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PATHWAYS

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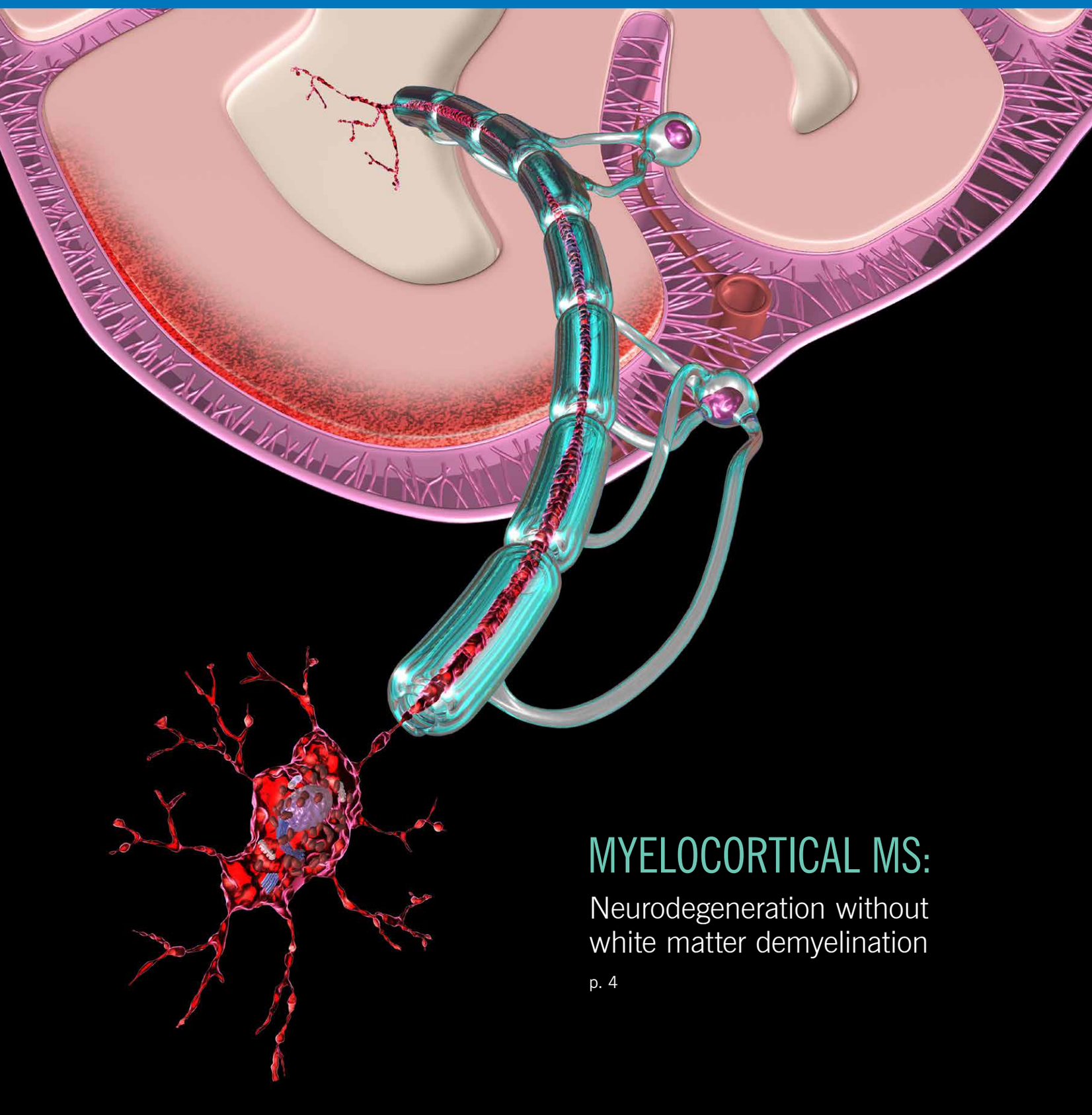

MYELOCORTICAL MS:

Neurodegeneration without white matter demyelination

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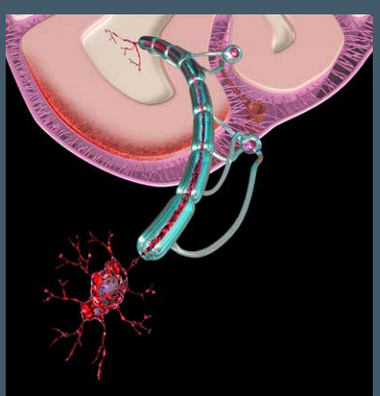

ON THE COVER: Myelocortical multiple sclerosis (MS) is a newly identified form of the disease with intact myelin in brain white matter. MRI shows lesions indistinguishable from those of typical MS. The illustration depicts the pathological findings of neurodegeneration with axonal swelling and intact myelin characteristic of white matter brain lesions in myelocortical MS. Myelocortical MS represents the first demonstration of neurodegeneration in the absence of demyelination. See page 4.

Neuroscience Pathways is produced by Cleveland Clinic's Neurological Institute.

