD type II lesions. In turn, the plastic changes of GAP-43-associated synaptogenesis and rearrangement of gap junction channels could account for the in situ expansion of local epileptic networks that may underlie the temporal progression of epilepsy in patients with type II FCDs.

Clinical Implications: A Biomarker for Epileptogenicity and Epileptogenesis?

Our research results showed increased GAP-43 expression in dysplastic neurons and that this increase is differentially expressed within the epileptic focus vs. adjacent nonepileptic brain regions. This rather specific expression of GAP-43 indicates fundamental pathophysiologic mechanisms for expression of epileptogenicity in FCD.

Assuming that GAP-43 expression is a biological correlate of disease progression/epileptogenesis — and considering our current findings indicating an increase in GAP-43 expression in relationship with longer epilepsy duration in patients with FCD type II — it is possible that early timing of resection of FCD type II lesions may halt epileptogenesis. Our preliminary findings suggest that GAP-43 may be considered as a pathology-specific biomarker for both epileptogenicity and the development/progression of epilepsy in patients with type II FCD. Further studies in a larger patient population are needed to confirm and validate these results.

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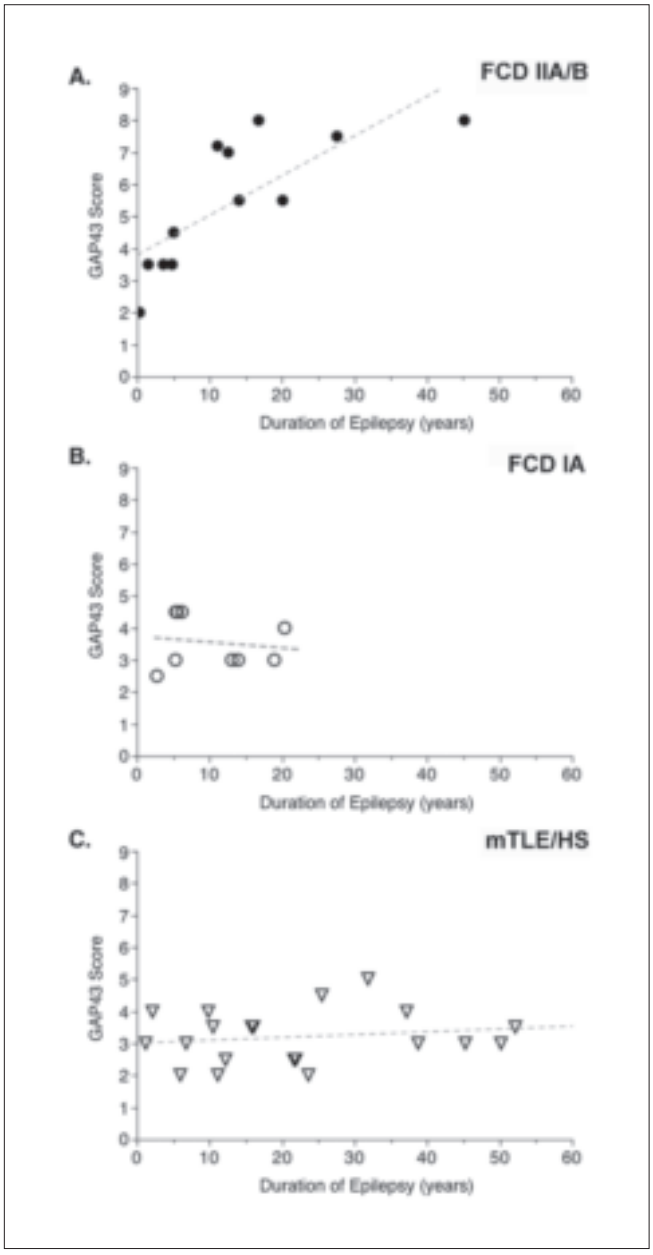


Figure 3. *Analysis of GAP-43 immunoreactivity and epilepsy duration in three groups of patients: (A) 12 patients with FCD type IIA/B pathology, (B) nine patients with FCD type IA pathology and (C) 20 patients with mTLE/HS. There is no significant difference in epilepsy duration between the FCD IIA/B and FCD IA groups despite the presence of two patients with epilepsy of more than 20 years' duration in the former group. Note that the association between epilepsy duration and GAP-43 score is significant only in the patients with FCD type IIA/B pathology* ($P < .0001$).

KEY POINTS

- Recent research from Cleveland Clinic's Epilepsy Center shows increased expression of growth-associated protein 43 (GAP-43) in dysplastic neurons. This protein is differentially expressed within the epileptic focus vs. adjacent nonepileptic brain regions.
- Our research also indicates an association between increased GAP-43 expression and longer epilepsy duration in patients with type II focal cortical dysplasia (FCD).
- These preliminary findings suggest that GAP-43 may prove to be a pathology-specific biomarker for epileptogenicity and the progression of epilepsy (epileptogenesis) in patients with type II FCD, but larger confirmatory studies are needed.

Introducing a Novel iPad® App to Screen for Cognitive Dysfunction in the MS Clinic

By Stephen M. Rao, PhD, ABPP/CN

At this year's annual meeting of the American Academy of Neurology (AAN), Cleveland Clinic investigators presented results of a study demonstrating the reliability and validity of a self-administered, computerized tool for screening for cognitive dysfunction in the multiple sclerosis (MS) clinic.[1] This novel assessment tool, called the Processing Speed Test (PST), takes advantage of Apple's iPad technology. The PST is one of a battery of iPad apps, called the Multiple Sclerosis Performance Test (see sidebar), designed to provide quantitative assessments of motor, vision and cognitive performance in MS.

Cognitive Deficits Loom Large in MS

Approximately 50 percent of MS patients experience mental symptoms — typically in the form of cognitive dysfunction — in addition to the hallmark physical symptoms of MS. The two most common cognitive deficits involve the ability to process information quickly and to retrieve recently learned memories. These cognitive deficits can have a deleterious impact on employment, driving and the ability to perform routine daily activities.

Longitudinal studies suggest that approximately 15 to 25 percent of patients with MS experience cognitive dysfunction during the early relapsing phase of the illness; this figure rises to 65 percent when patients enter the more progressive stage of the disease. Approximately 5 to 6 percent of patients will experience new cognitive symptoms or a worsening of existing cognitive symptoms in any given year.

The Quest for Practical Cognitive Assessment

The optimal method for assessing cognitive dysfunction is through standardized neuropsychological tests, which typically take two to three hours to complete and must be administered by a board-certified clinical neuropsychologist. Administering such a lengthy battery to all patients with MS is unrealistic.

The alternative is to use cognitive screening tests that identify those patients who may have experienced a worsening of their cognitive abilities. Unfortunately, simply asking the patient or his or her family members about changes in cognitive functioning has proved unreliable, since their responses do not correlate with those obtained from objective neuropsychological testing.

One solution is to have patients perform a brief neuropsychological test during their visits to the MS clinic. One such test, the Symbol Digit Modalities Test (SDMT), takes 10 minutes to administer, score and enter into the medical record. For busy MS clinics, such as Cleveland Clinic's Mellen Center for Multiple Sclerosis Treatment and Research, allocating even 10 minutes of personnel time to screen for cognitive dysfunction is impractical.

Enter the PST App

A multidisciplinary team of neurologists, bioengineers and neuropsychologists in Cleveland Clinic's Neurological Institute addressed this problem by developing the PST app, which resembles the SDMT (see Figure). Results reported at the AAN meeting[1] indicated that the self-administered PST has exhibited equal, if not better, test-retest reliability and sensitivity for identifying cognitive dysfunction in patients with MS compared with the technician-administered SDMT. Moreover, the PST and SDMT are highly correlated, indicating that they measure similar cognitive abilities.

We are now generating a nationwide normative database, derived from the performance of healthy individuals, to be completed in 2015. We are also conducting a study to determine whether test performance declines when a technician is not present in the evaluation room — a critical validation step for self-administration.

How It Will Work in Real-World Practice

We envision that the PST will be self-administered in the waiting area of the clinic before the patient sees his or her caregiver. Once the patient completes the test, the raw data will be transferred wirelessly to the cloud, scored and adjusted for demographic factors (age, education, sex, etc.) that might influence interpretation of the score.

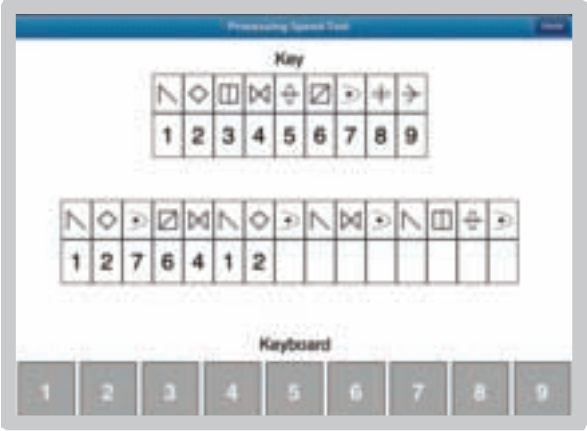
Our plan, not yet implemented, is to then integrate the results into the patient's electronic medical record. This transfer of information will be nearly instantaneous, allowing the clinician to view the results at the same patient visit. Depending on the evaluation results, the caregiver may refer the patient for a more comprehensive neuropsychological evaluation. The results may also suggest a "cognitive relapse" that might prompt changes to the patient's medical care plan.

Abundant Advantages

The PST offers several additional advantages over the SDMT:

- The SDMT has only one published test form, whereas the PST generates a unique test form with every administration, minimizing practice effects.
- The SDMT simply records the number of correct items; in contrast, the PST takes advantage of the iPad's processor to generate innovative response measures based on inter-response times. It is possible to generate a learning curve based on the two-minute administration time.
- The self-administered PST app can allow remote, and thus more frequent, cognitive assessments.

Figure. *Screen shot of the Processing Speed Test (PST) app for assessment of information processing and episodic memory in multiple sclerosis.*



Ultimately, our goal in developing this technology is to revolutionize the way cognitive problems are monitored and addressed in patients with MS.

ACKNOWLEDGMENTS

The author acknowledges Richard Rudick, MD, former Director of the Mellen Center, and Jay Alberts, PhD, Director of the Concussion Center, for their teams' leadership in the development of the PST app.

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The PST: One of Five Components of the Multiple Sclerosis Performance Test

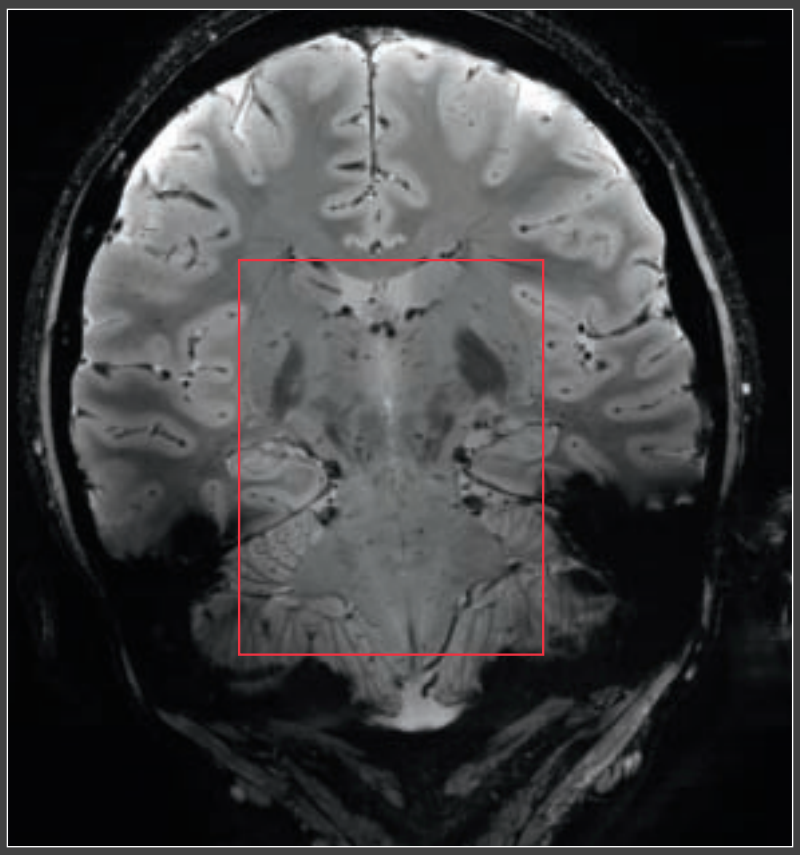
The Processing Speed Test is one of five apps for the iPad that constitute the Multiple Sclerosis Performance Test, which is detailed in a new video publication[2] by a team of Cleveland Clinic researchers in the *Journal of Visualized Experiments* (JoVE):

- Processing Speed Test — information processing speed and episodic memory
- Walking Speed Test — time to walk 25 feet
- Balance Test — ability to maintain postural stability
- Manual Dexterity Test — manual dexterity based on the nine-hole peg test
- Low Contrast Letter Acuity Test — contrast sensitivity (similar to Sloan charts)

Cleveland Clinic is exploring beta testing of the Multiple Sclerosis Performance Test app suite in clinical trials and MS centers beyond Cleveland Clinic, with potential plans for ultimate submission to the FDA for market clearance for broad clinical use.

