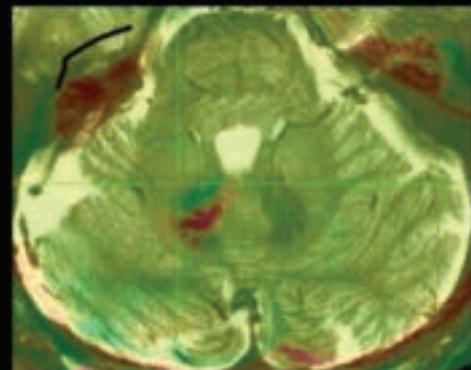


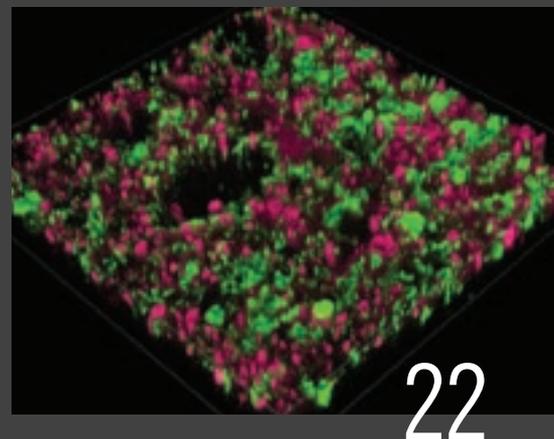
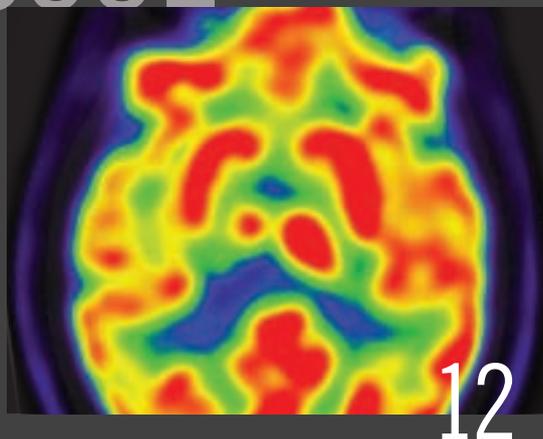
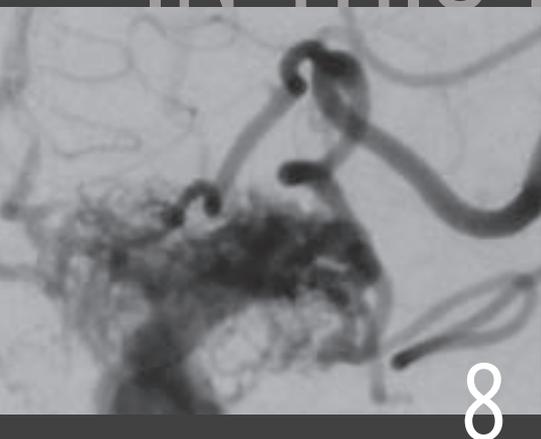
Deep Brain Stimulation for Stroke Rehabilitation

Initial Patient Shows
Promising Results in
First-in-Human Trial

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Medical Editors
Imad Najm, MD, and Robert Fox, MD

Managing Editor
Glenn R. Campbell

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Anne Drago

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ON THE COVER: Various images from throughout the course of investigation in Cleveland Clinic's first-in-human clinical trial of deep brain stimulation (DBS) for stroke rehabilitation. The main image is a baseline FDG-PET scan from the trial's first patient showing right hemisphere stroke. The top inset image is a patient-specific model revealing the relative angle of entry and location of the unilaterally implanted eight-contact DBS lead as determined through postoperative CT. The bottom inset image shows co-registered axial MR and CT scans of the cerebellum at the level of the cerebellar dentate nucleus.

DEAR COLLEAGUES,

In the two years that I've had the privilege of directing Cleveland Clinic's Neurological Institute, my colleagues and I have made three principles our touchstones: *excellence*, *discovery* and *innovation*.

I always enjoy working with our team across the institute to develop this annual *Neuroscience Pathways* publication because it showcases our pursuit of those three principles as well as any other communication that we produce. This year's issue is no exception.

Care excellence is at the core of a number of feature articles here. One standout example is on page 10, where staff from our Center for Spine Health share conclusions from several recent studies they've done examining determinants of a satisfying hospital experience for patients undergoing lumbar spine surgery. These are the first studies to explore HCAHPS scores in this setting and are intended to help providers everywhere understand how various factors may shape these patients' experience in an effort to improve overall care value.

Discovery is the essence of the work spotlighted in our cover feature on page 12, which reviews the encouraging results to date in our first-in-human clinical trial of deep brain stimulation for stroke rehabilitation. But it's equally at the heart of our leadership of the new Dementia with Lewy Bodies Consortium, detailed on page 16. The drive for discovery is likewise fueling our proteomic signature studies to elucidate links between obstructive sleep apnea and atrial fibrillation (page 20) as well as our pioneering research suggesting that blocking the source — rather than the target — of excitotoxic glutamate is a more feasible therapeutic strategy for central nervous system protection in multiple sclerosis (page 22).

Innovation is the middle ground between discovery and excellence, where we apply scientific advances to solve clinical problems more effectively. This issue is replete with examples of innovation in action. To cite just one, the feature on page 6 reviews our brain tumor team's recent publication of the largest series to date of patients with large brain metastases treated with two-staged stereotactic radiosurgery. Our staff outline how this treatment approach, which they are the first to apply broadly outside Japan, promises multiple advantages over alternate radiosurgery strategies for large brain metastases.

New to the publication this year is a sampling of brief reports — in addition to the usual features — on other notable research and clinical achievements within our Neurological Institute over the past year. Check it out on pages 24-29.

As you peruse these pages, let me or my colleagues know if any of these reports spur ideas for potential collaboration. We are always eager to work with colleagues around the nation and the world to advance our touchstone principles. Excellence, discovery and innovation are best pursued in good company.



Andre Machado, MD, PhD

Chairman, Cleveland Clinic Neurological Institute | machada@ccf.org



Negative 3T MRI? Here's What 7T MRI Can Bring to the Table

By Z. Irene Wang, PhD, and Stephen E. Jones, MD, PhD

MRI has been demonstrated as a reliable and accurate indicator for many of the pathologic findings underlying epilepsy. It has had a major impact on epilepsy surgery by delineating the extent of the epileptogenic zone. However, approximately 40 percent of the total epilepsy surgery population has a negative or “nonlesional” MRI, even using the 3-tesla (3T) epilepsy protocol. Surgery in the absence of a visible lesion is currently one of the greatest clinical challenges for tertiary epilepsy centers.

‘Nonlesional’ MRIs Are Not Truly Nonlesional

In the past few years, it has become increasingly clear that some focal epilepsies initially considered to be MRI-negative, or nonlesional, are not truly nonlesional. In fact, surgical series indicated that in 30 to 50 percent of patients with these epilepsies, histopathologic examination of the resected specimens revealed epileptogenic lesions, mainly focal cortical dysplasia (FCD).¹

The low detection rate of FCD by visual analysis stems from the fact that FCD can be quite subtle, with small lesions appearing buried in the complex convexities of the neocortex; some of these lesions have subtle signal changes on a single sequence or very few imaging slices, while others may be obscured due to artifacts. Given the practical constraints of time, MRI readers may miss those FCD lesions, which are only discernable with intense scrutiny. This is especially problematic when noninvasive clinical data, such as seizure semiology and scalp EEG, fail to point to a clear sublobar/lobar area of interest. In the presurgical evaluation of MRI-negative patients, identification of a “missed” FCD lesion may markedly simplify the evaluation process — and likely improve postresective seizure outcomes.

Initial Experience with 7T MRI

At Cleveland Clinic, ultra-high-field 7-tesla (7T) MRI has been available to patients with epilepsy since 2014 for use as a research study. The principal advantage of 7T MRI over lower-field MRI (3T or 1.5T) is its increased signal strength, which can translate to higher resolution. The latter is the factor most likely to be helpful for patients with subtle epileptic lesions. In our recent study published in *NeuroImage*, formal assessment of lesion conspicuity among 80 pairs of 7T and 3T images (from patients with a variety of neurological diseases, including epilepsy) found the 7T images to be mildly superior to 3T images overall and clearly superior in many cases.²

What 7T Brings to the Table in Epilepsy

Since 2014, 87 patients with epilepsy have undergone 7T MRI at Cleveland Clinic. Research is now underway to evaluate the clinical utility of 7T MRI for enhancing the diagnosis of epilepsy. Of particular interest is the group of 28 patients with negative 3T MRI. Preliminary results showed that visual assessment of these patients’ 7T images

revealed additional findings in a total of six patients (21 percent), including subtle FCD in three, FCD with coexisting polymicrogyria in two and vascular malformation in one.

Additional Yield from Postprocessing of 7T Data

Our previous research showed that postprocessing of MRI using a morphometric analysis program (MAP) can effectively increase the number of subtle lesions detected.³ We applied postprocessing methods uniquely adapted to 7T MRI on the scans acquired from the 28 patients with negative 3T MRI. Intriguingly, MAP not only reproduced the results of the visual assessment in the majority of cases but also detected subtle FCD abnormalities in an additional 10 patients (36 percent).

Correlation with Intracranial EEG and Histopathology

The gold standard for determining whether additional abnormalities detected by 7T are true positives or false positives is to examine their correlation with intracranial EEG, histopathology and postoperative seizure outcomes. We investigated all these measures in accordance with the 7T findings, and we continue to follow up with the patients for seizure outcomes.

A total of 11 patients who had additional positive 7T findings (visual or MAP) had already undergone intracranial EEG evaluation. In eight of these patients, the seizure onset zone from intracranial EEG overlapped with the imaging finding. In two patients, the seizure onset zone included the imaging finding but extended to a bigger cortical area. In the remaining patient, the imaging finding was not directly targeted by intracranial EEG, so the relationship could not be assessed.

A total of eight patients who had positive 7T findings (visual or MAP) had already undergone resective surgery. In six of these patients, resection completely included the imaging finding and the patients became seizure-free (five at one-year follow-up; one at six-month follow-up). Histopathology of resected tissue revealed a variety of FCD subtypes, including IIB in two cases, IIA in one, mild malformation of cortical development with oligodendroglial hyperplasia in two and malformation of cortical development type II in one. See Figure 1 for details from an example case. In two patients, resection did not include or only partially included the imaging finding, and both of these patients had recurring seizures.

Overall, our pilot data suggest that 7T visual and postprocessing analyses have the potential to generate a sizable percentage of additional findings in patients who present with 3T-MRI-negative epilepsy. These additional findings are likely relevant to the epilepsy, given their concordance with intracranial EEG and the pathological support of underlying FCD. Although this is a small, nonconsecutive

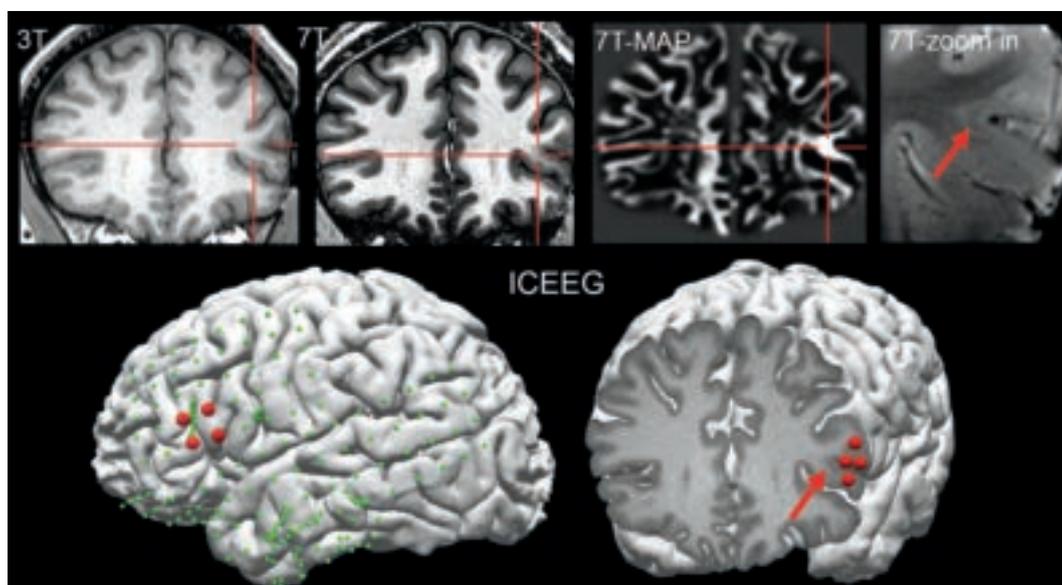


FIGURE 1. Imaging studies of a patient in whom both 7T MRI visual analysis and postprocessing analysis (MAP) identified a subtle FCD lesion. 3T MRI was negative. Retrospectively, the lesion (indicated by red crosshair and arrow) can be seen on the 3T MRI, but with much less conspicuity as compared with 7T MRI. Additionally, the lesion was seen with multiple sequences on 7T, including a T1-weighted sequence (top row, second panel) and a T2*-weighted sequence (top row, fourth panel). The lower row shows the intracranial EEG (ICEEG) findings in this patient, which were highly concordant with the lesion location. All implanted electrodes (subdural grids and depth) are indicated by green spheres; red spheres show those electrodes involved at ictal onset. The lower right panel shows the MRI slice at the exact location of ictal onset (for best viewing effect, only ictal onset is shown). This patient underwent resective surgery, which completely included the 7T finding; histopathology revealed FCD type IIB. The patient was seizure-free for six months at most recent follow-up.

cohort, these initial results encourage us to pursue further studies in larger numbers of patients. Seizure outcomes also need to be collected over a longer period.

Limitation of 7T

With our current setup, there is substantial bias field artifact at the inferior basal temporal regions, due to head coil geometry and sinus cavities. This artifact makes it difficult to image lesions located in those areas, and continuing improvements in the hardware are needed to alleviate this issue.

Potential Impact of 7T MRI for Epilepsy Surgery

Our initial experience showed that 7T MRI is useful for detecting subtle FCD lesions in 3T-negative patients with epilepsy, particularly those with extratemporal lobe epilepsies. Guidance from MRI postprocessing further assists FCD detection. These new noninvasive techniques have the potential to optimize seizure outcomes after epilepsy surgery, as well as to increase the number of favorable candidates who can be offered potentially curative surgery.