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CLEVELAND CLINIC NEUROLOGICAL INSTITUTE **AT A GLANCE**

WHO WE ARE

1 integrated institute

14 subspecialty centers for care

300+ professional staff

242 staff physicians

166 clinical residents and fellows

WHAT WE DO*

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15,491 annual admissions

12,723 annual surgical/ interventional procedures

78,862 annual neuroimaging studies

WHAT WE DO — BEYOND THE NUMBERS

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Offer distance-health options with virtual visits in 13 subspecialty areas and > 5,500 distance-health patient encounters in 2018 (through November)

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 has transported over 1,300 patients to date

Forge new paths in neuroimaging through pioneering applications of technologies like MR fingerprinting, myelin PET and computer-assisted MRI post-processing

HOW WE'RE ADVANCING NEUROSCIENCE KNOWLEDGE**

$31.1M in total research funding

79 federal grants/contracts

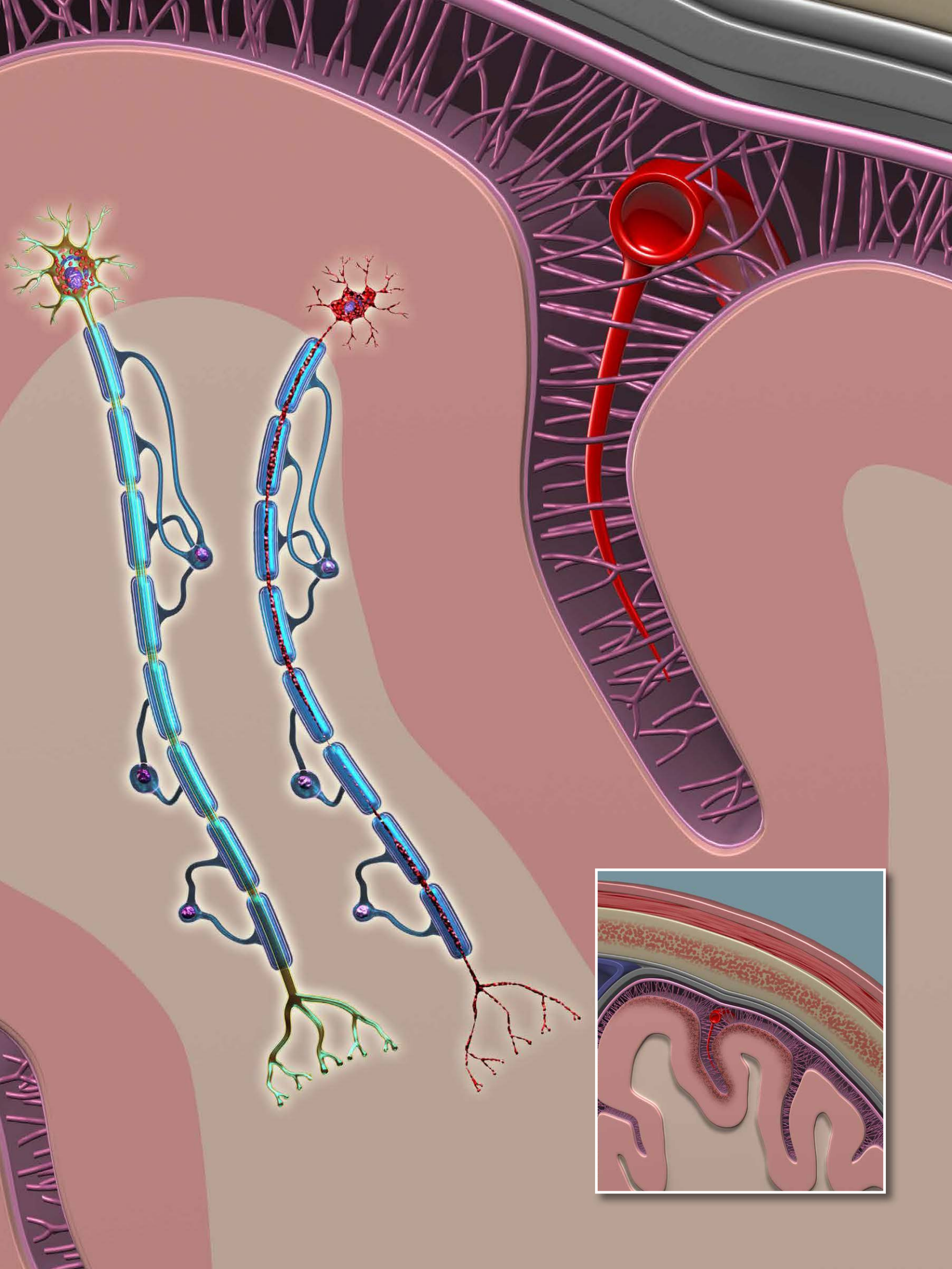
267 nonfederal grants/ contracts

544 active clinical research projects

86 new clinical research projects initiated (2017)

*2017 numbers

**2018 numbers unless noted otherwise



MYELOCORTICAL MULTIPLE SCLEROSIS:
NEURODEGENERATION WITHOUT WHITE MATTER DEMYELINATION

Discovery of new MS subtype suggests that the axon itself may be the primary site of injury

By Daniel Ontaneda, MD, MSc, and Bruce Trapp, PhD

Multiple sclerosis (MS) is well-established as being a highly heterogeneous disease, and now part of this heterogeneity can be better explained by the discovery of a new MS subtype characterized by the absence of demyelination in cerebral white matter.[1] This discovery was made using the rapid brain donation program at Cleveland Clinic, which involves in situ MRI followed by pathological examination of the brain within six hours of death.

We and our collaborators found that 12 of 100 cases of MS received for brain donation had no cerebral white matter demyelination but did have loss of myelin in the cerebral cortex and spinal cord, prompting us to name this new subtype *myelocortical multiple sclerosis* (MCMS) (Figure 1). We then conducted a comparative study between the 12 patients with MCMS and 12 cases of typical MS matched by age, sex, MRI protocol, MS disease subtype, disease duration and Expanded Disability Status Scale score. Clinical, MRI and histological features were compared between MCMS and typical MS cases. No significant differences were found in relation to the clinical history or MRI features of individuals with MCMS versus typical MS. The amount of cortical demyelination was similar between the groups (4.45 percent in MCMS vs. 9.74 percent in typical MS; $P = 0.5$), and spinal cord demyelination was present in both groups, although a greater demyelinated area was found in typical MS as compared with MCMS (13.8 percent vs. 3.8 percent, $P = 0.01$). MRIs were also compared between MCMS and typical MS patients, with no significant differences found between the groups.