KEY POINTS

- Cognitive dysfunction is a significant aspect of multiple sclerosis (MS), and practical, efficient methods for screening for cognitive deficits in the MS clinic are needed.
- Cleveland Clinic's self-administered Processing Speed Test (PST) app for the iPad exhibits equal or better test-retest reliability and sensitivity for identifying cognitive dysfunction in MS patients compared with the technician-administered Symbol Digit Modalities Test (SDMT).
- The PST offers several advantages over the SDMT — including remote administration, minimization of practice effects and generation of innovative response measures — and raises the prospect of better, more frequent and more cost-effective monitoring for cognitive dysfunction in MS.



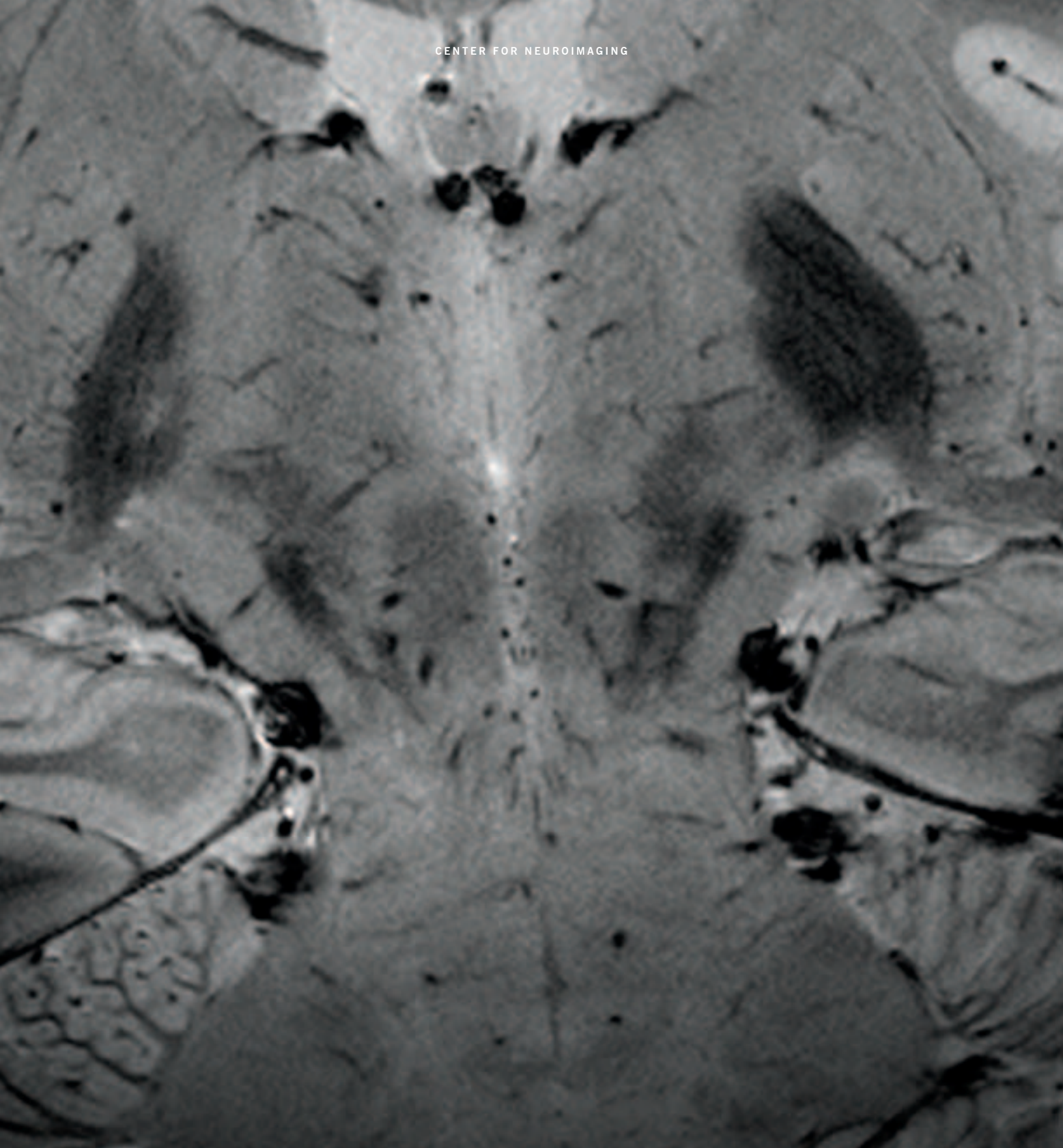
THE ART OF 7T IMAGING

Images provided by Mark Lowe, PhD, and Sehong Oh, PhD

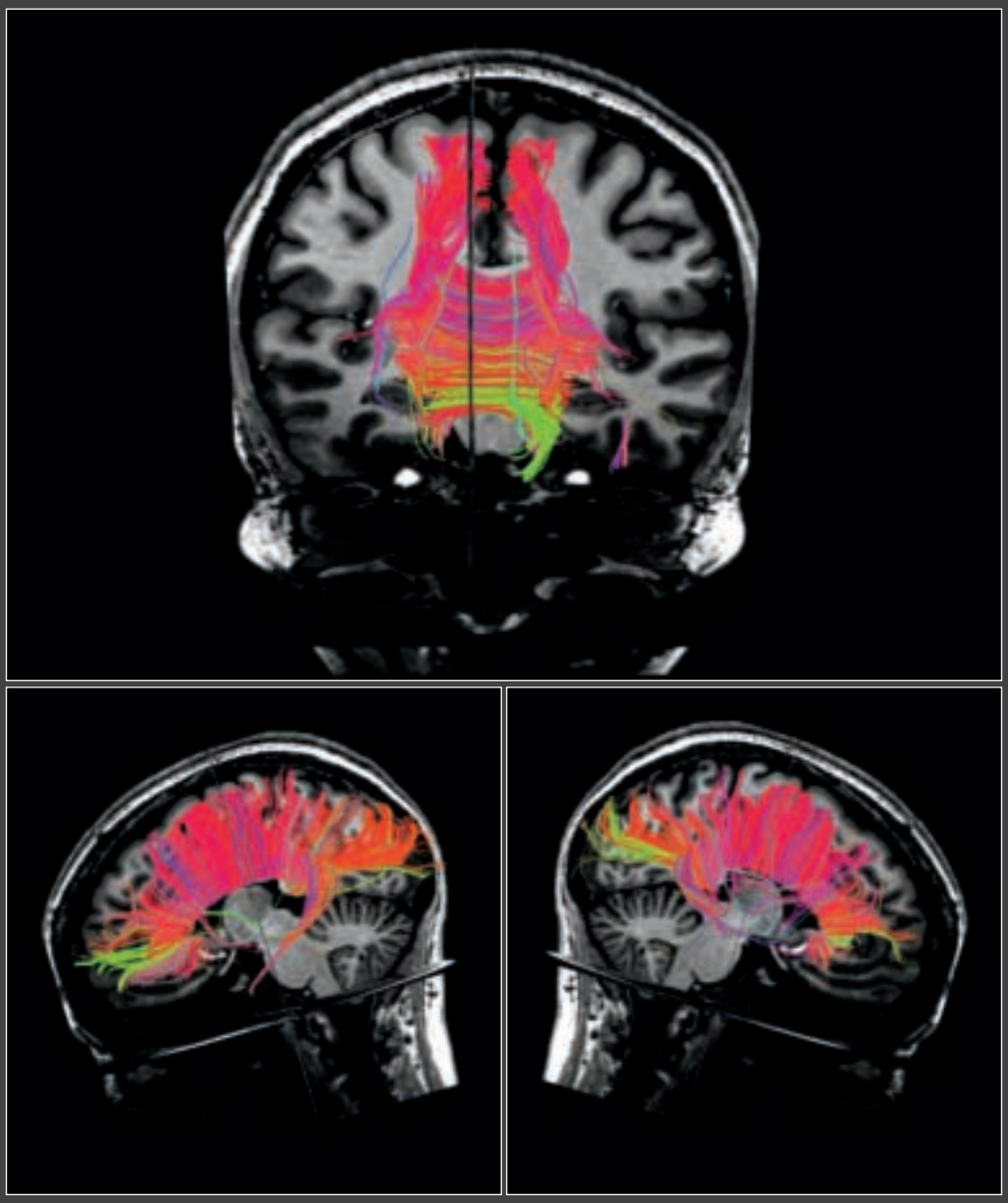
System-level brain study at a nearly microscopic scale. That's what Neurological Institute researchers have been relishing since the installation of a 7-tesla MRI scanner on Cleveland Clinic's main campus in mid-2013. With more than double the field strength of 3T MRI, 7T scanning — which the FDA currently restricts to research use only — produces in vivo images at spatial resolutions up to five times those possible at clinical field strengths. The result is imaging studies that marry the spatial resolution of CT with the superior soft-tissue contrast of MRI. Current Neurological Institute applications of 7T scanning range from studies in multiple sclerosis and amyotrophic lateral sclerosis to epilepsy to traumatic brain injury.

This photo essay presents a few glimpses of what 7T imaging has been allowing us to see — more clearly than ever before.

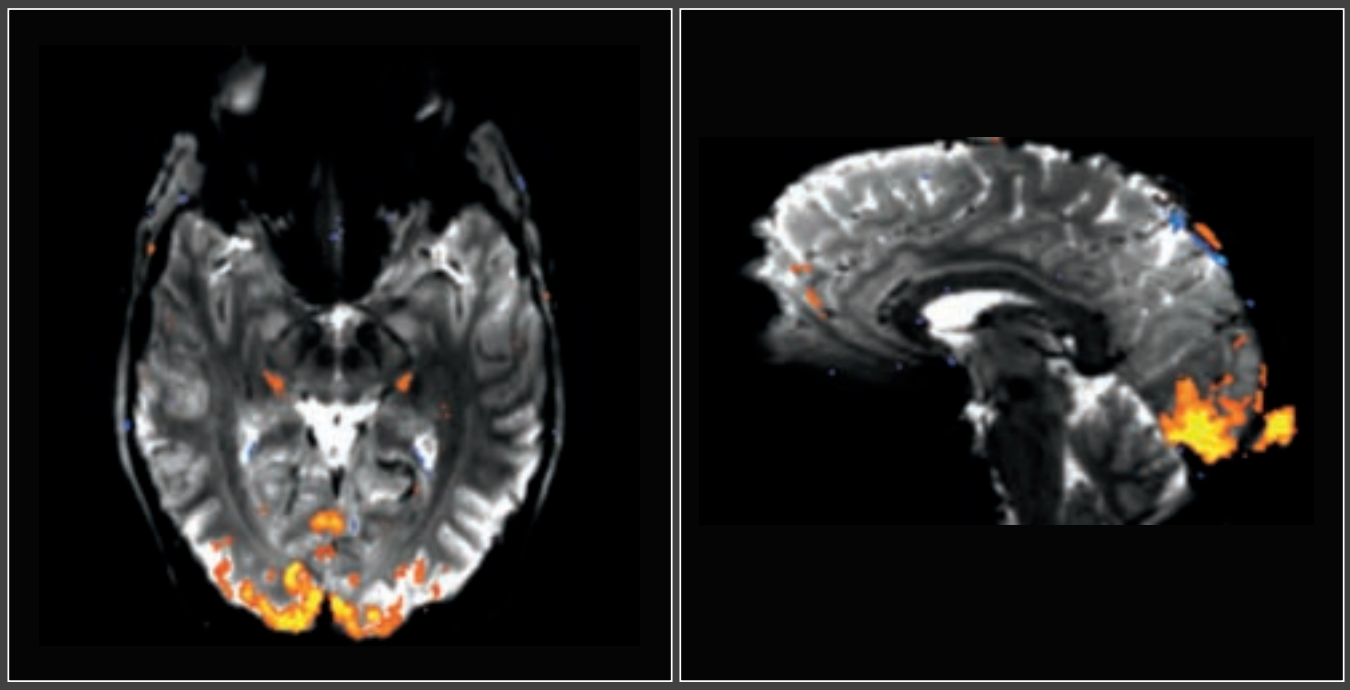
Dr. Lowe is Cleveland Clinic's Director of High-Field MRI. He can be reached at lowem1@ccf.org or 216.445.2661.
Dr. Oh is a project staff scientist in Cleveland Clinic's Imaging Institute.