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Dr. Wang (wangi2@ccf.org) is a staff scientist in Cleveland Clinic's Epilepsy Center and joint staff in the Department of Biomedical Engineering, Cleveland Clinic Lerner Research Institute.

Dr. Jones (jones19@ccf.org) is Vice Chair for Research and Academic Affairs in Cleveland Clinic's Imaging Institute and holds an appointment in the Epilepsy Center.

Two-Staged Stereotactic Radiosurgery for Large Brain Metastases: More Support from the Largest Series to Date

By Lilyana Angelov, MD; Samuel Chao, MD; and Gene Barnett, MD, MBA

Two-staged stereotactic radiosurgery has been shown to be a feasible, safe and effective modality for treating large brain metastases in the largest published series of metastases managed with this approach to date. These results, reported recently by our group in the *Journal of Neurosurgery*,¹ raise the prospect of enhanced local tumor control with decreased radiation-related morbidity in the setting of large brain metastases.

The Rationale for Staged Therapy

Effective control of large brain metastases (≥ 2 cm maximum diameter) with stereotactic radiosurgery (SRS) is a challenge, yielding local control rates of only 37 to 62 percent with an elevated risk of treatment-associated toxicity compared with smaller brain metastases. In recent years, two centers in Japan began reporting results with a novel strategy for treating large brain metastases known as staged stereotactic radiosurgery (SSRS).²⁻⁴ The approach involves delivery of SRS in two or more discrete treatment sessions rather than the traditional single session. The aim is to enable an increased overall dose to improve local tumor control while administering smaller individual doses in an effort to reduce toxicity.

In 2012, Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center became, to our knowledge, the first center outside Japan to offer two-staged SRS (2-SSRS). Our new paper¹ reports our experience with this approach from June 2012 through January 2016.

Our Study in Brief

We retrospectively analyzed all Cleveland Clinic patients during this period who underwent planned 2-SSRS for brain metastases ≥ 2 cm in maximum diameter secondary to systemic cancer. Patients were selected for planned 2-SSRS if they were not surgical candidates, or per surgeon and patient preference. The Gamma Knife® Perfexion system was used to deliver a total of 24 to 33 Gy (median, 30) across the two treatment sessions, resulting in a total biologic equivalent prescription dose of roughly 44 to 73 Gy (median, 62.5) if delivered in a single treatment session. The second SSRS session was typically scheduled approximately one month after the first (median interval, 34 days).

Our objective was to volumetrically assess the response of local brain metastases to the 2-SSRS strategy in terms of local control rates, treatment-related toxicity and impact on overall survival.

Key Results

Fifty-four patients received 2-SSRS during the study period, with a total of 63 treated brain metastases among them: 46 patients (85 percent) had one metastasis, seven (13 percent) had two and one (2 percent) had three. Patients with more than one metastasis had them treated concurrently. Median patient age was 63 years (range, 23-83).

The main outcome findings were as follows:

- › The median change in tumor volume at three-month follow-up MRI after 2-SSRS was a 54 percent reduction from baseline ($P < .001$). (See Figure 1 for an example case.)
- › Rates of local control were 95 percent at three months and 88 percent at six months.
- › Estimated overall survival rates (using Kaplan-Meier method) were 65 ± 7 percent at six months and 49 ± 8 percent at 12 months.
- › Seven lesions (11.1 percent) demonstrated adverse radiation effects (four lesions at grade 1/2 toxicity and three at grade 3).
- › Nine lesions (14.3 percent) showed local progression (median time, 5.2 months). Reduced time to progression was associated with greater tumor at baseline and smaller absolute and relative reductions in tumor volume from baseline to the second SSRS session.

Time for a Prognostic Model?

Our findings build on the initial results from Japan to support 2-SSRS as a feasible, safe and effective modality that yields excellent local control and similar or better overall survival and toxicity relative to many series (reviewed in our paper¹) in which large brain metastases were treated with single-session SRS or fractionated SRS. We also showed that multiple large brain metastases can be treated concurrently with 2-SSRS and that this strategy can be effective in treating large metastases arising from traditionally radiotherapy-resistant pathology.

These findings suggest that a prognostic model may well be in order to stratify patients with large brain metastases into favorable and unfavorable 2-SSRS response groups based on Karnofsky Performance Status, global intracranial disease and response of the tumor to initial SSRS treatment. Such a model could be a helpful guide to clinical decision-making.

Potential Advantages and Applications

At the same time, larger prospective trials are warranted to confirm these retrospective results, assess durability and directly compare 2-SSRS with alternative approaches for large brain metastases. Nevertheless,

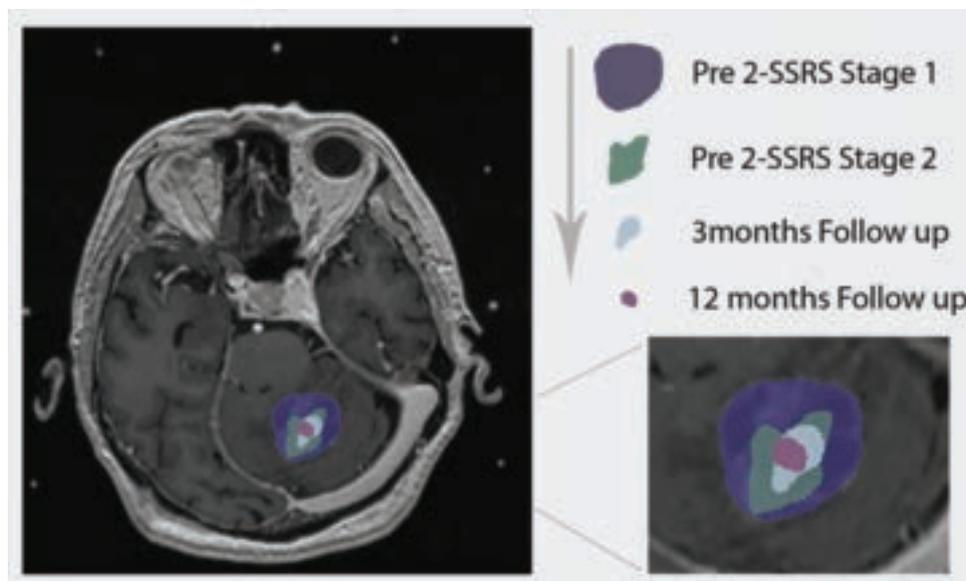


FIGURE 1. Tumor size over time in one of the patients from our study (image courtesy of neurosurgery resident Ghaith Habboub, MD).

2-SSRS appears to offer a number of advantages over other radiosurgery strategies in the setting of large brain metastases, including:

- › **Some of the best survival data to date.** As reviewed in our paper,¹ median survival in our study exceeded that of six of seven SRS cohorts with data from the published literature and exceeded that of seven of 12 fractionated SRS studies with data from the literature. Twelve-month survival in our study surpassed that of four of five single-fraction studies and six of 11 fractionated SRS studies with data from the literature.
- › **Convenience.** 2-SSRS use is independent of delivery platform (in contrast to the current limitation of fractionated SRS to frame-based platforms) and may be the least disruptive treatment approach in terms of the patient's overall care regimen.
- › **Possible radiobiological advantages.** These include the potential for enhanced tumor kill through higher doses per session relative to fractionated SRS, the potential for repair and repopulation of normal brain cells during the interval between first and second sessions, and the prospect of improved oxygenation to remaining tumor cells — and thus enhanced radiation sensitivity — resulting from decreased tumor size following the first session.

Apart from these broader potential advantages, 2-SSRS appears particularly well suited to several specific applications. These include treating tumors in eloquent brain or near critical structures where radiotoxicity is especially concerning, enabling deferral of whole-brain radiation therapy (WBRT) in patients who aren't surgical candidates, and use in patients with limited options who have already had WBRT and are not surgical candidates. We look forward to helping further define the role of this promising new approach to stereotactic radiosurgery.

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Dr. Angelov (angelol@ccf.org) is a neurosurgeon in Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center.

Dr. Chao (chaos@ccf.org) is a radiation oncologist in the Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center.

Dr. Barnett (barnetg@ccf.org) is a neurosurgeon and Director of the Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center.

Surgical Intervention for Unruptured Brain Arteriovenous Malformations: The Story Isn't Over Yet

By Mark Bain, MD, MS

Surgical treatment of unruptured brain arteriovenous malformation (ubAVM) is associated with a lower risk of stroke or death than a watch-and-wait approach, according to a new retrospective analysis of a large series of cases at Cleveland Clinic. These results add to the controversy generated with the 2014 publication of ARUBA (A Randomised trial of Unruptured Brain Arteriovenous malformations),¹ which came to the opposite conclusion. Our retrospective analysis of 105 patients between 2001 and 2014 who would have qualified for ARUBA was recently published in *Neurosurgery*.²

Optimal management of ubAVMs has been a topic of debate since brain imaging made possible the diagnosis of this often asymptomatic or mildly symptomatic condition (Figure 1). A no-treatment strategy entails a 2 to 5 percent annual risk of rupture. While this may seem low, over many years the cumulative chances become daunting. And the outcomes can be devastating: About one-third of patients with a bleed end up in a nursing home, and 10 percent die. But treatment is also not without risk.

What ARUBA Found

ARUBA, conducted at 39 clinical sites in nine countries, randomized patients to either interventional therapy (neurosurgery, embolization or stereotactic radiosurgery [Gamma Knife®], either in combination or alone, as determined by the treating physician) or medical management (symptomatic treatment with medications, as needed). The study, which started in 2007, was ended prematurely in 2013 because of superior outcomes in the medical management group. At that point, the study had randomized 223 patients (114 to intervention and 109 to medical management) and had a mean follow-up of 33.3 months. The primary end point, either stroke or death, had occurred in 10.1 percent of the medical management group versus 30.7 percent of the intervention group.

What Cleveland Clinic Found

Of the 105 cases in the Cleveland Clinic database that were ARUBA-eligible, 44 patients had undergone microsurgery and 61 patients had undergone stereotactic radiosurgery as their final treatment. Mean follow-up was 43 months (range, 4-136 months). A total of eight patients (7.6 percent) had a stroke or died, as detailed in Table 1.

This new Cleveland Clinic study² joins several other retrospective analyses published after ARUBA in finding substantially lower overall risk of stroke or death in the treatment arm than the 30.7 percent reported in ARUBA.³⁻⁶ Most important, overall risk was lower than the natural disease course, which justifies a strategy of surgical intervention for ubAVM.

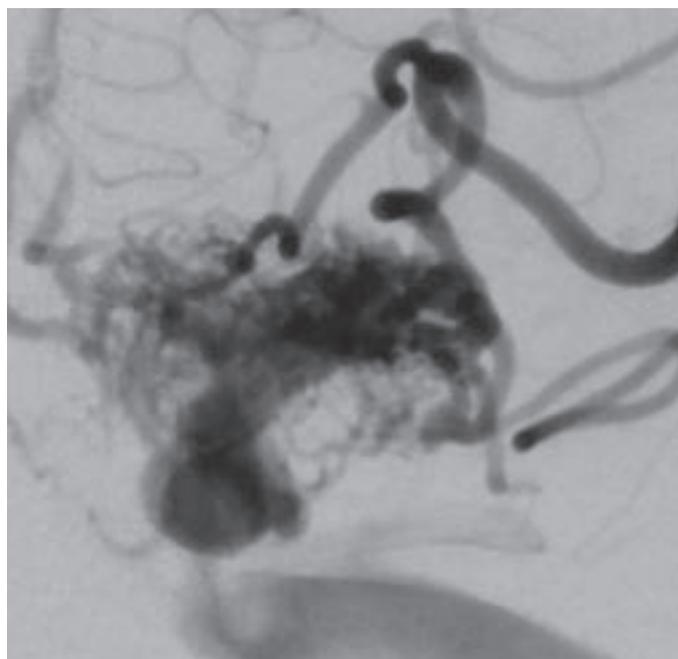


FIGURE 1. Angiogram showing an unruptured brain arteriovenous malformation.

Why the Difference?

Multiple issues have been identified that may account for the different conclusions reached by ARUBA and the other studies.

Treatment choices differed. ARUBA treated 26 percent of patients with endovascular embolization alone, a high rate that may partly explain the elevated rate of stroke or death relative to the subsequent studies. Because of the likelihood of complications from attempting to obliterate an AVM by embolization alone, many institutions, including Cleveland Clinic, reserve its use mainly to reduce AVM nidus size before surgery or stereotactic radiosurgery. With safer embolysates now available, the role of embolization in combined procedures is undergoing a further shift.

Cleveland Clinic uses the following rules of thumb to choose interventions for a patient with ubAVM:

- › Small AVM in a noneloquent area — microsurgery
- › Large AVM in a noneloquent area — embolization to slow the blood flow to the AVM rather than obliterate it, followed by microsurgery later
- › AVM in an eloquent area or deep in brain — stereotactic radiosurgery

Table 1. Risk of Stroke or Death After Surgical Intervention for ubAVM, Along with Success Rates

	All patients (N)	Microsurgery arm + embolization (N)	Radiosurgery arm + embolization (N)
Overall risk	7.6% (8)	11.4% (5)	4.9% (3)
Annual risk	2.1%	4.0%	1.2%
AVM obliteration	—	95.5%	47.5%

Short follow-up. Because most deaths from surgical intervention happen soon after the procedure and the risk of an untreated ubAVM is generally continuous over the years, a comparison of the risks within the first few years is likelier to favor no intervention.

Treatment of many patients outside the trial. ARUBA was designed such that not all patients who qualified for the trial were randomized, allowing surgeons to elect to operate on patients whose AVMs were deemed ideal for surgery. This ability to treat patients outside the trial could have introduced bias by steering disproportionate numbers of patients with complex or difficult-to-treat AVMs into the trial. This would not have been favorable for the trial's interventional arm.

How Can This Controversy Be Resolved?

Another randomized clinical trial would be ideal, using a more modern algorithm for treatment than was used in ARUBA. But because of the high expense, this is unlikely to happen soon. A second choice would be a prospective study conducted at multiple institutions to follow outcomes of different treatment strategies. Finally, a meta-analysis of the various retrospective studies that have followed ARUBA, including this Cleveland Clinic cohort, would be useful.

Patient Management in the Face of Uncertainty

We believe in providing our ubAVM patients with as much information as possible so that they can fully enter into the decision process for their treatment. They often have strong preferences based on the degree of risk they are comfortable with.