LEFT: *Illustration of a normal projection neuron (left) and a projection neuron in myelocortical MS (right). In myelocortical MS, lesions have the same MRI characteristics as in typical MS (T1 hyperintensity, T2 hyperintensity and low magnetization transfer), but on histological examination they show normal myelin content with normal internodal distances. Axons in myelocortical MS are swollen despite having intact myelin. Patients with myelocortical MS have intact myelin throughout the brain white matter, although clinical characteristics are similar to those in patients with typical MS.* ***Inset:*** *Myelocortical MS demonstrates normal white matter myelin content, but demyelination is present in both the spinal cord and brain cortex. In myelocortical MS, cortical neuronal loss is found in projection layers not connected to the spinal cord — evidence of neurodegeneration without demyelination.*

Neurodegeneration in the absence of demyelination

Despite the absence of demyelination in white matter, cortical neuronal density was decreased in MCMS as compared with control cases without neurological disease. Neuronal densities were examined in layers III, V and VI (cortical projection neurons), specifically from regions not receiving from or projecting to the spinal cord (inferior frontal gyrus, superior temporal gyrus, superior insula, inferior insula and cingulate gyrus) (Figure 2 and Table 1). This analysis provides evidence that neurodegeneration, manifested as cortical neuronal loss, occurs in MCMS independently from cerebral white matter demyelination. This is a significant finding, as it is *the first pathological evidence that demyelination and neurodegeneration can occur as independent events in MS*.

These results have significant implications for how we view the disease and potentially how we treat MS. They suggest that prevention of white matter lesions alone may not be sufficient to prevent neurological disability. Going forward, the mechanisms of neuronal loss require further exploration for identification of pathways that lead to neurodegeneration. The results also suggest that neuroprotective medications will be needed, in addition to anti-inflammatory medications, to fully treat the disease.

Axonal swelling in MCMS

Areas with normal myelin content but with abnormal signal on T2-weighted MRI, T1-weighted MRI and magnetization transfer ratio (MTR) images were identified and then histologically examined and compared with normal-appearing white matter. The most striking finding was the presence of swollen myelinated axons in the T1/T2/MTR abnormal regions (see illustration on facing page). *This significant observation suggests that brain white matter MRI abnormalities that are thought to reflect loss of myelin can reflect pathology of myelinated axons*. The findings that axonal pathology underlies what otherwise appear to be typical MS lesions may suggest that the axon itself, rather than myelin, may be the primary site of injury in MS. The next step of our research is to further interrogate these axons with electron microscopy and examine the underpinnings of why axonal swelling occurs.

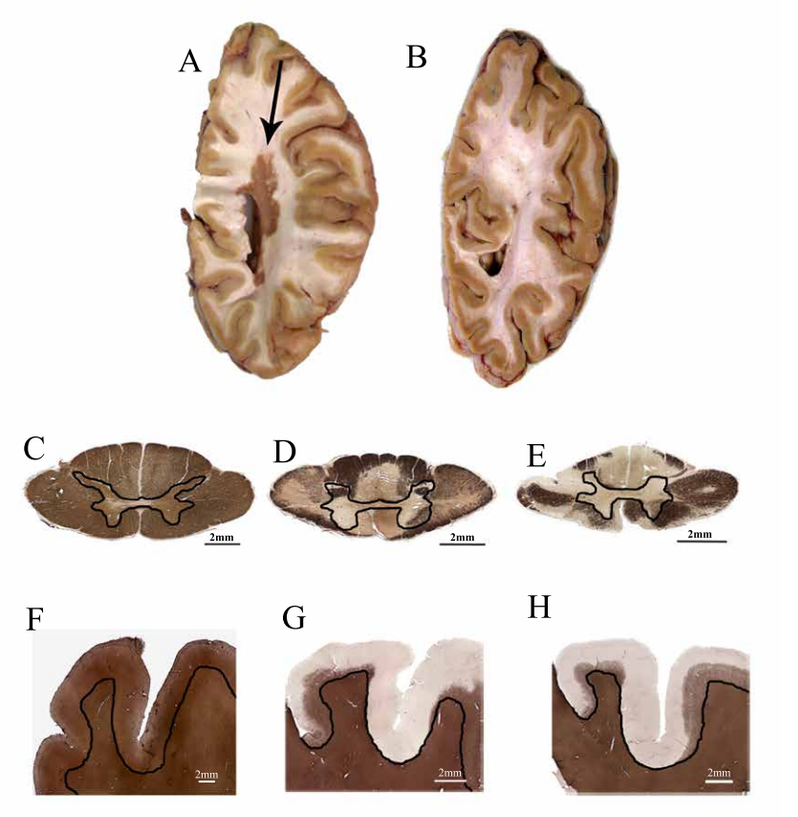


FIGURE 1. *Demyelination in myelocortical MS and typical MS. (A and B) Centimeter-thick slices from (A) a typical MS brain containing a large white matter lesion (arrow) and (B) a myelocortical MS brain without white matter lesions. (C) A normally myelinated spinal cord section labeled with anti-PLP antibodies. (D and E) Spinal cord demyelination was detected in tissue sections from individuals with typical MS (D) and myelocortical MS (E). (F) Normally myelinated cortex labeled with an anti-PLP antibody. (G and H) Subpial cortical lesions in typical MS (G) and myelocortical MS (H). Black lines separate spinal cord gray and white matter (C-E) and cortical and subcortical white matter (F-H). PLP = myelin proteolipid protein. Reprinted from Trapp et al.,* Lancet Neurol.[1] *Copyright 2018, with permission from Elsevier.*