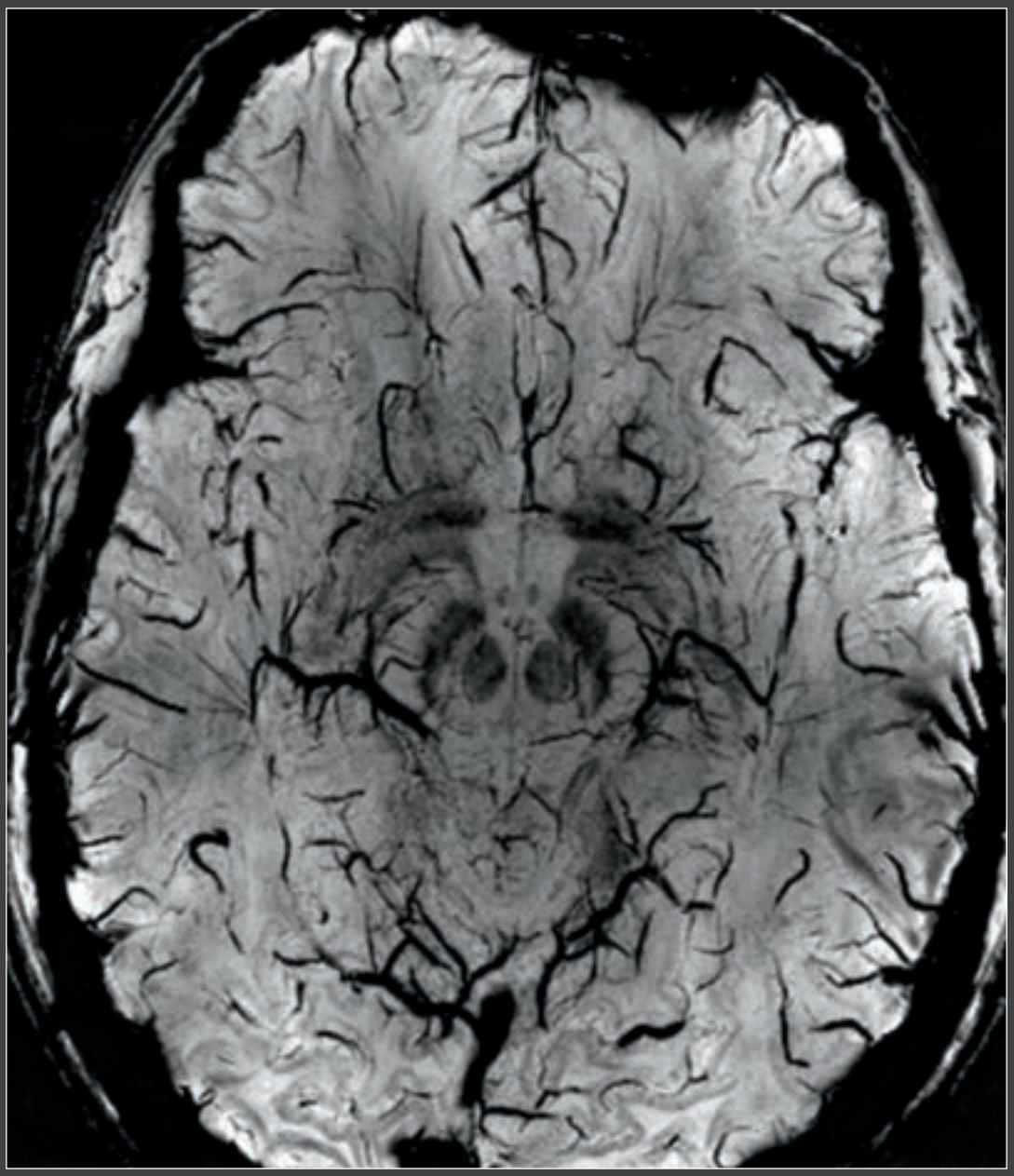
High-resolution two-dimensional T2-weighted gradient echo image obtained with 7T MRI (zoomed-in region above corresponds with the red box in the image on opposite page). The increase in static field to 7T from clinical field strengths provides a dramatic gain in signal and contrast. Images with this drastically improved resolution, sensitivity and contrast may enable more accurate diagnosis of diseases and help advance neuroscience research. (0.25 × 0.25 mm^2 in-plane resolution; 1.5 mm slice thickness; 9 min 54 sec scan time)*



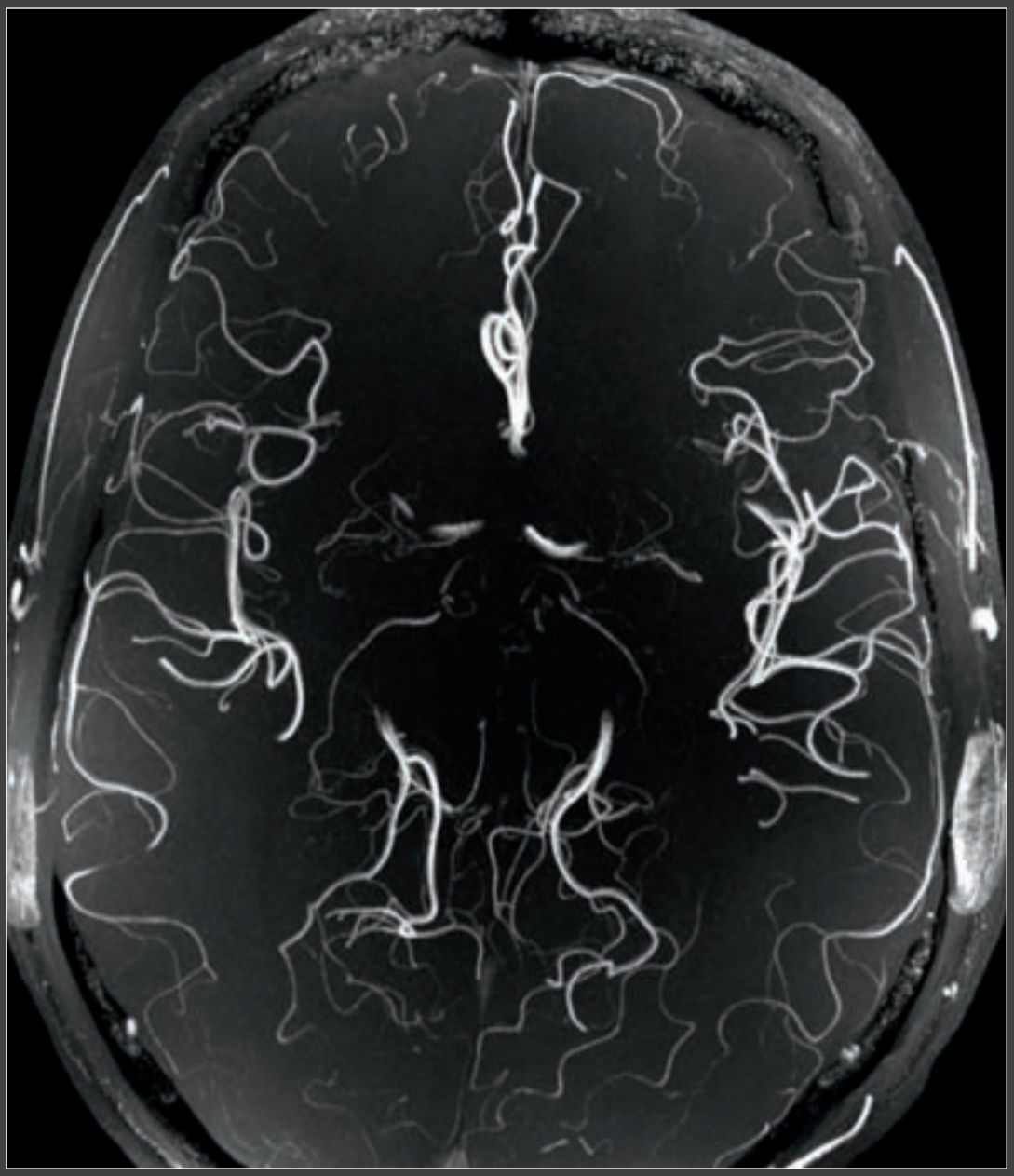
Fiber tractography images of the corpus callosum overlaid on the T1-weighted anatomic image. Using 7T MRI, we can visualize the submillimeter-size fiber tracts. Tractography results are color-coded according to the direction of the fiber. (1.0 mm^3 isotropic resolution, 12 min scan time)



Axial (left) and sagittal (right) views of functional MRI results at 7T using a flashing checkerboard visual stimulus. These results show activation in the visual cortex and the lateral geniculate nucleus. (1.25 mm^3 isotropic resolution)



Susceptibility-weighted imaging (SWI) in a healthy volunteer. SWI shows susceptibility differences between tissues and is sensitive to venous blood and iron. In general, higher-field-strength systems such as 7T MRI produce better contrast with SWI. (0.43 × 0.43 × 0.8 mm^3 resolution, 7 min scan time)



Magnetic resonance angiography (MRA) image without contrast in a healthy volunteer. At 7T, there is a higher contrast between blood vessels and tissue than at lower field strengths, making direct imaging of small vessels possible. 7T imaging promises to play an important role in the study of small-vessel abnormalities. (0.3 × 0.3 mm^2 in-plane resolution; 19 mm slab thickness; 5 min 16 sec scan time)

Improving Patient Experience in DBS Surgery: Intraoperative MRI for Real-Time Evaluation of Electrode Positioning

By Sean Nagel, MD; Caio Matias, MD; Michael Phillips, MD; Stephen E. Jones, MD, PhD; and Andre Machado, MD, PhD

Real-time or near-real-time intraoperative MRI is poised to revolutionize deep brain stimulation (DBS) surgery by simplifying the operation and enhancing the patient experience. Intraoperative MRI is now routinely offered and used as an option to guide electrode placement during DBS surgery in patients at Cleveland Clinic. Results of a preliminary evaluation of DBS leads placed in our intraoperative MRI suite indicate that actual lead location closely matched intended placement targets. This article reviews the rationale for the use of intraoperative MRI in DBS as well as the next steps in our assessment of this exciting treatment option.

Microelectrode Recording and the Awake Patient

DBS is a well-established treatment for Parkinson disease and essential tremor and is also FDA-approved under a humanitarian device exemption to treat refractory obsessive-compulsive disorder and dystonia. Microelectrode recording (MER) has been routinely used during stereotactic procedures for several decades to improve the localization of subcortical structures for DBS or for ablative treatments such as thalamotomy or pallidotomy. This standard technique has been refined gradually to improve the safety profile and increase the accuracy and precision of functional neurosurgical procedures for movement disorders and other applications. MER is typically carried out in the awake patient (Figure 1, left), along with evoked potentials. The recordings are then compared to surgical atlases and the patient's anatomy to infer electrode location.

In contrast, intraoperative MRI improves accuracy of lead location by assessing the relationship with anatomic landmarks instead of the physiological recordings obtained by MER. An important advantage of intraoperative MRI is that it allows the surgery to be done under general anesthesia, without any awake physiological measurements.

> Results of a preliminary evaluation of DBS leads placed in our intraoperative MRI suite in 24 patients indicate that actual lead location closely matched intended placement targets.

Building the Intraoperative MRI Suite

Cleveland Clinic constructed its intraoperative MRI suite with a special infrastructure consisting of two adjacent rooms — a leading-edge operating room and an MRI suite (Figure 1, right) — separated by mechanical doors. At any time during the operation, the surgeon can request an MRI to assess the location of DBS leads and make corrections as necessary. The mechanical doors open and the MRI machine moves on ceiling-mounted rails into the surgical field. Once images are acquired, they can be overlaid on the initial surgical plan to assess any deviation between the actual location of DBS leads and the intended plan.

The Likeliest Candidates

Patients who are offered or opt for asleep DBS with intraoperative MRI may have incapacitating claustrophobia, heightened anxiety, large-amplitude tremor or another medical comorbidity that increases the risk for awake surgery, such as respiratory disease, airway compromise or increased risk of seizures. Additional patients may simply elect to have surgery under general anesthesia because they are not comfortable with the idea of being awake for part of the surgery. This option is far more tolerable from a patient comfort standpoint, and we anticipate that most patients and surgeons will favor this approach if the outcomes are equal to awake implantation.

Reliable Principles Guide the Workflow

Although the workflow from one intraoperative MRI case to the next may vary based on multiple patient factors, the principles are unchanging. For many patients, the workflow proceeds as follows:

- A head-frame or frameless system is fitted to the patient's head, and a CT or MRI is completed.
- The patient is secured to the fixed intraoperative MRI table. Using the preplanned trajectory based on the preoperative MRI co-registered with the stereotactic images, the first lead is implanted.
- The doors are opened, the MRI machine is brought over the patient and a volumetric MRI (1.5T) is completed.
- These images are merged with the preoperative stereotactic CT using the planning software, and the actual trajectory is compared with the intended trajectory (Figure 2).
- After adjustments are made to account for brain shift, a second lead is implanted, followed by repeat intraoperative MRI imaging.