Our inclination to intervene stems from witnessing young, healthy patients meet with poor outcomes from a wait-and-see approach. Our data strongly argue that we have the tools to provide reasonable and safe strategies to improve outcomes for most patients.

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Dr. Bain (bainm@ccf.org) is a neurosurgeon in Cleveland Clinic's Cerebrovascular Center. He was primary investigator of the retrospective analysis discussed above.

Dissecting the Patient Experience of Lumbar Spine Surgery: Insights from the First Studies of HCAHPS Data

By Jay Levin and Michael Steinmetz, MD

The patient perspective of care is becoming an ever more integral component of how healthcare quality is defined. The Centers for Medicare & Medicaid Services has emphasized the importance of the patient experience by requiring hospitals to administer the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey. Results from these surveys are publicly reported and incorporated with other quality measures to adjust 2 percent of Medicare hospital reimbursement. As a result, hospital administrators and spine surgeons across the U.S. are being incentivized to improve HCAHPS scores.

However, the significance of high HCAHPS scores and the patient-level determinants of a satisfying hospital experience have never previously been studied in a lumbar spine surgery setting. Our research team in Cleveland Clinic's Center for Spine Health analyzed real-world HCAHPS data and correlated survey results with patient-level details in several recent publications in hopes of better understanding the patient experience of lumbar spine surgery. The results discussed here represent the forefront of patient experience research in the spine surgery literature.

Quality-of-Life Outcomes

While there is published evidence to support the idea that patients' perspectives of care can incentivize physicians to improve quality of care in the primary care setting, it is unclear whether this relationship exists in the surgical setting.¹⁻⁵ In our study assessing the relationship between top-box overall hospital rating⁶ — a 9 or 10 out of 10 — and validated quality-of-life (QoL) measures following lumbar spine surgery, we found no association between “satisfaction” and one-year QoL improvement as measured by the EuroQol 5 Dimensions instrument, the Pain Disability Questionnaire and the visual analog score for back pain. These results suggest that high satisfaction with the hospital experience may not necessarily correlate with favorable outcomes following lumbar spine surgery.

Key Drivers of Satisfaction

To elucidate which components of the hospital experience are most important to lumbar spine surgery patients, we analyzed 460 HCAHPS surveys to determine which individual survey questions were most strongly associated with top-box overall hospital rating (unpublished data). The strongest predictors were questions under the pain management dimension (odds ratio [OR] = 12.6 [95% CI, 6.7-23.8]) and the nursing communication dimension (OR = 11.7 [95% CI, 5.7-23.8]). These findings highlight opportunities for quality improvement efforts focused on the most relevant aspects of care in the lumbar spine surgery setting.

Preoperative Depression

Since untreated depression has been consistently associated with poor functional outcomes following spine surgery,⁷⁻¹⁰ we conducted a study of 237 patients who underwent lumbar fusion to determine whether preoperative depression was associated with HCAHPS scores.¹¹ Raw percentages of HCAHPS scores were significantly lower for depressed patients on several HCAHPS questions (Figure 1).

Furthermore, multivariable logistic regression analysis revealed that patients with preoperative depression had higher odds of feeling less respected by both physicians and nurses, as well as lower odds of satisfaction with nurses' response to their needs. These results collectively suggest that depression may be a modifiable risk factor for poor hospital experience of lumbar fusion, and that multidisciplinary intervention to treat concomitant depression may improve both hospital experience and HCAHPS scores.

Postoperative ED Visits

There are conflicting data on whether early readmission or postdischarge complications are associated with patients' HCAHPS responses.^{12,13} Since emergency department (ED) visits within 30 days after hospital discharge may reflect poor-quality care, we evaluated whether an association exists between ED visits and HCAHPS scores in a lumbar spine surgery population.¹⁴

Our results demonstrated a strong association between postdischarge ED visits and low HCAHPS scores for questions pertaining to doctor communication, discharge information and global measures of hospital satisfaction (Figure 2). However, given that ED visits occurred *prior* to patient completion of the HCAHPS survey in most patients seen in the ED after discharge, it is unclear whether early complications requiring ED visits influenced the low HCAHPS scores or whether a poor patient experience in the hospital led to early complications in this cohort.

Conclusions

No significant association was observed between high HCAHPS scores and one-year QoL outcomes in our lumbar spine surgery cohort, raising questions about whether HCAHPS can be used reliably as an indicator of quality surgical care. Additionally, pain management and nursing communication prevailed as the HCAHPS dimensions most strongly associated with a top-box overall hospital rating. In regard to patient-level associations, preoperative depression was identified as a modifiable risk factor for poor satisfaction with the hospital experience, while ED visits within 30 days after discharge were also associated with significantly lower HCAHPS scores.

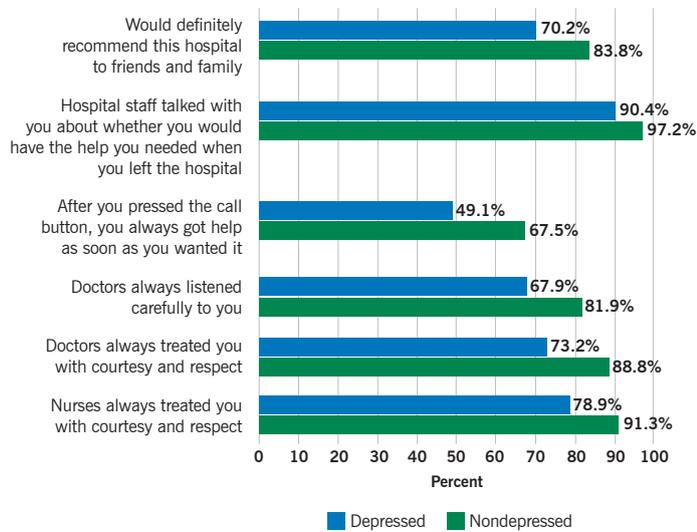


FIGURE 1. Raw percentages of top-box responses (i.e., 9 or 10 out of 10) by depressed and nondepressed patients on selected items from the HCAHPS survey. Between-group differences were statistically significant for all these items.

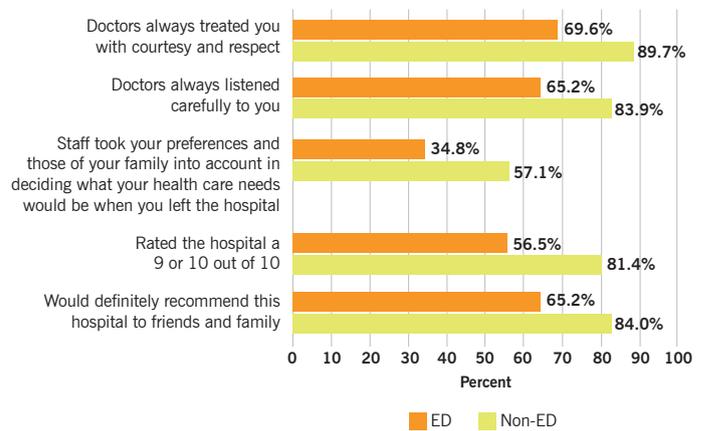


FIGURE 2. Raw percentages of top-box responses (i.e., 9 or 10 out of 10) on selected HCAHPS survey items by patients who did or did not visit the emergency department (ED) within 30 days after discharge. Between-group differences were statistically significant for all these items.

These findings have helped our spine surgery team more fully understand the possible implications of HCAHPS scores and how modifiable and nonmodifiable factors may influence patient experience. We hope to use this knowledge to continue to improve our high standard of patient-centered care while achieving excellent surgical outcomes.

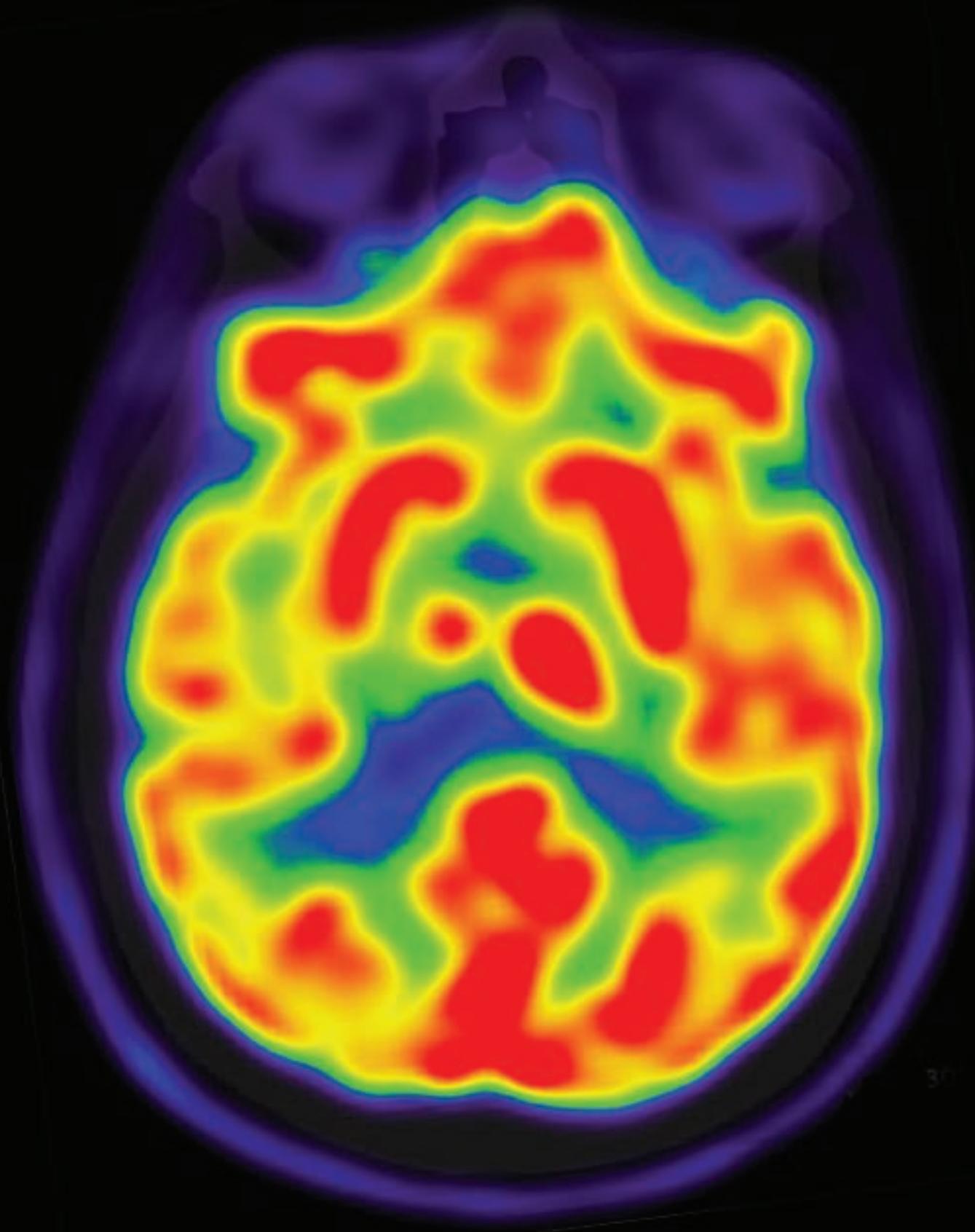
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Mr. Levin is a medical student at Case Western Reserve University School of Medicine with an interest in spine care.

Dr. Steinmetz (steinmm@ccf.org) is Chairman of Cleveland Clinic's Department of Neurological Surgery and a staff neurosurgeon in the Center for Spine Health.



Baseline ^{18}F -FDG-PET image from the trial's first patient showing a right hemisphere stroke, as indicated by the reduced FDG uptake across that hemisphere (red signifies highest uptake, blue signifies lowest). Study subjects are undergoing a series of four longitudinal FDG-PET imaging studies to test the hypothesis that metabolic activity along the brain pathway targeted with deep brain stimulation will increase in conjunction with any observed therapeutic improvements.

COVER STORY

First Trial of DBS for Stroke Recovery: Initial Patient's Functional Progress Continues Through Five Months

By Andre Machado, MD, PhD, and Kenneth Baker, PhD

The first patient to ever undergo deep brain stimulation (DBS) to enhance motor rehabilitation following hemiparesis after ischemic stroke has experienced significant and steady functional improvements throughout the first five months of management pairing DBS with rehabilitative therapy. The 59-year-old woman had a DBS electrode surgically implanted in her cerebellum in December 2016 as the first participant in a first-in-human clinical trial of DBS for stroke rehabilitation, which is being conducted at Cleveland Clinic. This article briefly reviews the patient's progress and our study's rationale, design details and current status.

Essentials of the Trial

Our trial is examining a novel strategy — stimulation of the dentatothalamocortical pathway to enhance excitability and plasticity across spared cerebral cortical regions — with the aim of promoting recovery of motor function following stroke. The primary hypothesis is that by applying DBS to the connections between the cerebellum and cerebral cortex, we can facilitate the plasticity that occurs in the surviving cortical regions around the stroke and thereby promote recovery of function beyond what rehabilitative therapy alone can accomplish.

For this initial trial, we plan to enroll 12 patients who, despite traditional rehabilitative therapy, have persistent, severe residual

hemiparesis from an ischemic stroke 12 to 36 months earlier. In addition to the patient reported here, a second patient has undergone DBS electrode implantation but hasn't completed enough subsequent therapy for results to be reported.

The study is being conducted solely at Cleveland Clinic with funding support from the National Institutes of Health's BRAIN Initiative.