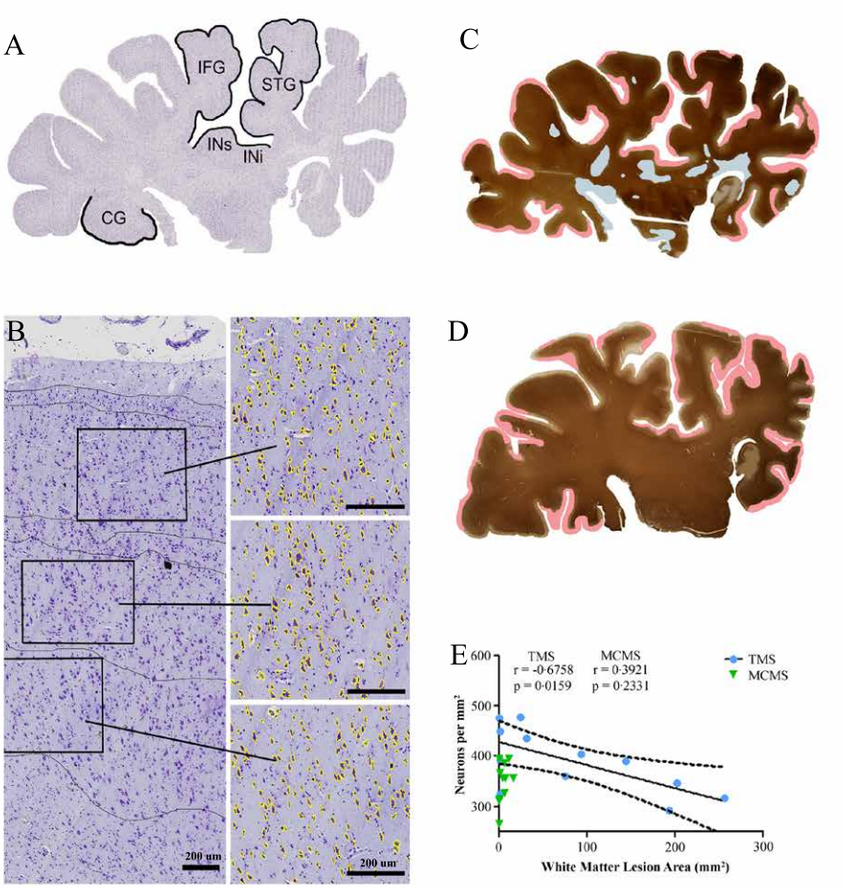


FIGURE 2. *Neuronal loss in the absence of cerebral white matter demyelination. (A) A cresyl violet-stained control hemispheric section from an individual classed as having typical MS. Neuronal densities were compared in cortical layers III, V and VI in each of the five labeled areas (IFG = inferior frontal gyrus; STG = superior temporal gyrus; INi = inferior insula; INs = superior insula; CG = cingulate gyrus). (B) Neurons with an area greater than 60 μm² (yellow) are shown in a representative image from the superior temporal cortex. (C and D) Labeling for myelin proteolipid protein and the distribution of demyelinated lesions (white matter demyelination is highlighted in blue, subpial demyelination in pink) in hemispheric sections from individuals with typical MS (C) and myelocortical MS (D). (E) A significant correlation between reduced cortical neuronal density and increased cerebral white matter lesion volume was found in typical MS but not in myelocortical MS (dashed lines indicate 95 percent confidence interval). Reprinted from Trapp et al.,* Lancet Neurol.[1] *Copyright 2018, with permission from Elsevier.*

Table 1. Neuronal Density* in Various Cortical Regions in Comparative Subject Groups

	Myelocortical MS	Typical MS	Control
Layer III	349.8 (51.9) *P* = 0.0104 vs. control *P* = 0.2040 vs. typical MS	381.5 (58.2) *P* = 0.1346 vs. control	419.0 (43.6)
Layer V	355.6 (46.5) *P* = 0.0006 vs. control *P* = 0.1533 vs. typical MS	392.5 (59.0) *P* = 0.0182 vs. control	454.2 (48.3)
Layer VI	366.6 (50.9) *P* = 0.0049 vs. control *P* = 0.2220 vs. typical MS	401.7 (74.7) *P* = 0.0589 vs. control	458.3 (48.4)

*Values are mean (SD) number of neurons per mm^2.
Adapted from Trapp et al., *Lancet Neurol*.[1]

Improving MRI specificity and identifying MCMS in live patients

Perhaps one of the most striking conclusions of our study is the relatively poor specificity of MRI for myelin content in cerebral white matter. The finding that almost 12 percent of patients with MS could have intact cerebral white matter will have important implications for the field.

A significant focus is now being placed on trials examining remyelinating agents, and many of those trials examine changes in purported myelin-sensitive imaging techniques in white matter brain lesions. MCMS patients will not be informative for such studies targeting myelin content in white matter.

The findings in MCMS patients may also be leveraged to look for MRI markers that are more specific to myelin using fixed tissue, with the aim of then translating these markers for use in live patients.

The ultimate goal of this research will be identification of MCMS patients in life, which may help discriminate differential treatment effects and perhaps better inform prognosis.

