Cleveland Clinic

Neuroscience

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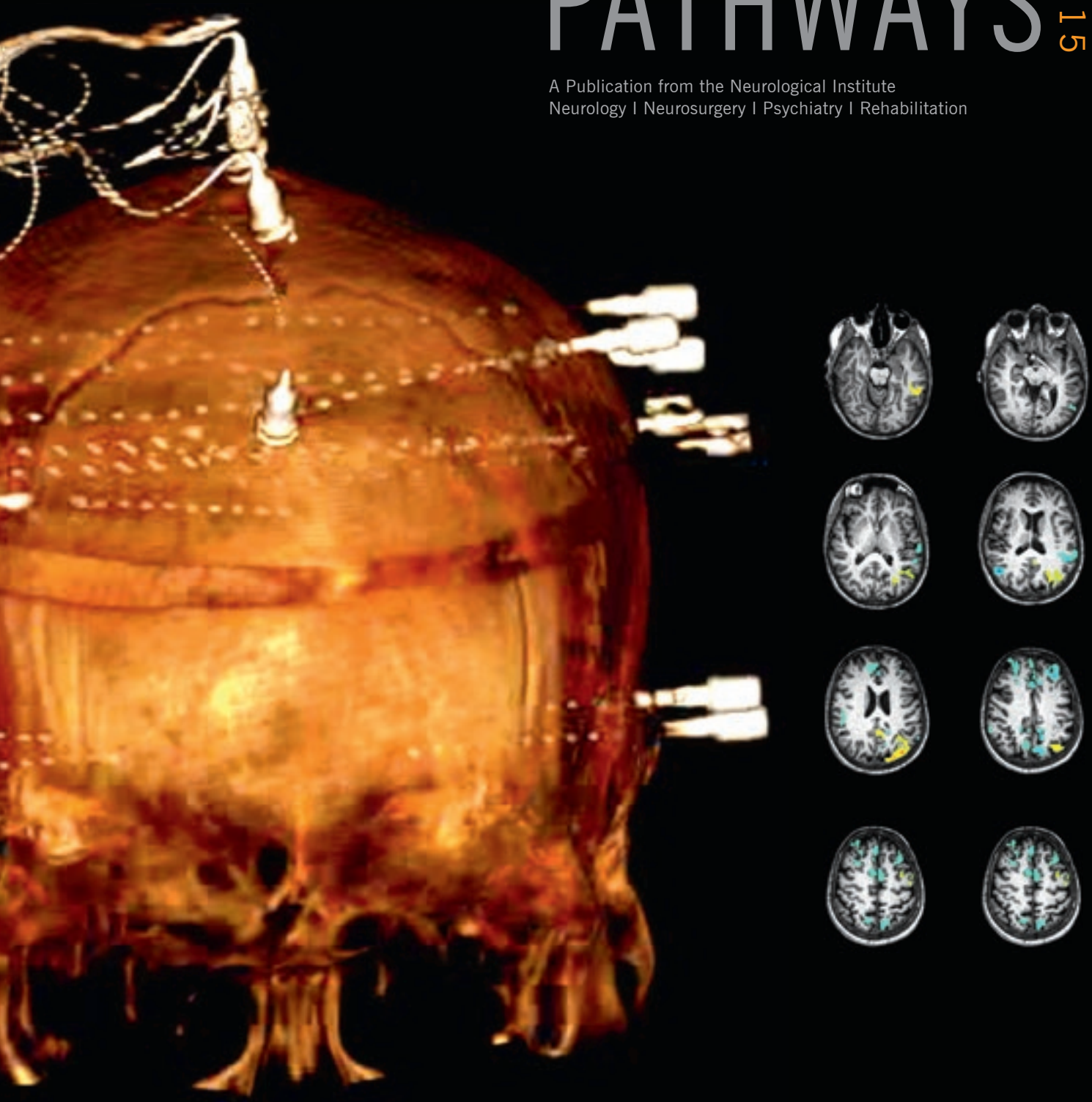
Neurology | Neurosurgery | Psychiatry | Rehabilitation



The Promise of Simultaneous Neural Stimulation and fMRI

From epilepsy to movement disorders and beyond | p. 18

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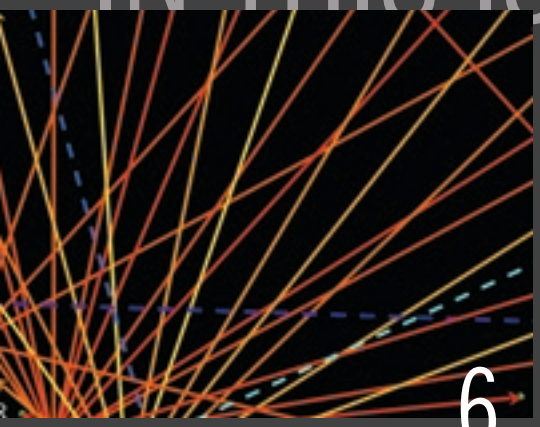
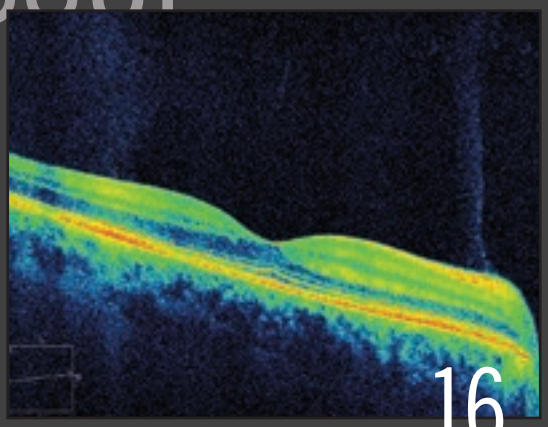
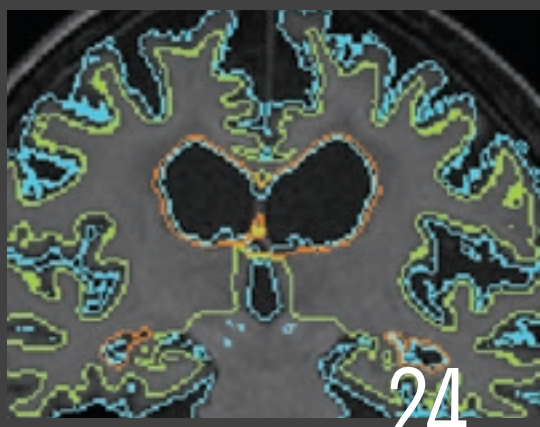






ON THE COVER: The next frontier in neurological therapies: Simultaneous use of neural electrical stimulation and functional MRI to study, diagnose and manipulate brain networks. *See article on page 18.*

DEAR COLLEAGUES,

Neuroscience is complex. Its reach sprawls across the spectrum of clinical disease, and the boundaries between its many subspecialties are often blurred and ambiguous.

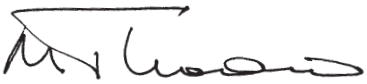
Yet that very complexity can be a powerful research asset, as the breadth of our discipline and the overlapping of its subspecialties mean that progress in one area of neuroscience often has wide-ranging implications. Advances in our field can pack an especially powerful punch.

This issue of *Neuroscience Pathways* is replete with examples from across Cleveland Clinic's Neurological Institute. First among them is the cover story (page 18), in which staff from diverse corners of our institute share how they are applying their novel technique for simultaneous neural electrical stimulation and functional MRI to more and more disease states. They show that stimulation of electrodes in neural tissue evokes a response in distal areas of the brain in similar ways across a range of diseases and clinical contexts — from epilepsy to Parkinson disease to sacral nerve stimulation for urinary incontinence. In each case much is revealed about patients' underlying brain networks. These findings lead them to conclude that techniques combining neural implants with advanced neuroimaging show great promise as the next frontier in the treatment of conditions across the spectrum of neurological disease.

A similarly promising dynamic underlies the article on page 26, which profiles exciting findings from the Trapp lab in Cleveland Clinic's Lerner Research Institute. These researchers recently published findings in the mouse that suggest for the first time that the protective role of microglia might potentially be harnessed to improve the prognosis for patients with traumatic brain injury and delay the advancement of progressive brain disorders from Alzheimer disease to multiple sclerosis. Their findings more broadly suggest that the innate immune system helps protect the brain following injury and during chronic disease — a hypothesis they believe may lead to targeted therapeutic strategies for a range of conditions.

Additional articles demonstrate how we're taking on neuroscience's complexities in increasingly collaborative ways. On page 30, we showcase how researchers from our Department of Physical Medicine and Rehabilitation are teaming with deep brain stimulation experts in our Center for Neurological Restoration to develop personalized rehabilitative care programs that draw on advanced brain mapping to adequately reflect brain plasticity. And the article on page 32 profiles the latest in a series of studies in which staff from our Sleep Disorders Center are working with Cleveland Clinic heart experts to untangle the complex, multidirectional relationships among sleep-disordered breathing, obesity and atrial fibrillation.

Neuroscience has grown far too broad and too complex for any of us to tackle its challenges alone. If you see areas for synergy in the following pages, please let us know.



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Implementing a Systemwide Delirium Management Program with EMR Tools and an Interdisciplinary Workflow

By Leopoldo Pozuelo, MD, FACP, FAPM, and Rachel Slosberg

Delirium in the hospital setting is a common and often challenging medical issue for our patients. We know of the short-term effects, such as increased morbidity, distress for the patient and caregivers, and an increased length of stay. Long-term effects have recently been described in the literature, including neuropsychological deficits that can persist for months after a patient's index hospitalization. Yet despite these substantial impacts of delirium among inpatients, education of medical professionals on the detection and management of delirium is erratic and inconsistent at best, with a more standardized approach clearly warranted.

A Delirium Task Force Is Born

In view of these challenges, Cleveland Clinic's Neurological Institute and Quality & Patient Safety Institute created a multidisciplinary and multispecialty delirium task force to achieve two goals:

- Implement systematic screening for delirium
- Develop a workflow for nurses and licensed independent practitioners (LIPs) to manage delirium more effectively

The task force took on this charge by focusing on several key component steps and accomplishments, as outlined below.

Ensuring Delirium Screening Throughout the Hospital Stay

The first step was to choose a delirium detection tool and build it into the electronic medical record (EMR) used by our health system (Epic). Nursing staff piloted and tested a selection of screening tools and chose the Brief Confusion Assessment Method (bCAM), which takes two minutes to administer. The patient is assessed daily on the medical and surgical floors, from admission through day of discharge. A similar tool (CAM-ICU) was previously implemented in our intensive care units, and assessments using it are also recorded in the EMR. The use of both of these tools allows clinicians to screen for delirium in our patient population throughout the entire hospital stay.

Building a 'Delirium Accordion' for Quick Display of All Relevant Data

Second, an electronic tool we named the Delirium Accordion was built with input from nursing, pharmacy and physician staff. This EMR-embedded tool captures all screening results for delirium and all potential causes of delirium for a given patient and displays them in a timeline fashion. Clinical data such as vital signs, laboratory values, imaging findings and medications that may be implicated in delirium are displayed in an easy-to-digest format that nurses and physicians can reference together when assessing why a patient is exhibiting delirium (Figure 1). In essence, the Delirium Accordion is a virtual tapestry into which key data points implicated in delirium cases are woven and can then be discovered.

Setting the Standard Through a Detailed Order Set

Third, a specific order set for delirium was created that contains both nonpharmacologic and pharmacologic interventions. Evidence-based interventions were reviewed and incorporated into the order set. The resulting menu of interventions, such as early patient mobilization and the use of selected medications, is designed to foster a more standardized approach that will limit inappropriate interventions and drive better outcomes. So far, early adoption of the delirium order set has been strong.

Putting It All Together

Finally, based on the foundations of the Cleveland Clinic Delirium Care Path for detecting and managing delirium, a delirium algorithm was created using the abovementioned EMR tools (Figure 2).

Together with education and online training materials, the delirium clinical tools and algorithm became available to all providers in the Cleveland Clinic enterprise in late 2014. All patients in the ICUs and on the medical and surgical floors of Cleveland Clinic hospitals are now screened daily for delirium.

The delirium management algorithm captures an enhanced workflow in which three key aspects are emphasized:

- Nursing personnel screen all patients for delirium and notify an LIP when the first delirium screening is positive.
- Nursing staff and the LIP jointly review the Delirium Accordion in the EMR to search for clues as to the cause of delirium as they examine the patient.
- The delirium order set with nonpharmacologic and pharmacologic interventions is implemented for the delirious patient.

Management of delirium in all phases (screening, detection and treatment) is a continuous process that requires nurses, pharmacists and physicians to work together, constantly ask questions and treat the delirium process. We believe that by providing delirium tools in the EMR and incorporating them in an efficient workflow, we have made these tools more user-friendly and better positioned Cleveland Clinic to ensure effective delirium management.

Current and Future Steps

An electronic dashboard was created and made available in the fall of 2015 to measure progress of the delirium management program. The dashboard captures core data such as the prevalence of delirium and the length of stay in each hospital unit. More individualized data, such as provider utilization of the delirium tools and workflow trends, are also displayed. In the context of delirium rounds and other targeted

educational efforts, we are now sharing the delirium dashboard with all clinicians to drive improved delirium care and standardization.

As familiarity with the delirium EMR tools and algorithm grows, we are better positioned to work on the next enterprise objective: delirium prevention. In keeping with the mantra of the delirium task force — "everyone owns delirium" — it is up to all caregivers to strive for continuous improvement in our approach to patients who experience delirium. The success of our initiative depends on precisely such widespread ownership, and we believe these EMR tools and algorithm are ideal tools for achieving it.

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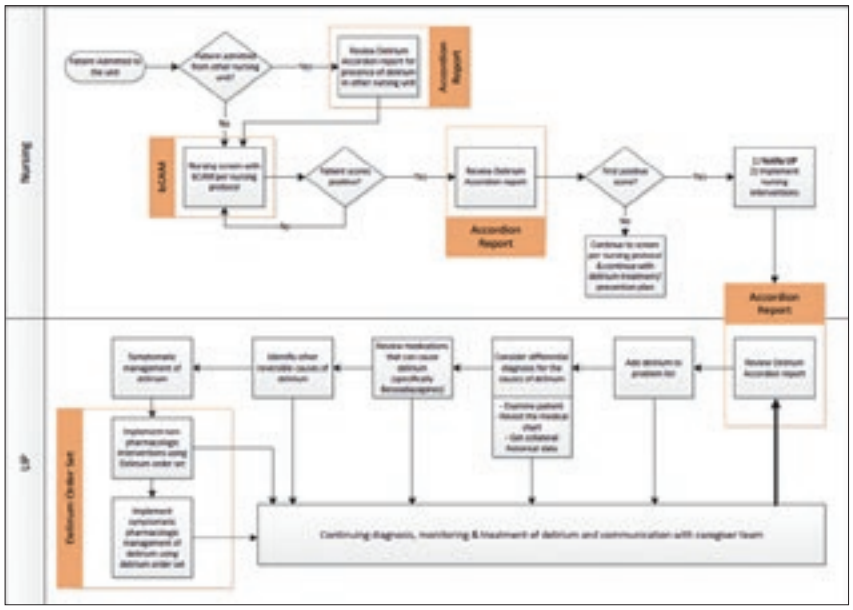
KEY POINTS

- Cleveland Clinic recently implemented a program to ensure systematic delirium screening of all inpatients and a workflow that empowers nurses and licensed independent practitioners to manage delirium more effectively.
- Key program components include the Delirium Accordion, a tool embedded in the EMR to capture all screening results and potential causes of delirium for a patient and display them in a timeline fashion; an order set to standardize delirium management; and a related delirium algorithm.
- The program's EMR tools and algorithm were deployed across the Cleveland Clinic enterprise in late 2014, and all medical and surgical inpatients are now screened daily for delirium. An electronic dashboard has been implemented to measure program progress and drive continuous improvement.

FIGURE 1. *Screenshot of a report from the Delirium Accordion.*

FIGURE 2. *The algorithm for delirium management on medical/surgical floors. LIP = licensed independent practitioner*



Uncovering Network Architectures Using Advanced Modeling Techniques in Functional MRI: An Olfaction Study in Sommeliers

By Dietmar Cordes, PhD; Karthik Sreenivasan, MS; Xiaowei Zhuang, MS; and Sarah Banks, PhD, ABPP/CN

A wealth of information has recently emerged on the topology of brain networks using graph-theoretical analysis of functional MRI (fMRI) data. For example, important network nodes have been characterized by defining so-called hubs, network connections have been described by efficiency of information processing, and network modularity has been discovered where different modules are interlinked. Graph-theoretical modeling can allow investigation of brain topology as the brain changes with age, development, training and sickness.

A Controlled Study of Olfactory Perception in Sommeliers

Building on this progress, the Cleveland Clinic Lou Ruvo Center for Brain Health has conducted an fMRI study to investigate brain networks during an olfactory perception task performed by Master Sommeliers (wine experts) and control subjects with no advanced training in identifying wines by taste.