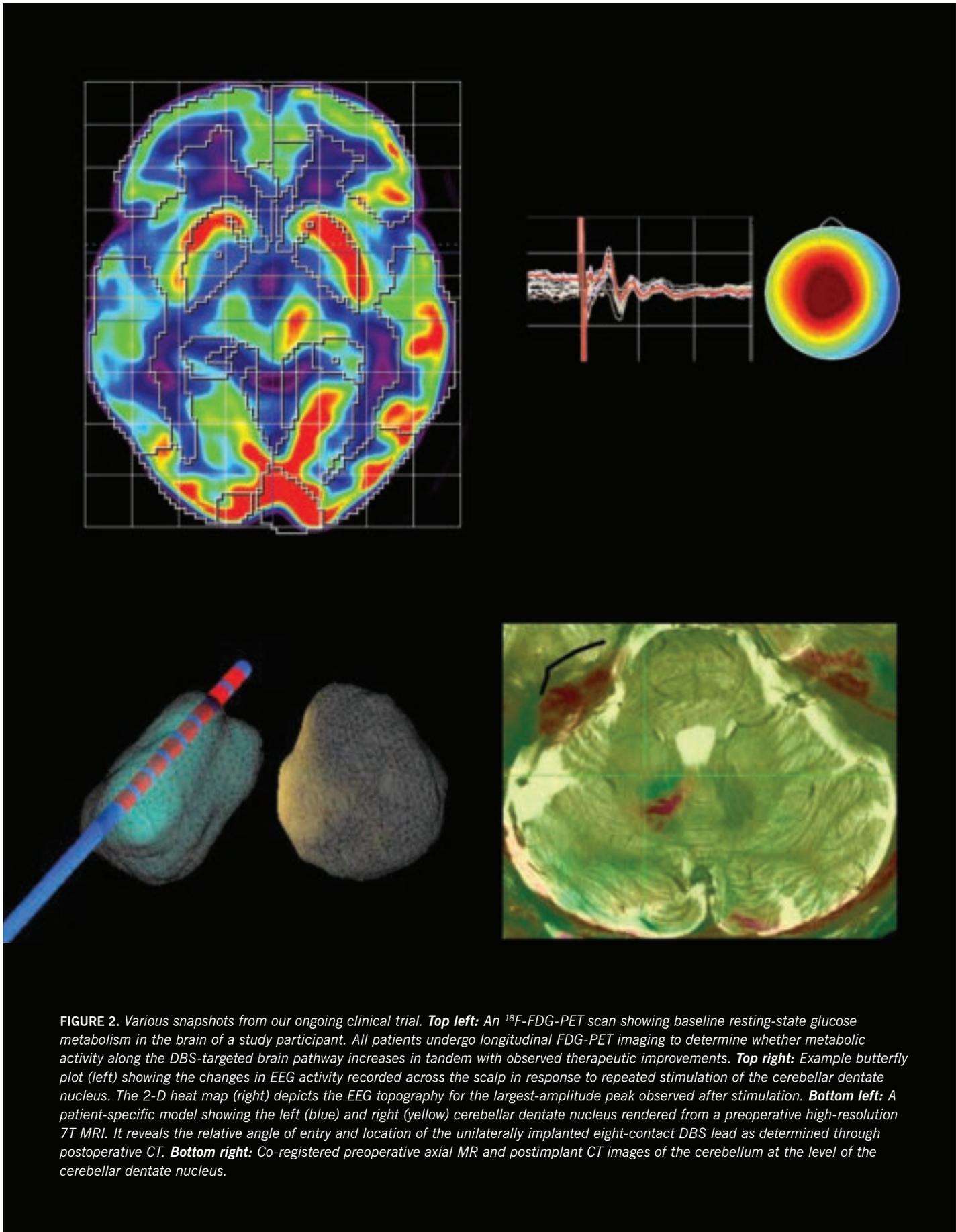
Initial Treatment Protocol — and First Patient's Response

The trial's initial protocol began as follows:

- › One month of twice-weekly rehabilitative therapy (physical plus occupational) to establish baseline function
- › Surgery to implant the DBS electrode and battery
- › Four-week resting period at home to recover from surgery
- › Eight weeks of therapy without the DBS device turned on, to establish a new functional baseline
- › Four weeks of programming the DBS device with the aid of transcranial magnetic stimulation
- › Four months of therapy with the DBS device turned on continuously



FIGURE 1. The trial's first patient uses her affected arm in a therapy session four months after the start of stimulation.



Within a few weeks of when the DBS device was turned on, the trial's first patient reported she could move her affected arm in ways she hadn't been able to since her stroke. Her function has steadily and progressively improved ever since, as measured by the upper extremity subscale of the Fugl-Meyer Assessment of Motor Recovery after Stroke. She reports that she is now able to use her affected arm to cook, play games with her grandchildren, fold laundry and perform many other routine tasks. Her functional progress had not yet plateaued as of this writing, approximately five months after stimulation was started.

Continuing Improvement Prompts Protocol Revision

The initial trial protocol called for a slow weaning from stimulation over the course of a month after completion of four months of concurrent DBS and rehabilitative therapy. However, continued progress by the first patient through even the fourth month of stimulation prompted us to obtain FDA approval to revise the protocol and extend therapy. Concurrent DBS and rehabilitative therapy will now continue for several additional months to afford the patient the opportunity for additional improvement, with stimulation weaned after nine months of treatment or when the patient's motor improvement appears to have plateaued (whichever comes first).

Additional Aspects of Our Investigation

In addition to the above functional outcomes that are the centerpiece of this trial, we are conducting many other investigations to better understand the relevant anatomy and refine the DBS technique used in this novel setting of stroke recovery (Figure 2). These investigations include the following:

7T magnetic resonance imaging (MRI). Each trial participant undergoes 7T MRI prior to surgery to allow optimal visualization of target brain structures. Our team's engineers use these images to develop patient-specific models of the pathways that we are attempting to modulate in order to achieve the therapeutic goal. These 7T images and the resulting models will help create a guidebook to elucidate the relevant anatomy for neuromodulation for stroke rehabilitation moving forward. While postoperative 7T MRI evaluation would be valuable as well, the DBS device used is currently incompatible with MRI.

Serial positron emission tomography (PET). All patients undergo a series of four FDG-PET imaging studies — at enrollment, after DBS electrode implantation, during DBS treatment and a month after stimulation is turned off. These studies will test our hypothesis that metabolic activity along the brain pathway being targeted with DBS will increase in conjunction with any observed therapeutic improvements.

Intraoperative somatosensory evoked potential (SSEP) and electroencephalographic (EEG) testing. We are supplementing our initial 7T imaging guidance with intraoperative SSEP and EEG recordings at the time of DBS lead placement. These techniques may allow us to determine which electrical contacts along the octopolar lead are showing

greater representation of motor-related neural activity and to assess changes in activity in response to acute stimulation in different areas. Given that neuromodulation for stroke rehabilitation — in contrast to movement disorders — does not allow immediate motor feedback once stimulation is started, this type of intraoperative testing can be invaluable in determining which contacts to use for chronic therapy.

Transcranial magnetic stimulation (TMS) to assess cortical changes.

Our team is using TMS as part of the acute programming sessions to assess whether DBS is enhancing excitability across the areas of cortex where we hope to achieve functional change. Additionally, TMS is being used to map the representation of motor activity for different regions of the body across those same spared cortical regions in order to identify whether any functional reorganization of the cortex is being achieved in response to therapy.

On the Horizon

We also plan to introduce several additional assessments for trial participants going forward, including:

- › Nonmotor testing by a neuropsychologist to ensure that there is no disruption of cognitive processes involving the stimulated brain region
- › Use of a robotic device on which patients perform video game-like tasks to assess reaction and movement time, jerkiness of movement and similar performance measures

An additional goal is to initiate the development of paired associative stimulation paradigms that use the electrophysiological information that we record from the dentate nucleus to provide stimulation in a timing-dependent manner. The result would be a “smarter” closed-loop system that actively reinforces a patient's attempted movements instead of relying on constant reinforcement.

Clearly, many questions remain, but we are encouraged by the positive results so far in our trial's initial patient. We look forward to learning much more as this study continues.

Dr. Machado (machada@ccf.org) is a neurosurgeon and Chairman of Cleveland Clinic's Neurological Institute.

Dr. Baker (bakerk6@ccf.org) is a neuroscientist in the Department of Neurosciences in Cleveland Clinic's Lerner Research Institute.

New Research Consortium Gives Dementia with Lewy Bodies Its Due

By James Leverenz, MD, and Babak Tousi, MD

In neurodegenerative disease, strength seems to lie in numbers. Understanding of both Alzheimer's disease (AD) and Parkinson's disease (PD) has benefited substantially from large consortia that have advanced research by harnessing the strengths of multiple academic centers to combine efforts, pool data and develop standardized approaches.

It is well past time to apply the same strategy to dementia with Lewy bodies (DLB), and Cleveland Clinic Lou Ruvo Center for Brain Health is proud to be the coordinating site for the newly formed nine-center Dementia with Lewy Bodies Consortium, funded by a \$6 million, five-year grant from the National Institutes of Health (NIH). This article briefly reviews the rationale for and objectives of this first-of-its-kind U.S. research consortium in DLB, along with some of its early initiatives.

Aiming to End a Dearth of Disease Markers

DLB is the second most common form of neurodegenerative dementia in the elderly, although it is likely underdiagnosed, as its symptoms can closely resemble those of AD and PD. This contributes to the condition's notoriously difficult diagnosis.

Diagnostic challenges, as well as the current absence of therapies, even for symptomatic management, stem in large part from a dearth of biomarkers for DLB. Impediments to biomarker development have included small subject numbers, a lack of systematic patient characterization and an absence of consistent longitudinal follow-up with autopsy.

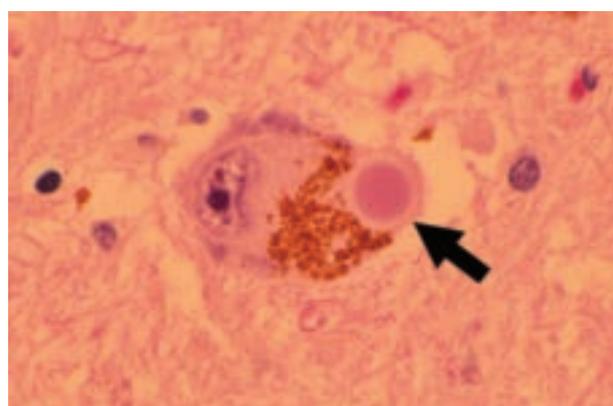
These traditional impediments are the main *raison d'être* of the national DLB Consortium, which has been established with the following primary objectives:

- › To conduct a national, coordinated study of DLB drawing on the extensive expertise available at nine centers across the U.S.
- › To systematically collect clinical, biofluid and imaging data from a large number of patients with DLB
- › To establish a large cohort of DLB cases readily available for observational research and clinical trials
- › To provide broad access to these data and materials to accelerate DLB research

The expectation is that the DLB Consortium will provide the foundation for a wide range of investigations into the future.

How It Will Work

The consortium will support and facilitate collection of clinical data through systematic patient assessments compatible with AD and PD programs, brain imaging studies (MRI and SPECT) and collection of



Lewy body inclusion (arrow) in a pigmented neuron of the substantia nigra.

biospecimens (blood and cerebrospinal fluid) from more than 200 individuals with DLB across the nine participating sites. Autopsy will also be offered in some cases. The aim is to create the foundation needed for biomarker development.

The consortium serves to formalize and strengthen existing collaboration among the participating centers, all of which have expertise in Lewy body disorders. In addition to Cleveland Clinic, the centers are Florida Atlantic University, Rush University, Thomas Jefferson University, University of California San Diego, University of North Carolina, University of Pennsylvania, University of Pittsburgh and VA Puget Sound Health Care Center/University of Washington. The consortium will further collaborate with the National Institute of Neurological Disorders and Stroke and the National Institute on Aging.

In addition to the five-year NIH grant, the consortium has received funding from the Lewy Body Dementia Association to convene an annual meeting of investigators, the first of which was held in February 2017, to develop study protocols and promote data sharing, collaboration and discovery in DLB. GE Healthcare has also provided a grant to support the cost of dopamine imaging (DaTscan™) performed on study subjects.

First U.S. Therapeutic Trials for DLB Underway

Investigators in Cleveland Clinic Lou Ruvo Center for Brain Health are excited to align our leadership in the national DLB Consortium with our participation in the first U.S. clinical trials designed to test investigational therapies for DLB. These studies are outlined below.

Table 1. Profile of First U.S. Clinical Trials of Therapies for Dementia with Lewy Bodies (DLB)

Agent	Trial design	Patients	Outcomes of interest
Intepirdine (RVT-101) (oral)	Phase 2, randomized, double-blind, placebo-controlled, 6 months	240 patients with DLB	Effect on CIBIC+ rating and cognitive battery performance; also safety and effect on visual hallucinations
Nelotanserin (oral)	Phase 2, randomized, double-blind, placebo-controlled, crossover, 28 days	30 patients with Lewy body dementia and frequent visual hallucinations	Safety, extrapyramidal signs, change in frequency and severity of visual hallucinations
Nelotanserin (oral)	Phase 2, randomized, double-blind, placebo-controlled, 28 days	60 patients with DLB or PD dementia and REM sleep behavior disorder	Safety, changes in frequency and proportion of severe REM sleep behaviors

CIBIC+ = Clinician's Interview-Based Impression of Change Plus Caregiver Input; PD = Parkinson's disease

HEADWAY-DLB study of intepirdine (RVT-101). Intepirdine (RVT-101) is a small-molecule 5-HT₆ receptor antagonist that has been shown to raise levels of acetylcholine. In January 2016, the phase 2 HEADWAY-DLB study began enrolling an anticipated 240 patients with DLB to compare six-month courses of intepirdine (35 or 70 mg orally once daily) or placebo for effect on the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+) rating and performance on a computerized cognitive battery. Secondary end points include visual hallucinations and safety measures. The randomized, double-blind trial completed recruitment in April 2017 and is offering a six-month extension to completers.

Two studies of nelotanserin for DLB symptoms. Nelotanserin is a selective inverse agonist of the 5-HT_{2A} receptor that has shown promise in calming neuropsychiatric disturbances seen with DLB, including visual hallucinations and sleep disturbances. It is now being investigated in two phase 2 randomized, double-blind, placebo-controlled studies focused on these symptoms.

One study, launched in late 2015, is using a crossover design to compare 28 days of nelotanserin 20 mg orally once daily with placebo among patients with Lewy body dementia who experience frequent visual hallucinations. Outcomes of interest are safety, extrapyramidal signs as assessed by the Unified Parkinson's Disease Rating Scale motor subsection and change in the frequency and severity of visual hallucinations. Target enrollment of 30 participants was achieved in summer 2017, and completion is expected by the end of 2017.

The second study, launched in early 2016, is comparing 28 days of nelotanserin 20 mg orally once daily with placebo among an anticipated 60 subjects with DLB or PD dementia who have REM sleep behavior disorder. End points are safety and changes in the frequency and proportion of severe REM sleep behaviors based on clinical evaluation. Completion is expected by the end of 2017. Participation at our institution is done in collaboration with colleagues in Cleveland Clinic's Sleep Disorders Center.

With further guidance on disease markers expected from the ongoing NIH-funded DLB Consortium biomarker study, we are hopeful that these are just the first in a wave of DLB therapeutic studies in the years ahead.