Conclusions and next steps

MCMS is a novel subtype of MS with intact brain white matter myelin and presence of cortical and spinal cord demyelination. Clinical and MRI features do not differentiate MCMS and typical MS, but these findings have significant implications for how we view the disease. We plan to leverage these results to identify better myelin markers, understand the role of the axon in MS, identify MCMS in live patients and further develop neuroprotective therapies in MS.

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DETECTING EPILEPTOGENIC SPIKES USING ULTRAFAST 7T EEG-FMRI WITH 3D PARADIGM FREE MAPPING

By Stephen E. Jones, MD, PhD

Patients suffering from intractable focal epilepsy potentially can be cured if the epileptogenic zone is identified and surgically resected. While current techniques such as scalp and intracranial EEG, structural MRI, MEG and PET are often helpful in identifying this zone, many patients remain untreated due to inadequacy of these techniques, a complicated disease presentation or both. For this reason, there is a continued need to develop new techniques to help identify the epileptogenic zone.

Promise and limits of EEG-fMRI

One promising technique is simultaneous EEG-fMRI, wherein sufficiently large epileptogenic spikes cause an associated change in local blood flow, which then can be visualized using a blood-oxygen-level-dependent (BOLD)-sensitive sequence during functional MRI (fMRI). This technique was first described nearly 20 years ago and classically requires EEG recordings to be obtained simultaneously during an MRI scan. These recordings then can be used to identify the time points of any spikes occurring during the MRI, which allows post-processing methods to visualize the three-dimensional location of the epileptogenic spike. The advantage of adding MRI to identify the location is that its spatial accuracy is far superior to that of scalp EEG recordings alone.

Nevertheless, there are several drawbacks to this promising method:

- The BOLD effect elicited by a spike can be weak and may not be reliably detectable.
- The time resolution of MRI (typically 2 seconds) is much longer than that of EEG (less than a millisecond), so MRI cannot identify the temporal evolution of a spike.
- Spikes are not necessarily frequent and may occur only a few times an hour. This means that patients must be scanned for up to an hour, which also requires an epileptologist to carefully review scans of the entire session for just a few spikes.

Taking the technique to ultrahigh field strength

At Cleveland Clinic, we have recently explored ways to address these difficulties by extending the earlier technique to ultrahigh-field MRI (7 tesla [7T], versus standard 1.5T or 3T), which first required developing a new head coil for safe operation and extensive testing (Figure 1). Using 7T MRI provides several advantages:

- The BOLD effect is inherently stronger at 7T than at 3T, by a factor of two to three.
- New multiband techniques can reduce the time resolution from 2 seconds to 0.3 seconds.

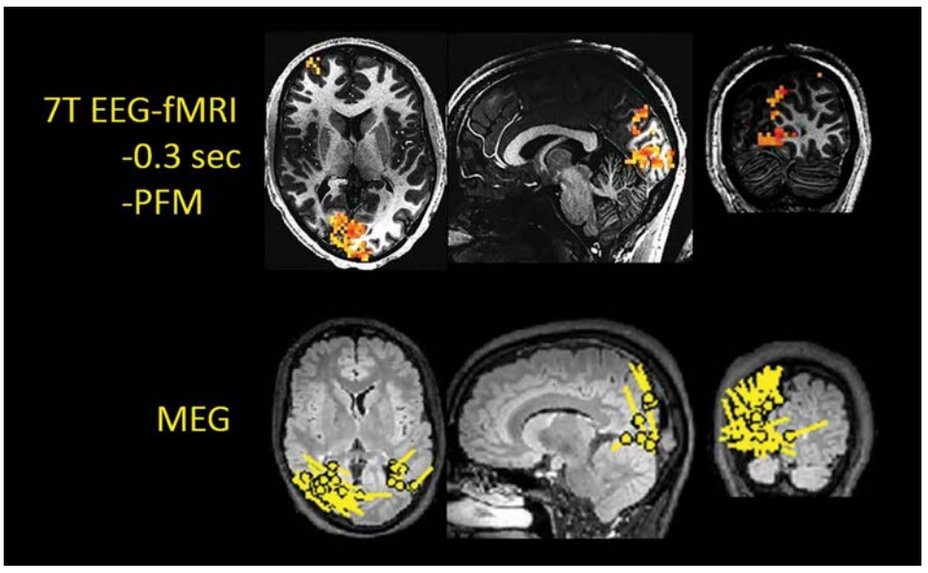

FIGURE 1. *Example of 7T EEG-fMRI applied to an epilepsy patient with a known occipital lobe focus, as displayed by the single-dipole models from a MEG study in the bottom row (performed before 7T EEG-fMRI). The top row shows three planes through the right occipital lobes, where the red overlaying the gray anatomy shows a strong focus of BOLD activation. Note the close correspondence of the BOLD location to that shown on MEG. PFM = paradigm free mapping.*