According to the notion of brain neuroplasticity, the brain has the ability to change its neural pathways in response to changes in environment, thinking or behavior. Since Master Sommeliers acquire their knowledge in identifying wines over years of training, we speculated that the brain circuitry associated with identifying the type and quality of wine would differ in the sommeliers relative to controls who are not wine experts. Specifically, in sommeliers we expected changes in the network topology involving the following areas:

- Olfactory cortex (smelling and discriminating wine scents)
- Medial temporal cortex (episodic memory in recalling characteristics of typical wine features)
- Visual association cortex (associating wine color with quality)
- Language areas (describing characteristic features of wine)

Methods and Key Findings

During fMRI scanning, participants were pseudorandomly presented odorants from two red wines, two white wines or one of three nonwines using an event-related design. Subjects used button presses to indicate whether the odorant was from a wine or a nonwine so that response accuracy could be assessed.

fMRI data were processed to obtain the underlying neuronal processes to find causal influence between brain regions. This process is technically described as a blind deconvolution operation applied to the neurovascular response using a cubature Kalman filter followed by Granger causality analysis. The resulting connectivity information obtained is a directional quantity and signifies the causal influence of one brain region on another. This type of causal connectivity information is also called effective connectivity in the fMRI literature.

After all data were brought into a common anatomical space, we performed an effective connectivity analysis using 76 regions and resulting in ~5,700 different directional connection measures.

The connection measures were populated into two samples corresponding to sommeliers and controls. A two-sided *t* test was used to identify the connections that were significantly different between the two groups ($P < .05$ corrected for multiple comparisons).

Since the *t* test does not guarantee generalizability or predictability of findings, we used a machine learning approach to accurately distinguish sommeliers from controls. Among all causal connections (features), the best features were chosen by lasso regularization.[1] These features were then input to a radial basis function network classifier,[2] which determined with very high accuracy whether a subject was a sommelier or control based only on these causal connectivity weights.

The findings of this new technique show that in addition to functional activation differences between sommeliers and controls, the effective connectivity networks significantly differed between the two groups (Figures 1 and 2). Furthermore, these directional connectivity measures can be used as features to accurately classify sommeliers from controls. Although the effective connectivity networks involve similar regions in the two groups, the complexity of these networks (strength of connection) was much higher in the sommeliers than in controls. Other graph-theoretic measures (global efficiency, small-worldness) are currently being investigated.

Potential Payoffs in Diagnosis, Monitoring of Cognitive Disease

This study demonstrates the usefulness of directional connectivity models for gaining a systematic understanding of neural circuits in the brain that underlie olfaction as well as their potential as a noninvasive neuroimaging biomarker to distinguish between groups of individuals with differences in a defined characteristic. These new techniques promise to enhance understanding of neural architecture and may ultimately help improve the diagnosis of patients with cognitive disorders and the monitoring of treatment effects.

SELECTED REFERENCES

For a full list of references, see the online version of this article at ***consultqd.org/olfaction****.*

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KEY POINTS

- Our group conducted an fMRI study to investigate brain networks during an olfactory perception task performed by sommeliers and control subjects. We employed Granger causality analysis using blind hemodynamic deconvolution to uncover underlying neuronal processes. A machine learning algorithm was used to improve generalizability and predictability of effective connectivity neural signatures.
- Our technique revealed significant differences between sommeliers and controls in functional activation and effective connectivity networks, demonstrating that directional connectivity measures can be used to accurately classify sommeliers (who had greater connectivity) from controls.
- These findings support the growing recognition that graph theory provides new measures to describe brain network topologies and discover network differences.

FIGURE 1. *Circle plot depicting the connections that differed significantly between sommeliers and controls. Points on the circle represent different brain regions. Solid lines (yellow/red) are paths that were stronger in sommeliers; dotted lines (blue) are paths that were stronger in controls. The color of the edge (connection) between two regions indicates the difference in the strength of connection between the two groups.*

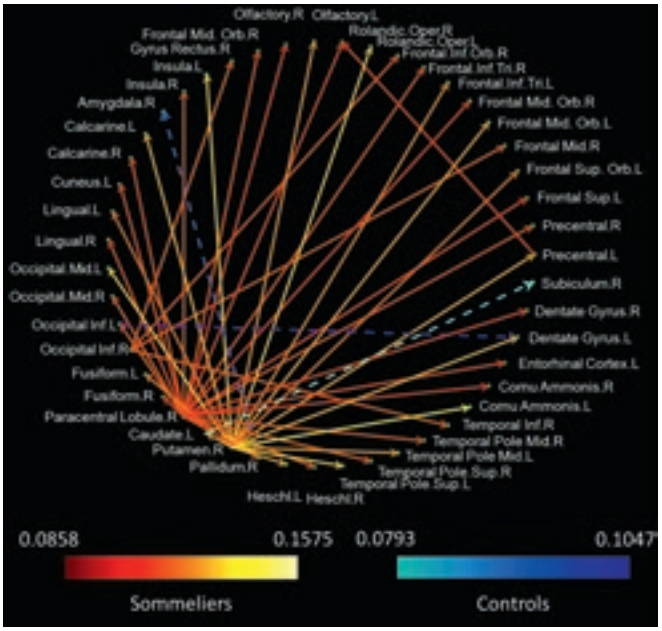
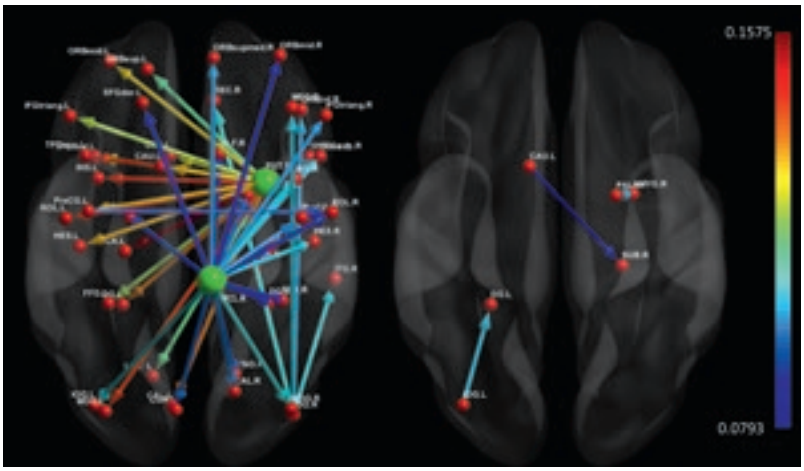


FIGURE 2. *Images showing connections that were stronger in sommeliers (left) and stronger in controls (right). The large green nodes are hubs (important regions with large numbers of connections). The color of the edge (connection) between two regions indicates the difference in the strength of the connection between the two groups. Blue indicates a small difference, and red indicates a large difference. Note that no hubs were found in control subjects. (To view the images as stereoscopic images, see the online version of this article at* ***consultqd.org/olfaction****.)*



The Cleveland Multiport Catheter: A New Take on Convection-Enhanced Delivery of Therapeutics to the CNS Yields Encouraging Early Results

By Michael A. Vogelbaum, MD, PhD, and Ghaith Habboub, MD

Despite exciting progress against many forms of cancer, brain tumors — particularly gliomas — remain one of the deadliest malignancies. Their lethality stems largely from the fact that glioma cells are highly infiltrative in the brain and resistant to DNA-damaging therapies such as radiation therapy and cytotoxic chemotherapy. These intrinsic cell properties underlie the failure of both surgery and radiation, even in combination, to prove curative.

The Challenge: Breaching the Blood-Brain Barrier

Gliomas are also resistant to most targeted anticancer therapies, which lack access to the cancer cells themselves because the blood-brain barrier (BBB) prevents their entry to the brain. Multiple strategies have been tried to at least temporarily open the BBB to allow passage of anticancer therapeutics, but these efforts have not produced clinical benefit for glioma patients. Moreover, attempts to re-engineer therapeutics to enter the brain via known endothelial transporters have yet to see clinical success.

Another approach for improving delivery of anticancer agents to the brain is convection-enhanced delivery (CED), in which therapeutic agents are introduced directly into brain parenchyma via surgically implanted catheters connected to low-rate infusion pumps. While this technique has been in use for nearly two decades, it remains investigational, as no therapeutics have been approved by the FDA for infusion directly into brain tissue.

A Fresh Take on Convection-Enhanced Delivery

Over the past decades, several large clinical trials identified a need for new CED-specific technology that would more reliably produce successful delivery to the brain. Now a partnership between Cleveland Clinic and the Cleveland-based multinational manufacturer Parker Hannifin Corp. has produced one of the first CED-specific catheter technologies to enter clinical trials — namely, the Cleveland Multiport Catheter™ (CMC).

The Story Behind the CMC

The new technology traces its origins to 2009, when Cleveland Clinic's technology commercialization arm, Cleveland Clinic Innovations, enlisted this article's senior author (Dr. Michael Vogelbaum) to lead a CED catheter development team including biomedical engineers, a patent attorney and a business development officer. The aim was to build on Dr. Vogelbaum's experience with CED in clinical trials and his proposals for multiple new catheter designs.

After extensive work to set design parameters, brainstorm device concepts and vet the concepts according to patentability and feasibility criteria, the team arrived at a design they called the "cat's paw" concept. It consisted of two microcatheters deployed from the wall of a central catheter implanted in the brain via conventional stereotactic neurosurgical techniques. Initial prototypes were created by Cleveland Clinic's Department of Biomedical Engineering, and functional testing was performed in Dr. Vogelbaum's laboratory using in vitro, ex vivo and in vivo models.

Following successful testing, the device concept was selected for further development by a joint development group formed with Parker Hannifin to commercialize new technologies from Cleveland Clinic Innovations. Dr. Vogelbaum's development team worked with Parker Hannifin engineers to create a clinical version of the new CED device (Figure 1), which now had four microcatheters and was named the Cleveland Multiport Catheter.

Extensive preclinical testing was followed by an IND approval from the FDA to conduct a first-in-human clinical study of delivery of the chemotherapeutic agent topotecan via the CMC in patients with recurrent high-grade gliomas. Cleveland Clinic Innovations formed a spinoff company, Infuseon Therapeutics Inc., to lead clinical development of the CMC.

First-in-Human Clinical Trial Shows Promise

The first-in-human study of the CMC is being conducted at Cleveland Clinic in patients with recurrent high-grade gliomas. The first patient was treated in December 2014, with three patients having completed treatment under the study protocol to date.

These procedures have involved placement of two CMC catheters into the brain using conventional stereotactic neurosurgical techniques. In all three cases, one catheter was placed into solid tumor and the other into tumor-infiltrated brain tissue surrounding the tumor mass. Topotecan cannot normally enter the brain but has shown activity against glioma cells; it was infused via the catheters, along with a gadolinium tracer visible on MRI, for a total of 96 hours. MRI was performed intermittently and showed that the infusions produced widespread distribution of the drug and tracer into the tumor-infiltrated brain in all three patients (Figure 2).

How the CMC Differs from Other CED Devices

While experience with the CMC is still developing, both the extent of brain tissue covered and the reliability of the technique in these three patients are largely unparalleled by past experience with CED.

Two other CED devices that recently entered the U.S. market each have a single infusion port and can be used only in an OR equipped with intraoperative MRI capabilities, whereas the CMC can be placed in any neurosurgical OR. Consequently, these other devices can be used only for several hours, which limits the amount of therapeutic that can be infused. The CMC, in contrast, can be left in place for

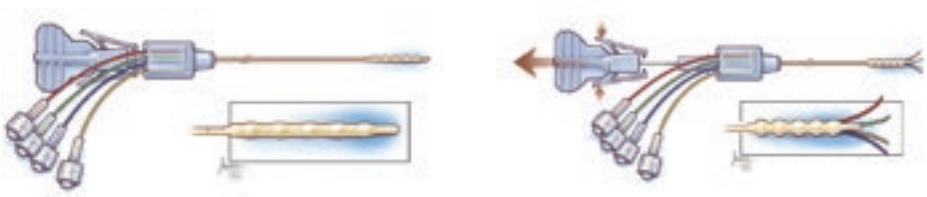


FIGURE 1. *Illustrations of the Cleveland Multiport Catheter in undeployed (left) and deployed (right) views.*

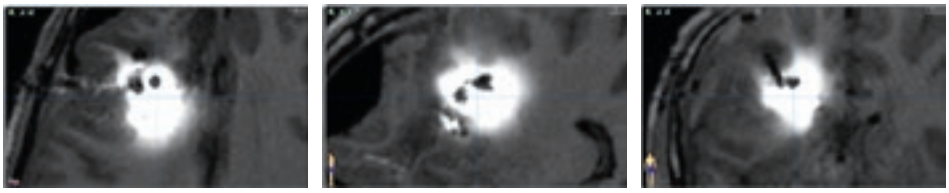


FIGURE 2. *Axial (left), sagittal (middle) and coronal (right) MRIs showing the distribution of infused topotecan and gadolinium in tumor-infiltrated brain 24 hours after the start of infusion via the Cleveland Multiport Catheter. No intravenous contrast was given; the white areas represent the distribution of the infused gadolinium.*

several days after implantation, which likely permits a larger volume of drug distribution within the tumor and tumor-infiltrated brain.

Next Steps in Testing and Development

Additional clinical evaluation of the CMC in patients with recurrent high-grade glioma is continuing. While the initial protocol called for CED infusions into both enhancing tumor and nonenhancing, tumor-infiltrated brain, experience with the first three patients indicated that the infusion rates and volumes would likely be different for those two locations. Accordingly, a new clinical protocol evaluating infusion into tumor-infiltrated brain only was launched in July 2015, and a separate protocol evaluating infusion into enhancing tumor only will be launched later in the year.

As the primary goal of these trials is to determine how best to maximize the CMC's delivery of therapeutics in the brain, the trials aim to maximize the volume of distribution (as assessed by MRI of the co-infused tracer) via manipulations of infusion rate and duration. Once use of the CMC has been optimized, Infuseon Therapeutics will reach out to the biotechnology and pharmaceutical industry to partner in the clinical development of therapeutics that require direct brain delivery. The Infuseon team expects that this initial optimization of the use of the CMC will require a total of 10 to 20 patients.

Other CNS Uses on the Horizon

Treatment of brain tumors is only a starting point on a broad spectrum of potential uses for this platform technology. The CMC has been designed to be capable of delivering any number of drugs, biologic therapies and cellular therapies to the brain, and Infuseon is pursuing partnerships with investigators and companies that are developing therapeutics for multiple neurologic conditions (including neurodegenerative diseases, stroke and epilepsy) in addition to brain tumors.

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Dr. Habboub (habboug@ccf.org) is a resident in the Department of Neurosurgery.

DISCLOSURE: *Dr. Vogelbaum is an inventor and patent holder of the Cleveland Multiport Catheter (CMC) as well as founder and Chief Medical Officer of Infuseon Therapeutics Inc. He holds equity and royalty interests in these entities. His participation in the CMC's clinical development is covered by a Cleveland Clinic-approved conflict management plan.*

KEY POINTS

- Gliomas remain one of the deadliest malignancies due to their highly infiltrative nature and location within the brain, which prevents chemotherapies and targeted anticancer therapies from reaching tumor cells.
- Cleveland Clinic has partnered with Parker Hannifin Corp. to develop a novel convection-enhanced delivery (CED) device, the Cleveland Multiport Catheter (CMC), which promises a larger volume of drug distribution to the glioma tumor and tumor-infiltrated brain tissue.
- Early human testing of the CMC at Cleveland Clinic has confirmed widespread distribution of topotecan and a tracer agent into tumor-infiltrated brain in patients with recurrent high-grade gliomas. While human trials of the CMC for glioma continue, its use for direct brain delivery of therapeutics for other conditions is being explored.

Mobile Stroke Unit Significantly Trims Time to Evaluation and Treatment in Acute Stroke

By M. Shazam Hussain, MD, FRCP(C)

Use of a mobile stroke treatment unit (MSTU) can significantly reduce the time to evaluation and treatment of patients with acute stroke in the United States compared with traditional models of acute stroke management.

That's the leading takeaway from the initial months of operation of Cleveland Clinic's MSTU following its launch in July 2014, as presented at the American Stroke Association's International Stroke Conference earlier this year.[1]

Cleveland Clinic's MSTU is only the second in the U.S. and among the first in the world, modeled in many ways on the success of the initial MSTUs in Germany. Our initial experience in time-to-treatment measures is encouraging because it closely replicates published data from those pioneering German MSTUs,[2,3] demonstrating that the success of mobile stroke therapy need not be a country-specific or healthcare system-specific phenomenon.

The MSTU at a Glance

Briefly, the MSTU is an ambulance that is specially equipped and staffed to function as a virtual ER dedicated solely to stroke diagnosis and management. Specifically:

- It houses a portable CT scanner and a telemedicine unit that enables rapid broadband transfer of brain scans and videoconferencing with neuroradiologists and stroke specialists on Cleveland Clinic's main campus, who direct patient management.
- An onboard mobile lab allows blood testing and immediate use of IV tissue plasminogen activator (tPA) when indicated.
- The unit is staffed by a paramedic, a critical care nurse (who administers tPA), a CT technologist and an EMS driver, all specially trained in acute stroke care.

The use of telemedicine and teleradiology are unique Cleveland Clinic adaptations of the German MSTU model.

The MSTU is based at Cleveland Clinic's main campus and dispatched via the 911 system in cases of suspected stroke. The aim is to essentially bring the ER to the patient, allowing evaluation and treatment to begin at the site of stroke onset and continue while the patient is transported to the nearest Primary Stroke Center or Comprehensive Stroke Center.