Dr. Leverenz (leverezj@ccf.org) is Director of Cleveland Clinic Lou Ruvo Center for Brain Health, Cleveland, and principal investigator of the NIH grant for the DLB Consortium.

Dr. Tousi (batous@ccf.org) is Head of the Clinical Trials Program at Lou Ruvo Center for Brain Health, Cleveland.

Observational Studies in the Emerging Landscape of Multiple Sclerosis Therapeutics: Harnessing Insights from Real-World Data

By Carrie M. Hersh, DO; Devon Conway, MD; and Daniel Ontaneda, MD

Clinical trial data, while valuable from a regulatory standpoint for approval of new medications, have limited applications in clinical settings. At Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research, we are using our large patient experience to derive real-world evidence for multiple sclerosis (MS) patients and providers. These studies use data from our clinical practice and do not have the rigid constraints of clinical trials. As such, the results are more generalizable for the neurologist in clinic and provide patients more realistic insights into the efficacy and safety of medications and interventions.

Here we highlight two such observational real-world studies: a comparison of two commonly prescribed MS disease-modifying treatments (DMTs), and an evaluation of the use of MRI in clinical practice to ascertain treatment response.

Comparative Efficacy of Two Disease-Modifying Therapies

In the rapidly advancing landscape of novel neurotherapeutics for MS, it has become increasingly challenging and important to compare the effectiveness and safety of DMTs. While randomized controlled trials are the standard for regulatory approval of DMTs, the cost and time involved make such trials impractical for providing these comparisons. Observational studies are thus valuable for comparing the effectiveness and safety of DMTs to inform decision-making in routine practice.

Despite the pragmatic utility of observational studies, they are prone to confounding and bias, making it necessary to limit baseline imbalances in demographic and disease characteristics before direct comparisons are made. Propensity score analysis is a statistical method that reduces the impact of confounding and certain biases, thereby approximating a randomized study design. Propensity studies commonly use standardized difference plots (Figure 1) to show how adjustments improve covariate balance and make study groups more comparable.

In this context, we conducted a retrospective observational study using propensity score analysis to investigate the comparative effectiveness and discontinuation rates of fingolimod (FTY) and dimethyl fumarate (DMF), two commonly used oral DMTs for relapsing MS.¹ In total, 395 DMF-treated and 264 FTY-treated patients had 24-month follow-up data available for analysis.

At 24 months, patients treated with DMF and FTY showed comparable effectiveness on multiple outcome measures, including the following:

- Annualized relapse rate (odds ratio [OR] = 1.45; 95% CI, 0.53-3.99)
- Time to first relapse (hazard ratio [HR] = 1.26; 95% CI, 0.87-1.81) (Figure 2)

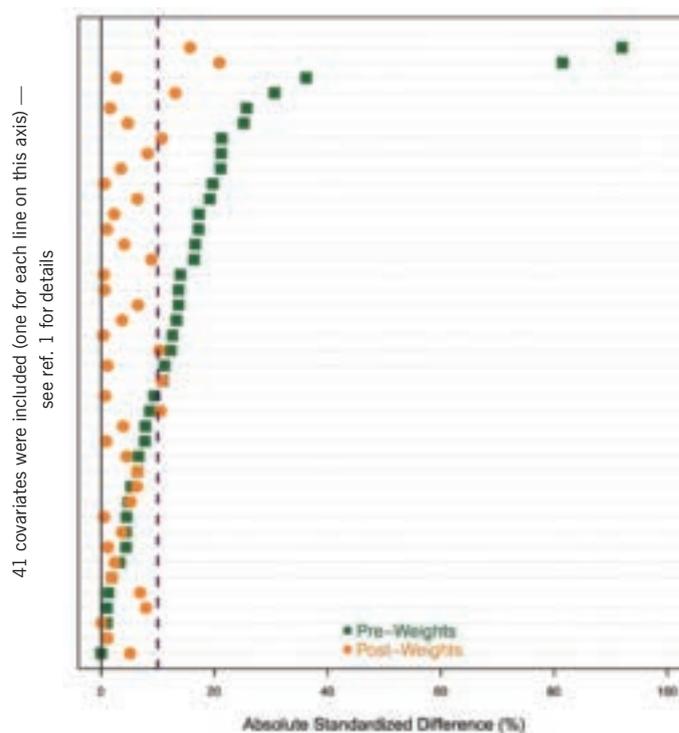


FIGURE 1. Covariate balance before (green) and after (orange) propensity score adjustment. Improved balance (i.e., reduced standardized differences) was obtained after propensity adjustment. Individual covariate listings on the y-axis are omitted here for reasons of space, but each line represents a different covariate. See original for full details. Adapted from Hersh et al. in *Multiple Sclerosis Journal — Experimental, Translational and Clinical*, SAGE Publishing.¹

- Proportion of patients with new T2-weighted brain MRI lesions (OR = 1.60; 95% CI, 0.80-5.12)
- New gadolinium-enhancing brain MRI lesions (OR = 1.64; 95% CI, 0.82-5.63)
- Proportion of patients with disability progression, measured as 20 percent worsening on the timed 25-foot walk (OR = 1.23; 95% CI, 0.72-2.13) and 20 percent worsening on the 9-hole peg test (OR = 0.79; 95% CI, 0.34-1.80)

At 24 months, DMF-treated patients discontinued DMT earlier than did FTY-treated patients, with the difference mostly driven by early mild-to-moderate side effects (HR = 1.40; 95% CI, 1.11-1.77) (Figure 2). The primary reasons for discontinuation due to intolerability were gastrointestinal side effects for DMF and headaches for FTY.

Our results showed clinical and radiologic outcomes similar to those observed in the pivotal clinical trials of each DMT (CONFIRM and DEFINE for DMF, and TRANSFORMS and FREEDOMS for FTY), confirming treatment effects in clinical practice.

This real-world comparative effectiveness data should assist clinicians in treatment decisions regarding DMF and FTY in the management of MS. Our investigation also highlights the utility of propensity score-adjusted observational studies that reflect treatment effects in real-world settings while minimizing confounding and bias.

MRI as Treatment Target

In a separate study, we used an observational design to investigate MRI stability as a treatment target in MS.² A treat-to-target approach to MS management has gained increased acceptance, with “no evidence of disease activity” (NEDA) — in which patients are free of relapses, disability progression and MRI activity — as the preferred target.³ While NEDA seems a sensible goal, there is limited evidence that achieving NEDA leads to better long-term outcomes.

Our study utilized the Knowledge Program[®], a Cleveland Clinic-developed database used to electronically collect patient- and clinician-reported outcomes longitudinally.⁴ We identified 417 patients who had activity on their MRIs and then determined whether they remained on the same DMT or were switched to an alternative therapy. After propensity score matching, we compared clinical and radiologic outcomes after 18 months in 78 switchers and 91 nonswitchers. No significant differences were observed between the groups.

Our study did not show a short-term benefit of switching treatment, but it is possible that efficacy differences are apparent only after longer follow-up. It is also worth considering the possibility that zero tolerance of new MRI lesions, which is required to achieve NEDA, may be too stringent a goal. To reach such a target, most patients will require escalation to treatments with more safety concerns,⁵ so it will be important to justify that risk by demonstrating that achieving NEDA leads to better long-term outcomes.

Conclusions

Observational studies based on real-world data from clinical practice can answer clinically relevant questions that have broad applicability and may not be addressed by randomized trials. Structured collection of clinical data, such as through our Knowledge Program tool, enables implementation of this type of research.

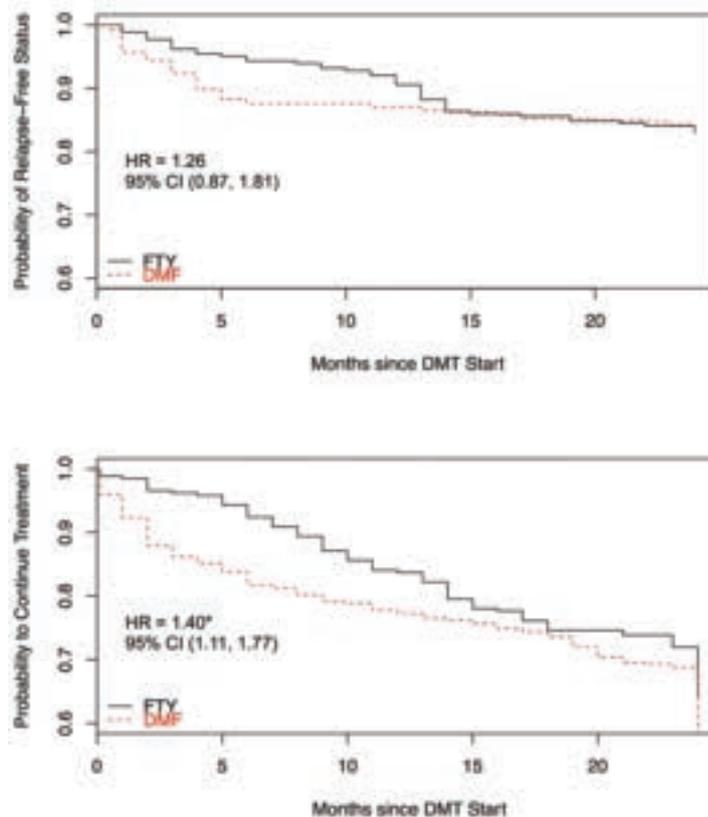


FIGURE 2. Kaplan-Meier plots of relapse-free status and discontinuation with dimethyl fumarate (DMF) and fingolimod (FTY) therapy through 24-month follow-up. Reprinted from Hersh et al. in *Multiple Sclerosis Journal — Experimental, Translational and Clinical*, SAGE Publishing.¹

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Dr. Hersh (hershcc@ccf.org) is a neurologist at Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas.

Drs. Conway (conwayd2@ccf.org) and Ontaneda (ontaneda@ccf.org) are neurologists with Cleveland Clinic's Mellen Center for Multiple Sclerosis Treatment and Research.

Proteomic Signatures Help Illuminate Links Between Obstructive Sleep Apnea and Paroxysmal Atrial Fibrillation

By Reena Mehra, MD, MS

Research at Cleveland Clinic exploring the relationship between obstructive sleep apnea (OSA) and paroxysmal atrial fibrillation (AF) has uncovered specific proteomic signatures — namely, blood proteins — indicating inflammation, fibrosis and oxidative stress in patients with both conditions. In addition, three months of treatment of OSA with continuous positive airway pressure (CPAP) therapy in patients with OSA and paroxysmal AF was associated with improved protein biomarker signatures.

These novel investigations, presented at the American Thoracic Society's 2017 International Conference,^{1,2} shed new light on these two conditions and point to further directions for research in diagnostics and therapy. While the association between OSA and AF is well established, the underlying mechanisms linking the conditions have been poorly understood. These intriguing results from Cleveland Clinic's Sleep Disorders Center, together with other emerging evidence, may help elucidate these mechanisms and ultimately lead to identification of specific therapies to treat OSA and/or AF.

Why the OSA-AF Link Matters

Previous epidemiologic studies have shown that AF is two to four times more common in patients with OSA than in the general population. Because of its sporadic nature, paroxysmal AF (defined as recurrent episodes of AF that self-terminate within seven days) is particularly difficult to diagnose. But as a precursor to continuous AF, the paroxysmal form is important to recognize: OSA-related AF is believed to have multiple negative consequences on the autonomic nervous system and on the heart's structure and electrical system, leading to increased risk of stroke and permanent heart damage.

Proteomics — An Emerging Research Tool

New technology in the field of proteomics allows rapid, unbiased identification and quantification of more than 1,000 proteins in a blood sample, enabling researchers to examine diseases in novel ways. Previous research by other investigators has separately observed upregulation of circulating pathologic biomarkers in patients with OSA and in patients with AF. The studies by our Cleveland Clinic team are the first to examine biomarkers in patients who have both conditions — and the first to analyze the effects of sleep apnea treatment on AF.

Biosignatures of OSA and Paroxysmal AF Revealed

Our studies involved rigorous phenotyping of paroxysmal AF and OSA, as well as standardized methods of blood collection, including the timing of sampling, to strengthen the reliability of the findings.

The investigations involved aptamer-based proteomic studies using the SOMAscan[®] assay of 24 patients with paroxysmal AF and 24 patients

without AF. Subjects represented a range of OSA, from absence of OSA to mild, moderate or severe OSA as defined by apnea-hypopnea index categories. Participants were predominantly male (63 percent), with a mean age of 61. The majority were obese.

Analysis of this 48-patient sample revealed the following primary findings:¹

- Relative to patients without paroxysmal AF, those with paroxysmal AF had altered levels of specific chemokines, interleukins, phospholipases and markers of fibrosis (Figure 1). Levels of some biomarkers correlated with degree of hypoxia and severity of OSA.
- Among patients with paroxysmal AF, those with OSA had the same biosignature findings above while also having abnormal endothelial markers and lymphocyte activation markers relative to their counterparts without OSA.

This proof-of-principle study represents the first large-scale proteomic analysis involving patients phenotyped for both OSA and AF. Our findings suggested an upregulation of macrophages and fibroblast proteomic signatures in AF and overall moderate levels of OSA.

CPAP Therapy Alters Biosignatures

In a second study,² we conducted additional proteomic analysis on 12 participants with paroxysmal AF and OSA after three months of CPAP treatment. These subjects had the highest CPAP adherence in the study profiled above.

Results showed that inflammatory biomarkers were quantitatively reduced from baseline levels after three months of CPAP therapy. Moreover, these reductions were accompanied by quantitative changes in (1) atrial and vascular remodeling proteins, (2) factors important to fibrosis development and (3) proteins implicated in thrombosis and stroke risk.

Next Steps: Validate and Extend

The biomarkers we identified are biologically plausible and could indicate pathological processes directly related to OSA and AF. These inflammatory biomarkers might one day serve as excellent tools for diagnostics and disease monitoring or even as therapeutic targets.

But caution in interpretation is indicated in light of these small sample sizes, and verification is needed via replication and validation studies. As we pursue validation studies, our Cleveland Clinic team expects to publish full results from these initial investigations in the coming months. We likewise intend to investigate the relationship between protein profiles and ECG findings as well as echocardiographic left atrial structure in patients with paroxysmal AF and OSA.