Figure 1. *Options for electrode placement during DBS surgery are evolving from traditional microelectrode recording in the awake patient (left) to intraoperative MRI in the patient under general anesthesia (right).*

Promising Preliminary Outcomes Assessment

Our preliminary results, described below, indicate that outcomes are similar with preserved safety. At this time, long-term follow-up will be necessary before definitive conclusions can be drawn.

We recently conducted an assessment of lead location in 24 patients who underwent DBS lead implantation in the intraoperative MRI suite. We used stereotactic planning software (iPlan® 3.0, Brainlab, Munich, Germany) to fuse preoperative MRI and CT scans with intraoperative MRI images. All images were normalized to two midline anatomic landmarks, the anterior commissure and the posterior commissure, which allowed a comparison between the intended preoperative x, y and z coordinates and the actual intraoperative electrode coordinates. In the stereotactic space, the x-axis represents the medial-lateral position, the y-axis represents the anterior-posterior position and the z-axis represents the superior-inferior position.

The average differences between the intended target and the actual electrode tip were as follows:

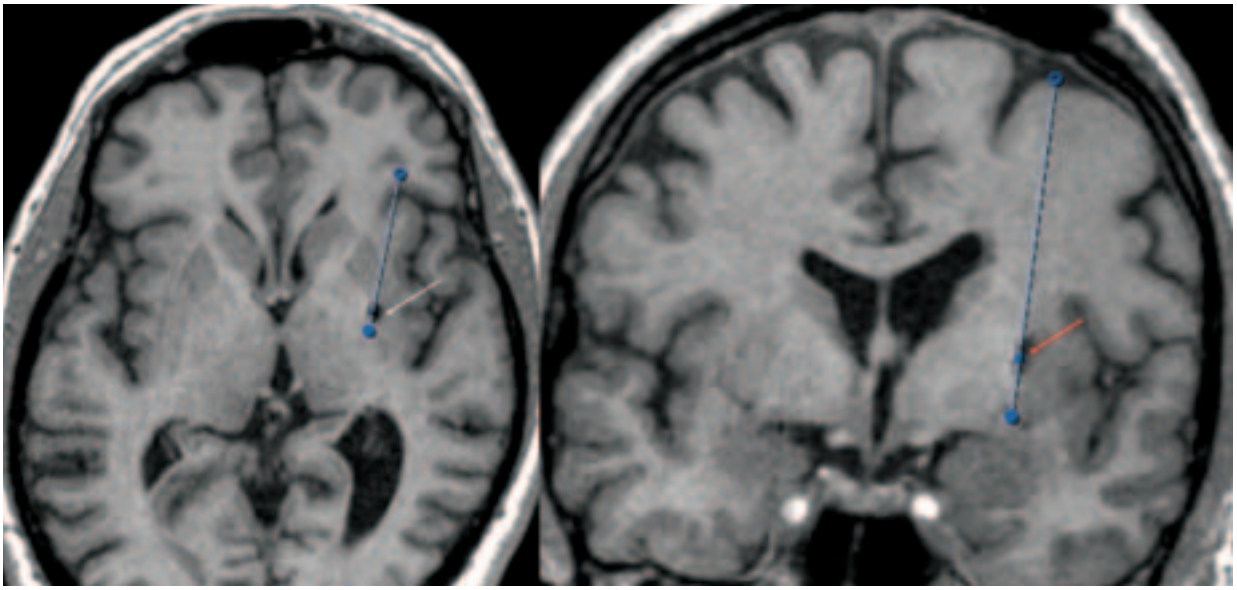
- 1.1 ± 0.9 mm for the x-axis
- 0.7 ± 0.04 mm for the y-axis
- 0.8 ± 0.9 mm for the z-axis

These differences are within the expected error range for stereotactic neurosurgical operations. Furthermore, since the electrode used for DBS has a diameter of 1.27 mm, errors of approximately 1 to 2 mm are considered acceptable.

Next Steps and Implications

The next step will be to compare motor and nonmotor outcomes between patients with Parkinson disease undergoing DBS with intraoperative MRI vs. MER.

Figure 2. *Axial (left) and coronal (right) T1-weighted intraoperative MRIs following implantation of a unilateral right-sided DBS electrode into the globus pallidus internus with preplanned trajectory overlay (dashed blue line, which shows the entirety of the trajectory, including portions lying outside the planes). The actual position of the electrode crossing into these two planes is shown by the hypointense (dark) focus denoted by the arrows. Note how the actual lead tracks with the intended trajectory in both planes. There was no appreciable error in targeting, and adjusting the target for the contralateral side was not necessary.*



We anticipate that the role of intraoperative MRI for DBS will expand over the next several years, for a couple of reasons. The number of potential candidates for DBS is expected to increase, not only as a result of new indications but also because those previously not offered awake DBS may now be candidates for this new method using intraoperative MRI under general anesthesia. In addition, real-time lead evaluation will likely enhance patient safety.

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Dr. Matias was a research fellow in the Center for Neurological Restoration when this was written.

Dr. Phillips is a staff physician in the Center for Neuroimaging and the Department of Neurosciences as well as Vice Chair of Research and Academic Affairs in Cleveland Clinic's Imaging Institute. He can be reached at phillim@ccf.org or 216.445.0557.

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KEY POINTS

- Deep brain stimulation (DBS) conducted with real-time intraoperative MRI allows assessment of lead location with anatomic landmarks instead of the physiological recordings used with microelectrode recording during awake surgery.
- The advantages of DBS with intraoperative MRI include the ability to perform the surgery with the patient under general anesthesia and real-time anatomic evaluation of lead placement.
- A preliminary analysis of DBS leads implanted in Cleveland Clinic's intraoperative MRI suite found differences from target lead placement to be modest and within expected error ranges. We now plan to compare clinical outcomes in patients undergoing DBS with intraoperative MRI vs. microelectrode recording.

Neuromuscular Ultrasound: Defining Its Growing Utility in Managing Peripheral Nerve Disease

By Steven Shook, MD

High-resolution ultrasound has emerged as a useful tool to guide the management of patients with peripheral nerve entrapments, tumors, trauma and other surgically amenable pathology. The procedure is a valid and reliable method of evaluating peripheral nerves,[1] offering excellent resolution and a flexible, dynamic field of view.

A Complement to Other Diagnostic Modalities

Neuromuscular ultrasound offers particular utility when skillfully combined with clinical examination findings and electrodiagnostic techniques. When paired with electromyography (EMG), the traditional gold standard for evaluating peripheral nerve disease, ultrasound meaningfully impacts the clinical approach in up to 43 percent of cases, typically by identifying potentially surgically amenable intraneural and adjacent pathology as well as variant anatomy.[2] In patients with suspected traumatic nerve lesions, ultrasound modifies the treatment plan in 58 percent of cases, primarily by providing early evidence of nerve discontinuity.[3] Ultrasound can also identify symptomatic peripheral nerve lesions not apparent by EMG.

Ultrasound and MRI are both increasingly used for visualizing peripheral nerves. A recent study comparing the two modalities suggested that ultrasound is more sensitive than MRI, has equivalent specificity and is better at identifying multifocal lesions.[4] For these reasons, ultrasound is typically the initial imaging modality for peripheral nerve assessment, except when nerves lie very deep within the body or beneath bone.

At the Fore of Shaping Ultrasound Use

Neuromuscular ultrasound is used as part of the comprehensive evaluation offered by Cleveland Clinic's Peripheral Nerve and Plexus Surgery Program, a specialized multidisciplinary clinic designed to diagnose and treat brachial and lumbosacral plexus disorders as well as focal neuropathies of the upper and lower extremities, including peripheral nerve tumors, trauma and entrapment.

This clinic is directed out of Cleveland Clinic's Neuromuscular Center, which is actively involved in neuromuscular ultrasound guideline development through participation in the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Ultrasound Task Force.[5]

Neuromuscular Center staff have likewise trained numerous medical professionals in neuromuscular ultrasound technique through lectures and hands-on instruction at Cleveland Clinic's main campus, at the Wake Forest Baptist Medical Center Program for Medical Ultrasound, and at annual meetings of the American Academy of Neurology, the American Society for Neuroimaging and the International Society of Peripheral Neurophysiological Imaging.

The remainder of this article surveys some leading indications to which specialists in the Neuromuscular Center and elsewhere are applying neuromuscular ultrasound as its use continues to evolve.

Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) is the most common peripheral nerve entrapment. Increased cross-sectional area of the median nerve at the level of the pisiform bone (a marker of the proximal carpal tunnel) is considered the most reliable and clinically useful parameter, and it is accurate for the diagnosis of CTS.[5]

In addition to diagnosing CTS, ultrasound can identify structural causes of CTS and important anatomic variations that impact the surgical approach. Persistent median artery (PMA) within the carpal tunnel (estimated incidence of 10 to 26 percent) can also be demonstrated. When not identified preoperatively, PMA can complicate an endoscopic carpal tunnel release — or an open release if a tourniquet is used. Ultrasound imaging may thus guide CTS surgical planning and improve patient outcomes.

Ulnar Nerve Entrapment

There is increasing evidence that ultrasound can localize ulnar nerve entrapment at the elbow when EMG is equivocal and that it can identify relevant pathology and anatomic variants.[6] At the same time, interest is growing in the use of ultrasound to guide surgical intervention for patients with ulnar nerve entrapment and to diagnose patients with deterioration after ulnar nerve transposition.[7]

Intraneural Ganglion Cysts

Patients with foot drop may be diagnosed with a common peroneal neuropathy at the fibular head based on EMG findings. Although either long-standing compression or acute trauma affecting the nerve may be the cause, an intraneural ganglion cyst is identified in up to 18 percent of these patients (see Case Profile 1, next page).

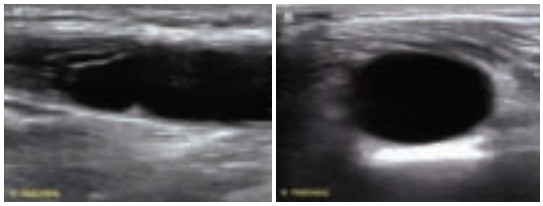
When identified in a timely manner, intraneural ganglion cysts are surgically amenable, with good postoperative outcomes. The presence of pain at the knee or neuropathic pain in the peroneal nerve distribution, a mass lesion, and fluctuating symptoms increase the pretest probability of finding an intraneural ganglion cyst, particularly in patients with no history of weight loss, immobility or leg crossing.[8]

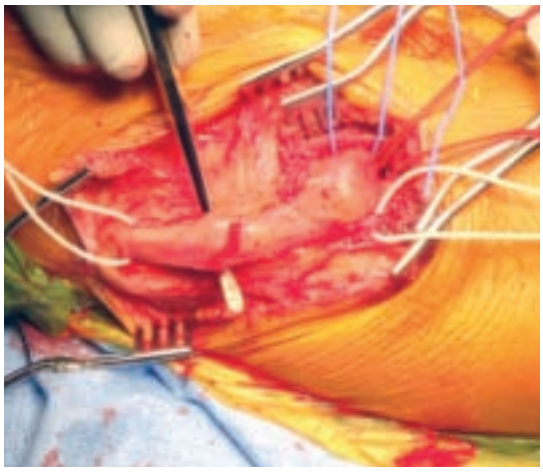
Peripheral Nerve Tumors

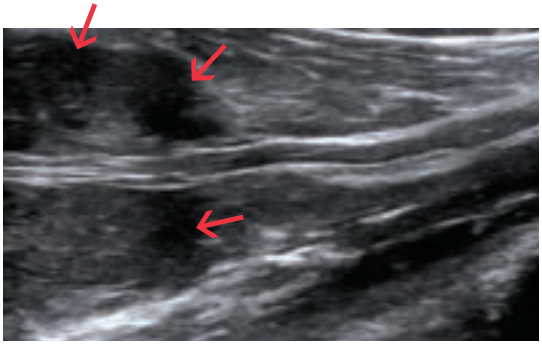
Peripheral nerve tumors are also readily identified by ultrasound. Tumor types include lesions derived from adjacent non-neural sheath tissues, such as desmoid tumor and nodular fasciitis (see Case Profile 2, next page), as well as benign peripheral nerve sheath tumors (e.g.,

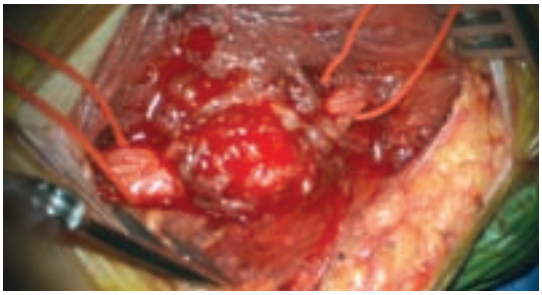
Case Profile 1: Painful Foot Drop

A 49-year-old man presented with a painful right foot drop. He had no history of prior weight loss, immobility or leg crossing. EMG showed severe axon loss affecting the tibialis anterior and peroneal longus muscles. Ultrasound revealed an oblong tender, hypoechoic, power-Doppler-negative lesion within the peroneal nerve with significant posterior acoustic enhancement (longitudinal and transverse views below), consistent with an intraneural ganglion cyst. Surgical decompression of the peroneal nerve with external and internal neurolysis and removal of the intraneural ganglion cyst were performed (intraoperative image below), with resolution of pain and improvement of ankle and toe dorsiflexion to near full power.