Study Design and Key Findings

Our team's recent presentation compared intervention times between the first 100 patients evaluated in the MSTU (from July 2014 through late 2014) and 53 comparable patients presenting to ERs at Cleveland Clinic hospitals in or adjacent to the city of Cleveland during 2014. All control patients had a stroke alert called within 30 minutes of their hospital arrival, and all presented within the window during which the MSTU operates (8 a.m. to 8 p.m.).

The 100 MSTU patients were diagnosed in the MSTU as follows:

- 33 patients with probable acute ischemic stroke
- 30 with possible acute ischemic stroke
- 4 with transient ischemic attack
- 5 with intracerebral hemorrhage
- 28 with other diagnoses

IV tPA was given to 16 of the 100 MSTU patients, and all of them were among the 33 patients initially diagnosed as having probable acute ischemic stroke.

As detailed in the table, the median time from alarm (vehicle dispatch) to various management milestones was significantly shorter in the MSTU group than in the control group, including for the primary end point, time from alarm to IV tPA. Similarly significant reductions were observed in the MSTU group for the median time from door (of the MSTU or the ER) to these same milestones, including time from door to IV tPA.

Among other noteworthy findings:

- The rate of IV tPA administration among patients with probable acute ischemic stroke was 48.4 percent (16/33) based on initial diagnosis in the MSTU and 31.0 percent (9/29) based on patients' final diagnosis at discharge. Both rates compare favorably to the national average of approximately 3 to 5 percent and to the approximately 20 percent achieved by specialized centers.
- 16 of 19 patients (84 percent) in the MSTU group who were eligible for IV tPA were successfully treated. Of the remaining three eligible patients, IV access could not be obtained in the MSTU for two patients, and telemedicine failure (due to crew error) prevented tPA administration in the other patient, who was rushed to the closest Primary Stroke Center and received tPA there.
- Four patients in the MSTU group were given IV tPA within one hour of their last known well time (the "platinum hour"), which is extremely rare in traditional stroke care models.

The New and the Next: Outcomes Study Underway, CT Angiography

The reduction in time to evaluation and treatment observed in these first 100 MSTU patients has been confirmed by our experience with subsequent MSTU patients (Figure), which exceeds 300 patients at the time of this writing.

Table. Median Times to Key Management Milestones			
Metric	MSTU Group (N = 100)	Control Group (N = 53)	*P* value for difference
Alarm to CT completion	33 min (IQR 29-41)	56 min (IQR 47-68)	< .0001
Alarm to CT reading	44 min (IQR 39-52)	64 min (IQR 54-76)	< .0001
Alarm to INR result	25 min (IQR 22-34)	79 min (IQR 70-105)	< .0001
Alarm to IV tPA	55.5 min (IQR 46-65)	94 min (IQR 78-104)	< .0001
INR = international normalized ratio; IQR = interquartile range			

Next steps in the research surrounding our MSTU program include:

- An outcomes study looking at 90-day modified Rankin Scale scores among IV tPA recipients and 30-day outcomes in all stroke patients managed in the MSTU. We expect to include approximately 400 patients in that study. Results should be available in 2016.
- A cost-effectiveness analysis of the MSTU. This should follow soon after outcomes data are available.

Meanwhile, we have begun performing CT angiography in the MSTU, which allows us to identify emergent large vessel occlusions more swiftly and expedite the transfer of such cases to an angiography suite for intra-arterial therapy. We look forward to reporting on our experience in this area soon.

Another Challenge: Keeping Up with Demand

The positive initial experience with the MSTU has prompted expansion of the unit's dispatch area into two suburban municipalities in addition to Cleveland, with more municipalities coming on board soon. Expanded hours of operation are being explored, as is the possible launch of a second unit.

As word gets out about the promise of mobile stroke therapy, keeping up with demand may be a challenge. But given the increased timeliness of interventions, that's a very good problem to have.

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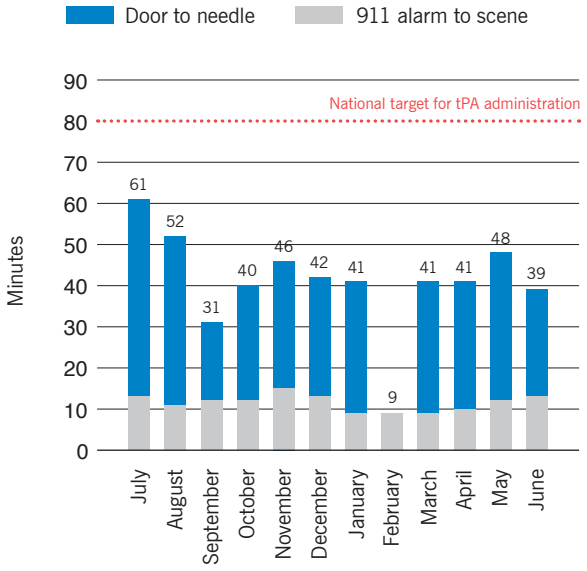
FIGURE. *Mean time (by month) from 911 alarm to administration of IV tPA for patients managed in the mobile stroke treatment unit (MSTU) during its first year of operation (2014-15). The national target for administering IV tPA within 80 minutes is based on targets of 20 minutes from EMS dispatch to arrival at the hospital door plus 60 minutes for administration of tPA ("door to needle" time). The MSTU has allowed tPA to be given in approximately half the national target time.*



KEY POINTS

- Cleveland Clinic introduced one of the nation's first mobile stroke treatment units (MSTUs) in July 2014 to "bring the ER to the acute stroke patient" and accelerate patient evaluation and treatment.
- A case-controlled analysis of the first 100 patients managed in the MSTU found a statistically significant reduction in time to patient evaluation and initiation of thrombolysis compared with traditional acute stroke management models.
- We are currently accumulating data to assess clinical outcomes and total treatment costs among several hundred patients managed in the MSTU to confirm whether the unit's promotion of swifter management translates to superior patient outcomes and overall treatment savings.

The Intelligent Mouthguard: A Valid Tool to Meet Growing Demand for Accurate and Precise Head Impact Data

By Adam Bartsch, PhD, PE

The ability to measure single human head impacts with accuracy and precision has been the holy grail of concussion research for at least four decades, dating back to the pioneering work of Col. John Paul Stapp, MD. The quest has never shown more promise than today, with recent laboratory and human validation studies demonstrating Cleveland Clinic's Intelligent Mouthguard to be a valid single-event head impact dosimeter.

This article traces the development and testing of the Intelligent Mouthguard and outlines next steps in our efforts to make it available as a trustworthy clinical tool for monitoring concussion risk after individual head impacts.

Head Impact: Focusing on Magnitude, Location, Direction

The Intelligent Mouthguard is equipped with sensors to measure linear and rotational head movement in real time. Since its development began at Cleveland Clinic in 2008, it has evolved through several iterations to its current wireless version (Figure 1) with Bluetooth data transmission and an inductively charged battery.

Development of the Intelligent Mouthguard has been guided by the hypothesis that trustworthy information on three aspects of head impacts — magnitude, location and direction/orientation (e.g., glancing blow vs. direct blow) — is necessary for effective concussion risk monitoring. Two principles are central to this hypothesis:

- Concussion risk is based on combinations of spatial (x-, y- and z-axes) and temporal parameters.
- Measurements must reliably couple accuracy and precision across individual impact events to provide a clinically useful degree of certainty about concussion risk (a "dose response" measure) and avoid false positives.

Ensuring that Sensors and Head Move as One

Design of the Intelligent Mouthguard was shaped by our team's early recognition that placement of impact sensors in a mouthpiece — as opposed to a helmet, skullcap, skin patch or other head gear — is the optimal way to combine accuracy with precision in head impact measurement to ensure that sensor movement is reliably coupled with actual head movement.

That recognition is not trivial, because managing to couple sensor movement with head movement is not as easily achieved as it may seem. Although a number of published head impact studies have captured impressive-looking data using helmet- or skin-mounted sensors, these approaches yield erroneous head impact measures. That's because a helmet or skullcap often moves very differently from how the head moves, as demonstrated in a short video produced using a crash test dummy in our lab (see clevelandclinic.org/impactvideo). This results in measurement artifacts as opposed to measures of actual head impact. This sometimes produces data that suggest degrees of head acceleration or deceleration that physics models indicate are simply impossible for the human head to undergo.

No Devices Tested to Date Meet NFL Validity Specs

Poor dosimeter-head coupling was among the limitations of commercially available dosimeters recently tested by the National Football League (NFL) when it assessed an instrumented helmet and a sensor-laden mouthguard for use in on-field head impact quantification. Neither device met the NFL's validity specifications based on a 2014 NFL scientific presentation.[1] In February 2015, the NFL announced the indefinite postponement of its on-field dosimeter work.

Promising Laboratory Validation Findings

While it may seem straightforward to use a mouthguard firmly coupled to the teeth to mount sensors to the skull, the failure of the commercial mouthguard dosimeter in the NFL tests independently confirms that this approach is not without difficulty. We had to complete several difficult engineering tasks — developing theoretical equations of motion, testing gyroscopes, smashing accelerometers, whacking crash test dummies, instrumenting human volunteers — to ensure that the Intelligent Mouthguard produced accurate, precise and trustworthy data.

After successfully completing these tasks, we recently published test data demonstrating that the Intelligent Mouthguard meets NFL validity specifications as a single-event head impact dosimeter.[2] Our published data confirm that the Intelligent Mouthguard can measure head impacts within 5 percent of the true value.

On to Human Validation Studies

We have since built on this laboratory validation with human studies designed to confirm the Intelligent Mouthguard's performance within tested ranges. We have tested it in the following populations:

- Four amateur boxers ages 15 to 18 during five three-minute sparring rounds
- Eight American football players ages 11 to 20 during four practices and scrimmages

Our reporting of head impact data is limited to "true positives," or those impacts for which we have video confirmation of a corresponding hit as well as data that are consistent with the physics of head motion after an impact.

Although there were no concussions or clinical symptoms in this cohort, many of the head impacts measured by the Intelligent Mouthguard were near the concussive ranges reported in literature studies from the NFL and Virginia Tech. Figure 2 presents a graphical depiction of the head impacts captured in our human study.

Publication and Next Steps

We have submitted data from this human validation study for publication. With the finer resolution now provided by Intelligent Mouthguard data, we can, for the first time, accurately and precisely determine the following:

- Where the impact force is acting on the skull
- How hard the impact was
- The direction of the impact

These parameters will be critical in the future as we tie impact magnitude, direction and location to clinically measured behavioral changes.

Our next steps include working with Cleveland Clinic Concussion Center clinicians to design experiments to determine how best to quantify concussion threshold as a function of the magnitude, direction and location of head impacts. These efforts will likely pair data from the Intelligent Mouthguard with relevant data available from MRI studies, neurocognitive assessments, blood tests, etc.

We will also work with our clinician colleagues to identify how we might supplement the three core variables captured by the Intelligent Mouthguard with other important variables in concussion risk, such as individual susceptibility and individual brain adaptability to head impacts.

These steps will inform our ongoing efforts through Cleveland Clinic's commercialization arm, Cleveland Clinic Innovations, to refine the Intelligent Mouthguard hardware to make it commercially available. The demand for accurate and precise head impact measurement to guide clinical concussion assessment is real and large. We are hopeful this is an important step in meeting that growing demand.

Dr. Bartsch (bartsca@ccf.org; 216.363.5749) is a researcher in the Department of Biomedical Engineering in Cleveland Clinic's Lerner Research Institute and in the Neurological Institute's Concussion Center and Center for Spine Health. He acknowledges the following collaborators in the work reported here: ***From Cleveland Clinic:*** *Sergey Samorezov, research engineer with the Medical Device Solutions Engineering Core, Lerner Research Institute; and Edward Benzel, MD, Center for Spine Health.* ***From the University of Pittsburgh:*** *Vincent Miele, MD.* ***From Sportsguard Laboratories Inc:*** *Daniel Brett, DDS.*

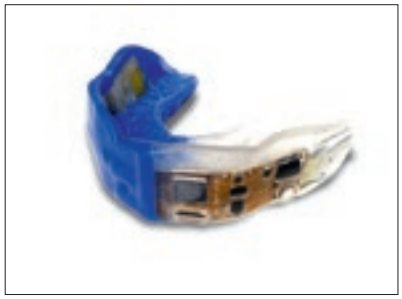


FIGURE 1. *The Intelligent Mouthguard.*

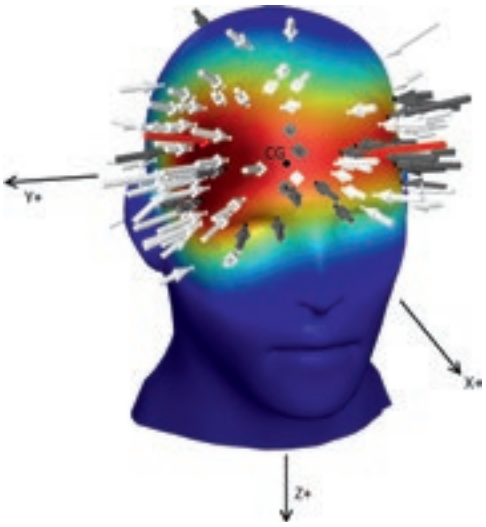


FIGURE 2. *Graphical depiction of the impacts from our human study showing the location (arrow tip), magnitude (arrow length) and direction (arrow orientation) of impacts.*

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KEY POINTS

- There is a long-standing unmet need for a validated tool for collecting accurate and precise single-event head impact information to help identify individuals requiring concussion assessment.
- Cleveland Clinic's Intelligent Mouthguard has been developed to meet this need through placement of sensors that move as one with the head and output data within 5 percent of the true impact value.
- Laboratory testing recently has shown the Intelligent Mouthguard to be a valid single-event head impact dosimeter that meets NFL validity specifications, and human validation data have been submitted for publication. We hope to ultimately make the Intelligent Mouthguard available for widespread use in concussion monitoring.

The Epilepsy Surgery Nomogram: A Promising, Unprecedented Instrument for Individualized Outcomes Prediction

By Lara Jehi, MD

Brain surgery is the only available curative option for drug-resistant focal epilepsy, but identifying good surgical candidates remains a major challenge. While many patients who could benefit from this procedure are missed and never referred for surgical evaluation, others see multiple specialists and undergo highly complex evaluations before realizing that epilepsy surgery is inappropriate for them. The crux of the problem is the healthcare community's inability to adequately predict the outcomes of epilepsy surgery, which prevents us from optimally targeting the use of this potentially lifesaving intervention.

An Attempt at a Comprehensive Tool for Individualized Prediction

In an unprecedented effort to address this prognostication conundrum, Cleveland Clinic's Epilepsy Center led an international collaboration of major epilepsy centers in the U.S., France, Italy and Brazil to develop a novel statistical tool that we call the Epilepsy Surgery Nomogram (ESN). This simple nomogram uses six clinical patient characteristics (see below) and provides an objective, individualized prediction of postoperative seizure outcomes. Our nomogram and its initial retrospective validation were recently described in *Lancet Neurology*.[1]

Defining the Need

To understand the value of the ESN, it's helpful to trace the path by which patients currently get to the point of having epilepsy surgery:

- **Step 1:** The community neurologist recognizes that a patient's epilepsy is drug-resistant.
- **Step 2:** The community neurologist refers the patient to a comprehensive epilepsy center for more specialized treatment options, including brain surgery.
- **Step 3:** At the comprehensive epilepsy center, the patient undergoes extensive testing, the results of which are discussed in a multidisciplinary patient management conference where experts reach a consensus recommendation to operate or not based on their subjective interpretation of the available data.
- **Step 4:** The chances of surgical success (seizure freedom) are provided to the patient based on compiled rates of seizure freedom from large published surgical cohorts.

This bird's-eye view of the typical path to epilepsy surgery reveals the unquestionable need for process improvements that could be fostered by a tool like the ESN.

The Limits of Current Practice

Determining drug resistance (Step 1) is now facilitated by guidelines from the International League Against Epilepsy, which define drug resistance as failure of sustained seizure control following adequate use of two appropriate antiepileptic medications. In contrast, all the subsequent steps of the path above are currently highly subjective.

For instance, the referral decision is driven by many factors, including the local neurologist's coarsely estimated risk-vs.-benefit calculation regarding possible brain surgery. Yet recent data show a knowledge gap that often leads to overestimation of risks in this calculation, preventing many potentially good candidates from getting the appropriate surgical treatment.

Additionally, even when a patient is seen in a tertiary care center, various specialists may interpret his or her clinical picture differently. This is understandable, given that the value of any given test in guiding patient care up to that point has essentially been studied in relation to the prognostic value of the test *in isolation* rather than in the general clinical context.

'What About Patients Like Me?'

Based on the current medical literature, a physician can find that test A predicts an X percent chance of postoperative seizure freedom, test B predicts a Y percent chance and so on. The ideal scenario, in which all tests are aligned, with little variation between X and Y, happens in less than one-third of cases.[2] This means the remaining two-thirds of patients fall into a limbo where nobody knows exactly how well surgery will fare in controlling their seizures.

That's why physicians often cite numbers reflecting how often *all patients* who had epilepsy surgery became seizure-free. While these are helpful data, what a patient needs to know is how the surgery will affect *him or her*, rather than the hundreds of strangers who had the procedure done. "How did *patients like me* do?" is the question they care about far more than "How well does this work in general?"