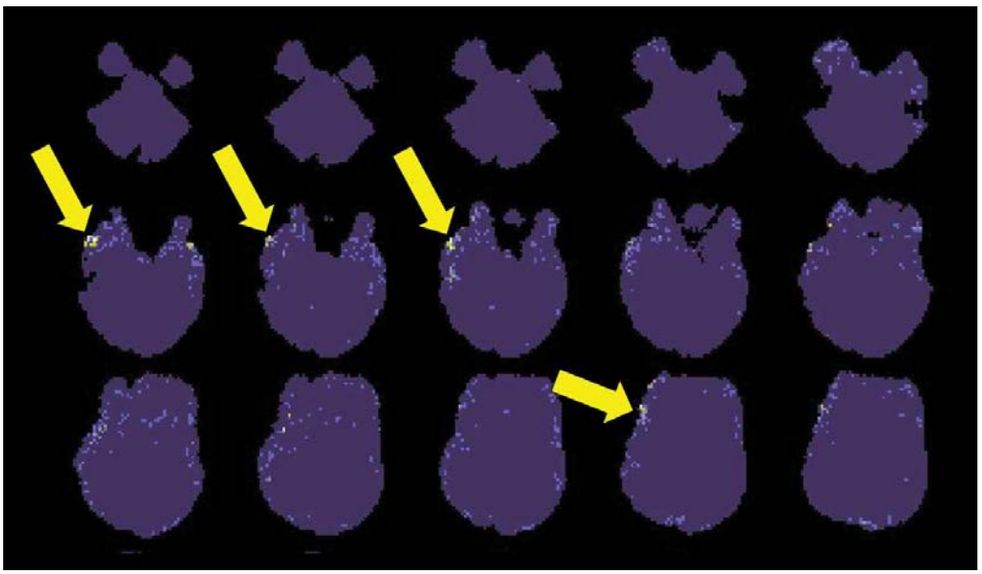

FIGURE 2. *Findings of 7T EEG-fMRI recently applied to a 24-year-old right-handed man with a three-year history of epilepsy now treated with multiple medications. While the structural MRI is negative, both PET and video-EEG indicated focal epilepsy likely arising from the right temporofrontal regions. The displayed EEG-fMRI maps were obtained without timing information from EEG, as computed from four BOLD spikes. Corresponding to the other findings, these maps indicate a small network of activation (yellow arrows) in the right frontotemporal region.*

- We incorporate a new detection algorithm called paradigm free mapping (PFM),[1] which searches for the BOLD signature of any potential spikes within the data rather than requiring simultaneous EEG. Due to the long time required to scan these patients, special motion correction algorithms also have been adopted.[2]

We have tested the method using a simple model of a spike and its associated network: Volunteers have been scanned while in the resting state except for performing a single volitional tap of the index finger in response to an auditory stimulus. This method can easily detect the known BOLD activation maps for the associated auditory and motor networks. Thus we hypothesize that the method should be able to detect any spike whose BOLD response is at the level of a single finger tap or greater.

After confirming the model with tests, we have now applied this method to eight patients with epilepsy. Example findings from two patients are presented in Figures 1 and 2, both of which show close correspondence of EEG-fMRI localization to other localization modalities, as detailed in the captions. These early data provide evidence to support future studies to thoroughly investigate this noninvasive method.

Conclusion

Any noninvasive MRI technique that can guide neurosurgeons to resect the region of brain tissue causing epilepsy holds enormous potential benefit. We are addressing the need for such a technique by extending traditional EEG-fMRI methods to 7T MRI, which markedly increases detection sensitivity and temporal resolution of epileptogenic spikes and can be performed in a data-driven manner.

Acknowledgments. *The author acknowledges contributions to this work from César Caballero-Gaudes (Basque Center of Cognition, Brain and Language, San Sabastian, Spain) and from Anna Crawford; Mark Lowe, PhD; Sehong Oh, PhD; Wanyong Shin, PhD; Balu Krishnan, PhD; and Imad Najm, MD (Cleveland Clinic).*

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DEEP BRAIN STIMULATION FOR EPILEPSY: AN IMPORTANT EXPANSION OF NEUROMODULATORY THERAPY FOR INTRACTABLE SEIZURES

By Dileep Nair, MD; William Bingaman, MD; Jorge Gonzalez-Martinez, MD, PhD; Sean Nagel, MD; and Andre Machado, MD, PhD

The past year has seen an expansion in the use of neuromodulation for epilepsy with the April FDA approval of deep brain stimulation (DBS) for adjunctive treatment of medically intractable partial-onset seizures in adults. The approved device (the Medtronic DBS System for Epilepsy) is becoming available to patients at approximately 20 level IV epilepsy centers in the U.S. starting in December 2018. Cleveland Clinic is one of those centers, and this article outlines why we are eager to offer this new therapy option to appropriate patients and how we plan to ensure its effective use.

Neuromodulation for epilepsy isn't new

Approximately 30 percent of patients with epilepsy have seizures that are deemed medically intractable, defined as failing to respond to two or more appropriately chosen and taken anti-seizure medications. Many of these patients are candidates for epilepsy surgery, yet some are not good candidates for surgical resection of their seizure focus, for various reasons. For this group, neuromodulation may be a treatment option.

The first neuromodulatory therapy for epilepsy was vagus nerve stimulation, which was approved by the FDA in 1997. This was followed by responsive neurostimulation (RNS), which was approved by the FDA in 2013.

DBS represents the third neuromodulatory approach to epilepsy treatment. It is an open-loop therapy that relies on placement of leads in the anterior nucleus of the thalamus deep within the brain for delivery of electrical stimulation on a duty cycle of one minute on and five minutes off. FDA approval is for use in conjunction with anti-epileptic medications in adults with frequent and disabling partial-onset seizures (with or without secondary generalization) that have been unresponsive to three or more antiepileptic drugs.

Although initially thought of as an approach best suited for temporal lobe epilepsy, DBS appears to have yielded benefit in patients with various forms of focal epilepsy. These include patients in whom the epilepsy is hard to localize or hard to restrict to one or two specific regions. Whereas RNS is indicated for epileptic foci within one or two regions, DBS can be considered a useful method of neuromodulation in patients whose epilepsy is more widely distributed. Similar to RNS, DBS requires placement of electrodes within the brain.

Insights from the SANTE trial: Efficacy grows over time

The pivotal study that evaluated the efficacy and safety of DBS for epilepsy was the SANTE trial conducted among 110 patients randomized to receive active stimulation or sham stimulation.[1] At the end of the study's three-month blinded phase, median seizure frequency was reduced by 30 percent in the active stimulation group (n = 53) relative to the sham stimulation group (n = 54) (adjusted difference; $P = 0.0017$). At the end of the blinded phase, all patients had their deep brain stimulator turned on for active stimulation over several more years of follow-up.