Case Profile 2: Progressive Radial Neuropathy

A 31-year-old woman presented with dorsal left hand and forearm numbness that progressed to wrist and finger drop over several months. Neurological exam revealed sensory loss in the distribution of the left radial nerve and weakness of left wrist/finger extension. EMG showed a left radial neuropathy. Ultrasound (longitudinal view above) revealed a hypoechoic, noncompressible, power-Doppler-negative soft tissue mass (arrows) within the antecubital fossa completely surrounding and compressing the radial nerve. The epineurium was intact within the mass. The mass was surgically resected with decompression and internal/external neurolysis of the radial nerve (intraoperative image above). Pathology revealed nodular fasciitis, a benign mesenchymal tumor arising from fascia. The patient's pain resolved, and weakness was significantly improved at her four-month follow-up appointment.

Ultrasound is increasingly used for visualizing peripheral nerves. A recent study suggested ultrasound is more sensitive than and equally specific as MRI in this setting and also better at identifying multifocal lesions.

schwannomas, neurofibromas, perineurioma and granular cell tumor) and malignant peripheral nerve sheath tumors.

The primary role of ultrasound in nerve tumor management is localization for biopsy/surgical planning. It has also been suggested that serial evaluation of asymptomatic lesions — monitoring for change in size or morphology — may prove useful in patients with known neurocutaneous disorders, such as neurofibromatosis.

Nerve Trauma

Identification of complete nerve transection can guide the decision to pursue earlier surgical intervention in patients with nerve trauma. EMG cannot differentiate complete nerve transection until reinnervation begins beyond six weeks. Ultrasound is both sensitive and specific for early identification of transection, and is used in acute presurgical planning to localize the injury site and proximal/distal nerve stumps. For management of remote nerve trauma, ultrasound can identify stump neuromas and reveal excessive perineural scar tissue.

Patients who remain symptomatic after peripheral nerve exploration and surgical intervention present a special clinical challenge. Although delayed recovery is expected, early identification of graft discontinuity, nerve encasement by scar tissue or neuroma formation prompts surgical revision and potentially improves patient outcomes.

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KEY POINTS

- When combined with clinical findings and electrodiagnostic techniques, neuromuscular ultrasound can significantly impact management and improve outcomes in patients with a variety of peripheral nerve disorders.
- Ultrasound can identify symptomatic peripheral nerve lesions that are not apparent by electromyography. It has been shown to be more sensitive than and equally specific as MRI and also better at identifying multifocal nerve lesions.
- Neuromuscular ultrasound brings distinct advantages to the management of carpal tunnel syndrome and other peripheral nerve entrapments, intraneural ganglion cysts, peripheral nerve tumors and various forms of nerve trauma.

What Does the Macrophage See? A Study of Inflammatory Demyelination

By Richard M. Ransohoff, MD, and Haiyan Lu, MD, PhD

Recent investigations by a Cleveland Clinic-led multicenter research team are yielding high-resolution representations of how inflammatory demyelination — the process underlying multiple sclerosis (MS) — begins. This article reviews the rationale behind this research, the essentials of our findings so far, and a glimpse ahead to potential implications and our next research goals.

The Imperative for Preventing Myelin Damage

In its simplest form, inflammatory demyelination results from the generation of autoimmune T lymphocytes, which can be stimulated by fragments of myelin, the fatty/proteinaceous membrane wrapped around nerve fibers. Once stimulated, the T cells communicate to macrophages, which then carry out the direct attack on myelin membranes. This attack results in patches of damage to myelin and nerve fibers, and this damage underlies the symptoms of MS.

The myelin membrane carries responsibility for ensuring energy-efficient, accurate communication among nerve cells as well as guaranteeing nourishment to nerve fibers. It is therefore critically important for proper nervous system function. Myelin damage can be repaired through endogenous recovery mechanisms, but this repair process is uncertain. As a result, prevention of myelin damage is a priority of MS research.

Tapping EAE to Explore Lingering Questions

Despite nearly a century of research and much gratifying, clinically relevant progress, certain fundamental questions about inflammatory demyelination remain unresolved. A major engine driving MS research involves a similar disease, experimental autoimmune encephalomyelitis (EAE), that can be induced in mice by an immunization procedure that makes the mice "allergic" to their own myelin. About 2.5 weeks after the immunization, mice develop hind limb weakness very similar to the limb weakness experienced by MS patients. Several currently used MS treatments emerged directly from EAE studies.[1]

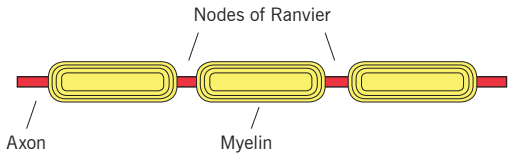


Figure 1. *Our recent study revealed that nodes of Ranvier, the 1-μm gaps between myelin segments along the axon, are where macrophages localize in experimental autoimmune encephalomyelitis, an animal model of MS.*

Assembling a Picture of a Macrophage Attack

Using this EAE model, our Cleveland Clinic-led multicenter research team set out to evaluate how macrophages attack myelin during EAE in the mouse in a newly published study.[2] We used serial block-face scanning electron microscopy (SBFSEM) with three-dimensional (3-D) reconstruction to make pictures of macrophages attacking myelin at micrometer (millionths of a meter) resolution.

Surprising Findings

These images showed a dramatic, unexpected representation of how inflammatory demyelination begins — namely, with macrophages being attracted to nodes of Ranvier. The nodes of Ranvier are basic to the structure of nerve fibers: They are the 1-μm gaps between myelin segments, where one myelin segment ends and the next begins (Figure 1). It was surprising and provocative to find macrophages localizing to these gaps in the myelin sheath. Our interest was strongly engaged because this feature of inflammatory demyelination might provide clues about the molecular signals that attract macrophages.

> It was surprising and provocative to find macrophages localizing to these gaps in the myelin sheath.

Focusing in Further with Confocal Microscopy

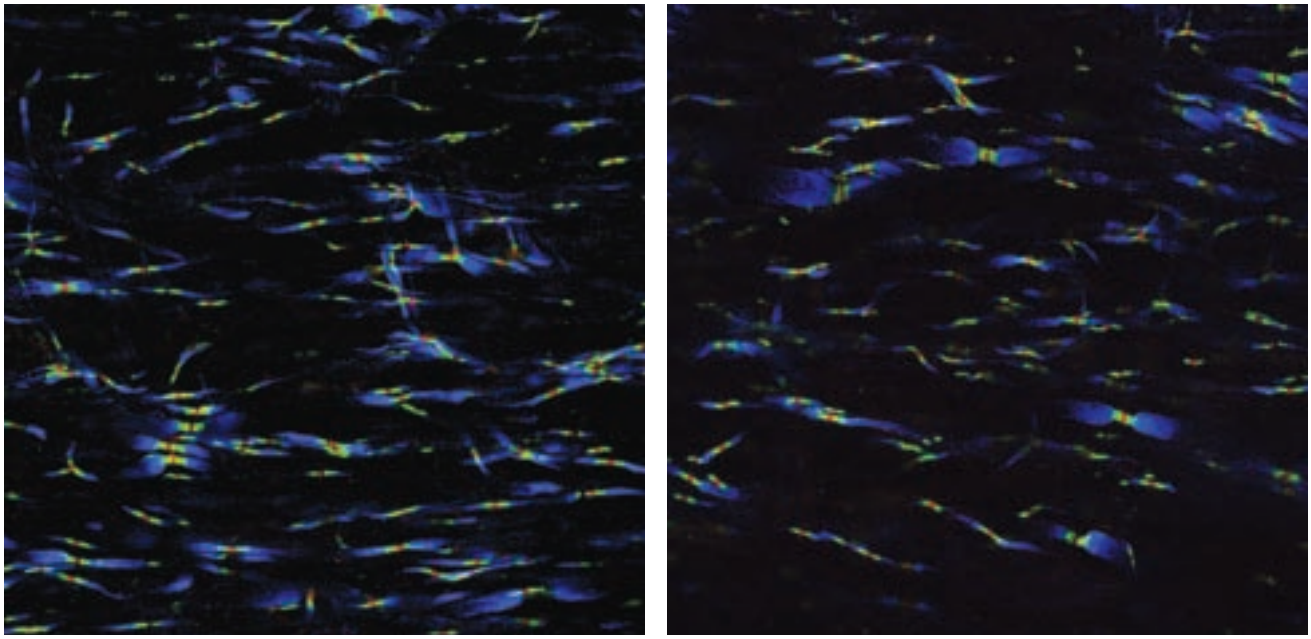
We set about to develop a method for visualizing the nodes of Ranvier, both in healthy and in inflamed mouse spinal cord sections. We used confocal microscopy, which allowed us to focus on a flat focal plane less than 0.5 μm thick. This approach enabled us to see very small structures at quite high resolution. We performed pilot studies using dozens of tissue markers and many different ways of preparing spinal cord tissues for our studies.

Finally, we arrived at our goal: sharp, clear pictures showing nodes of Ranvier and the adjacent myelin structures in mouse spinal cord, from both healthy and inflamed tissues (Figure 2).

Next Goal: Illuminating the Macrophage Attack

We are now ready to embark on our next adventure: illuminating the macrophages as they attack these tissues and searching for their molecular targets. Stay tuned.

Figure 2. *Confocal microscopy images showing nodes of Ranvier in the spinal cords of a healthy mouse (left) and a mouse at the earliest stage of EAE (right). The blue, green and red structures in the left panel show the nodal elements as they should appear. The right panel shows swelling of the blue structures and lengthening of the green structures in some nodes. We hypothesize that these changes may expose markers recognized by invading macrophages.*



Dr. Ransohoff recently retired from long-standing appointments in Cleveland Clinic's Neurological Institute and Lerner Research Institute to continue in the private sector his research into the pathogenesis and treatment of neurological disease. He remains Adjunct Professor of Molecular Medicine at Cleveland Clinic Lerner College of Medicine. He can be reached at rransohoff@gmail.com.

Dr. Lu is a research associate in the Department of Neurosciences. She can be reached at luh@ccf.org or 216.444.0637.

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KEY POINTS

- Using serial block-face scanning electron microscopy and confocal microscopy, our research team obtained high-resolution images showing that inflammatory demyelination in a mouse model of MS begins with attraction of macrophages to nodes of Ranvier.
- This provocative finding has prompted our team to begin related studies to illuminate macrophages as they attack nodes of Ranvier and adjacent myelin structures and to search for their molecular targets.

SEEG in Pediatric Patients with Refractory Epilepsy: Growing Experience Supports Safety and Efficacy

By Deepak Lachhwani, MD, and Jorgé Gonzalez-Martinez, MD, PhD

Stereoelectroencephalography (SEEG) is a methodology for exploring surgical resection strategy in medically refractory patients suspected of having focal epilepsy. SEEG involves the temporary surgical implantation of electrodes that enable simultaneous recording of electrical activity from many parts of the brain at high temporal resolution (~ 1 ms), which is used to identify the epileptogenic zone.

SEEG involves relatively minimal risk of morbidity and mortality, and its results have aided the planning of surgical resection in appropriate candidates and the decision to avoid resection in patients deemed to have a poor prognosis.

Cleveland Clinic's SEEG Experience

Our institution has seen steady growth in the use and acceptance of this methodology based on some distinct merits of SEEG relative to other methods of invasive evaluation, such as subdural grids.

In our recently published series[1] of 28 pediatric patients who underwent SEEG evaluation, 18 of 28 were able to undergo resection; of these 18 patients, 13 had improvement in their seizure control and five became seizure-free.

An Illustrative Case

Careful review of patient profiles highlighted that SEEG-related advantages are especially relevant in young patients, such as patient BB featured in Figures 1 and 2. By the age of 2 years 5 months, BB had failed to respond to multiple seizure medications and the first attempt at tailored resection (guided by subdural grids) of the presumed seizure focus in her left frontal lobe. Frequent and intense daily seizures significantly impaired her quality of life.

BB's family arrived at our institution for a second opinion, and we recommended SEEG as the methodology of choice to explore surgical treatment options. At the age of 3 years 4 months, BB became the youngest of our patients to undergo successful SEEG implantation, which was followed by resection within six weeks. She has remained seizure-free for more than 18 months since the surgery.