Enter the Epilepsy Surgery Nomogram

In this context, we developed the ESN to meet these needs for more objective prognostication, more scientific decision-making and more individualized patient counseling. Community neurologists may use the ESN to better inform their initial estimates of potential surgical success, and specialized epileptologists can use it to provide individualized patient counseling.

Its potential is huge, considering the possibility of infinite improvements through incorporation of additional outcome determinants from imaging or electrophysiologic data — work that our team currently has underway.

The ESN is a Web-based (Figure), user-friendly, clinically driven tool that uses these six easily defined variables to estimate the likelihood

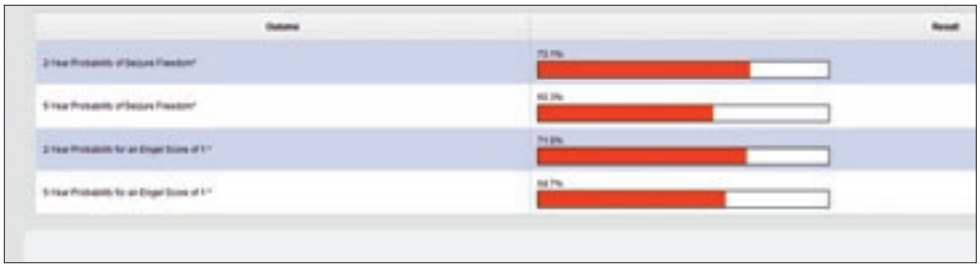

FIGURE. *Screenshots of the Web-based Epilepsy Surgery Nomogram. The top image shows fields where the provider enters patient-specific data for the six required variables. The bottom image shows how the patient-specific surgical outcome predictions are displayed. The online risk calculator is available at* ***clevelandclinic.org/epilepsycalculator****.*

of seizure freedom at two and five years after epilepsy surgery:

- Age
- Gender
- Seizure frequency
- Presence/absence of convulsions
- Epilepsy etiology
- Expected broad localization

First Proof of Concept for Individualized Outcomes Assessment

The ESN was developed after a careful analysis of 846 patients who underwent epilepsy surgery at Cleveland Clinic over an 18-year period. It was then tested in a retrospective external validation cohort of 604 patients operated on over a similar period at Mayo Clinic; the University of Campinas in Brazil; the Ospedale Niguarda surgery program in Milan, Italy; and two hospitals in Marseilles, France. It performed reasonably well, as reported in our recent paper,[1] and provided the first-ever proof of concept that individualized outcome prediction is possible in epilepsy surgery. Next steps include prospective validation studies.

From Educated Opinion to Science

Physicians learn tremendously from personal experience, but such experience is still limited to the relatively small number of patients an individual physician has treated. The ESN allows us to bring patient counseling into the 21st century and expand it beyond our best "educated opinion" to actual science. Our patients deserve it.

Dr. Jehi (jehil@ccf.org; 216.444.3309) is Head of the Outcomes Research Group and Director of Clinical Research in Cleveland Clinic's Epilepsy Center.

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KEY POINTS

- No known validated instrument exists to comprehensively combine potential predictors of epilepsy surgery outcomes in a reliable measure for guiding decision-making in individual cases.
- To address this need, Cleveland Clinic's Epilepsy Center led an international collaboration to develop the Epilepsy Surgery Nomogram (ESN), a statistical tool that uses six clinical characteristics to provide an objective, individualized prediction of postoperative seizure outcomes.
- The ESN performed reasonably well in a retrospective external validation cohort and provided the first proof of concept that individualized outcome prediction is possible in epilepsy surgery.

SPRINT-MS Trial: A New Front in the Quest for a Therapy and Imaging Biomarkers for Progressive Multiple Sclerosis

By Robert J. Fox, MD, and Ken Sakaie, PhD

Despite dramatic advances in the treatment of relapsing-remitting multiple sclerosis (MS), there remains no effective therapy to slow the insidious neurologic decline in progressive forms of MS. To compound the problem, there are no effective biomarkers to screen putative therapies for progressive MS.

To help fill this void, Cleveland Clinic is leading a phase 2 clinical trial with a dual objective: (1) to evaluate a potential therapy for progressive MS and (2) to identify the best imaging biomarker for use in progressive MS trials. If successful, the multicenter trial will provide proof-of-concept evidence supporting the efficacy of a new therapy and guide the conduct of future phase 2 trials in progressive MS.

Study Backdrop: A Dearth of Therapies and Biomarkers for Progressive Disease

MS typically starts as a relapsing-remitting disease, with intermittent bouts of inflammation that manifest as new lesions on conventional MRI. Over the past 20 years, more than a dozen therapies have been approved to treat relapsing-remitting MS, reducing this form of MS to an eminently treatable condition.

After 10 to 20 years, however, relapsing-remitting MS often transitions into a gradually progressive form — secondary progressive MS — in which neurologic disability accumulates little by little over time. In about 10 percent of MS cases, relapses are not seen and the disease goes directly into a progressive form, known as primary progressive MS.

None of the therapies that have proved effective in relapsing-remitting MS have demonstrated efficacy in either secondary progressive or primary progressive MS (collectively referred to as "progressive MS"). This is likely because progressive MS is a degenerative disorder that arises from the inflammatory injury of relapsing-remitting MS but is separate and independent from that inflammatory injury.

New lesions on MRI are commonly used as a biomarker to screen potential anti-inflammatory therapies in phase 2, proof-of-concept clinical trials in relapsing-remitting MS. Unfortunately, new lesions are uncommon in progressive MS, and they appear to have little relationship to the degeneration that drives progressive MS. A different biomarker is needed to screen for potential therapies in progressive MS.

The Trial at a Glance

Investigators from Cleveland Clinic are leading a multicenter clinical trial to address both of these problems — the lack of effective therapies and the lack of validated biomarkers for proof-of-concept studies.

The Secondary and Primary pRogressive Ibudilast NeuroNEXT Trial in Multiple Sclerosis (SPRINT-MS) is a two-year, 250-subject, randomized, placebo-controlled trial enrolling at 28 centers across the U.S. It will evaluate the safety and efficacy of ibudilast — an inhibitor of both phosphodiesterase and macrophage migration inhibitory factor (MIF) — in patients with either primary or secondary progressive MS.

The $13 million study is funded principally through the National Institutes of Health (NIH), with additional support from the National Multiple Sclerosis Society and the pharmaceutical company MediciNova. It is being conducted through the NIH-funded NeuroNEXT network, a phase 2 clinical trial network intended to accelerate development of therapies for neurologic conditions.

A Range of Outcome Measures

The trial's primary outcome measure is whether ibudilast treatment can slow the progression of whole brain atrophy compared with placebo treatment.

Key secondary outcomes include cortical atrophy and brain changes on diffusion tensor imaging (DTI) and magnetization transfer ratio (MTR) imaging, all of which are thought to be sensitive metrics of neurodegeneration. Another key secondary outcome is thinning of the retinal nerve fiber layer as measured by optical coherence tomography (OCT), which is a quick and inexpensive tool for measuring MS injury in the back of the eye.

Additional outcomes include clinical disability and patient-reported outcomes.

The Long View: Better Progressive MS Trials

Regardless of whether ibudilast is effective in slowing the progression of degeneration in progressive MS, SPRINT-MS also provides an opportunity to directly compare the five key outcomes:

- Whole brain atrophy
- DTI changes
- MTR imaging changes
- Cortical atrophy
- Thinning of the retinal nerve fiber layer on OCT

By evaluating the longitudinal change in these measures — several of which are depicted in Figures 1 to 4 — and their correlation with disability, the study will identify the best biomarker for use in future phase 2 trials of progressive MS.

An Interdisciplinary Initiative

SPRINT-MS leverages several Cleveland Clinic strengths:

- The trial is led by the Mellen Center for Multiple Sclerosis Treatment and Research, which is a world leader in the study of MS and the care of MS patients.
- Support for the advanced imaging outcome measures is provided by the High-Field Imaging Laboratory in Cleveland Clinic's Imaging Institute, led by Mark Lowe, PhD. This lab has extensive experience implementing and analyzing advanced imaging tools like DTI.
- The whole brain atrophy and cortical atrophy outcomes will be derived from image analysis algorithms developed and applied by the Department of Biomedical Engineering in Cleveland Clinic's Lerner Research Institute. These efforts are directed by Kunio Nakamura, PhD.

Thus, the SPRINT-MS trial assimilates assets from diverse disciplines across Cleveland Clinic for a unified purpose: testing a new drug for a currently untreatable disease. And the study's greatest significance may ultimately lie in its objective of identifying the best imaging biomarker for future progressive MS trials. In short, SPRINT-MS aims not only to catch a fish, but to teach researchers how to fish better.

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Dr. Sakaie (sakaiek@ccf.org; 216.445.5096) is an assistant staff member in the Department of Diagnostic Radiology and the Mellen Center for Multiple Sclerosis Treatment and Research.

KEY POINTS

- Despite advances in therapies for relapsing-remitting MS, progressive forms of MS still lack an effective therapy and effective imaging biomarkers for use in clinical trials.
- Cleveland Clinic investigators are leading a new phase 2 multicenter clinical trial, SPRINT-MS, to evaluate the investigational therapy ibudilast for treatment of progressive MS.
- The two-year study is also designed to evaluate longitudinal changes in multiple outcome measures, including several advanced neuroimaging modalities, to identify the best biomarker for use in future clinical trials of progressive MS.

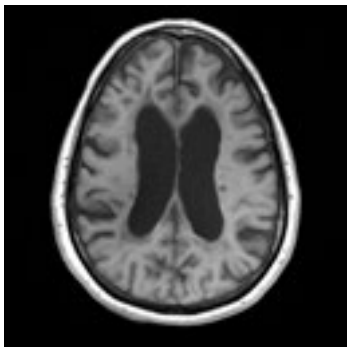


FIGURE 1. *A conventional MRI showing severe brain atrophy, with enlarged lateral ventricles and cortical sulci.*

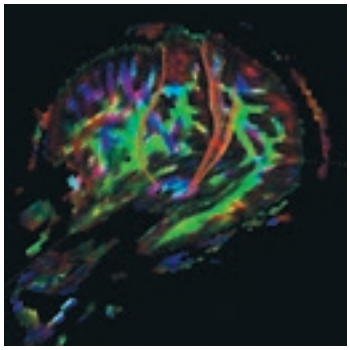


FIGURE 2. *Rendering of corticospinal tracts from a diffusion tensor imaging (DTI) study acquired in the SPRINT-MS trial.*

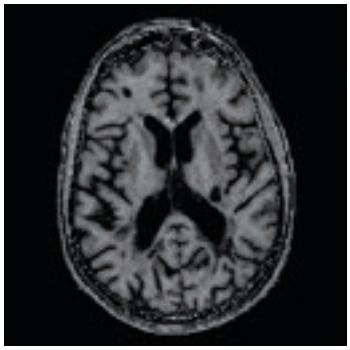


FIGURE 3. *Magnetization transfer ratio (MTR) imaging, with MS lesions showing decreased magnetization transfer. (Image courtesy of Sridar Narayanan, PhD, McGill University.)*

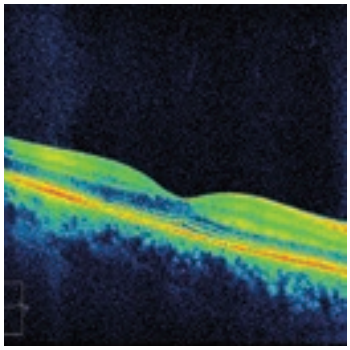
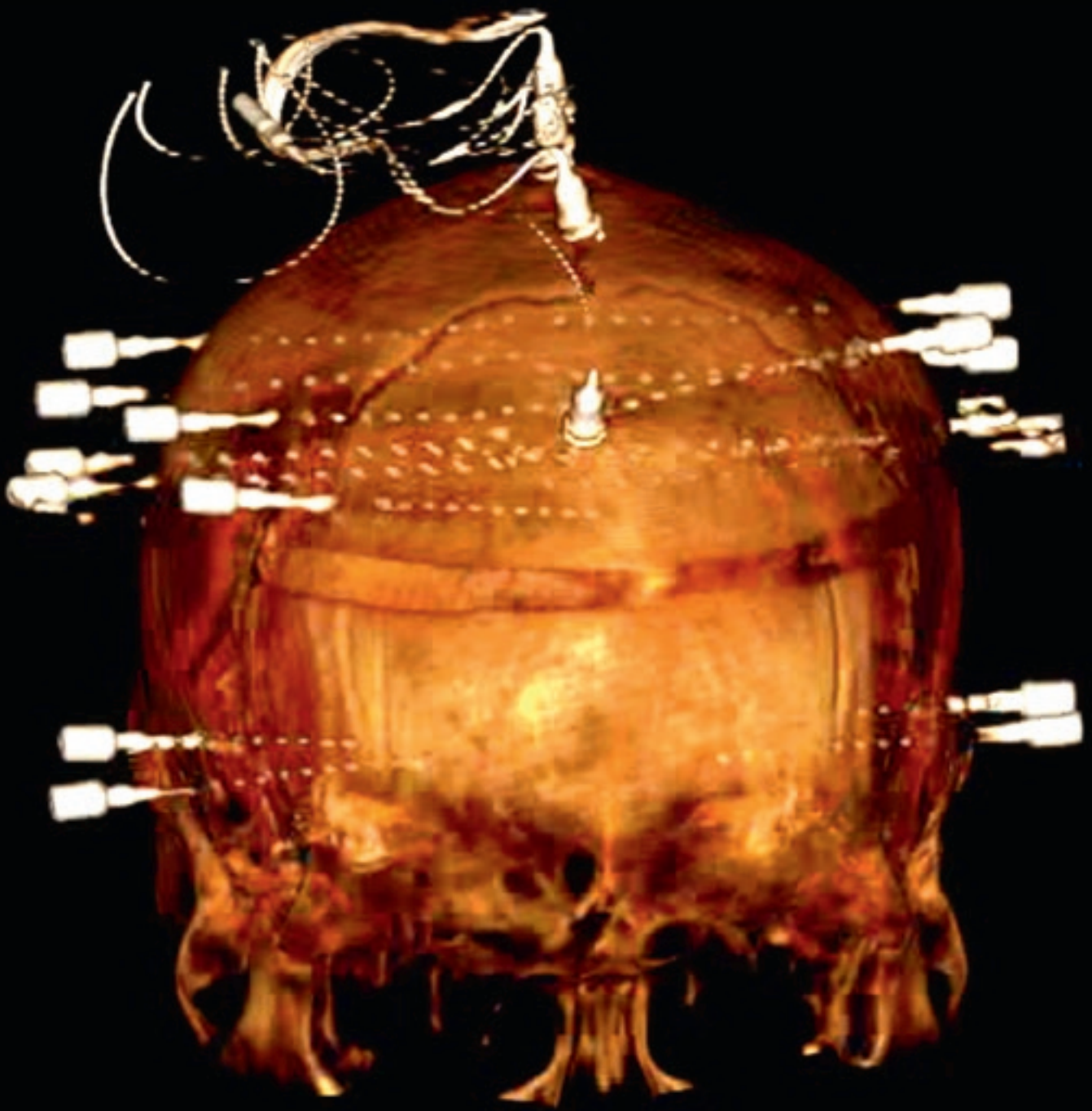


FIGURE 4. *Optical coherence tomography (OCT) showing the retinal nerve fiber layer in the back of the eye.*



COVER STORY

Simultaneous Neural Electrical Stimulation and Functional MRI: The Promise of Neuroimaging for Improving Clinical Neurostimulation

By Stephen E. Jones, MD, PhD; Jorge Gonzalez-Martinez, MD, PhD, FACS, FAANS; Andre Machado, MD, PhD; and Howard B. Goldman, MD

The collaborative use of neuroimaging and neurological interventions continues to grow more exciting with the ongoing development of techniques that run the gamut from structural imaging to functional imaging. Its promise looms even larger when considered in the context of the rapid development of new functional neurosurgical procedures aimed at treating neurological conditions such as movement disorders, epilepsy, dementia, stroke, chronic pain and psychiatric diseases.

Although it may sound like science fiction, in the near future neural implants are likely to play a significant role in treating many neurological diseases. Today we are witnessing the genesis of the techniques that will make this possible. After discussing the context in which these techniques are evolving, this article summarizes some leading contributions our group at Cleveland Clinic has made to these techniques.

Promise Tempered by Technical Challenges

Despite the flurry of progress in the use of neuroimaging to improve neurostimulation, many technical problems remain to be addressed. One is that an individual's structural anatomy may not fully explain or predict the functional changes of the neural networks in his or her disease state.[1] For example, the exact functional brain tissue controlling the hand may slightly differ from the expected location as determined by the brain's folds. Likewise, the processing of motor control in patients with Parkinson disease is expected to differ from that in normal individuals, but structural anatomy is insufficient to identify such differences.

Can Functional Imaging Overcome the Limits of Structural Anatomy?

We expect that functional neuroimaging will be of critical importance to the development of neuroprosthetic interventions, not only because these techniques are hoped to guide electrode placement but also because they may serve as biomarkers for response. Preliminary data from our group show that functional neuroimaging can be utilized during electrode implantation and directly image the function of brain tissue located at the electrode tip as well as its relationship with the neural networks. This knowledge can then be used to adjust the electrode position or to refine the stimulation electrodes or parameters.