Five-year follow-up showed a median reduction in seizures of 69 percent from baseline among the 83 SANTE trial participants who continued to be followed.[2] Seven-year follow-up results from SANTE, presented in abstract form at the American Epilepsy Society annual meeting in December 2016, showed a median seizure reduction of 75 percent.[3]

The most notable finding from the SANTE trial is that efficacy of DBS for seizure reduction was shown to cumulatively grow over time with continued DBS therapy, as median seizure reductions rose from 40 percent at one year to 53 percent at three years to 69 percent at five years (with preliminary evidence of greater reductions at seven years).[1-3] Among other notable findings from SANTE:

- 8 percent of patients seemed not to respond to DBS therapy and had a greater than 50 percent increase in seizures by the seventh year of follow-up.
- 11 percent of patients were seizure-free at the time of last follow-up.
- Almost two-thirds of patients saw their seizures reduced by half.

What about safety?

The safety profile of DBS for epilepsy appears to be no different from that of DBS for other disorders, such as Parkinson disease. The serious adverse effects associated with DBS include surgical adverse effects, including an implantation site infection rate of about 10 percent. There were no symptomatic intracranial hemorrhages noted at five-year follow-up in the SANTE trial,[2] and there is no evidence of increased rates of sudden unexplained death in epilepsy using the DBS device. Other notable side effects during clinical testing

resulted from stimulation and included cognitive side effects and mood disorders. Depression was noted in 37.3 percent of patients and memory impairment in 27.3 percent.[2] In rare instances, seizures can be exacerbated by stimulation. Many of these stimulation-induced side effects can be controlled by altering stimulation parameters.

Identifying candidates for DBS

Patients interested in considering DBS or other neuromodulatory therapies need to be evaluated by a level IV epilepsy center that ideally is part of a neurology/neurosurgery program with broad DBS experience and expertise. Determining which therapy is appropriate for an individual is a highly personalized decision.

At Cleveland Clinic, this determination is based on recommendations from a multidisciplinary epilepsy management conference weighing various therapeutic options for an individual patient's case following a series of tests to analyze the patient's epilepsy type. Various surgical options are discussed in the context of expected efficacy and safety based on the patient's epilepsy type. Epilepsy surgery is usually the first and best option for those patients who are good surgical candidates. However, DBS and other modes of neuromodulation allow new treatment alternatives for some patients who previously have had no options.

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TAKING ON GLIOBLASTOMA THROUGH TRANSLATIONAL RESEARCH: THREE PROMISING BENCH-TO-BEDSIDE INITIATIVES

By Manmeet S. Ahluwalia, MD

Glioblastoma (GBM), the most common and lethal primary malignant brain tumor, still has limited effective treatment options. Current standard therapies — including surgery, radiation and conventional chemotherapies — have not been able to extend survival much beyond 15 to 18 months.

Physicians and basic scientists from Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center and Lerner Research Institute are closely collaborating on efforts across multiple fronts to find a breakthrough to combat this daunting disease. Their multidisciplinary partnership has contributed to Cleveland Clinic's status as home to one of the largest and most active brain tumor clinical trial programs in the U.S. (Figure 1).

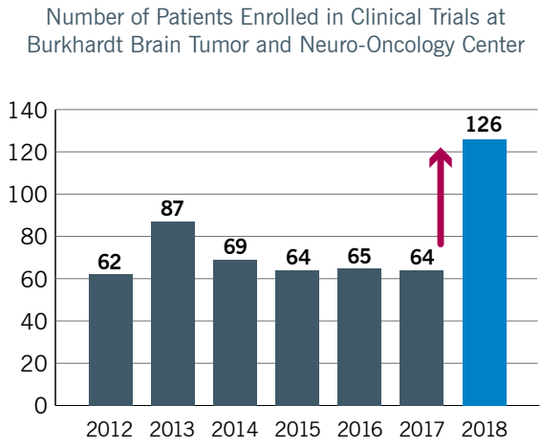

FIGURE 1. *Cleveland Clinic's brain tumor clinical trials program is one of the nation's largest, with enrollment of 126 patients in 2018.*

Our institution's large, international patient population and deep, broad scientific and clinical resources promote the rapid translation of promising basic research findings to clinical trials. This article profiles three representative examples of ongoing GBM clinical trials that stem from translational research projects and highlight the bench-to-bedside efforts of our multidisciplinary teams.

Combating tumor-mediated immunosuppression

GBM confounds conventional therapies by suppressing the host immune system and bouncing back from the guns fired at it. Medical oncologist David Peereboom, MD, and stem cell biologist Justin Lathia, PhD, both with the Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, are leading efforts to understand the mechanism of immunosuppression and develop innovative therapies to address it. Rather than targeting tumor cells — the usual focus of GBM therapeutics — their strategy is to reverse the immunosuppressed microenvironment of GBM to reduce tumor growth.

Their research is focused on human myeloid-derived suppressor cells (MDSCs), which have potent immunosuppressive qualities. The work is built on our findings that MDSCs are elevated in the blood of patients with GBM and also present close to self-renewing cancer stem cells in the tumors themselves. It is believed that the tumor secretes factors that promote migration of host MDSCs to the brain, where they are activated by cancer stem cells, resulting in blocking of beneficial host anti-tumor immune responses. The result: promotion of GBM growth and metastasis.

Enter capecitabine — an oral analogue of 5-fluorouracil (5-FU) — which is cytotoxic to MDSCs. Currently used to treat colorectal cancer, metastatic breast cancer and (off-label) several other cancers, capecitabine offers a possible novel approach to treating GBM.