Heatmap of Sparse-Cluster Selected Proteins from PAF-noAF CC Study

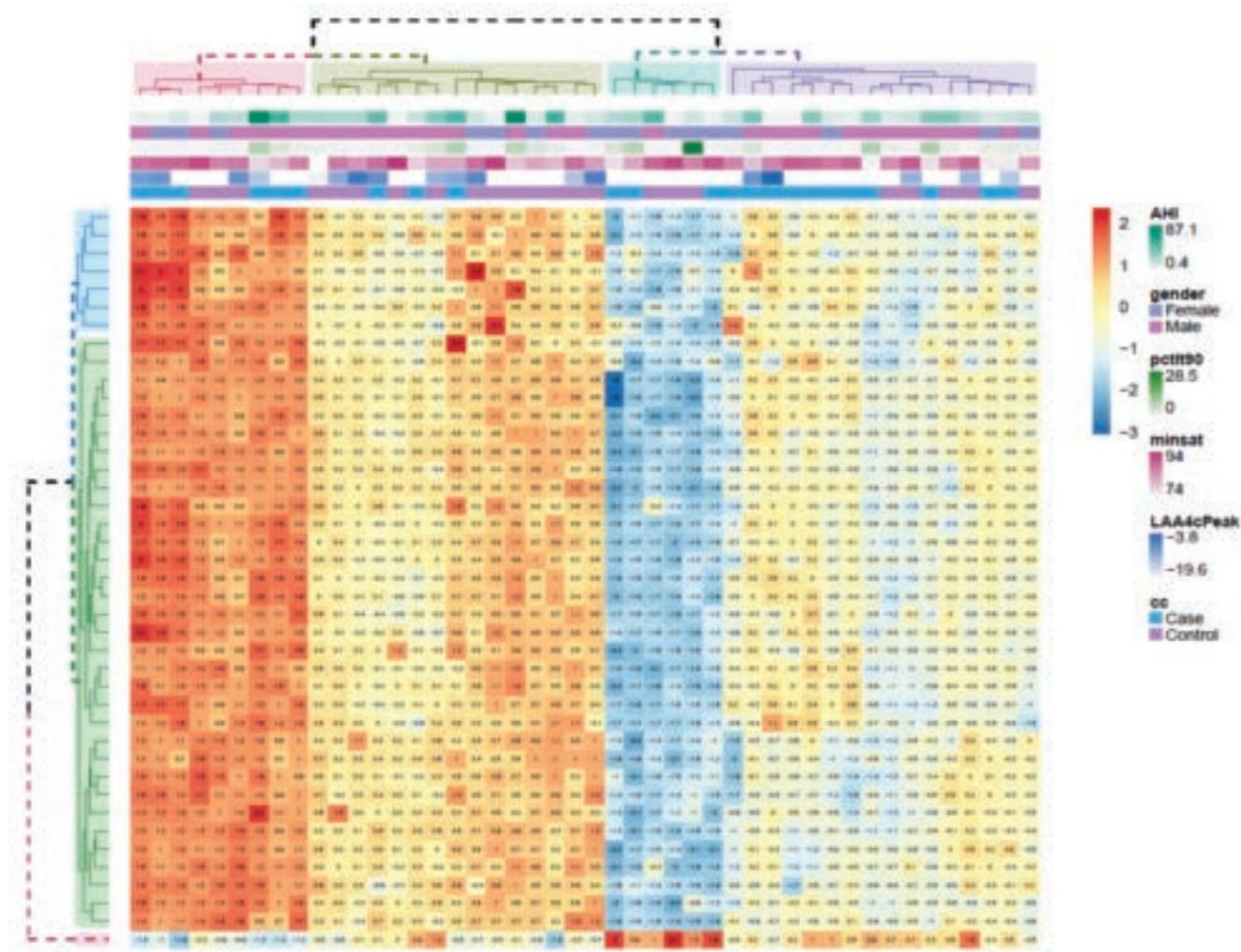


FIGURE 1. Pathway and network analyses displayed using the sparse clustering method selected 21 proteins showing separation into two primary clusters in paroxysmal AF and non-AF.

At this point, proteomic signature studies are discovery-based avenues of research that promise to be especially relevant in generating new hypotheses for understanding the interplay between OSA and AF. A more perfect understanding of that important interplay may pave the way for development of personalized medicine strategies based on biomarker predictors.

This research was supported by the National Heart, Lung, and Blood Institute (R01HL109493) and by a Cleveland Clinic Lerner Research Institute Center of Excellence honorable mention award. Dr. Mehra acknowledges collaborative contributions to this work from functional atrial fibrillation genomics expert David Van Wagoner, PhD, and senior biostatistician John Barnard, PhD, both of Cleveland Clinic's Lerner Research Institute.

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Dr. Mehra (mehrar@ccf.org) is Director of Sleep Disorders Research in Cleveland Clinic's Sleep Disorders Center. She also has appointments in Cleveland Clinic's Respiratory Institute and Miller Family Heart & Vascular Institute as well as in the Department of Molecular Cardiology in Cleveland Clinic's Lerner Research Institute.

Excitotoxic Glutamate Release: Is This What Stymies Oligodendrocytes' Protective Role in Multiple Sclerosis?

By Tara DeSilva, PhD

Inflammation and MS

The major hallmark of demyelinating diseases such as multiple sclerosis (MS) is immune cell infiltration into the central nervous system (CNS) resulting in axon-myelin damage and eventual neurodegeneration. In addition to slowing propagation of nerve impulses, demyelination of the neuronal axon makes the axon more vulnerable to injury, resulting in motor and visual impairments, bowel and bladder dysfunction, pain sensation and cognitive decline.

Current treatments for MS focus on attenuating immune cell infiltration into the CNS. While these treatments reduce the number of relapses, they do not completely eliminate disease activity in the CNS, so long-term disability is not improved. This underscores the importance of understanding mechanisms of CNS protection as a potential add-on therapeutic strategy for MS.

Evidence for Glutamate Dysregulation in MS

Our laboratory at Cleveland Clinic focuses on mechanisms that regulate glutamate as a therapeutic strategy for neuroprotection in MS. Excitotoxicity is a pathological consequence of prolonged activation of glutamate receptors resulting in excessive influx of calcium into the cytosol, leading to cell death. Oligodendrocytes, the cells that make up the myelin sheath, contain glutamate receptors, rendering them potentially vulnerable to excitotoxicity.

Glutamate levels are elevated in the cerebrospinal fluid, acute lesions and plasma of patients with MS, and elevated glutamate levels (as measured by MRI) have been associated with reduced brain volume in patients with MS. These findings provide evidence that glutamate homeostasis may be altered, thereby contributing to excitotoxic mechanisms.

Causal Link Between Inflammation and Glutamate Dysregulation

To address the efficacy of blocking glutamate release in MS, we targeted the system x_c^- transporter as a potential source of glutamate release in experimental autoimmune encephalomyelitis (EAE), an animal model of MS.

Blocking the source of excitotoxic glutamate is a more feasible therapeutic strategy for CNS protection than blocking the target, since AMPA receptor signaling is necessary for both remyelination and synaptic function in neurons.

System x_c^- functions as an exchanger that imports cystine into the cell for synthesis of glutathione, a major antioxidant, in exchange for release of glutamate. Our group showed that genetic or pharmacologic inhibition of the system x_c^- transporter resulted in abrogation of clinical disease and demyelination in the CNS in both chronic and relapsing-remitting models of EAE.¹ An interesting finding from this work is that glutamate also regulates immune cell infiltration into the CNS. Mechanisms regulating how immune cells are able to gain access to the CNS are an important area of research interest in neuroinflammatory diseases. Inhibiting system x_c^- transporter function attenuated T cell infiltration into the CNS, which prevented clinical disease presentation and myelin destruction but not T cell activation in the periphery. Further studies identified expression of system x_c^- on peripheral macrophages as well as dendritic cells, suggesting a novel role for glutamate signaling in activating T cell entry into the CNS.

To further explore the hypothesis that excitotoxicity contributes to demyelination independent of immune cell modulation, we performed pharmacologic inhibition of the system x_c^- transporter after immune cell infiltration in the relapsing-remitting model of EAE. Our results provide evidence that myelin-specific T helper cells provoke microglia to release glutamate via the system x_c^- transporter, causing excitotoxic death to mature myelin.

Taken together, these studies support a novel role for the system x_c^- transporter in mediating T cell infiltration into the CNS and in promoting myelin destruction after immune cell infiltration in EAE. These studies led to an important conceptual idea that modulation of immune cell infiltration must be considered when evaluating CNS neuroprotective strategies, resulting in a methodology to differentiate these two important mechanisms, as outlined in a recent paper by our group.²

Blocking the Target for Glutamate Release Prevents Myelin and Axonal Damage

This prompted the next experimental question: "Does inhibiting the target for glutamate on mature myelinating oligodendrocytes prevent demyelination and correspond with improved clinical scores in EAE?" Data being prepared for publication show that mice genetically deficient in AMPA-type glutamate receptors on mature oligodendrocytes have improved clinical scores and reduced myelin degradation compared with littermate controls subjected to EAE. Furthermore, deleting AMPA-type glutamate receptors from myelin also prevents axonal injury and loss as evidenced by 3-D confocal imaging (Figure 1).

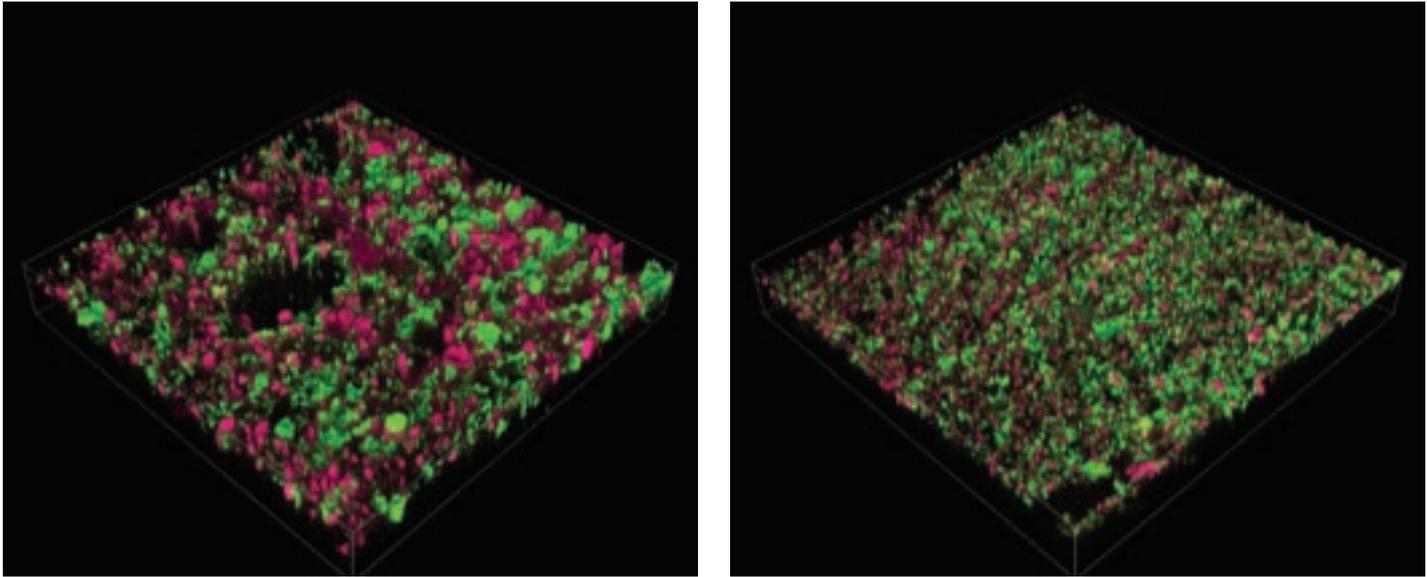


FIGURE 1. Reduction of AMPA receptors in myelin attenuates demyelination and axonal damage in EAE. 3-D representations of 15- μ m confocal z-stacks of spinal cord sections from littermate control mice (left panel) and AMPA receptor-deficient mice (right panel). Far-red immunofluorescence represents SMI-312 (neurofilament) staining of axons, and green immunofluorescence represents MBP (myelin) staining. Axon swelling and myelin loss are reduced in the AMPA receptor-deficient mice (right panel) compared with controls (left panel). Unpublished data from the DeSilva laboratory.

To confirm that abrogation of disease activity was CNS-specific, we analyzed CNS-infiltrating immune cells by flow cytometry and demonstrated no changes in AMPA receptor-deficient mice compared with controls. These data, currently being prepared for publication, support the idea that AMPA receptors expressed on myelin mediate damage to both the myelin sheath and the neuronal axon, suggesting the importance of myelin maintenance for axonal health in MS.

Glutamate and Regeneration in MS

In MS, new early-stage myelin-producing cells (oligodendrocyte progenitor cells) proliferate but fail to rebuild the insulation around nerve fibers as they would during normal development. Our work suggests that AMPA receptors on oligodendrocyte progenitor cells sense glutamate release from axons as an instructive signal to start myelinating axons. Therefore, excessive glutamate release could negatively regulate differentiation, myelin formation and remyelination in MS.

A Perfect Storm?

Excitotoxic glutamate release from the system x_c^- transporter may provide the perfect storm in MS by facilitating immune cell infiltration into the CNS to promote excitotoxic death of myelin and inhibit remyelination of newly proliferated oligodendrocyte progenitor cells.

Blocking the source of excitotoxic glutamate is a more feasible therapeutic strategy for CNS protection than blocking the target, since AMPA receptor signaling is necessary not only for remyelination but also for synaptic function in neurons. This insight underlies our active pursuit of clinically relevant therapeutic strategies for blocking the system x_c^- transporter to protect and promote regeneration in the CNS in MS.

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Dr. DeSilva (desilvt@ccf.org) is an associate staff member in the Department of Neurosciences in Cleveland Clinic's Lerner Research Institute.