A Novel Technique for Studying Brain Connectivity

We recently developed a technique to image the patterns of brain function associated with an electrode by simultaneously stimulating the electrode while the patient undergoes functional MRI scanning.[2] These studies represent the first such experiments with external stimulation in humans with epilepsy or under general anesthesia.

These efforts build on early work led by our Cleveland Clinic colleague Michael Phillips, MD, in 2006 on Parkinson disease patients with implanted devices for deep brain stimulation (DBS).[3] The technique is effectively able to show brain activity through its surrogate of increased blood flow. The advantage of this method is that it can reveal in three dimensions the patterns of activity superimposed on the brain's structural anatomy, which necessarily also contains the stimulating electrodes. Extensive safety tests were performed in advance to ensure patient safety, given the strong electromagnetic environment of an MRI scanner.

> We recently developed a technique to image the patterns of brain function associated with an electrode by stimulating the electrode while the patient undergoes functional MRI scanning.

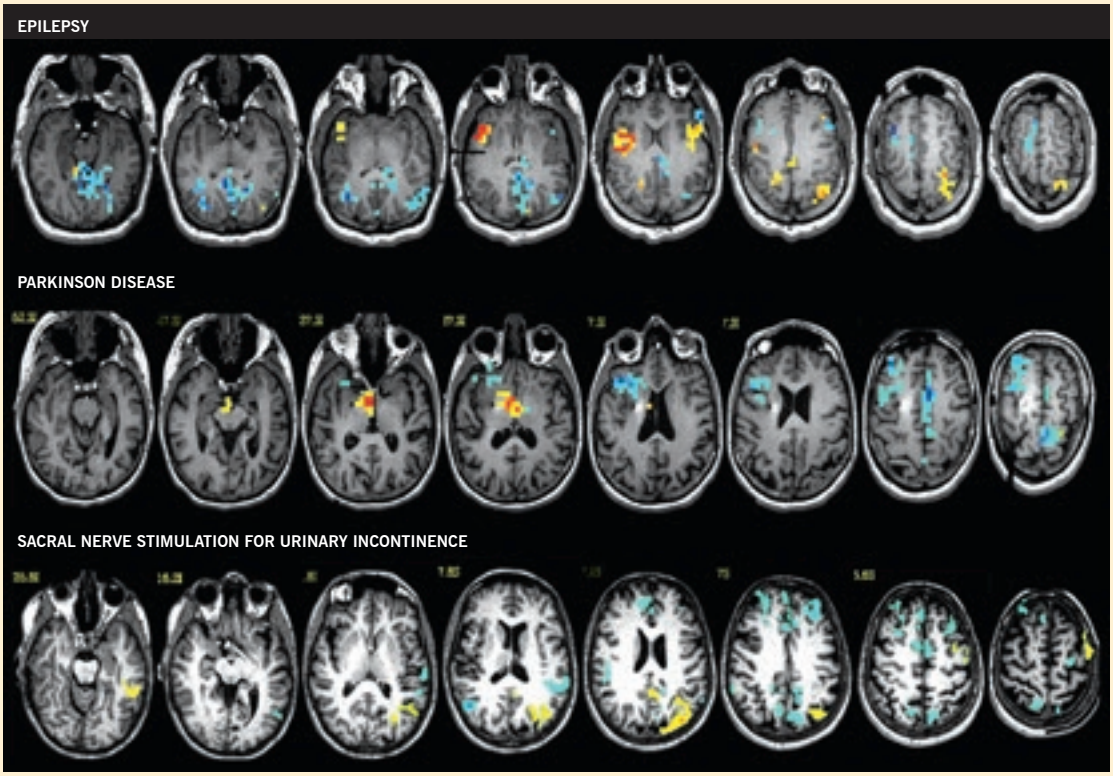


FIGURE 1. *Functional MRI activation maps during intracranial stimulation of a patient with epilepsy (top row), deep brain stimulation of a patient with Parkinson disease (middle row) and sacral nerve stimulation of a patient with urinary urgency incontinence (bottom row). In all cases, stimulation of an electrode in neural tissue evoked a response in distal areas of the brain. These patterns reveal much about underlying brain networks. The study, diagnosis and manipulation of brain networks represents the next frontier for neurological therapies.*

Initial Applications in Three Diverse Conditions

Epilepsy. This technique was first applied by our group during the invasive evaluation of epilepsy patients for determining the epileptogenic zone triggering their disease.[2] As shown in the top row of Figure 1, this method beautifully shows underlying networks of activity related to the location of stimulation, providing evidence for the networked nature of epilepsy. Furthermore, the exuberance of activity seems to be related to the degree of epileptogenesis associated with the electrode site.

This method may benefit many patients with a focal form of epilepsy wherein the seizures are generated at a focal abnormality that is often invisible on routine MRI. The ability to identify and surgically remove these foci can potentially result in a cure. Application of our technique to these foci can help verify their epileptogenicity and associated networks.

> The study, diagnosis and manipulation of brain networks represents the next frontier for neurological therapies.

Movement disorders. Another recent application involves the placement of DBS electrodes for movement disorders such as essential tremor or Parkinson disease. As shown in the middle row of Figure 1, stimulation again excites brain networks that reveal the functional location of the electrode tip relative to the rest of the brain. This pattern of generated activation can reveal whether the electrode is in the most appropriate location. If the technique is performed intraoperatively, the electrode can be adjusted for maximal benefit.

In the future, this technique could markedly increase the rate of successful electrode implantations since they would be based on the patient's functional networks rather than structural anatomy. In addition to increased successful motor improvement (Figure 2), expected benefits include a reduction of nonmotor side effects, including cognitive and emotional effects. Our group recently presented some of our early experience in this area,[4] and we are completing a major grant submission to expand on this work.

Urinary urgency incontinence. An additional example uses stimulation of the peripheral nervous system rather than stimulation from electrodes implanted in the brain. Sacral stimulation is now routinely

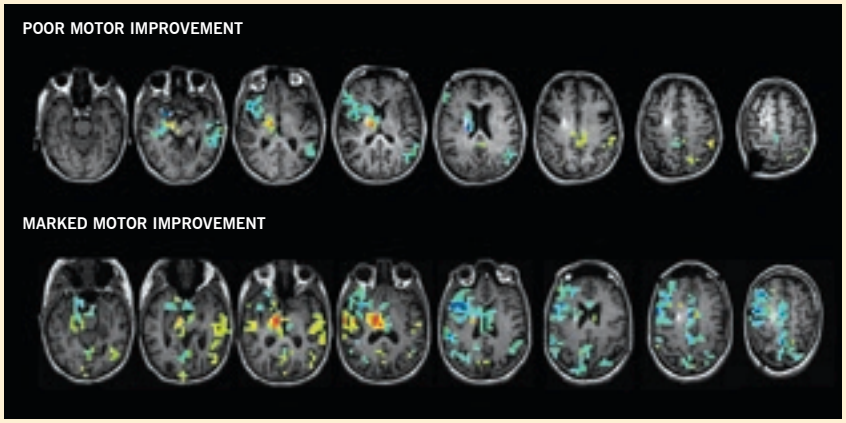


FIGURE 2. *Functional MRI activation maps showing different patterns in two patients with differing outcomes after undergoing deep brain stimulation (DBS) for Parkinson disease. Both patients had a right DBS electrode in the internal globus pallidus; the DBS-fMRI stimulus for each was 8 volts between, C1-C3 contacts, 130 Hz. The patient in the top row had poor motor improvement, whereas the patient in the bottom row had marked motor improvement.*

used for the treatment of refractory urinary urgency incontinence in females. Similar to our findings in the DBS experiments assessing electrode efficacy, we have found that simultaneous stimulation of the sacral nerve causes patterns of brain activation (bottom row of Figure 1) that might one day help assess the efficacy of stimulator placement in addition to stimulation parameters.

What Lies Ahead

Our work holds further exciting potential applications, such as in DBS treatment for major depression. The technique will also be advanced with the addition of new head coils that permit imaging at 3 Tesla, the introduction of multiple electrodes that permit stimulation and recording, and protocols that enable imaging of awake patients. The utility of neuroimaging to improve clinical neurostimulation is expanding at an exhilarating pace.

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KEY POINTS

- In the near future, neural implants are likely to play a significant role in treating various neurological diseases, largely thanks to the use of functional neuroimaging during electrode placement to reveal the activity of localized brain tissue and its relationship with neural networks.
- Our group recently developed a technique for imaging patterns of brain function associated with an electrode by simultaneously stimulating the electrode while the patient undergoes functional MRI scanning.
- We first applied this novel technique in epilepsy patients during invasive evaluation for determining the epileptogenic zone, and we have since applied it during placement of DBS electrodes for treatment of movement disorders and during sacral nerve stimulation for urinary urgency incontinence.

First-in-Human Study of DBS for Thalamic Pain Syndrome Proposes a Paradigm Shift in Targeting Neural Networks for Pain Management

By Andre Machado, MD, PhD

My colleagues and I recently conducted a 10-patient study at Cleveland Clinic that stands as the first-ever prospective, randomized, double-blind, controlled clinical trial of deep brain stimulation (DBS) for the management of chronic pain.

While the literature offers many case series reporting the effects of DBS in patients with various chronic pain conditions, most studies are limited by failure to account for placebo effects, which can be significant in this population. Furthermore, neurostimulation techniques such as DBS and spinal cord stimulation have thus far been aimed largely at the sensory pathways, which mediate only a portion of the overall pain experience. In our initial human study, we aimed to alleviate pain-related suffering in patients with thalamic pain syndrome (TPS), a devastating and often refractory condition that can follow a stroke. The study was funded by the NIH Director's New Innovator Award.

TPS: A Disruption of Sensory Pathways and the Neuromatrix

Chronic neuropathic pain in TPS is associated with lesions of somatosensory thalamic nuclei or somatosensory thalamocortical projections, typically from a stroke. TPS is characterized by unrelenting, disabling anesthesia dolorosa (painful numbness) on one side of the body, with or without associated allodynia. Patients often avoid using the affected extremity due to pain, which contributes to disability. TPS is often intractable and proves extraordinarily frustrating for patients and physicians alike.

The neuromatrix theory, first described by Melzack,[1] proposes that pain is processed by an integrated network of somatosensory, limbic and cognitive pathways. Therefore, targeting only the sensory pathways may not be a viable option, particularly when little substrate may be available after extensive lesions to this network.

A New DBS Target for Chronic Pain

Our study targeted structures that process emotion and affective behavior: the ventral striatum/anterior limb of the internal capsule. We had prior experience with this target from studies evaluating DBS for treatment-refractory depression led by Donald Malone, MD, Chairman of Psychiatry and Psychology at Cleveland Clinic.[2]

While previous studies have examined DBS for chronic pain conditions, all of them targeted sensory pathways of the brain rather than emotional ones. These traditional approaches targeting sensorimotor substrates have mostly failed to produce pain relief or improve disability. The offending lesion in TPS that almost invariably destroys sensory pain pathways may render these classical approaches ineffective. Our novel approach focuses instead on alleviating the affective sphere of pain to reduce pain-related disability from TPS.[3]

The lessons we learned from the initial phase of our ongoing study have paved the way for future research in this area. We presented preliminary findings at the most recent Biennial Meeting of the American Society for Stereotactic and Functional Neurosurgery. Those findings will be published in a forthcoming peer-reviewed article.

Study Design

As detailed previously,[4] inclusion criteria for our 10-patient, double-blind, randomized, controlled study of ventral striatal/ventral capsular stimulation for TPS included:

- Severe hemibody pain for greater than six months
- Lesion in the thalamic region (or immediately ventral or dorsal to the thalamus)
- Failure of at least one antidepressant, one antiseizure medication and one narcotic

After implantation, patients were randomized to receive active DBS to the ventral striatum/anterior limb of the internal capsule or sham stimulation for three months, followed by crossover. The crossover approach was used to mitigate the ethical/scientific dilemma of a control group that would not receive a potentially beneficial intervention as well as to control for placebo effects.

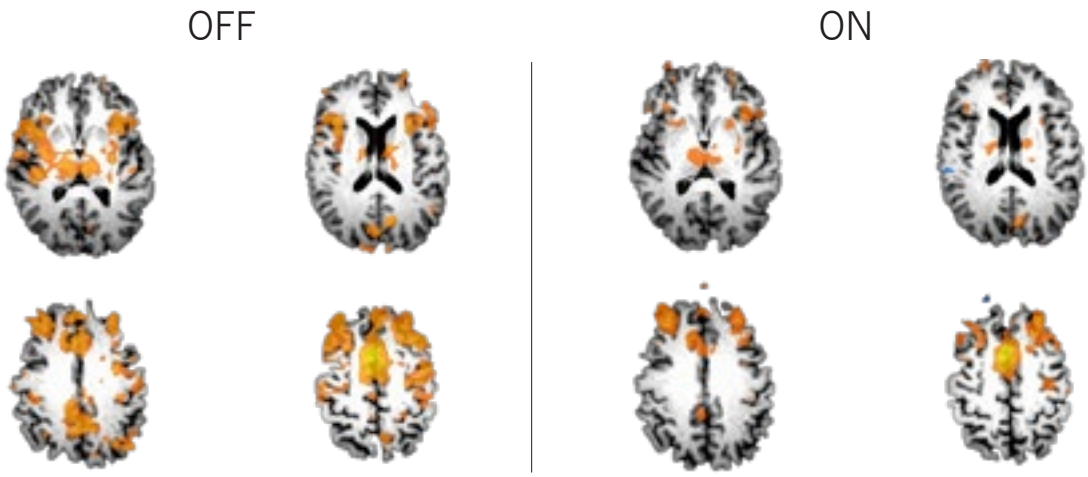
The primary end points were the Pain Disability Index and a visual analog scale of pain. Additional end points included quality-of-life measures, functional neuroimaging, and depression and anxiety inventories.

Lessons from the First Randomized Trial of DBS for TPS

While more research clearly lies ahead, our study provided important lessons. Most notably:

- We demonstrated for the first time that it is safe to surgically intervene with DBS on the emotional networks of the brain in patients with chronic pain.
- We showed that it is possible to successfully complete a randomized controlled trial in patients with chronic pain.
- Our preliminary results show that patients with severe and refractory TPS can respond to DBS of the ventral striatal and ventral capsular pathways. Patients have shown improvements in pain levels and changes in depression scores.
- These findings are particularly relevant because they were achieved under a double-blind design, thus largely controlling for placebo- and study-related effects.

FIGURE. *Example of fMRI resting-state imaging showing the effects of DBS of the ventral striatal and ventral capsular areas on limbic networks.*



› We showed that it is possible to safely conduct fMRI studies in patients with fully implanted DBS systems. fMRI data were acquired during the blinded phase of the study and can therefore be correlated with the observed clinical improvements. The figure above shows an example of how fMRI can detect patterns of brain activity in a patient with an implanted DBS system. A striking difference is noted when comparing the fMRI data acquired when DBS was "on" vs. "off."

Next Steps: More Centers, More Pain Types

Shifting attention from the sensory pathways of the nervous system to target areas that modulate emotion could provide a clinical breakthrough with potential to help many patients. When patients are disabled by long-standing chronic pain, their suffering can be magnified by desperation, frustration and anxiety. Patients tend to become consumed not so much by their pain in the moment as by its relentlessness and the expectation that they may remain in pain indefinitely.

It's incumbent on the field to incorporate well-controlled, blinded trial designs into ongoing research to explore current and novel DBS targets for chronic neuropathic pain conditions like TPS. We are now working to secure funding for a larger multicenter study that could take several years to complete. As our research continues, we hope to expand it to additional medical centers and extrapolate our findings to populations with chronic pain conditions beyond TPS. This work goes hand in hand with current nationwide efforts to reduce opioid use in the management of noncancer chronic pain.

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KEY POINTS

- Cleveland Clinic researchers recently completed the first human clinical trial of DBS for refractory thalamic pain syndrome (TPS), which also represents the first prospective randomized controlled trial of DBS in any chronic neuropathic pain condition.
- The study involved stimulation of the ventral striatum/anterior limb of the internal capsule, structures representing emotion and affective behavior, in recognition that pain is not solely a somatosensory phenomenon.
- Results from this phase 1 study revealed that intervening in the emotional networks of the brain in patients with chronic pain is safe and can be effective in some patients with TPS.

Pairing MRI with Histopathology to Probe the Pathogenesis of ALS

By Jacqueline Chen, PhD, and Erik P. Pioro, MD, PhD

More than 150 years after the initial description of amyotrophic lateral sclerosis (ALS) by Dr. Jean-Martin Charcot, its cause remains unknown and current treatments improve survival by only a few months. How will this disease be stopped?

An interdisciplinary team at Cleveland Clinic believes the answer lies in a better understanding of ALS pathogenesis through coordination of longitudinal brain MRI studies with histopathologic analyses following rapid autopsy. Our team has initiated an innovative research program to bring that coordination to bear across a growing series of ALS patients, with the goal of illuminating ALS pathogenesis and identifying new therapeutic targets.