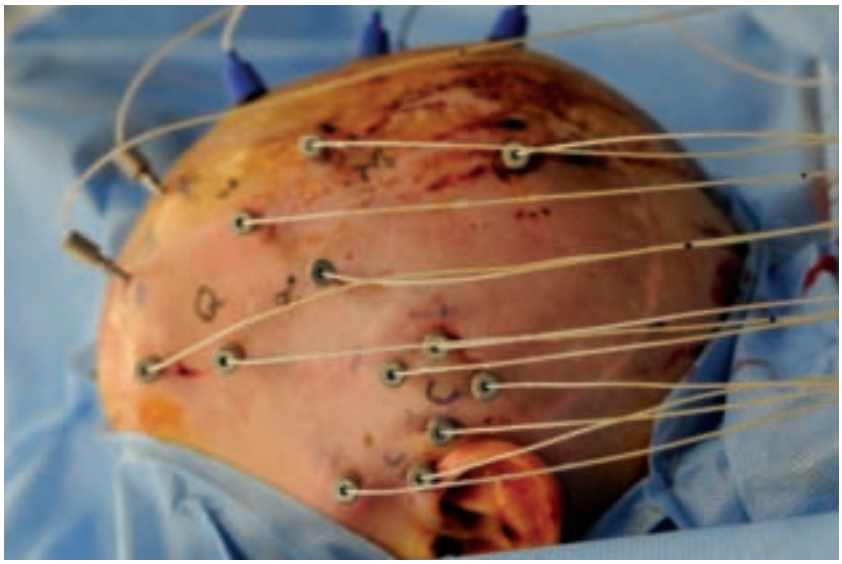
SEEG's Advantages

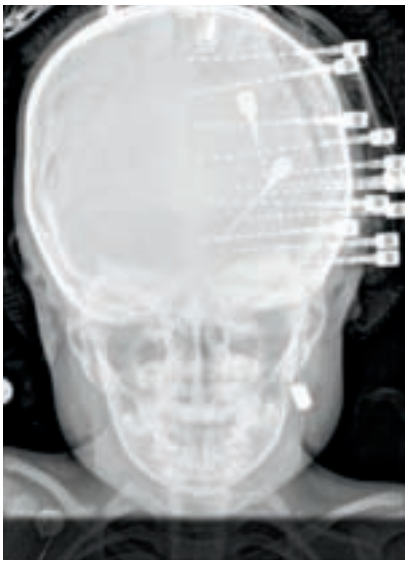
Our experience with SEEG has provided these insights:

- **SEEG is effective.** Invasive recordings are intended for the very specific result of identifying or excluding surgical candidacy. In epilepsy patients with difficult-to-localize epilepsy, it is sometimes necessary to sample widely separated candidate areas within one hemisphere (e.g., the frontal and occipital lobes) or to exclude potential bihemispheric epileptogenicity before offering a tailored resection. SEEG allowed us to offer resection to 64 percent of the patients in our published series (18 of 28); poor surgical candidacy was confirmed in the remaining patients due to nonlocalizable or multifocal ictal onset or location of the epileptogenic zone within the eloquent cortex. SEEG allowed us to strategically sample and evaluate depths of cortical gyri and widely separated and even bilateral regions with the help of small burr holes.
- **SEEG is efficient.** Exploring surgical candidacy with SEEG methodology does not require craniotomy. Electrodes are placed by robotic technology with the help of stereoscopic guidance in an angiography suite. This process is completed within two to three hours. Compared with a craniotomy carried out in an operating theater — requiring more than six hours and deployment of many more resources — SEEG stands out as an efficient procedure.
- **SEEG has reduced morbidity.** Subdural grid electrode placement requires exposure of the brain surface using a large craniotomy. Placement of SEEG electrodes is performed through small pinholes. Obviating the need for craniotomy reduces blood loss and pain. Young patients are less likely to need aggressive pain control and 24 to 36 hours of recovery in the ICU before transfer to the monitoring unit to initiate seizure recording. These aspects make SEEG a less morbid procedure.
- **SEEG is safe.** Only one of the patients in our series experienced complications related to lead implantation, monitoring or lead removal. This patient experienced a CSF leak that was successfully treated. There were no other serious morbidity or mortality issues.
- **SEEG extends the time to resection, allowing for a more thoughtful informed consent process.** In the typical course of invasive evaluation with subdural grids, the patient undergoes a craniotomy for implantation of electrodes based on the preoperative hypothesis of seizure foci. After a variable delay of seven to 10 days during which seizures and cortical mapping data are analyzed, the patient undergoes a second craniotomy for removal of electrodes and resection of the proposed epileptogenic zone. SEEG does not involve a craniotomy at the time of electrode implantation or explantation. Implantation is carried out via small burr holes based on preplanned strategy, and explantation

SEEG allowed us to offer resection to 64 percent of the patients in our published pediatric series.

Figures 1 and 2. *Images of patient BB at 3 years 4 months of age. Figure 1 (left) is an operating room photo showing the implanted SEEG electrodes. Figure 2 (right) is a skull X-ray demonstrating positioning of the SEEG electrodes. BB has remained seizure-free for more than 18 months since her surgery.*





involves a sterile pullout of these electrodes. Resection of the proposed epileptogenic zone is carried out after a minimum delay of six weeks postimplantation to allow the brain to heal from the procedure and to minimize infection risk. The delay to surgery may be perceived as a disadvantage, but the chance to evaluate gathered data without the rush to proceed to resection at the time of a second craniotomy is a definite upside. Moreover, the postimplantation period allows additional time for a more detailed and thoughtful informed consent process. Patients can return home and then decide regarding surgical intervention.

A Solid Method for Identifying Surgical Candidates

We conclude that our ongoing experience weighs strongly in favor of SEEG as a safe and effective methodology for identifying young candidates who are suitable for surgical treatment of refractory epilepsy.

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KEY POINTS

- Stereoelectroencephalography (SEEG) uses temporarily implanted electrodes to perform simultaneous, multisite, high-resolution recording of electrical activity in patients with medically refractory epilepsy, aiding in decision-making regarding surgical resection.
- Cleveland Clinic's experience with SEEG in pediatric patients has shown SEEG to be safe, efficient and effective at identifying resection candidates while reducing patient pain and morbidity relative to subdural grid electrode placement and craniotomy.

6 Clicks Tool: Validation Studies Confirm Its Reliability in Promoting Appropriate Rehab Referrals and Discharge Planning

By Frederick S. Frost, MD; Mary Stilphen, PT, DPT; and Vinoth K. Ranganathan, MSE, MBA

Since 2011, rehabilitation professionals across the Cleveland Clinic health system have systematically employed 6 Clicks, a pair of electronically administered questionnaires designed to measure the functional status of patients in the acute care hospital. Hospital systems across the United States have embraced the tool as a means of rationalizing therapy delivery and improving patient-centered discharge planning.

6 Clicks at a Glance

6 Clicks, conceived and designed at Cleveland Clinic in collaboration with Boston University's Rehabilitation Outcomes Center, is named for the six questions in each of two outcomes measurement tools that standardize the assessment of hospitalized patients' mobility and self-care abilities. To date, Cleveland Clinic staff have logged more than a half million outcomes measurements using the tools.

This screening instrument helps determine appropriate patient referrals for physical and/or occupational therapy, aids in discharge planning, and improves the allocation of treatment resources and personnel. The objective is to reduce overall hospital therapy costs while maintaining quality.

6 Clicks' queries are derived from the Activity Measure for Post-Acute Care™ (AM-PAC™), a comprehensive set of patient outcome measures developed by Boston University researchers.

6 Clicks' questions address a patient's ability to turn in bed, sit, transfer from bed to chair, stand, walk, eat, dress, bathe, perform personal care and use the bathroom. The questions can be answered by a patient or a surrogate and are scored from 1 to 4 by physical or occupational therapists using direct observation of the activity in question or the therapist's clinical judgment about the patient's probable ability. The scores are entered into the patient's electronic medical record and kept as discrete data fields.

Nurturing a 'Culture of Mobility'

Cleveland Clinic's experience to date with 6 Clicks in more than 577,000 patients has produced a number of insights. The tool has:

- Increased productivity without sacrificing clinical care. We have reduced the number of unnecessary physical therapy visits (Figure 1) and have consequently been able to reposition resources, such as providing an increased physical therapy presence in the intensive care unit, enabling earlier intervention.
- Streamlined the patient discharge process through early identification of discharge disposition to long-term acute care, a skilled nursing facility, an inpatient rehabilitation facility or home.
- Helped educate physicians and nurses about which patients are appropriate referrals for physical and/or occupational therapy.
- Nurtured a "culture of mobility" among the nursing staff by providing guidance on which patients are capable of ambulating without a physical therapist present. Patients with a 6 Clicks score of 18 or above need only minimal help with activities, and the nursing team is tasked with mobilizing them before consulting physical therapy.

Validation Studies Confirm Value

Two studies published in 2014[1,2] have validated 6 Clicks' accuracy in predicting patients' need for therapy in the acute care setting and in predicting the appropriate discharge setting. A third study[3] verified the interrater reliability of 6 Clicks' measures. The research was a collaboration involving Cleveland Clinic, Boston University and the University of Vermont.

We confirmed the validity of 6 Clicks' basic mobility and daily activities scores in assessing the activity limitations of patients with a wide variety of medical and surgical conditions in an acute care setting. We also found that 6 Clicks scores derived from the initial physical therapy and occupational therapy visits showed fair accuracy in determining patients' discharge destination (Figures 2 and 3). Finally, using pairs of physical and occupational therapists rating the same patients and blinded to each other's 6 Clicks scores, we found that overall intraclass correlation coefficients were very high, with levels of agreement that varied across the pairs of raters, from large to nearly perfect for physical therapists and from moderate to nearly perfect for occupational therapists.

Taken together, the findings further verify 6 Clicks' ability to provide valuable guidance in rehabilitation patient care and resource allocation decisions.

In the future, we hope to validate the use of 6 Clicks by nursing personnel and other members of the medical team.

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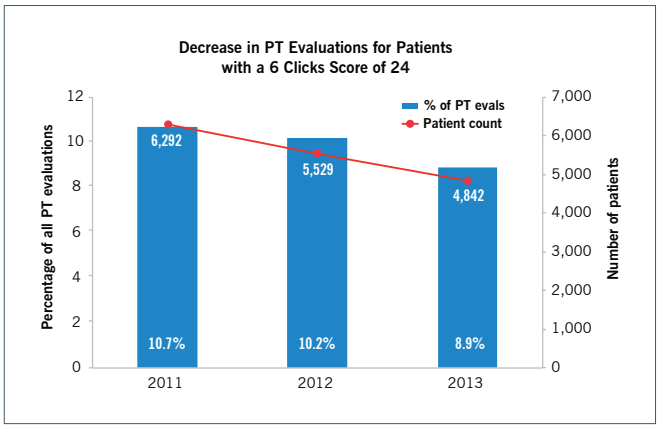

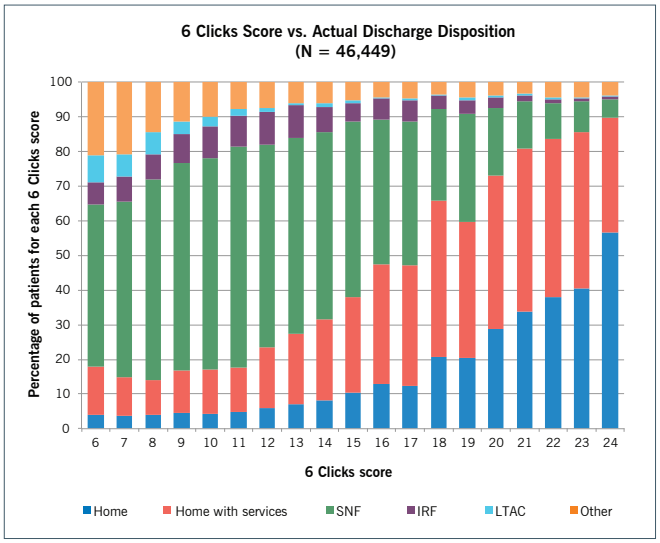

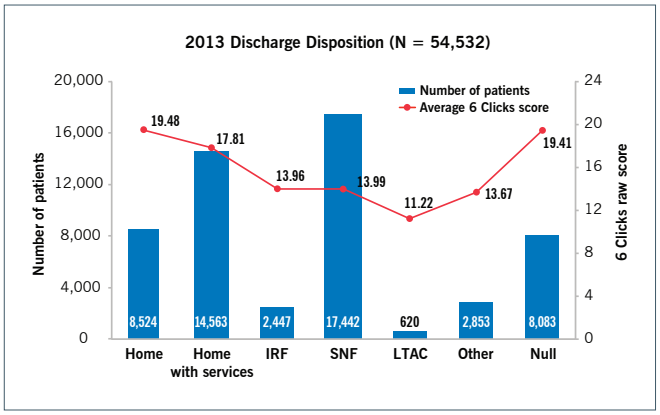

Figures 1, 2 and 3 *(top to bottom).*

PT = physical therapy;
SNF = skilled nursing facility;
IRF = inpatient rehabilitation facility;
LTAC = long-term acute care.