More 2017 Research and Clinical Achievements

A sampling of notable developments from across Cleveland Clinic's Neurological Institute

NIA-Funded Study of Exercise for Curbing Alzheimer's Risk

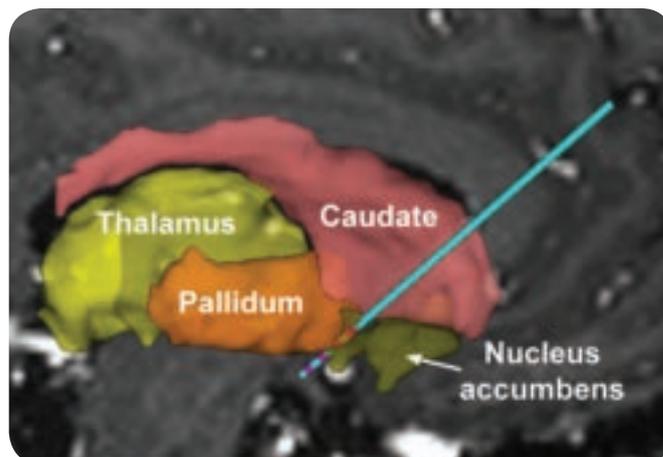
Cleveland Clinic investigator Stephen Rao, PhD, received a five-year, \$8.75 million National Institute on Aging grant to study how exercise might modify genetic risk for Alzheimer's disease (AD) and reduce AD-associated cognitive decline. The award funds the IMMUNE-AD project that Dr. Rao is leading to examine mechanisms by which physical activity counteracts negative inflammatory effects of the *APOE ε4* allele (*APOE4*), a genetic risk factor for late-onset AD.

He and colleagues at Cleveland Clinic Lou Ruvo Center for Brain Health will track the physical activity of 150 cognitively intact healthy older adults with and without the *APOE4* gene over 24 months. Assessments include the effects of physical activity on various indicators of AD pathology, including functional and structural MRI, amyloid PET imaging, analysis of CSF and blood biomarkers, and tests of memory and cognition. Subjects with and without *APOE4* will be compared to determine whether physical activity confers greater neuroprotection in the genetically at-risk group. "If exercise shows positive effects and this is validated by others, it could help significantly reduce the number of people who develop Alzheimer's," says Dr. Rao, Director of Cleveland Clinic's Schey Center for Cognitive Imaging. More at consultqd.clevelandclinic.org/adexercise.

Trimming Time to Stroke Care with a Mobile Stroke Unit

A telemedicine-enabled stroke ambulance equipped with a CT scanner allows delivery of thrombolysis 38.5 minutes sooner than does a traditional model of stroke care delivery. That was a key takeaway from a study of Cleveland Clinic's early experience with its mobile stroke treatment unit (MSTU), as reported in *Neurology* (2017;88:1305-1312).

The study compared process measures between the first 100 patients treated with Cleveland Clinic's MSTU (over several months in 2014) and a control group of 53 patients with suspected stroke brought to a Cleveland Clinic ED by traditional ambulance during the same period. Results showed that MSTU management yielded highly significant reductions in median alarm-to-CT completion time, median alarm-to-thrombolysis time and median door-to-thrombolysis time. "We also found that a greater proportion of patients on the MSTU were given the treatment they needed, and they got it faster," says principal author M. Shazam Hussain, MD, Director of the Cerebrovascular Center. "Overall, people transported in the MSTU received thrombolysis nearly 40 minutes faster." His team expects to report its subsequent MSTU experience, including clinical and cost-effectiveness outcomes, in the future. More at consultqd.clevelandclinic.org/mstu100.



Deep Brain Stimulation for Chronic Pain: Study Makes the Case for a New Paradigm

When Cleveland Clinic researchers published their 10-patient study of deep brain stimulation (DBS) for long-standing post-stroke pain syndrome in May (*Ann Neurol.* 2017;81:653-663), they were reporting on the first prospective, randomized, controlled trial of DBS for neuropathic pain. But they were also doing much more: "We showed that active versus sham DBS of the ventral striatum/anterior limb of the internal capsule produced significant improvements in multiple outcome measures associated with the affective sphere of chronic pain, such as depression, anxiety and quality of life," says lead investigator Andre Machado, MD, PhD. "This trial represents a paradigm shift in chronic pain management in that it targeted neurostimulation to brain structures related to the affective, rather than sensory, sphere of chronic pain."

The implication is that analgesia may not be the appropriate treatment goal in central pain syndromes. "We propose a shift in surgical targeting away from neural networks underlying the sensory-discriminative domain toward networks that mediate the affective-motivational sphere of chronic pain," says Dr. Machado, a neurosurgeon and Neurological Institute Chairman. His team hopes to initiate a multicenter study to confirm their findings and potentially expand the approach to other chronic pain types. More at consultqd.clevelandclinic.org/dbsforpain.

17.1%

Growth in Neurological Institute research program funding over past 5 years

Leading a PCORI-Funded Project to Guide Treatment Philosophy in Multiple Sclerosis

Escalate or hit hard early? That's the dilemma when choosing a disease-modifying treatment (DMT) strategy for patients with relapsing-remitting multiple sclerosis (RRMS). No evidence exists comparing these DMT approaches in a head-to-head trial. So Cleveland Clinic neurologist Daniel Ontaneda, MD, is leading a team of researchers to change that. Their efforts got a boost in 2017 with a \$10.6 million funding award from the Patient-Centered Outcomes Research Institute (PCORI).

The funded project will directly compare two DMT strategies:

- **Escalation**, or starting with a medication considered safe but not highly likely to control the patient's MS activity, and then escalating to progressively more-potent therapies if disease activity continues
- **"Early highly effective treatment,"** or first-line use of a medication with high rates of efficacy but also the potential for rare significant adverse effects (i.e., one of the monoclonal antibodies used in MS)

The five-year project will measure changes in brain volume and monitor patient-reported outcomes in a randomized trial involving 400 patients and an observational cohort of 400 more patients. All will be treatment-naïve individuals with RRMS from 16 sites in the U.S. and U.K. "It's a test of two philosophical approaches to treating RRMS, beyond just a comparison of individual medications," says Dr. Ontaneda, of the Mellen Center for Multiple Sclerosis. "Discussions with patients inevitably come around to the lack of comparative data between these approaches. We want to fill that gap." More at consultqd.clevelandclinic.org/mspcori.



Upping the Game in Predicting Epilepsy Surgery Outcomes

Patients considering epilepsy surgery traditionally are told what the "average" chance of success is, but not what their *individual* chance is. Cleveland Clinic epileptologist Lara Jehi, MD, wants to improve that model of patient counseling, and in 2017 she and her Epilepsy Center colleagues garnered a \$3.4 million National Institutes of Health grant to aid their efforts.



The five-year award will support development of a comprehensive epilepsy surgery nomogram that uses diagnostic technology and predictive modeling to project individual outcomes in epilepsy surgery. The work builds on Cleveland Clinic's first epilepsy surgery nomogram, published in *Lancet Neurology* in 2015, which used basic patient characteristics to predict postoperative seizure outcomes. With the new grant, researchers led by Dr. Jehi will enhance the tool by integrating additional clinical, imaging, genetic, electrophysiologic and histopathologic data. "This project will generate the first objective, validated, user-friendly epilepsy surgery prediction tool," says Dr. Jehi. "It should improve patient counseling through a more scientific decision-making process." More at consultqd.clevelandclinic.org/epinomogram.

Bringing Overdue Guidance to Management of Mitochondrial Disease

For the first time, physicians who care for individuals with primary mitochondrial disease have formal recommendations for these patients' preventive care and routine management. That's thanks to the 2017 publication of a consensus statement on the topic from the Mitochondrial Medicine Society, with Cleveland Clinic pediatric neurologist Sumit Parikh, MD, serving as lead author.

The milestone document, published online by *Genetics in Medicine* in July, is organized by the various organ systems involved in mitochondrial disorders, with focused sections providing screening and management recommendations in neurology and many other specialty areas. "We used the Delphi method to form consensus-based recommendations in areas where data are insufficient on treatment of this rare group of genetic disorders," explains Dr. Parikh, who led a writing team of 35 international experts. He and his co-authors plan to work with the Mitochondrial Medicine Society to implement the recommendations via an expanded network of mitochondrial disease centers across the U.S. to promote more standardized practice. More at consultqd.clevelandclinic.org/mitochondrial.



Transcranial Direct Current Stimulation Improves Function in Chronic Tetraplegia

Patients with chronic incomplete tetraplegia realized gains in motor function below the level of injury after a two-week program pairing transcranial direct current stimulation (tDCS) with massed practice training in a new Cleveland Clinic pilot study. The gains were still evident three months after the intervention, and motor map characteristics showed increased excitability of residual pathways.

Results were reported at an Academy of Spinal Cord Injury Professionals conference in September, where the study was selected as the event's prestigious Jayanthi Lecture. The study also was published online by the *Journal of Spinal Cord Medicine*.

The double-blind investigation randomized 12 patients to tDCS or sham stimulation plus two hours of physical therapy five days a week for two weeks. "We observed significant functional benefits in these very disabled patients in the chronic stage of injury after only a short intervention with tDCS plus massed practice training," says Cleveland Clinic research scientist Kelsey Potter-Baker, PhD, who led the effort that included staff from the Department of Physical Medicine and Rehabilitation.

"Our findings provide evidence that stimulation helps restore cortical representation of paralyzed and weak muscles," Dr. Potter-Baker adds. "They strongly suggest the potential for adaptive plasticity long after injury." Preparations for a phase 2 trial are underway. More at consultqd.clevelandclinic.org/tDCS.

Probing Mechanisms of Lithium's Bipolar Benefits in NIH-Funded Study

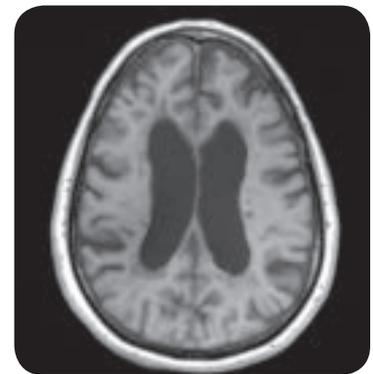
Cleveland Clinic researchers were awarded a \$3.7 million National Institutes of Health grant to investigate the effects of lithium on the brains of patients with bipolar disorder. "Lithium is one of the most specific and effective treatments we have for bipolar disorder, but no one has demonstrated how it works," says lead investigator Amit Anand, MD, Vice Chair for Research in the Center for Behavioral Health. "This research will address important knowledge gaps by exploring changes in the brain and at the molecular level in patients on lithium therapy."

The five-year study is recruiting 90 patients with bipolar II disorder and assessing them with MRI and blood testing after two, eight and 26 weeks of lithium monotherapy. Findings will be compared with those in 30 untreated healthy controls. Investigations include resting-state functional MRI using Cleveland Clinic's 7T scanner, diffusion-weighted structural imaging and assessment of gene expression changes via RNA from peripheral blood lymphocytes. Dr. Anand is particularly interested in characterizing the "connectomes" (neural networks) between various brain regions. Preliminary results are expected in about three years.

More at consultqd.clevelandclinic.org/lithium.

Marked Slowing of Brain Atrophy Demonstrated in Progressive Multiple Sclerosis

The investigational drug ibudilast slowed progression of brain atrophy in patients with progressive multiple sclerosis (MS) by nearly half relative to placebo, according to initial, top-line results of the phase 2 SPRINT-MS study presented by Cleveland Clinic neurologist Robert Fox, MD, at the 7th JointECTRIMS-ACRIMS Meeting in October. The 48 percent reduction in brain atrophy over two years seen with ibudilast compares favorably with the 18 percent reduction reported in separate studies of ocrelizumab, which earlier this year became the first FDA-approved therapy for progressive MS.



Ibudilast, a small-molecule compound that takes on progressive MS via novel mechanistic pathways, was also found to be well-tolerated. The oral therapy has been approved in Japan since 1989 for use in asthma and cerebrovascular disorders. "The SPRINT-MS results are very encouraging," says Dr. Fox, principal investigator of the 28-center trial. "Our hope is that ibudilast's benefit in slowing brain volume loss will translate to slowed progression of physical disabilities." Phase 3 testing to explore that question is expected to follow. Publication of full results from SPRINT-MS will be forthcoming. More at consultqd.clevelandclinic.org/sprintms.



Plasma Elevations of Two Brain Proteins Linked to Repeated Head Blows

Plasma concentrations of two brain proteins — tau and neurofilament light chain — are elevated in individuals exposed to repetitive head impacts, according to an analysis of longitudinal results from a 438-subject cohort of Cleveland Clinic's Professional Fighters Brain Health Study. "We found that higher levels of both proteins may be associated with repetitive head trauma," says lead investigator Charles Bernick, MD, who presented the findings at the American Academy of Neurology's Sports Concussion Conference in July.

The analysis is part of the larger Professional Fighters Brain Health Study, designed to ultimately determine whether pro fighters are at risk of long-term neurological complications — and which fighters are at greatest risk. Its findings included a significant increase in tau levels over time among active fighters, and this increase was associated with a substantial 7 percent lower baseline thalamic volume on MRI. "Longer follow-up is needed to determine whether increasing tau levels over time indicate a risk of long-term neurological decline," says Dr. Bernick, a neurologist with Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas. "But measurement of both of these brain proteins may one day help us detect brain injury early, predict who will develop complications and better monitor brain injury over time." More at consultqd.clevelandclinic.org/tau.



Advancing a Novel Convection-Enhanced Delivery Catheter for Direct Drug Delivery to the CNS

A novel convection-enhanced delivery (CED) device developed under the leadership of Cleveland Clinic neurosurgeon Michael Vogelbaum, MD, PhD, won FDA 510(k) clearance in March as a therapeutic delivery device. Known as the Cleveland Multiport Catheter (CMC), the device features four microcatheters and was designed for higher-volume drug distribution to glioma tumors and tumor-infiltrated brain tissue. While no therapeutic has yet received FDA approval for direct delivery into brain parenchyma, "this clearance of the CMC is important to developers of drugs and biologics for direct delivery to the CNS, as they want to use an FDA-cleared catheter for IND-based clinical trials," says Dr. Vogelbaum of the Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center.

He and colleagues are gaining experience with the CMC in a first-in-human clinical trial of the catheter at Cleveland Clinic. To date, 12 patients with glioma have completed treatment with the device under the trial's protocol. Encouraging results from the trial were reported at a Society for Neuro-Oncology meeting in November. More at consultqd.clevelandclinic.org/cmc510k. (Dr. Vogelbaum is chief medical officer of Infuseon Therapeutics Inc., a Cleveland Clinic-owned spinoff company funding clinical development of the CMC; his roles in this effort are covered under a Cleveland Clinic-approved conflict-of-interest management plan.)