These efforts are directed out of the Department of Neurosciences and the Section of ALS and Related Disorders in the Neurological Institute's Neuromuscular Center, with collaboration from the departments of Anatomic Pathology, Diagnostic Radiology and Biomedical Engineering.

The Obstacle of an Incomplete Picture of Pathogenesis

Degeneration of motor neurons in the brain, brainstem and spinal cord is the central feature of ALS. The inability to directly observe why and where the motor neurons degenerate has proved to be an important obstacle to the discovery of effective therapies.

In the absence of direct observation of motor neuron degeneration, a biomarker that is directly associated with the disease process would be invaluable. Biomarkers of disease progression in ALS clinical trials and drug development to date have included demographics, clinical presentation, functional testing and — increasingly — analysis of biofluids or other tissues. Although such metrics may be associated with disease progression, they do not elucidate the pathological processes that cause motor neuron degeneration.

MRI of the brain and spinal cord of patients with ALS can be performed in vivo to potentially reveal underlying pathology at one or more time points. MRI provides a noninvasive and high-resolution method of investigating various aspects of pathology (demyelination, degeneration, inflammation, etc.) during a single imaging session. Although MRI can identify ALS pathology, its sensitivity is not well characterized and we do not fully understand which aspects of such pathology it detects.

Pursuing Pathogenesis Through a Coordinated Research Approach

Cleveland Clinic's interdisciplinary approach addresses this need for a better understanding of ALS pathogenesis and for identification of new therapeutic targets. The program is unique in the high-quality data acquired throughout the disease course and postmortem.

The model for acquiring imaging and pathology data is outlined in Figure 1. Newly diagnosed patients are recruited to undergo brain MRI soon after diagnosis and approximately one year later. Patients may also consent to postmortem MRI and rapid autopsy of their brain and spinal cord. These procedures are performed immediately after death so that the MRIs are of similar quality to those acquired in vivo and tissues are in optimal condition for highly sensitive and specific immunostaining to characterize the pathology.

Within this research program, 12 patients are currently being monitored with brain MRI and 13 patients have undergone postmortem MRI and rapid autopsy.

Using Histopathology to Identify MRI Biomarkers

Presently, we are determining which MRI metrics calculated from postmortem MRIs correspond with the ALS pathology observed on immunostained tissues (Figure 2). Preliminary results suggest:

- Brain atrophy is associated with decreased neuronal and myelin density in the primary motor cortex (PMC) (Figure 2, A-C).
- Decreased average cortical thickness is associated with diffuse astrocytosis and superimposed foci of reactive astrocytes in the PMC as well as in the non-motor cortex (Figure 2, D and E).
- Reduction in volume of the pons (mid-brainstem) is associated with reduced neuron density in the cervical spinal cord and PMC.

When data sets of in vivo MRIs, postmortem MRIs and histopathology are completed, our goal will be to identify in vivo MRI biomarkers of ALS pathogenesis. Histopathologic evaluation will be performed on the brain tissue to identify regions of ALS pathology. Both in vivo and postmortem MRIs will be aligned with the brain tissue so that tissue regions that exhibit pathology can be mapped onto the MRIs. This will effectively allow us to look back in time and identify the earliest MRI abnormalities that eventually evolve into the pathology observed postmortem.

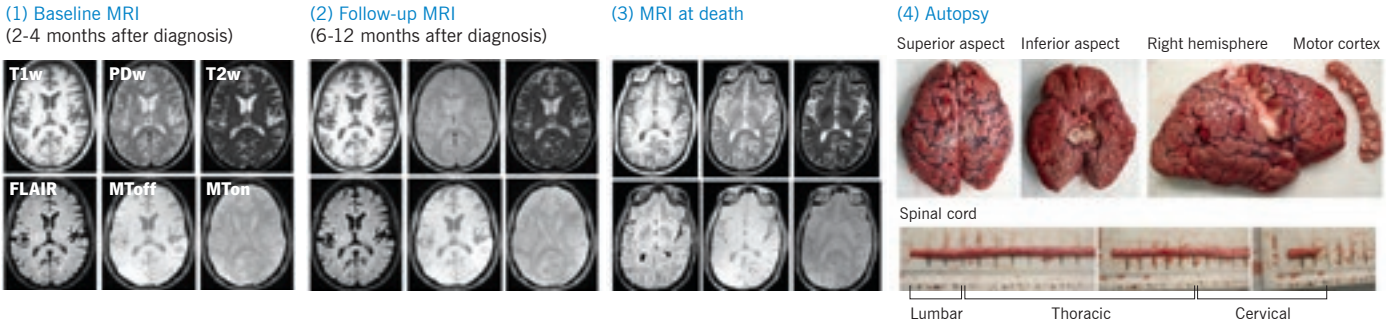
Using MRI and Histopathology to Identify Therapeutic Targets

We are also using histopathological techniques to characterize the ALS motor neuron microenvironment. Preliminary results show:

- Spinal cord motor neuron loss is variable, with relative sparing of lumbar motor neurons in some patients.
- Myelin is reduced in the PMC.
- Oligodendrocyte progenitors and microglia are activated in the PMC.
- Astrocytes exhibit variable patterns of reactivity.

In the future, we aim to classify ALS patients into categories based on their pathology pattern and to determine the MRI features that correspond with each category.

FIGURE 1. *Model and timeline for imaging and histopathologic data acquisition in ALS patients. (1) Six different in vivo MRI modalities at baseline in an ALS patient. (2) One-year follow-up in vivo MRI in the same patient. (3) Postmortem in situ MRI in an ALS patient. (4) Example photographs documenting the autopsy of an ALS patient.*



Looking Ahead

Our ongoing efforts are predicated on the following principles and suppositions:

- Histopathologic analyses of brain and spinal cord tissues will reveal candidate therapeutic targets.
- In vivo MRI biomarkers will be used by clinicians for diagnosing, prognosticating, and stratifying patients in clinical trials to optimize outcomes by matching the therapeutic mechanism to the predicted pathology.
- In vivo MRI biomarkers will be used to assess therapeutic efficacy.

We look forward to sharing insights we gain in the months and years ahead.

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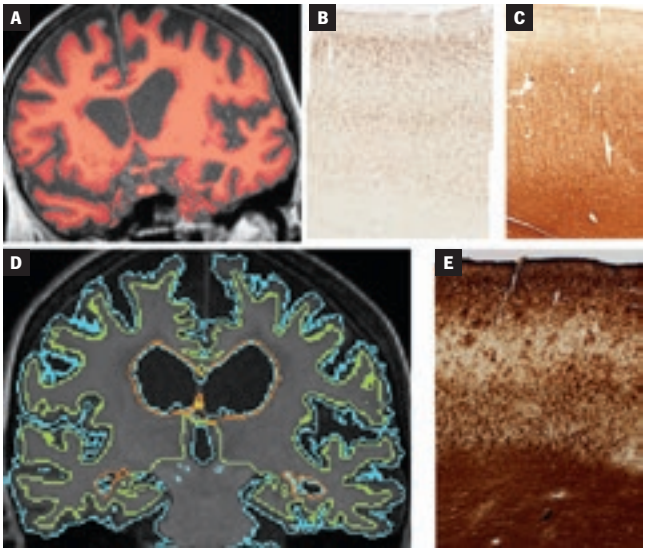
FIGURE 2. *Postmortem MRI and associated histopathology findings in ALS patients. (A) Segmentation of the brain from MRI for atrophy quantification. (B and C) Immunostaining for neurons (B) and myelin (C) in the primary motor cortex. (D) Segmentation of the cerebral cortex from MRI for cortical thickness quantification. (E) Immunostaining for astrocytes.*



KEY POINTS

- An interdisciplinary team at Cleveland Clinic has developed an innovative research program aimed at revealing ALS pathogenesis and identifying new therapeutic targets.
- Under the program, patients with ALS undergo brain MRI soon after diagnosis and approximately one year later. They may also consent to postmortem MRI and rapid autopsy of brain and spinal cord.
- Our objective is to find MRI biomarkers of in vivo ALS pathogenesis by mapping tissue pathology onto all MRIs, allowing retrospective identification of the earliest MRI abnormalities that eventually evolve into the postmortem pathology.

Harnessing the Intrinsic Neuroprotective Functions of Microglia: Novel Insights and Next Steps

By Zhihong Chen, PhD, and Bruce D. Trapp, PhD

Resident macrophages exist in almost all organs, where they are the first-line defenders against infection or disease. In the brain, this innate immune response is performed by microglia (Figure 1). Numerous microglia cover the entire brain parenchyma in a nonoverlapping, mosaic fashion by spreading their delicate processes.

Modern multiphoton imaging techniques have allowed glial biologists to directly study the brain of the living mouse. What is astonishing is that microglial processes can be observed constantly extending or retracting a minute distance, making them arguably the fastest-moving structures (~1.5 μm/min) in the brain.[1]

These observations aroused strong curiosity about what microglia actually do and why they do it — questions that remain to be fully addressed today. However, at least one hypothesis is that these movements allow microglia to actively gauge the health of surrounding central nervous system (CNS) cells within their microdomains.

Microglia: Misunderstood Guardian Angels?

Microglia are activated by acute insults and chronic diseases. This activation induces hypertrophy of their cell bodies, asymmetrical distribution of their processes and increased expression of activation molecules.

Activated microglia can be observed in many neurologic diseases, such as those surrounding the core plaques in an Alzheimer disease brain. Because of their frequent presence in various disease states, activated microglia traditionally have been considered to be destructive.

This "guilt by association" view has recently been revisited, however, as more and more studies have begun to demonstrate that microglia are actually essential defenders against many CNS diseases.[2] This is particularly the case in chronic brain diseases, where the majority of microglia are activated. If these activated microglia were exclusively destructive, these conditions would not be "chronic" because microglia would have essentially destroyed much of the tissues.

Even more convincing evidence supporting a neuroprotective role for microglia lies in conditions where microglial activation occurs in the absence of frank pathology, such as when "rod cells" encapsulate healthy-appearing neurons, as observed in subacute sclerosing panencephalitis, multiple sclerosis (MS) or amyotrophic lateral sclerosis.[2]

The Quest to Find the Neuroprotective Mechanism of Microglia

In our previous work, we found that microglial activation, as a critical part of immune responses in the CNS, can be mediated by a preconditioning paradigm induced by injecting the gram-negative bacteria outer membrane component lipopolysaccharide (LPS). We further showed that LPS-induced microglial activation contributes to neuroprotection against experimental traumatic brain injury, as the brain lesion size is much smaller when microglia are activated by LPS.[3] This novel finding has facilitated revision of prior perceptions of the role and mechanism of microglial activation in the brain.

Following our findings in 2012, we were interested in the specific actions that activated microglia exert on neurons in order to provide protection. Our continued investigations involved applying several novel technologies, including three-dimensional electron microscopy and wireless telemetric electrophysiology.

In a breakthrough observation published in *Nature Communications* last year,[4] we demonstrated for the first time that microglia, when activated, migrate to and dislodge inhibitory synapses between neurons. This "synaptic stripping" increases neuronal firing activity and leads to a cascade of events that enhance the survival of brain cells (Figure 2). We further demonstrated that these events are one of the underlying mechanisms by which activated microglia contribute to neuroprotection after traumatic injury.

Potentially Sweeping Implications

Given that physical interactions between microglia and neurons exist in a variety of neurologic diseases, such as Alzheimer disease, MS and stroke, our discoveries may have a profound impact across the whole spectrum of neurologic disease. They suggest that the protective role of microglia could potentially be harnessed to improve the prognosis for patients with traumatic brain injury and delay the progression of diseases such as Alzheimer disease, MS and stroke. On a broader scale, our findings suggest that the innate immune system helps protect the brain after injury or during chronic disease, and this role should be further studied.

Next Steps: Elucidating the Pathways of Microglial Activation

We are now working to elucidate the pathways and molecular mechanisms of microglial activation in the model we have established. We are using RNA microarray profiling techniques to define the molecular signature of neuroprotective microglia. Identifying the profile of the protecting microglia will aid the design of targeted therapeutic strategies.

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KEY POINTS

- Although activated microglia traditionally have been considered destructive to CNS health, increasing numbers of studies are demonstrating that they are actually essential defenders against many CNS diseases.
- Our lab recently demonstrated for the first time that microglia in the adult mouse, when activated, migrate to and dislodge inhibitory synapses between neurons. We also showed that the resulting cascade of events is one mechanism by which activated microglia contribute to neuroprotection.
- These discoveries suggest that the protective role of microglia might be harnessed to improve prognoses across a wide spectrum of neurologic disease. We are now working to elucidate the pathways and molecular mechanisms of microglial activation in our model, with the ultimate goal of targeted therapeutic strategies.

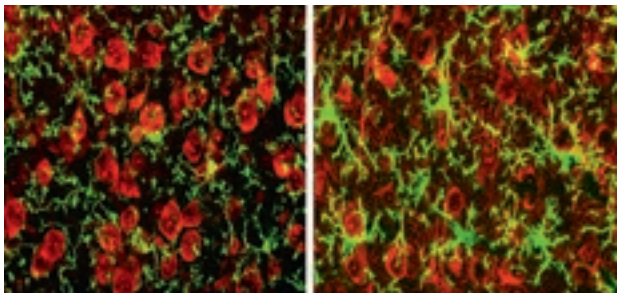

FIGURE 1. *Morphological appearance of microglia in the mouse brain (visualized in green by immunofluorescent staining with anti-Iba1 antibody). In control mice (left), microglia have small cell bodies and long and slender processes. When activated (right), microglia enlarge their cell bodies and thicken their processes, which closely enwrap neuronal cell bodies (red, Nissl staining). Reprinted from Chen et al.[4]*

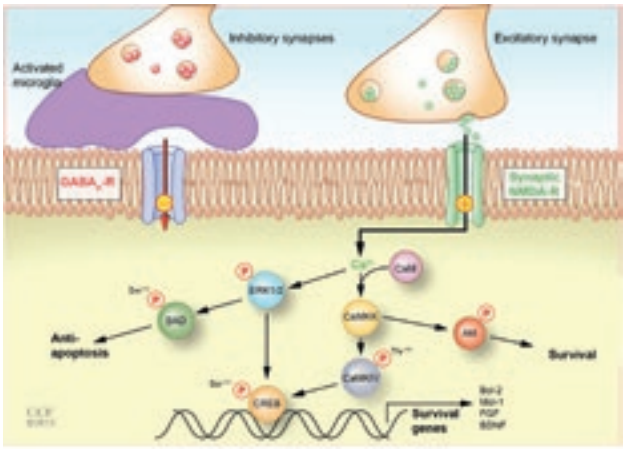

FIGURE 2. *Model of activated microglia-mediated neuroprotection. Activated microglia displace presynaptic GABAergic terminals, which lowers the threshold for firing of excitatory synaptic NMDA receptors. Increased firing of synaptic NMDA receptors (+) elevates intracellular Ca^{2+} levels, which leads to activation (phosphorylation) of signaling molecules and transcription factors, culminating in production of anti-apoptotic and neurotrophic proteins. Reprinted from Chen et al.[4]*

Converging Robotic SEEG with Laser Ablation: A Minimally Invasive Approach for Difficult-to-Localize Pediatric Epilepsy

By Jorge Gonzalez-Martinez, MD, PhD, and Ahsan N.V. Moosa, MD

Laser ablation guided by real-time MRI, initially described in 2006 as a treatment for metastatic tumors, has shown promising results in the treatment of multiple intracranial pathologies including primary and metastatic lesions, epileptogenic foci and radiation necrosis.

Advantages of Laser Ablation

The use of laser ablation for treatment of epileptogenic areas such as tubers (in tuberous sclerosis) and in mesial temporal sclerosis (via selective laser amygdalohippocampotomy), focal cortical dysplasias, hamartomas and post-stroke epilepsy has been described in the literature. The advantages of laser ablation are attributed to several factors:

- The small opening required to accommodate the probe
- The precision related to the probe's final location
- The relatively short ablation time associated with each treatment (< 5 minutes, on average, after placement of the laser catheter)

All these attributes result in a potentially safer, more cost-effective and more efficient treatment option than other approaches for pediatric patients with medically intractable focal epilepsy. Additionally, laser ablation provides access to areas where surgical treatment using conventional therapies would be contraindicated.

Pioneering Integration of SEEG with Laser Therapy

While Cleveland Clinic's Epilepsy Center has previously published cases of laser ablation of epileptogenic lesions, the use of the robotic stereoelectroencephalography (SEEG) technique in combination with laser ablation to disrupt a specific epileptic network in patients with nonlesional epilepsy has not been reported. We have been performing this innovative work in adult and pediatric patients for the past year, with promising results in terms of seizure control and safety. We share here an illustrative case report of a pediatric patient.

Representative Case Description

Epilepsy history. A 17-year-old male presented with a history of intractable epilepsy since age 9. He described his seizures as a "cold chill down the whole body" followed by partial awareness of subsequent events. His caregivers reported that the seizures began with a stare, changes in facial expression and pouting of the mouth, accompanied by changes in breathing pattern. He often walked aimlessly or made quick "robotic" movements. His seizures ended with a scream that startled anyone nearby and disrupted the patient's social life. Although the seizures lasted only 15 to 20 seconds, they occurred as frequently as 20 times a day, and almost hourly during sleep.

The patient presented to Cleveland Clinic after having failed eight different antiepileptic drugs and vagal nerve stimulation. His neurologic examination was normal.