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KEY POINTS

- 6 Clicks is a short set of electronically administered questions that assesses mobility and basic functional capabilities.
- Cleveland Clinic's experience with 6 Clicks in more than 577,000 patients has demonstrated its value in aiding rehabilitation referrals and discharge planning, as well as in improving resource allocation.
- Three recent studies have confirmed 6 Clicks' accuracy and reliability.

Targeting Sleep Disorders to Improve Neurologic Outcomes: Impact of PAP Therapy in Epilepsy Patients with Obstructive Sleep Apnea

By Nancy Foldvary-Schaefer, DO, MS

Obstructive sleep apnea (OSA) is highly prevalent, affecting a reported 24 percent of U.S. men and 9 percent of U.S. women.[1] As those rates are based on studies from the 1990s, when obesity rates were lower than current estimates, OSA prevalence today may be even higher.

The potential impact of OSA and other sleep disorders on patients with neurological disorders is becoming increasingly apparent. OSA has been observed to be highly prevalent in those with pharmacoresistant focal epilepsy, which suggests that ongoing untreated OSA may contribute to epilepsy pathophysiology.[2] In a recent study of 130 adults with epilepsy unselected for sleep complaints, we found a 30 percent prevalence of OSA and a 16 percent prevalence of moderate to severe OSA.[3]

OSA Therapy and Seizures: What Do We Know?

Although several studies show that treatment of OSA with positive airway pressure (PAP) therapy or upper airway surgery improves seizure control in some cases, these studies are limited by small sample sizes.[4,5] While not directly confirmed, sleep deprivation and fragmentation are proposed mechanisms for the seizure-promoting effects of OSA in epilepsy and the reduction in seizures observed with PAP therapy. Whether exposure to intermittent hypoxia, autonomic dysregulation and upregulation of systemic inflammation — mechanisms by which OSA contributes to cardiovascular and metabolic disorders — impacts epilepsy outcomes is unknown.

To shed light on this and related questions, our group recently sought to examine the effect of PAP therapy on seizure frequency in a large cohort of adults with epilepsy and suspected OSA referred for polysomnography.[6]

Our Analysis at a Glance

We undertook a retrospective review of adults with epilepsy who underwent polysomnography at Cleveland Clinic from 1997 to 2010.[6] Patients were divided into three groups for comparison of seizure outcomes based on the presence/absence of OSA (apnea-hypopnea index [AHI] ≥ 5) and whether it was treated, as follows:

- Those without OSA (AHI < 5)
- Those with PAP-treated OSA
- Those with untreated OSA (intolerant of PAP or declined treatment)

Adherence to PAP therapy was defined as complete (≥ 4 hours/night for ≥ 70 percent of nights) or partial (lesser amounts of use). The following seizure measures were calculated for all groups:

- Percentage change in monthly seizure frequency from baseline to one-year follow-up (for all subjects)
- Percentage of subjects with ≥ 50 percent seizure reduction ("responder rate," for subjects not seizure-free at baseline)
- Percentage of subjects with successful outcomes (≥ 50 percent total seizure reduction in patients not seizure-free at baseline, or continued seizure freedom in those seizure-free at baseline)

Results: Promising Effects from PAP Therapy

The analysis included 132 subjects (65 percent female) with a mean age of 40.2 ± 13 years. Among the overall sample, 76 patients (57.6 percent) had OSA; of these, 43 (56.6 percent) were on PAP therapy and 33 (43.4 percent) were untreated. Within the PAP-treated group, 83.7 percent of patients were fully adherent.

Subjects without OSA were significantly younger, were significantly more likely to be female and had significantly lower body mass index (BMI) compared with the two OSA groups. Age, gender and BMI did not differ between the PAP-treated OSA and untreated OSA groups.

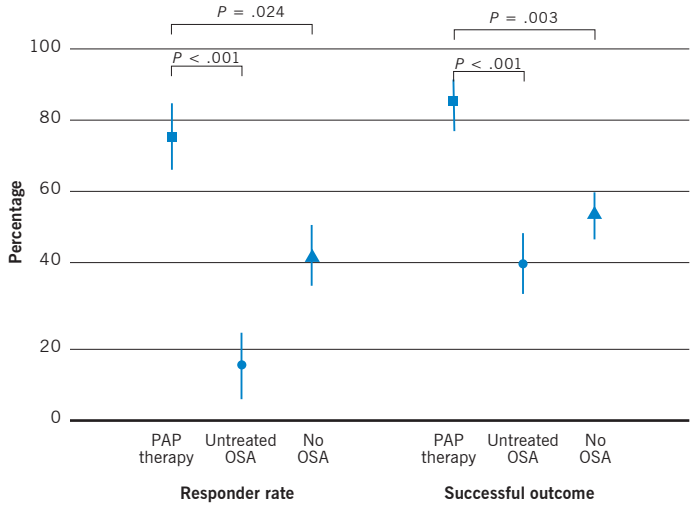
Mean monthly baseline seizure frequency was 3.9 and did not differ significantly among the groups. The standardized antiepileptic drug dose change from baseline to follow-up, a measure of drug burden, was minimal and not significantly different among groups.

Key seizure outcomes[6] were as follows:

- Seizure reductions at follow-up were significantly greater in the PAP-treated OSA group compared with the other groups.
- Among subjects not seizure-free at baseline, the responder rate was highest in the PAP-treated OSA group (73.9 percent), although the difference vs. the other groups reached statistical significance only compared with the untreated OSA group (14.3 percent; $P < .001$), not the group without OSA (40.5 percent) (Figure).
- In contrast, the successful outcomes rate (defined in above bullet list) was significantly higher in the PAP-treated group (83.7 percent) relative to both the untreated OSA group (39.4 percent; $P < .001$) and the group without OSA (53.6 percent; $P = .003$) (Figure).

Seizure outcomes were not significantly different between subjects with mild vs. moderate to severe OSA, or between those with focal vs. generalized epilepsy.

Figure. *Graph showing responder rate (i.e., percentage of subjects achieving ≥ 50 percent seizure reduction) and successful outcomes rate (i.e., percentage of subjects achieving ≥ 50 percent seizure reduction or maintaining seizure freedom if seizure-free at baseline) among the three patient groups (N = 132). The significance threshold for between-group comparisons was* P < *.017.*



Bolstered Support for Seizure Control as an OSA Treatment Benefit

OSA is characterized by recurrent sleep-related respiratory events associated with arousal or oxygen desaturation. The result is typically a state of chronic sleep deprivation and a host of medical and psychosocial comorbidities. Although weight loss and lifestyle modification are central to OSA treatment, PAP therapy is first-line treatment for moderate to severe disease. PAP therapy eliminates respiratory events, arousals and oxygen desaturations, thereby reducing daytime sleepiness, cognitive impairment and blood pressure while also improving mood and metabolic and cardiovascular outcomes.[7]

Given that seizures are incompletely controlled in 30 to 40 percent of individuals with epilepsy, the need for a better understanding of the impact of sleep comorbidities in epilepsy is compelling.[8] Taken together with prior investigations, our work supports adding seizure control to the list of beneficial effects of treating OSA and underscores the importance of routine OSA screening in epilepsy populations regardless of epilepsy type or seizure status.

ACKNOWLEDGMENTS

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KEY POINTS

- A large retrospective analysis at Cleveland Clinic found that positive airway pressure therapy appears to produce beneficial effects on seizures in adults with epilepsy and obstructive sleep apnea (OSA).
- Our findings, taken together with prior studies, support counting seizure control among the beneficial effects of treating OSA. They also underscore the importance of routine OSA screening in epilepsy populations regardless of epilepsy type or seizure status.

Concurrent Multiple Sclerosis and Cervical Stenosis: Insights into a Treatment Dilemma from the Largest Study to Date

By Daniel Lubelski, BA, and Thomas E. Mroz, MD

A Confounding Combination

The clinical presentation and symptom progression of multiple sclerosis (MS) can overlap with those of other pathologies, making the underlying condition difficult to diagnose and treat. Specifically, cervical stenosis with myelopathy (CSM) can present with MS-like symptoms including gait ataxia, extremity weakness, spasticity and sensory loss due to spinal cord compression. When the two diseases occur concurrently (Figure), management is exceedingly difficult. While MS therapy involves immunomodulatory medications, CSM is often treated with surgical decompression. Furthermore, it is difficult to discern which disease process is responsible for the symptoms.

A literature search is not particularly helpful, as only a small number of case series with few patients have addressed this clinical dilemma. Assessment of outcomes in this unique patient cohort is difficult, as most institutions lack a sufficiently large patient volume to allow data aggregation and meaningful analysis.

Leveraging Volume and Expertise for Guidance

To overcome these challenges, researchers from two areas within Cleveland Clinic's Neurological Institute — the Center for Spine Health and the Mellen Center for Multiple Sclerosis Treatment and Research — pooled our centers' respective high patient volumes and specialized clinical expertise in treating these patients. Specifically, we performed a retrospective cohort-controlled analysis of postoperative outcomes of all patients with coexistent MS and CSM who underwent cervical decompression surgery at Cleveland Clinic from 1996 to July 2011.[1]

We collected data on patient demographics, preoperative symptoms and presentation, and pre- and postoperative severity of myelopathy as measured using the Nurick scale and the modified Japanese Orthopaedic Association (mJOA) classification of disability. Diagnoses of CSM were made by Center for Spine Health spine surgeons, and MS diagnoses and classifications were made by Mellen Center neurologists specializing in MS.

Largest Study to Date

The study included 154 patients in all — 77 patients with concurrent MS and CSM plus 77 individually matched control patients with CSM alone who underwent cervical decompression surgery. Mean postoperative follow-up was 58 months and 49 months for the respective groups. This was the largest such study in the literature, as previous studies have included between seven and 17 patients. It was also the first to include a matched control population.

Findings: Presentation and Symptom Resolution

We found that patients with CSM alone (control group) were significantly more likely to present with a main complaint of neck pain (78 percent vs. 47 percent, $P = .0001$) and radiculopathy (90 percent vs. 75 percent, $P = .03$) relative to those with both MS and CSM.

Following surgery, patients with MS and CSM had significantly lower rates of resolution of myelopathic symptoms. In the short term, 23 percent of patients in the control group did not improve vs. 39 percent in the MS/CSM group ($P = .04$); in the long term, 19 percent of the control group did not improve vs. 44 percent of the MS/CSM group ($P = .004$).

Findings: Myelopathy Scores

Analysis of Nurick and mJOA scores showed that although there were no significant between-cohort differences in the short term following surgery, there was a significant difference in the long term (i.e., at last follow-up visit):

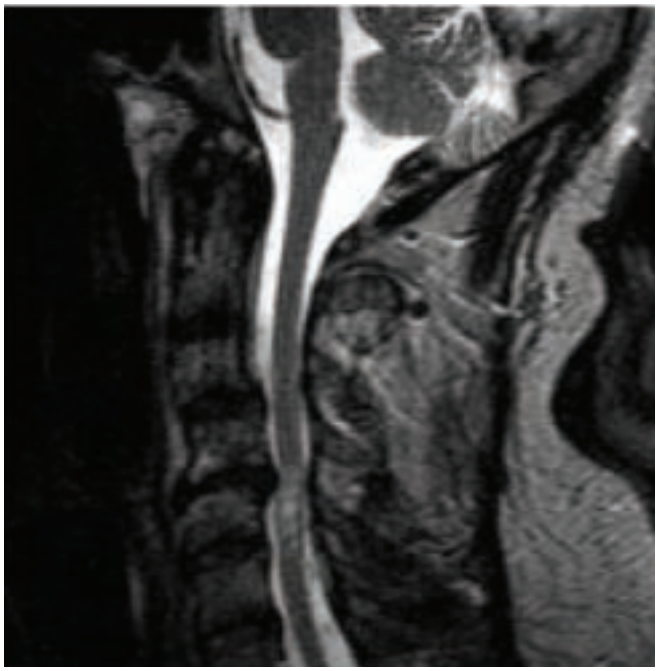
- For patients with both MS and CSM, the mean change in Nurick and mJOA scores from preoperative levels to last follow-up was a worsening of scores by 0.5 points and 1.3 points, respectively.
- For control patients, the mean change was an improvement of scores by 0.3 and 1.3 points on the respective scales.

This translates to a between-cohort difference in mJOA score change of 2.6 points (i.e., a decrease of 1.3 for the MS/CSM group and an increase of 1.3 for the control group). This difference is greater than the 2-point minimal clinically important difference that has been previously described,[2] suggesting that this difference is not only statistically significant ($P < .0001$) but also clinically relevant.

Impact of MS Subtype

Further analysis aimed to determine the impact of MS subtype on postoperative outcome. We found a strong trend toward higher rates of long-term improvement or resolution of myelopathic symptoms in patients with the milder relapsing-remitting form of MS compared with more severe MS subtypes, but it did not reach statistical significance. By the last follow-up visit, 64 percent of patients with relapsing-remitting disease showed improvement or resolution of myelopathic symptoms vs. 47 percent of patients with primary progressive MS and 27 percent of patients with secondary progressive MS.