BRAIN Neuroethics Grant Enables Deep Dive into Personality in Parkinson's Disease

A Cleveland Clinic researcher is the recipient of a funding award in the first wave of neuroethics grants issued by the National Institutes of Health's BRAIN Initiative. Cynthia Kubu, PhD, will receive \$1.6 million over four years to study perceptions of personality in the context of Parkinson's disease (PD) and its treatment with deep brain stimulation (DBS). Objectives include identifying whether existing measures capture valued personality characteristics, determining if PD results in changes in patients' perceived personality, evaluating concordance between patients' and their family members' ratings of personality change, and learning whether DBS results in changes in

individually meaningful personality characteristics. The hope is to yield insights for developing personality measures that mirror patients' values and to help shape informed consent for DBS.

"We hypothesize that patients will report changes to personality associated with Parkinson's disease," says Dr. Kubu, a neuropsychologist in the Center for Neurological Restoration. "And we suspect that deep brain stimulation will result in a return to pre-illness personality and allow a patient to be his or her more authentic self." More at consultqd.clevelandclinic.org/pdpersonality.



Trial Aims to Enrich Options for Intracerebral Hemorrhage

Can early surgical hematoma evacuation in intracerebral hemorrhage be done in such a minimally invasive fashion that it promises significantly more benefit than risk? That's what Cleveland Clinic and nine other U.S. centers hope to learn by participating in the recently launched phase 3 ENRICH study comparing a novel surgical system for clot removal within 24 hours of a hemorrhagic stroke to standard medical management.

"Historically, surgery was not a viable option for intracerebral hemorrhage because of damage caused by the surgery itself," says neurosurgeon Mark Bain, MD, who is leading the study in Cleveland Clinic's Cerebrovascular Center. "The system tested in ENRICH offers a minimally disruptive approach to the hematoma, fine control and a gentle way to remove the hemorrhage." He says that if this minimally invasive approach fares well in the 300-patient trial, "the results could revolutionize hemorrhagic stroke treatment and avoid devastating outcomes for many patients." More at consultqd.clevelandclinic.org/enrich.



Clarifying the Role of Home Sleep Testing for OSA

New clinical practice guidelines released in 2017 provide the clearest recommendations to date on when home sleep apnea testing is an appropriate alternative to polysomnography for assessing adult obstructive sleep apnea (OSA), and a Cleveland Clinic sleep disorders specialist was one of seven experts who developed the guidelines.

"There's now good evidence supporting home testing as a viable alternative to polysomnography and a reliable method for diagnosing OSA in uncomplicated adults with a high probability of having moderate to severe OSA based on clinical signs and symptoms," says Reena Mehra, MD, MS, Director of Sleep Disorders Research. She served on the American Academy of Sleep Medicine (AASM) task force that drafted the guidelines after a systematic literature appraisal using GRADE methodology to standardize recommendations. Details of when home testing is and isn't appropriate are at consultqd.clevelandclinic.org/osa. The AASM guidelines are published in the *Journal of Clinical Sleep Medicine* (2017;13:479-504).

Exploring the Behavioral-Biological Reasons Why Bariatric Surgery Comes Up Short

Despite the weight-loss and health benefits for many of the nearly 200,000 Americans who undergo bariatric surgery each year, a subset of patients experience suboptimal weight loss or substantial weight regain after initial success. Now a newly launched trial co-directed by Cleveland Clinic is aiming to understand why, with help from a \$4.5 million, five-year NIH grant.

The seven-center study will prospectively follow 144 patients for 24 months after they undergo bariatric surgery to assess for correlates and predictors of observed weight loss trajectories. "The etiologic contributors to weight loss success following bariatric surgery are not well understood," explains co-principal investigator Leslie Heinberg, PhD, of Cleveland Clinic's Department of Psychiatry and Psychology

and Center for Behavioral Health. "Weight change likely involves complex interactions between behavioral and biological factors, and it's difficult to predict outcomes in bariatric surgery patients."

She and co-investigators will examine interrelationships among factors ranging from eating disorders to the gut's bacterial composition to physical activity, mood symptoms and cognitive function. The aim is to generate data to better identify those bariatric surgery candidates most likely to have suboptimal outcomes — and perhaps help target modifiable risk factors through interventions. "We hope to enable a shift toward more individualized medicine in the care of patients with obesity who are considering bariatric surgery," Dr. Heinberg says. More at consultqd.clevelandclinic.org/bariatricbehavior.



An Eager Embrace of Distance Health

Cleveland Clinic's Neurological Institute is moving thoughtfully but vigorously into various forms of distance health in appropriate clinical settings. The institute offers virtual visits in at least 13 subspecialty areas ranging from headache to movement disorders to epilepsy and more. Here's how the institute's 2,700+ distance health patient encounters in the first three quarters of 2017 broke down by type:

952 virtual visits

883 virtual inpatient consults

881 telestroke consults

10 telepsych emergency department consults (launched Sept. 2017)

Selected Additional Activities of Note in the Neurological Institute

- › Leadership of a four-site clinical trial comparing ketamine vs. electroconvulsive therapy for treatment-resistant depression with support of an \$11.8 million Patient-Centered Outcomes Research Institute (PCORI) award
- › Participation in an eight-center study of exercise delivery for patients with multiple sclerosis (MS) that received a \$5.7 million PCORI funding award
- › Continued leadership of an NINDS-funded project to develop a brain atlas of cortico-cortical evoked potential responses from hundreds of epilepsy surgery patients who have undergone SEEG
- › Presentation of phase 3 results from the pivotal RADIANCE and SUNBEAM trials of ozanimod for relapsing MS at the 2017 American Academy of Neurology andECTRIMS-ACRIMS meetings
- › Continuation of three research projects in Alzheimer's and Parkinson's diseases under a five-year, \$11.1 million Center of Biomedical Research Excellence (COBRE) grant from the NIH awarded to Cleveland Clinic Lou Ruvo Center for Brain Health and the University of Nevada, Las Vegas
- › Further rollout of an innovative population health pilot launched in 2016 to prioritize functional outcomes over opioid- and procedure-based care for patients with chronic low back and leg pain
- › Continued leadership of the multicenter MS PATHS initiative to use clinical and imaging data from office visits to develop better outcome measures and improve care for patients with MS
- › Receipt of a \$100,000 grant from the Prayers From Maria Foundation to support Cleveland Clinic pediatric glioma research
- › Leadership of the multicenter ARM-TD study of deutetrabenazine (*Neurology*. 2017;88:2003-2010), which supported the drug's 2017 clearance as the second FDA-approved therapy for tardive dyskinesia
- › Continuation of basic research into how MS develops and progresses in the human brain through two large NINDS grants for work in remyelination and axonal and neuronal degeneration
- › Ongoing participation as one of four leading sites for the NIH-funded DIAGNOSE CTE study to help enable in vivo detection of chronic traumatic encephalopathy
- › Expansion of Cleveland Clinic's regional rehabilitation footprint with the opening of two new 60-bed inpatient rehabilitation hospitals east and south of Cleveland, to be operated in a joint venture with Select Medical Corp.
- › Receipt of a \$400,000 donor fund to support autonomic research focusing on biofeedback, psychological support tools and rehabilitation services
- › Leadership of the 2017 revision of the McDonald diagnostic criteria for MS, with Jeffrey Cohen, MD, of the Mellen Center for Multiple Sclerosis serving as revision co-chair

CLEVELAND CLINIC NEUROLOGICAL INSTITUTE AT A GLANCE

WHO WE ARE



1 integrated institute

300+ professional staff

14 subspecialty centers for care

155 clinical residents and fellows

26 research fellows

WHAT WE DO*



228,548 annual outpatient visits

16,289 annual admissions

14,215 annual surgical/ interventional procedures

82,780 annual neuroimaging studies

WHAT WE DO — BEYOND THE NUMBERS



Provide multiregional care access

with sites in 3 U.S. regions: Northeast Ohio, Southeast Florida and Las Vegas



Provide expanding distance health access

with virtual visits in 13 subspecialty areas and >2,700 distance health patient encounters in Q1-Q3 2017



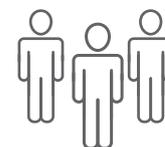
Transform care with data

through our innovative Knowledge Program® platform for collecting patient-reported outcomes for real-time integration into clinical workflows



Pioneer novel delivery methods

like our telemedicine-enabled mobile stroke treatment unit, which cared for 299 patients in 2016



Forge new paths in population health

with initiatives like our Back on TREK program prioritizing pain rehabilitation and functional outcomes for patients with chronic low back pain

HOW WE'RE ADVANCING NEUROSCIENCE KNOWLEDGE*

\$23.5M in total grant/contract research funding

79 federal grants/contracts

258 nonfederal grants/contracts

413 active clinical research projects

77 new clinical research projects initiated



*2016 totals

2018 Continuing Medical Education from the Neurological Institute

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DEC. 3-7, 2018

Cleveland Clinic Gamma Knife Center,
Cleveland, Ohio

Directors: Gene Barnett, MD; Lilyana Angelov,
MD; John Suh, MD; Gennady Neyman, PhD

11th Annual International Symposium on Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery

FEB. 23-25, 2018

Loews Portofino Bay Hotel, Orlando, Florida

Directors: Lilyana Angelov, MD; Gene Barnett,
MD; Edward Benzel, MD; Samuel Chao, MD;
John Suh, MD

(see back cover for more information)

Cleveland Clinic Neurological Institute Summit 2018: MS Treatment Strategies

MARCH 22-24, 2018

InterContinental Hotel & Conference Center,
Cleveland, Ohio

Director: Robert Bermel, MD

Cleveland Clinic Innovations in Cerebrovascular Care 2018

JUNE 7-8, 2018

InterContinental Hotel & Conference Center,
Cleveland, Ohio

Directors: M. Shazam Hussain, MD; Mark
Bain, MD; Andrew Russman, MD; Ken
Uchino, MD

(see back cover for more information)

Mellen Center Update in Multiple Sclerosis

JUNE 29, 2018

InterContinental Hotel & Conference Center,
Cleveland, Ohio

Director: Alex Rae-Grant, MD

Cleveland Spine Review

JULY 10-17, 2018

Cleveland Clinic Lutheran Hospital,
Cleveland, Ohio

Directors: Edward Benzel, MD;
Douglas Orr, MD; Richard Schlenk, MD;
Michael Steinmetz, MD; Jason Savage, MD;
Greg Trost, MD

(see back cover for more information)

2018 Neurology Update – A Comprehensive Review for the Clinician

AUG. 3-5, 2018

The Ritz-Carlton, Washington, D.C.

Directors: Alex Rae-Grant, MD, and
Glen Stevens, DO, PhD

Leksell Gamma Knife Perfexion® Course

AUG. 20-24, 2018

Cleveland Clinic Gamma Knife Center,
Cleveland, Ohio

Directors: Gene Barnett, MD; Lilyana Angelov,
MD; John Suh, MD; Gennady Neyman, PhD

SEEG Brain Mapping Workshop

SEPT. 5-8, 2018

Cleveland, Ohio

Directors: Andreas Alexopoulos, MD; Juan
Bulacio, MD; Patrick Chauvel, MD; Jorge
Gonzalez-Martinez, MD, PhD

Wake Up to Sleep Disorders 2018: A Cleveland Clinic Sleep Disorders Center Update

SEPT. 7-8, 2018

Cleveland Clinic Administrative Campus,
Beachwood, Ohio

Directors: Nancy Foldvary-Schaefer, DO, MS;
Reena Mehra, MD, MS; Harneet Walia, MD;
Tina Waters, MD

Spasticity and Neuromotor Rehabilitation: Pediatric and Adult Symposium 2018

SEPT. 13-15, 2018

Corporate College East,
Warrensville Heights, Ohio

Directors: Francois Bethoux, MD,
and Douglas Henry, MD

Midwest Spine Symposium

SEPT. 22-23, 2018

Cleveland Clinic Lutheran Hospital,
Cleveland, Ohio

Director: Michael Steinmetz, MD

Cleveland Clinic Epilepsy Update and Review Course 2018

SEPT. 22-24, 2018

InterContinental Hotel & Conference Center,
Cleveland, Ohio

Director: Ajay Gupta, MD

(see back cover for more information)

These activities have been approved for *AMA PRA Category 1 Credit™*.

For many additional online neuroscience-related CME activities from Cleveland Clinic, visit ccfcm.org.

2018 CME from the Neurological Institute

Selected highlights of upcoming live activities. For the full slate of Cleveland Clinic's 2018 live neuroscience CME offerings, see inside back cover.

11th Annual International Symposium on Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery

FEB. 23-25, 2018

Loews Portofino Bay Hotel, Orlando, Florida

Directors: Lilyana Angelov, MD; Gene Barnett, MD; Edward Benzel, MD; Samuel Chao, MD; John Suh, MD

More than two dozen expert faculty explore advances in the treatment of benign and malignant tumors involving the brain, spine and other organ sites. Technical and clinical expertise will be emphasized, with many opportunities for faculty and vendor interaction.

Information/registration: ccfcme.org/sbirt18

Cleveland Clinic Innovations in Cerebrovascular Care 2018

JUNE 7-8, 2018

InterContinental Hotel & Conference Center, Cleveland, Ohio

Directors: M. Shazam Hussain, MD; Mark Bain, MD; Andrew Russman, MD; Ken Uchino, MD

As the management of cerebrovascular conditions advances rapidly, this course focuses on how clinical care is impacted by the field's technological advances. It also features a multidisciplinary discussion of the greatest challenges posed by complex cerebrovascular cases.

Information/registration: ccfcme.org/IICC18

Cleveland Spine Review

JULY 10-17, 2018

Cleveland Clinic Lutheran Hospital, Cleveland, Ohio

Directors: Edward Benzel, MD; Douglas Orr, MD; Richard Schlenk, MD; Michael Steinmetz, MD; Jason Savage, MD; Greg Trost, MD

This weeklong intensive is a perennial favorite for surgical and medical spine specialists alike. Hallmarks include a serious devotion to problem-based learning, nonoperative strategies, and hands-on education in the cadaver lab. And the legendary social functions can't be beat.

Information/registration: ccfcme.org/spinereview18

Cleveland Clinic Epilepsy Update and Review Course 2018

SEPT. 22-24, 2018

InterContinental Hotel & Conference Center, Cleveland, Ohio

Director: Ajay Gupta, MD

Invited national faculty will join Cleveland Clinic experts in reviewing the latest in epilepsy diagnosis and medical and surgical treatment for adult and child neurologists, epileptologists and trainees. In addition to CME, the course is approved for credits in the American Board of Psychiatry and Neurology maintenance of certification (MOC) program.

Information/registration: ccfcme.org/epilepsyupdate18

These activities have been approved for *AMA PRA Category 1 credit*[™].

See page 31 (inside back cover) for our full slate of live neuroscience CME in 2018.