Presurgical, noninvasive workup. Video EEG evaluation suggested a diagnosis of left frontal epilepsy based on interictal spikes and ictal patterns in a few seizures. Several other seizures, however, were poorly localized, with bifrontal involvement. A 3T MRI brain scan did not reveal any lesion. Fluorodeoxyglucose positron emission tomography (FDG-PET) showed focal hypometabolism in the left frontal region. Ictal single-photon emission computed tomography also showed hyperperfusion in the left anterior medial frontal region. Magnetoencephalography confirmed epileptiform discharges in the same region (Figure 1).

The absence of a lesion on brain MRI and localization in the dominant frontal lobe led to consideration of invasive monitoring with SEEG. This procedure was performed to map the epileptogenic zone and to determine the margins of the resection.

Invasive monitoring with robotic SEEG. During SEEG monitoring, the electrode in the left anterior mesial frontal area (L′, contacts 2, 3 and 4) showed focal and persistent repetitive spikes throughout the evaluation (Figure 2). All recorded seizures also arose from the same region (Figure 2). This was concordant with the presurgical suspicions. Stimulation of the same regions elicited habitual seizures, further reinforcing the hypothesis. After discussion with the patient and his family, we elected to perform laser ablation of the focus at the time of removal of the SEEG electrodes.

Laser ablation. With the patient under general anesthesia, a small lesion centered at the previous location of the L′ electrode (left mesial frontal area, contacts 2, 3 and 4) was created, approximately 1 cm^3 in volume (Figure 3). The treatment period, from insertion of the laser probe to the end of the lesioning phase, was five minutes. Afterward, the probe was removed, the incision was closed with one stitch and anesthesia was reversed. The patient was discharged from the hospital the next morning.

Outcome. At three-month postoperative follow-up, the patient was seizure-free. He has had no change in personality or memory. However, his family reports a new "problem": "Since surgery, we don't know if he is at home or not!" they relate (because his seizure-associated screams have ended).

Conclusions: A Promising Diagnostic-Therapeutic Combination

Our preliminary experience with the described method clearly illustrates the feasibility of a unique combination of robotic SEEG, laser ablation and intraoperative MRI in the management of pediatric

FIGURE 1

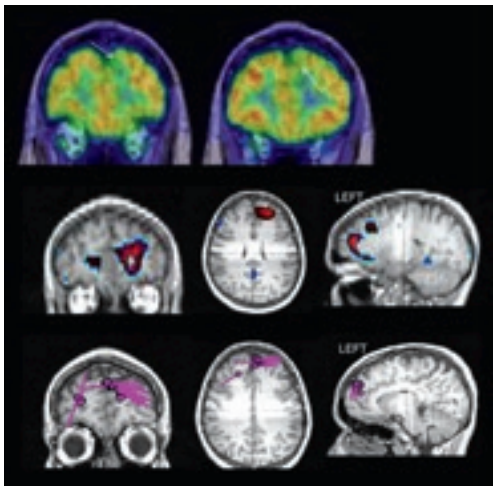

FIGURE 2

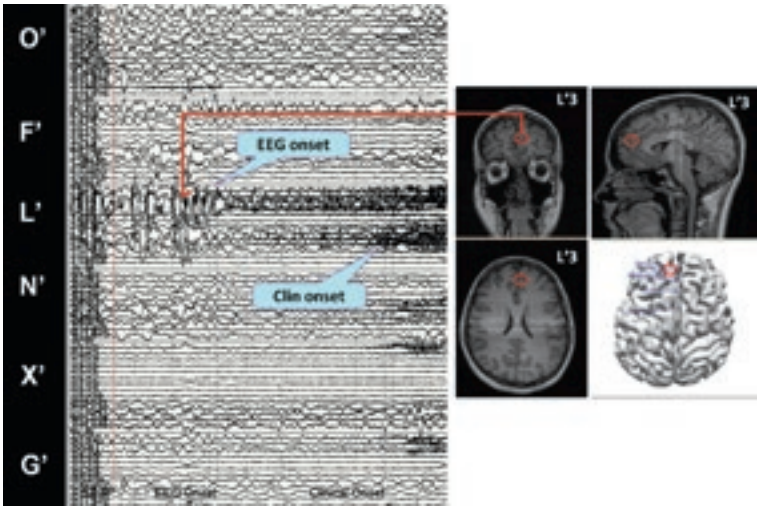

FIGURE 3

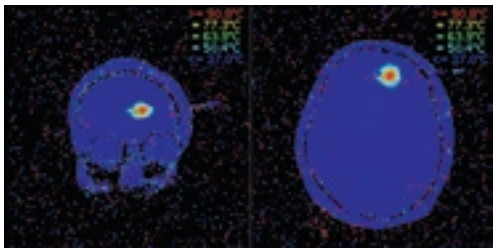

FIGURE 1. *Left frontal localization supported by noninvasive testing with FDG-PET (top), ictal single-photon emission computed tomography (middle) and magnetoencephalography (bottom).*

FIGURE 2. *Localization of ictal onset to the left anterior mesial superior frontal gyrus (L' 2-4) as confirmed by intracranial SEEG.*

FIGURE 3. *Intraoperative coronal and axial thermograms during MRI-guided laser ablation of the left mesial frontal area.*

patients with difficult-to-localize epilepsy. While further study is needed, the success of this procedure raises the possibility of a diagnostic-therapeutic combination unparalleled in its minimal invasiveness, reduction of treatment time and brevity of recovery time — all apparently without compromising efficacy.

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Dr. Moosa, aka Ahsan Moosa Naduvi Valappil (naduvia@ccf.org; 216.445.6746), is a pediatric epilepsy specialist in the Epilepsy Center.

SUGGESTED READING

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Quigg M, Harden C. Minimally invasive techniques for epilepsy surgery: stereotactic radiosurgery and other technologies. *J Neurosurg.* 2014;121(suppl):232-240.

KEY POINTS

- Laser ablation of epileptogenic foci employing SEEG is a feasible treatment option in pediatric patients with difficult-to-localize epilepsies, even in the most difficult clinical scenarios, such as patients with "nonlesional" scans.
- The combination of laser therapy with SEEG may also be particularly suitable for deep, difficult-to-access lesions such as insular lesions, hypothalamic hamartomas and periventricular heterotopias.
- Short-term results of laser ablation/SEEG epilepsy surgery have been promising. Precise localization is key to a successful outcome.

Personalizing Rehabilitation and Brain Stimulation: The Patient as a Guide to Maximizing Neurologic Recovery

By Ela Plow, PhD, PT; Vishwanath Sankarasubramanian, PhD; David Cunningham, MS; Kelsey Potter-Baker, PhD; Ken Sakaie, PhD; and Andre Machado, MD, PhD

As the neurologic rehabilitation community looks to apply principles of personalized medicine, it faces a particular challenge: a lack of information about which clinical or diagnostic characteristics are appropriate for deriving tailored therapies. After all, a hallmark of personalized medicine is its emphasis on interventions that are biologically or genetically tailored to maximize outcomes on initial use, without need for trial and error.

A project called the BRAIN initiative (Brain Research through Advancing Innovative Neurotechnologies℠), recently launched by the federal government in conjunction with the National Institutes of Health, promises to yield the first interactive map of the neural circuitry of the human brain. This type of mapping may provide the key to tailored rehabilitation treatments.

In our work at Cleveland Clinic, we are leveraging concepts of the BRAIN initiative to develop personalized rehabilitation care programs. This work is based on our creation of an interactive map of the diseased or damaged brain.

Confronting Variance in Brain Plasticity

Although stroke is the most common and well-studied condition leading to persistent disability, the field of stroke rehabilitation is plagued with generic, nonspecific therapies. A good example is the scattershot approach seen with noninvasive brain stimulation.

Although the technology was initially considered promising as a means to increase adaptive neuroplasticity, the latest clinical trials have failed to demonstrate a consistent improvement in outcomes. Noninvasive brain stimulation using magnetic fields or direct current may ultimately prove helpful, but its current indiscriminate use — driven by a one-size-fits-all approach based on the assumption of a generic substrate for brain plasticity — is likely to produce only variable outcomes, given differences in the nature and extent of stroke-related disability among individual patients.

Rather than discounting the potential of brain stimulation to dramatically maximize and accelerate outcomes of rehabilitation in stroke, we instead operate on a conceptual framework based on tailoring stimulation to an individual's neurologic characteristics.

Guided by our empirical understanding that mechanisms of neuroplasticity vary from patient to patient, we use advanced neuroimaging technologies to investigate individual characteristics that generate such variance. These techniques include functional MRI to illustrate brain perfusion and function during real-time limb movement, diffusion tensor imaging to visualize the structure of white matter pathways devoted to moving the paralyzed limb, and transcranial magnetic stimulation to map the physiology of pathways and cortices (Figures 1 to 3).

Through these imaging innovations, we are able to determine which substrates remain spared in the damaged brain, how they interact with other regions and how they contribute to the potential to move paralyzed limbs. We process this information in concert with information regarding the patient's pattern and severity of impairment, collected using validated clinical scales that track deficit and recovery.

We then process these neural and clinical characteristics via a hypothesis-driven decision tree, with the goal of developing treatment interventions unique to the patient's pathology. Our aim is to identify whether substrates on the injured or damaged side of the brain are spared adequately to be entrained with rehabilitation of the paretic upper limb, or if they are disrupted to such a degree that it would be best to rely on compensatory therapies such as those involving use of the less-affected side.

Considering that rehabilitation interventions are customized to individual impairment and etiology, it is necessary to similarly customize stimulation therapies. After all, stimulation therapies seek to facilitate processes adopted in recovery with rehabilitation. Brain stimulation customized to a patient's pathology will likely offer the most consistent boost to paired rehabilitative therapy.

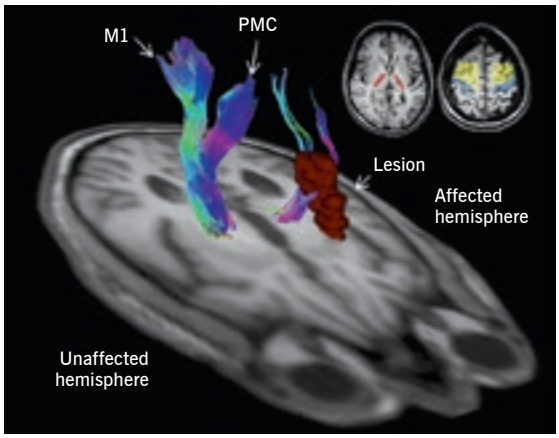
In a clinical trial and two other clinical studies underway at Cleveland Clinic, we are attempting to understand how clinical and neural characteristics predict which substrates are likely inherent to a patient's expression of plasticity. We are testing stimulation of such candidate substrates against traditional approaches and validating whether stimulation of the "patient-specific" substrate is most effective for recovery.

Tailoring Stimulation for a Range of Deficits

If this approach is successful in stroke, it holds potential across other disease states. Our framework could be translated to tailor stimulation in conditions such as pain, vision loss and depression as well as to potentiate therapies in brain injury, cerebral palsy and multiple sclerosis, where generic approaches have rendered rehabilitation arduous, varyingly effective and poorly funded.

In a much larger context, using a simple, noninvasive, inexpensive treatment tailored to what NIH Director Francis Collins, MD, PhD, has termed "brain types," we challenge the long-standing assumption of generic plasticity.

With recent drastic cuts in Medicare reimbursement for therapies, neurologic rehabilitative practice demands more effective, precise and accelerated outcomes. Brain stimulation guided by characteristics that maximize individual patients' mechanisms of neuroplasticity would yield promising, consistent and prompt gains in neurologic rehabilitation.



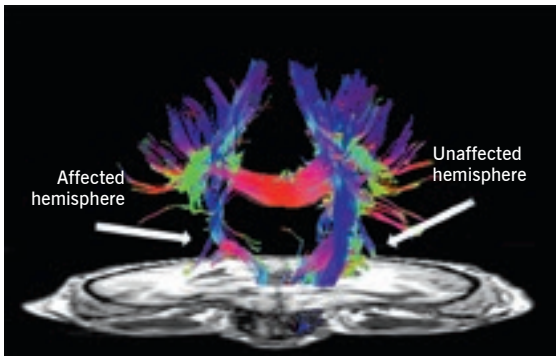


FIGURE 1. *Advanced diffusion tensor imaging methods help reconstruct all surviving pathways in the lesioned areas of the stroke-affected hemisphere. Differences between integrity of pathways in the affected vs. unaffected hemispheres serve as an important baseline characteristic for predicting levels of recovery and the type of brain stimulation therapies that can be used. The images at the top right represent pivot points used for the analysis (internal capsule and motor cortices). Pathways are reconstructed between these nodes to form our analyses.*

FIGURE 2. *Like Figure 1, this image illustrates our ability to reconstruct all surviving pathways in the lesioned areas of the stroke-affected hemisphere. It also demonstrates our ability to map key transcallossal pathways that connect bilateral motor cortices. Survival and physiology of these pathways are key to dictating recovery from chronic stroke.*

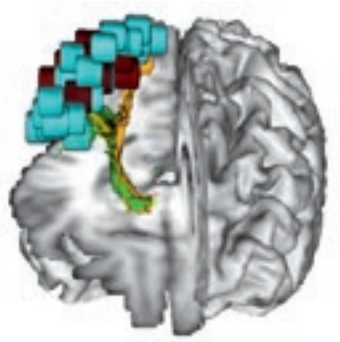


FIGURE 3. *This image illustrates our ability to interface two mapping methodologies. Cuboid cells in blue and red represent points on the brain surface that are mapped with a neurophysiologic technique (transcranial magnetic stimulation, or TMS); red cells represent sites on the surface that were responsive to TMS (i.e., able to elicit neurophysiologic responses in the corresponding muscles of the hand). Pathways emerging from these sites have been reconstructed with diffusion tensor imaging (DTI). A combined TMS-DTI approach demonstrates regions of the brain that offer structurally and neurophysiologically sound pathways.*

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KEY POINTS

- Although noninvasive brain stimulation is a promising technology for treating neurologic deficits, its one-size-fits-all application based on the assumption of generic brain plasticity has produced inconsistent outcomes.
- Plasticity varies greatly among patients, yet advanced mapping of the damaged or diseased brain may reveal unique characteristics that help determine plasticity variances.
- Advanced mapping may enable clinicians to determine which patients have adequate potential for plasticity and which surviving regions likely contribute to such potential. This knowledge could support development of targeted brain stimulation as an aid to rehabilitation following stroke or other deficit.
- Cleveland Clinic researchers are working to interface advanced mapping from multiple MR-based and neurophysiologic sources with therapeutic brain stimulation within the framework of personalized rehabilitation medicine.

Sleep-Disordered Breathing and Obesity Increase Atrial Fibrillation Following Cardiac Surgery

By Reena Mehra, MD, MS

The Sleep Disorders Center at Cleveland Clinic has developed a focus in the area of sleep-disordered breathing (SDB) and atrial fibrillation (AF), identifying a strong magnitude of association in large population-based studies.[1,2] Our investigations have also explored the intersection of both conditions with obesity. Yet an enduring knowledge gap surrounds interrelationships among SDB, obesity and AF following cardiac surgery.

This gap prompted us to embark on a collaboration with Cleveland Clinic's Miller Family Heart & Vascular Institute to examine the interrelationships of SDB, obesity and post-cardiac surgery AF. We share an overview of our study rationale and findings here.

SDB, Obesity and AF: Untangling a Web of Related Effects

SDB, which encompasses both obstructive and central sleep apnea, is characterized by repetitive upper airway collapse or cessation of breathing that is either complete (resulting in apneas) or partial (resulting in hypopneas). These sleep-related respiratory events are accompanied by intermittent bouts of hypoxemia, hypercapnia, autonomic dysregulation and intrathoracic pressure swings, leading to long-term adverse cardiovascular sequelae.

Our group has documented twofold to fourfold higher odds of AF in patients with a severe degree of SDB relative to those without SDB.[1,2] We have also demonstrated an immediacy to the relationship of respiratory events with discrete arrhythmic events such as paroxysms of AF. These findings suggest an acute impact of the physiology of SDB superimposed on the likely chronic adverse influences of SDB pathophysiology in terms of cardiac remodeling. The result is creation of the ideal milieu for atrial arrhythmogenesis (Figure 1).

Although obesity is a recognized risk factor for both SDB and AF, parsing out the complex and multidirectional relationships of SDB and obesity in relation to cardiac outcomes remains a substantial challenge.[3] In addition to an increase in parapharyngeal fat pads resulting from obesity-related mechanical load, leptin resistance and an increase in systemic inflammation may also represent risks for SDB. Bidirectional relationships are likely at play, with pathways of metabolic dysregulation and insulin resistance that may represent intermediate factors contributing to obesity in SDB. Additionally, the literature has increasingly implicated obesity in AF development, likely via pathophysiologic mechanisms related to genetic susceptibilities, coronary artery disease, ventricular adaptation and visceral/epicardial adiposity leading to cardiac electrical and structural remodeling.

AF After Cardiac Surgery: Common, Prognostically Ominous

The prevalence of AF following cardiac surgery is high: 33 percent among patients undergoing coronary artery bypass graft surgery (CABG) and 50 percent among those having valvular surgery. Identification of risk factors is key, as post-cardiac surgery AF portends a poor prognosis and is associated with adverse outcomes including increased rates of postoperative stroke, increased hospital stay and healthcare costs, and a trend toward lower survival rates.