Figure. *Sagittal T2-weighted MRI of a patient with MS and cervical stenosis with myelopathy.*



Implications for Clinical Practice

Myelopathic patients with coexisting MS and CSM have a distinct presentation relative to those with only CSM. Our data suggest that surgery should be considered for patients with this unique presentation of MS and CSM. These patients should be informed that their MS confers a greater likelihood that their myelopathic symptoms may not be alleviated or be alleviated only temporarily, but that surgery can help alleviate neck pain and radicular symptoms, if present. Finally, the strong trend toward better outcomes in patients with relapsing-remitting MS relative to those with primary and secondary progressive MS should inform patient counseling as well.

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Dr. Mroz is Director of the Spine Surgery Fellowship and a spine surgeon in the Center for Spine Health in Cleveland Clinic's Neurological Institute. He can be reached at mrozt@ccf.org or 216.445.9232.

We found a strong trend toward higher rates of long-term improvement or resolution of myelopathic symptoms in patients with relapsing-remitting MS compared with more severe MS subtypes.

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KEY POINTS

- Patients with concurrent MS and cervical stenosis with myelopathy (CSM) are less likely to present with preoperative neck pain and radiculopathy compared with patients who have CSM alone.
- A significantly higher proportion of patients with MS and CSM do not have improvement in myelopathic symptoms following cervical decompression surgery compared with matched patients with CSM alone.
- Among patients with concurrent MS and CSM, those with relapsing-remitting MS have better outcomes following surgery for CSM relative to those with primary or secondary progressive MS.

Lessons from the Care Path: Insights on the Neurological Institute's Lead Quality and Value Initiative

By Irene Katzan, MD, MS, and Nancy Papesh, RN, MBA

Over the past three years, Cleveland Clinic has put great effort into developing condition-specific care paths for each of the health system's clinical institutes. The initiative emphasizes value-oriented care through the use of process-based tools to operationalize evidence-based practice guidelines and guide clinical work flow. The Neurological Institute is leading the charge, with more than two dozen care paths completed or under development.

By design, the care paths align with national initiatives centered on value-based care and reimbursement, patient satisfaction, and leveraging healthcare IT to measure patient-centered outcomes and drive quality. As providers and payers place ever more emphasis on these factors, we share here some lessons learned from development of the Neurological Institute's care paths to date.

Illuminating a Dark Room

The timeline from conceptualizing a care path to implementing it within the electronic medical record (EMR), if appropriate, stretches over about 18 months. The process involves:

- **Developing consensus-driven care path guides** based on literature evidence, clinical guidelines and clinician experience
- **Pilot testing algorithms developed from the care path guides** and analyzing meaningful patient outcomes and relevant process metrics before and after implementation
- **Making updates as needed,** based on the pilot tests
- **Implementing a technology "build-out"** to integrate care path algorithms into the EMR and incorporate them into the clinical work flow

As of mid-2014, three Neurological Institute care paths — for spine care, stroke and concussion — had reached the EMR integration stage.

We sometimes compare the creation of care paths, and their related guides and algorithms, to switching on a light in a dark room. If the care path ends up being electronically implemented as well, the brightness in the room can be particularly illuminating. Below are topically grouped insights that have come to light as the Neurological Institute has developed and implemented its care paths thus far.

Lessons from Care Path Guide Development

Care path guides have proved to be game-changers in reducing variability of care and unnecessary cost. The guides serve as critical, consensus-based road maps. Together with related algorithms and work flows, the guides are "exportable" across all Cleveland Clinic practice settings — and potentially to other health systems in the future. They are adaptable enough to be integrated into any institution's EMR system and can even be used as a nonelectronic clinical tool.

What Is a Care Path?

Cleveland Clinic care paths start with evidence- and consensus-based care path "guides" — succinct documents detailing the appropriate steps in patient management for the condition at hand, with supporting rationales. The guides, which are developed by multidisciplinary teams of Cleveland Clinic experts, are then translated into algorithms and work flows for practical application. The care path initiative then focuses on three main objectives:

- Standardizing clinical management around the care path guide, with a focus on value-based, patient-centered care
- Integrating work flows and algorithms into the electronic medical record where appropriate
- Tracking patient-reported outcomes to drive care

The overarching goal is to make it easier to consistently deliver the most evidence-based care possible — and to continually measure and improve care quality, with an emphasis on patient-reported outcomes.

We've learned that:

- **Care path guides are not to be applied generically.** Care path guides are essential to create a standardized system of care that emphasizes algorithms that everyone agrees are important, but care still must be individualized. "Cookie-cutter care" is not part of the equation.
- **"Usual suspects" emerge — and need to be addressed.** Regardless of the disease, improving value often involves similar themes. These include overprescribing (and sometimes underuse) of therapies, medications or imaging. We are finding better ways to integrate the concept that "less care is sometimes better care" into our work flows while always honoring the principle that appropriate care must never be reduced.
- **Ownership among all stakeholders is key.** Development of care path guides must be driven by those who will use them. It involves unified input and buy-in from all key stakeholders and specialists across relevant disciplines. Stakeholders are kept current on pilot testing and updates to the guides. This approach tends to produce a sense of ownership and support that will drive successful implementation following care path rollout.

Lessons from Pilot Projects

Care paths undergo pilot testing, typically at Cleveland Clinic community hospitals, to ensure that they are achieving their goals of improving consistency with evidence-based practice and avoiding unnecessary costs.

We've learned that:

- **Pilot testing provides proof of concept and allows fine-tuning before implementation.** A pilot study of the Headache Care Path in the emergency department of one community hospital achieved a 75 percent reduction in opioid prescribing. In pilot testing of the Spine Care Path, opioid prescriptions and premature imaging were both reduced by about 50 percent. Other pilot tests have flagged algorithms or processes that needed refining, prompting changes before full care path rollout.
- **Initial pilot data demonstrate cost reductions.** Our pilots have shown that in the acute phase of care, consistent use of a care path can reduce costs by up to 50 percent. Future efforts will aim to determine whether such cost reductions are maintained over time without reductions in care quality.

Lessons in EMR Integration

When a care path is integrated into the EMR work flow, data are collected to (1) carry out ongoing analysis; (2) generate condition-specific metrics for individual physicians, departments and facilities; and (3) drive continuous quality improvement. Care path tools tied to the EMR include standardized documentation templates, order sets, and clinical decision-support and predictive analytic tools.

We've learned that:

- **We must choose which care paths to prioritize for full EMR integration.** Not all care paths require full EMR integration. Those that span several subspecialties with a focus on multidisciplinary care (e.g., the Stroke Care Path) are the best candidates, to help support coordinated and consistent delivery of especially complex care. In contrast, other care paths may serve chiefly to guide primary care referral to a specific type of specialist for a given condition, which typically doesn't require EMR integration. Prioritizing care paths for EMR integration promotes the best use of resources to maximize impact on patient outcomes and the value of care delivered.
- **Patient "red flags" should be considered in EMR algorithms.** For example, in the Spine Care Path, 12 red-flag questions are included to detect the potential for serious underlying causes of back pain that may require earlier imaging or other testing than is generally recommended.
- **Measuring patient-reported outcomes (PROs) is essential.** PRO tracking is critical to patient-centered care. Traditional collection of only objective outcomes — such as the number of seizures a patient on antiepileptic medication is having — does not serve patients well enough. Value-oriented care requires capturing outcomes on functional and quality-of-life measures as well, such as whether the medication makes a patient sleepy or dizzy. PRO tracking — which Cleveland Clinic achieves via its Knowledge Program© data collection system — goes beyond traditional end points to regularly assess how patients are faring on measures they deem important so we can better guide their care.

The Present and the Future

As the Neurological Institute develops care paths for additional disease states, we are continuously refining existing care paths, as follows:

- **Staying current.** Care paths are updated at least annually — and more often when needed to reflect serious FDA warnings or new clinical guidelines.
- **Coordinating care.** We are examining the interface between various care paths for patients with comorbidities. For example, if a patient with diabetes and hypertension has a stroke, three care paths need to be coordinated, both logistically and electronically, and guidance is needed on which care path takes priority.
- **Ongoing monitoring.** We continue to monitor care paths' operation in real-world practice and collect information on resource utilization for comparison with pre-implementation levels.

Stay tuned. The value-based future of medicine is here, and care paths will play a pivotal role.

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KEY POINTS

- Cleveland Clinic's Neurological Institute has over two dozen condition-specific care paths completed or in development to operationalize evidence-based practice guidelines and guide clinical work flow.
- Care paths start with development of consensus-driven and evidence-based "guides," which are translated into algorithms and work flows. Next comes pilot testing and resulting refinements, followed by a technology "build-out" for integration into the EMR and clinical work flows.
- Initial care path pilot testing has demonstrated reductions in the overall cost of care delivery, and insights from our early experience include recognition that care paths must be applied flexibly, not generically; the need to judiciously prioritize care paths for EMR integration; and the importance of tracking patient-reported outcomes.

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CEO and President, Cleveland Clinic

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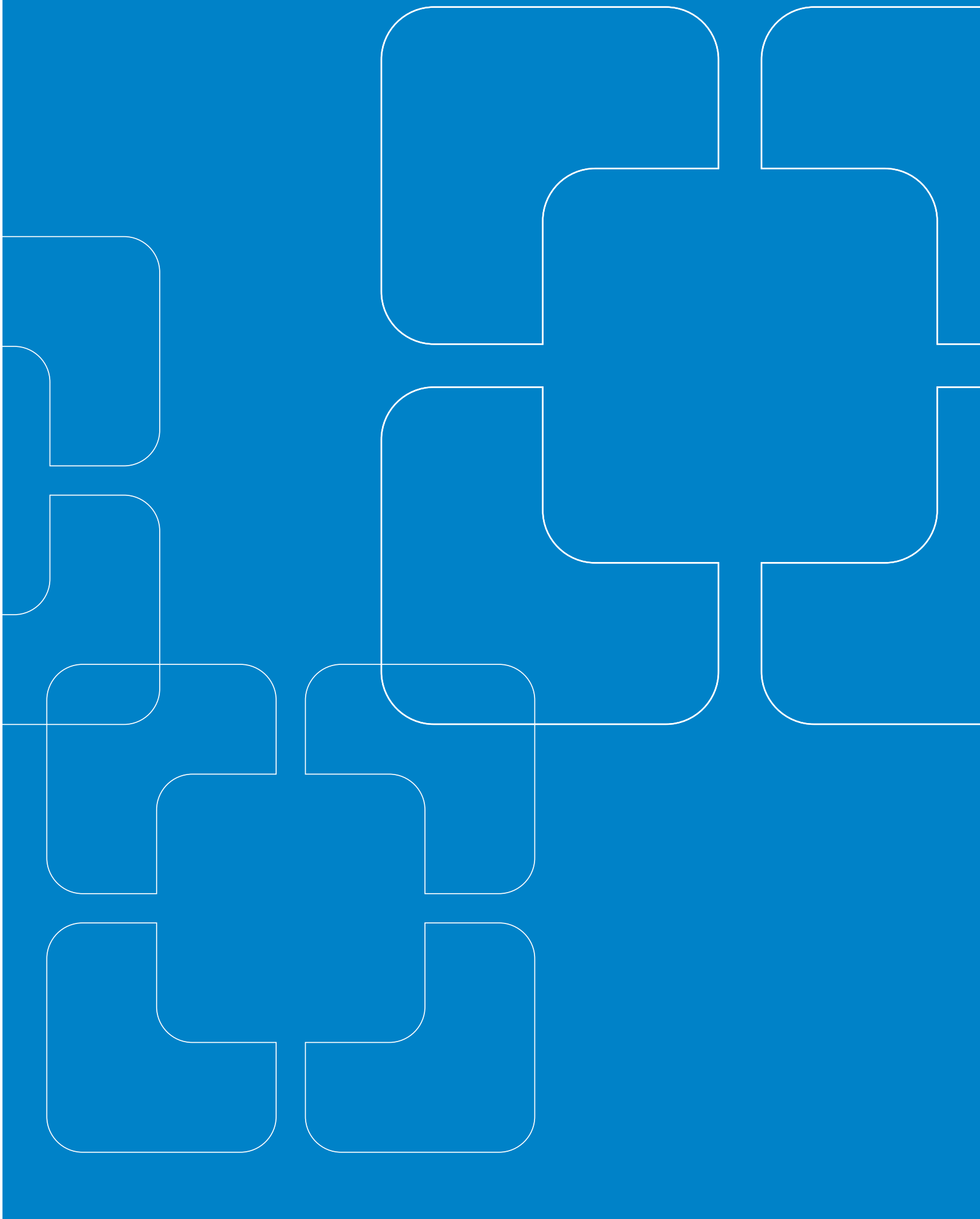

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