Despite the substantial impact of post-cardiac surgery AF, studies to date have been limited by at least three factors: (1) consideration of only CABG, with no examination of valvular surgery, (2) lack of consideration of confounding factors such as obesity and (3) failure to collect refined, detailed polysomnographic data (e.g., use of a screening questionnaire for obstructive sleep apnea).

Our Study in Brief

Our collaborative study with the Miller Family Heart & Vascular Institute set out to address these limitations by examining the interrelationships of SDB, obesity and post-cardiac surgery AF among patients who underwent both cardiac surgery (CABG and/or valvular surgery) and polysomnography within three years of each other at Cleveland Clinic from 2009 to 2014. We restricted the study to patients 18 or older without known AF or atrial flutter, which yielded a sample of 190 patients.

SDB was defined by the apnea-hypopnea index (AHI), using the 3 percent oxygen desaturation scoring rule, or alternately by the oxygen desaturation index. Indices to characterize obstructive sleep apnea (obstructive apnea-hypopnea index) and central sleep apnea (central apnea index) were also examined.

Overall, the patient sample was relatively old (60.6 ± 11.4 years) and obese (body mass index 33.3 ± 7.5 kg/m^2). Ninety-three percent of patients had an AHI of 5 or greater, and the prevalence of postoperative AF was 30 percent, which was in line with existing reports.

We identified a statistically significant association of postoperative AF with AHI-defined SDB but not specifically with obstructive or central sleep apnea. After adjusting for obesity and other confounding factors, the relationship was slightly attenuated. Notably, obesity was found to be an effect modifier of the relationship, in that SDB was more closely associated with post-cardiac surgery AF in those who were more obese, a finding particularly pronounced in patients with the most severe degree of SDB (Figure 2).

Implications and Next Steps

These findings were recently highlighted as a platform presentation at SLEEP 2015, the annual meeting of the Associated Professional Sleep Societies, and are being submitted for publication. They are important

FIGURE 1. *Polysomnogram in a patient with atrial fibrillation demonstrating an obstructive apnea (blue tracing and arrow) and a hypopnea (green tracing and arrow) with accompanying oxygen desaturations and an EEG microarousal.*

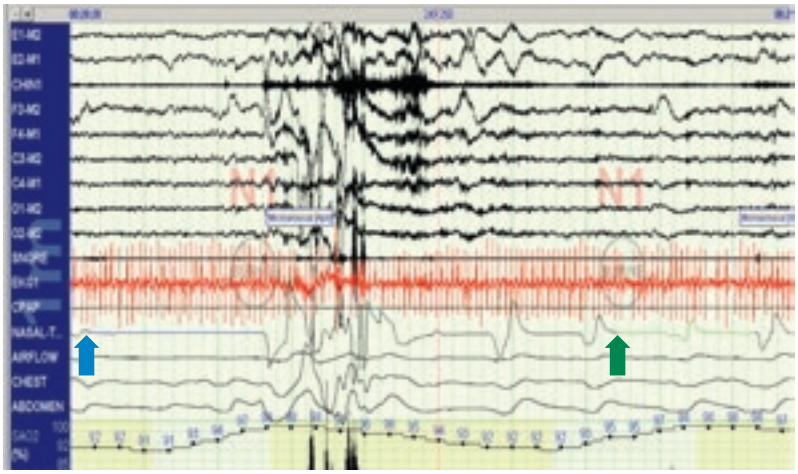
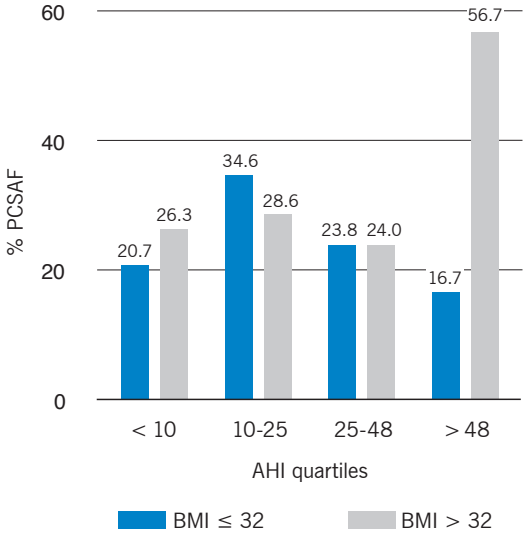


FIGURE 2. *Rates of post-cardiac surgery atrial fibrillation (PCSAF) by apnea-hypopnea index (AHI) quartiles and stratified by median BMI (N = 190).*



because they suggest that patients with both SDB and obesity may represent a particularly vulnerable group that merits targeting to reduce post-cardiac surgery AF and its attendant morbidity.

These findings also serve as a springboard for future investigations to examine their reproducibility in other patient populations, to enhance understanding of the mechanisms by which SDB and obesity may operate together to increase AF risk following cardiac surgery, and to evaluate the effectiveness of interventions targeted at SDB and obesity to reduce post-cardiac surgery AF.

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KEY POINTS

- Atrial fibrillation (AF) is common after cardiac surgery and confers an increased risk of morbidity. Despite recognition of the strong association of AF with sleep-disordered breathing (SDB) and obesity, understanding of the interrelationships among SDB, obesity and post-cardiac surgery AF remains limited.
- A new Cleveland Clinic analysis of 190 patients who underwent both cardiac surgery and polysomnography found a statistically significant association of postoperative AF with SDB. The association was particularly pronounced among patients who were obese.
- These findings suggest that patients with SDB and obesity are particularly vulnerable to AF following cardiac surgery and may merit targeting to reduce AF risk.

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Assessing Thoracic Spine Biomechanics After Decompressive Surgery: An Intact Rib Cage Bolsters Clinical Relevance

By Andrew T. Healy, MD, and Thomas E. Mroz, MD

Procedures that decompress the thoracic spinal cord are common and inevitably convey some degree of change to spinal kinematics at the surgical level. Whether or not to proceed with instrumented fusion following these procedures — to prevent spinal instability or long-term degeneration and pain — is a critically important yet largely unexplored question. Recent research[1-3] from Cleveland Clinic's Spine Research Lab has begun to help quantify the biomechanical effects of these types of procedures in the thoracic region. That research and its potential implications are summarized here.

Traditional Testing Has Been Limited by Rib Disarticulation

Despite its specialized and resilient design, the spinal column is a frequent source of pain and disability from degeneration, disk herniation, infection, tumor and traumatic pathologies. The thoracic spine, as the longest of the spinal segments, frequently incurs these pathologies.

Part of what makes the thoracic spine unique are the stenocostovertebral articulations and continuity of the rib cage, which afford increased stiffness and stability relative to the cervical and lumbar spine. As a testament to the contribution of the rib cage, in vitro testing shows that the thoracic spine will achieve over 700 percent greater motion in extension simply if the sternum is removed.[4]

Because previous platforms for cadaveric spinal testing were not equipped to test the full thoracic spine with associated rib cage, the bulk of the historical data on thoracic biomechanics has been obtained by testing specimens disarticulated from the rib cage. Therefore, biomechanical data quantifying the consequences of decompressive procedures on the thoracic spine in the clinically relevant scenario — with an intact rib cage — have been limited, in contrast to biomechanical data regarding the cervical and lumbar spine.

Methods of Our Novel Thoracic Biomechanics Studies

In 2013 we set out to fill some of this knowledge gap surrounding the stability of the thoracic spine following decompressive procedures. Specifically, we utilized an industrial robot manufactured by KUKA Systems GmbH (Augsburg, Germany) to perform multidirectional flexibility tests on 19 fresh frozen human cadaveric thoracic spine specimens with the rib cage intact (Figure 1).

The specimens were tested first in their intact state, then after each of three sequential surgical decompressive procedures at T4-5 or T8-9 — (1) laminectomy, (2) unilateral facetectomy and (3) unilateral costotransversectomy — and then after instrumented fusion from T3 to T7 (Figure 2).

CT and dual-energy X-ray absorptiometry (DXA) scans of each specimen were carried out to determine pre-existing spinal pathology

FIGURE 1.
The robotic spine testing system with a cadaveric specimen.

or fusion and the bone mineral density of each specimen. Custom-designed spinal fixtures were used to secure the spine cranially and caudally onto the robotic spine testing system. The cranial (C7-T1) and caudal (T12-L1) levels were mounted onto the custom test fixtures using pedicle screws and rods.

A six-axis, force-moment sensor (Gamma, ATI Industrial Automation, Apex, North Carolina) was used to measure the applied load and provide feedback for the robot. Three-dimensional motion was monitored continuously using an optoelectronic camera system (Optotrak Certus®, Northern Digital Inc., Waterloo, Ontario, Canada) at a rate of 20 Hz. The camera system measured the vertebral motion by tracking the relative motion between infrared markers placed on rigid body vertebral segments. This system has a measurement accuracy of ±0.1 mm in translation and ±0.1 degrees in rotation.

Collectively this testing enabled us to measure the change in range of motion across the surgical levels.

Surprising Results

We found that in all three planes of motion, the sequential decompressive procedures caused no statistically significant change in motion across the surgical level when compared with the intact state, likely due to the tremendous stability afforded by the thoracic rib cage.

We also found that despite the presence of the semirigid rib cage, the addition of pedicle screw fixation dramatically and effectively decreased the range of motion across surgical levels if necessary (see Figure 3). Complete results are available in our full-length publications.[1-3]

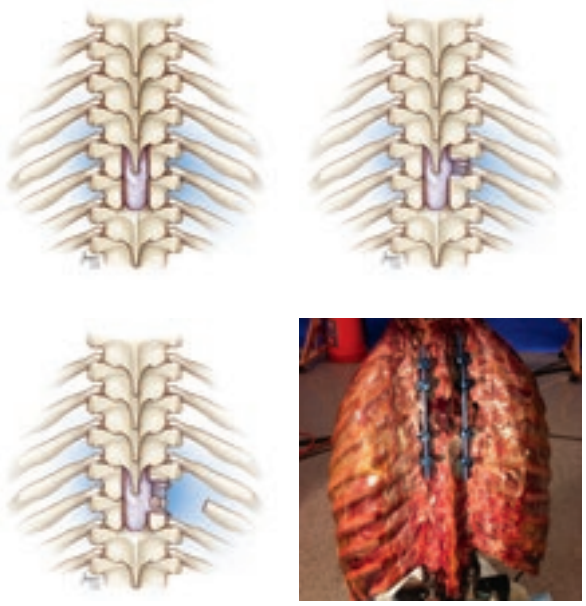

FIGURE 2. *The sequential decompressive procedures used in the study: laminectomy (top left), unilateral facetectomy (top right), unilateral costotransversectomy (bottom left) and instrumented fusion (T3 to T7) (bottom right). Reprinted from Healy et al.*[1]

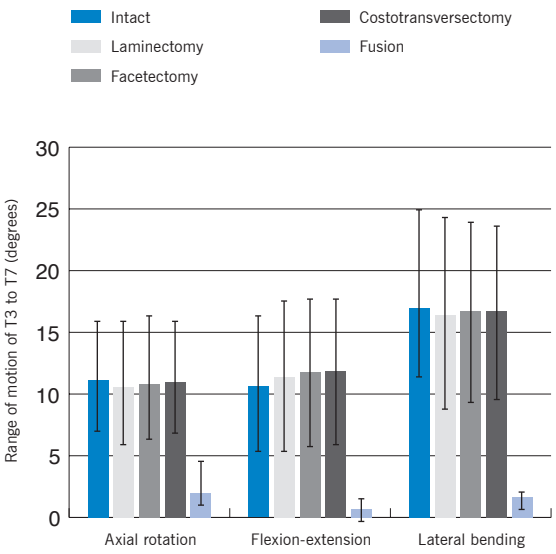

FIGURE 3. *Mean range-of-motion values for all specimens in the intact state and after each of the surgical decompressive procedures. Reprinted from Healy et al,*[1] *©2014, with permission from Elsevier.*

Future Directions and Implications

Our studies showed that laminectomy, unilateral facetectomy and unilateral costotransversectomy at the level of both the true and false ribs did not significantly alter the range of motion in our cadaveric model, suggesting that such procedures may not require instrumentation. The potential to avoid instrumentation, if confirmed, would be significant, since proceeding with instrumentation carries additive operative risk for the patient and added cost to the healthcare system.

At this stage of investigation, long-term consequences such as gradual deformity or patient discomfort cannot be ruled out and require future investigation. Since the completion of these studies, we continue to use the robotic testing system to answer fundamental biomechanical questions directly translatable to spinal surgery and patient care.

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Dr. Mroz (mrozt@ccf.org; 216.445.9232) is a spine surgeon and Co-Director of the Center for Spine Health.

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KEY POINTS

- Whether or not to proceed with instrumented fusion following surgical decompressive procedures in the thoracic spine is a critical yet largely unexplored question with implications for patient risk and healthcare costs.
- Most historical data on thoracic spine biomechanics have been obtained by testing specimens disarticulated from the rib cage, which limits their clinical relevance.
- Recent Cleveland Clinic biomechanical studies on human cadaveric spine specimens with intact rib cages found that sequential decompressive procedures caused no statistically significant change in motion across the surgical level when compared with the specimens' intact state.
- While these preliminary observations warrant further investigation, if confirmed, they suggest that certain decompressive procedures in the thoracic spine of appropriately selected patients may not require instrumentation.

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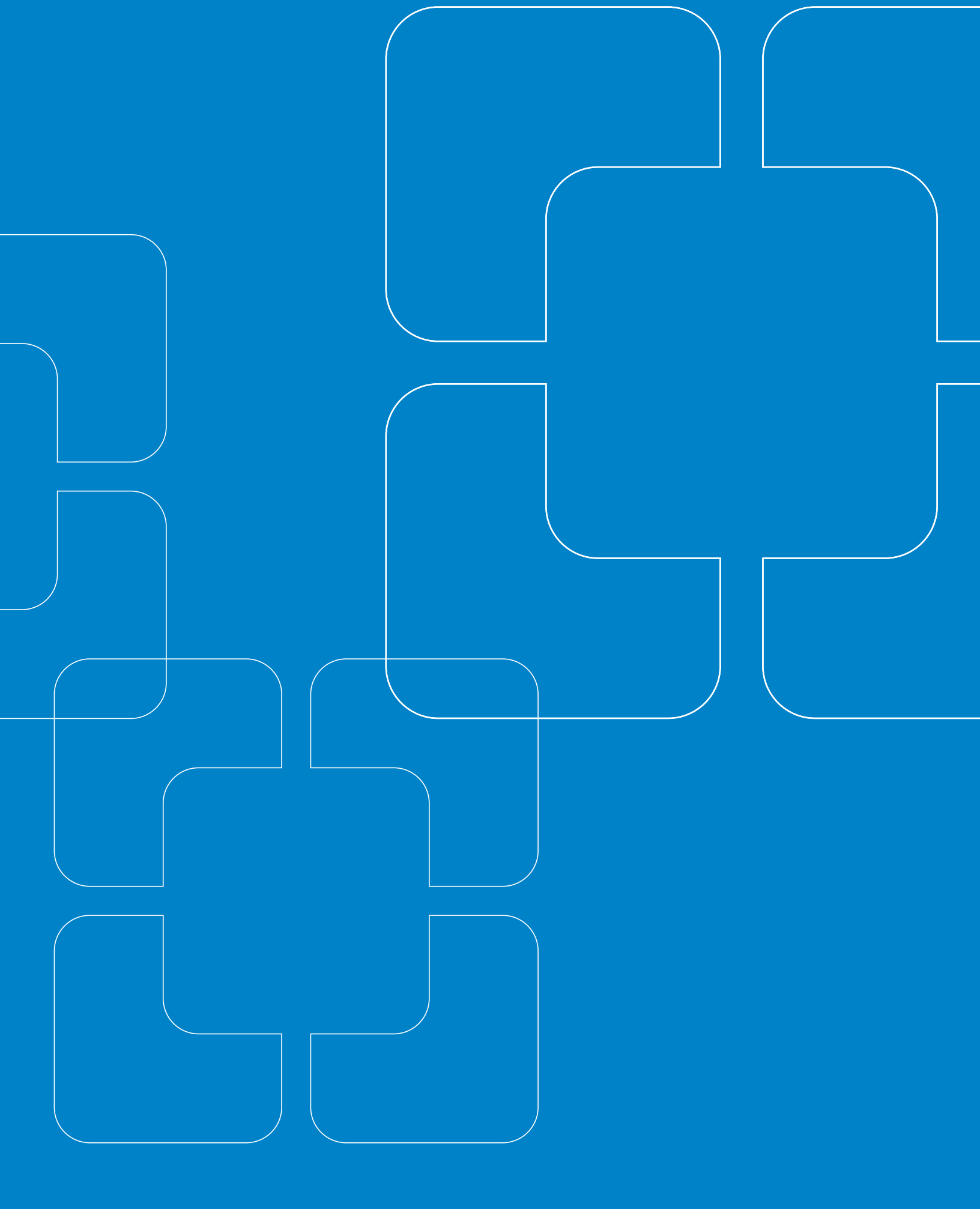

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