In the current phase 0/1 clinical trial for which Dr. Peereboom is principal investigator, patients with recurrent GBM and planned tumor resection are treated with a seven-day cycle of capecitabine, then surgery, then capecitabine again, combined with bevacizumab. Bevacizumab is a standard therapy for GBM; although it blocks angiogenesis and slows tumor growth, it does not extend survival.

This proof-of-concept study will help determine whether MDSC suppression is feasible by evaluating the change in concentration of circulating MDSCs following treatment. The concentration of MDSCs in the resected tumor and blood will also be evaluated, as will the concentration of T-regulatory cells, using new technology such as mass cytometry time of flight, which allows simultaneous assessment of more than 30 parameters. This approach, recently reported in a large-scale analysis of brain tumor patients,[1] will allow the team to further pinpoint key changes in the immune system associated with favorable response. Progression-free survival and adverse effects will be assessed as well.

Dr. Peereboom presented preliminary results of this trial at the Society for NeuroOncology's annual meeting in November 2018. Early evidence is encouraging, and his team expects to continue advancing this strategy.

Inactivating glioma stem cells — a key to resistance

Ibrutinib, a small-molecule compound recently approved by FDA to treat various forms of lymphoma and leukemia, is being evaluated by Shideng Bao, PhD, in a phase 1 study for its application to GBM. Dr. Bao is a researcher in Cleveland Clinic's Department of Stem Cell Biology and Regenerative Medicine.

A major challenge in GBM treatment has been the inability to effectively target the glioma stem cell (GSC) population that gives rise to tumor recurrence. Earlier work by Dr. Bao's group found that GSCs have high levels of BMX (bone marrow and X-linked nonreceptor tyrosine kinase). BMX activates signal transducers and promoters of transcription 3 (STAT3), which resist radiation therapy and enable GSCs to replicate, spread and promote tumor growth. Ibrutinib specifically disrupts the BMX-mediated STAT3 activity.[2]

In a preclinical mouse model of GBM and cultured human GBM cells, Dr. Bao's team found that ibrutinib suppressed GSC-driven tumor growth and potently induced GSC death. It was significantly more effective in slowing tumor growth than temozolomide, the current standard-of-care chemotherapy for GBM. Average survival increased significantly in preclinical models. His team's work has also demonstrated that ibrutinib has excellent blood-brain barrier penetration.

The current phase 1 clinical trial is testing various ibrutinib dosages for safety and efficacy in patients with newly diagnosed methylated or unmethylated MGMT GBM. The study is combining ibrutinib with radiation in the patients with unmethylated MGMT promoter. Patients with methylated MGMT GBM will have temozolomide added to their treatment regimen.

Patient accrual is ongoing and expected to be completed in the summer of 2019.

Interfering with the JAK-STAT signaling pathway

Another investigation targeting GSCs uses ruxolitinib, a drug currently used to treat myelofibrosis and polycythemia vera. A Janus kinase (JAK) inhibitor (specifically of JAK1 and JAK2), ruxolitinib targets the JAK-STAT pathway, which has been implicated in GBM as a promoter of tumor cell survival, growth and invasion. Levels of JAK 1/2 and STAT3 are increased in GBM tissues.

Our group and others have found that inhibiting JAK2 reduces survival and proliferation of glioma cells in vitro and that JAK2/STAT3 inhibition slows disease progression in animal models of GBM. We have since initiated a phase 1 trial testing efficacy, safety and tolerability of ruxolitinib combined with radiation and temozolomide for newly diagnosed grade 3 gliomas and GBM. The study's combination of ruxolitinib and radiation is anticipated to facilitate breakdown of the blood-brain barrier and delivery of ruxolitinib to the tumor in the unmethylated MGMT promoter arm. Patients with methylated MGMT promoter will receive various doses of ruxolitinib, temozolomide and radiation.

New strategies offer new hope

These three innovative translational studies are the direct result of basic research that yielded greater understanding of cellular mechanisms of GBM. Our hope is that targeted cellular and immunotherapy approaches will soon make headway against this disease that has so far confounded conventional therapeutic approaches.

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ARTIFICIAL INTELLIGENCE IS STARTING TO REDEFINE VALUE-BASED SPINE CARE

By Thomas Mroz, MD, and Ghaith Habboub, MD

As the exponential expansion of computing capacity converges with unsustainable healthcare spending, a promising opportunity has emerged: the use of artificial intelligence (AI) to enhance healthcare value.

At Cleveland Clinic and elsewhere, clinicians and data scientists are taking steps to leverage AI to improve patient outcomes while reducing healthcare costs, particularly among candidates for surgical care. An AI-driven decision platform is under development in Cleveland Clinic's Center for Spine Health, and we recently reported an analysis indicating that use of this AI platform across a historical cohort of lumbar laminectomy patients at Cleveland Clinic would have improved the cohort's clinical success rate by 50 percent and lowered total treatment costs.

This article reviews the rationale for our embrace of AI to help guide spine care decision-making, details of our recent analysis and next steps in our use of AI.

Standardization of spine care remains elusive

Today computing capacity advances more in a single hour than it did in the first 90 years of the information age. By the year 2045, computing capacity is expected to exceed the cognitive ability of all human brains on earth combined, with parallel increases in the data generated.

Despite having so much data at our fingertips, vast discrepancies remain in how patients are treated for various medical conditions. Perhaps no therapeutic area shows more heterogeneity in the delivery of surgical and nonsurgical care than spinal disorders. For instance, recent national surveys of U.S. spine surgeons conducted by our center found high rates of disagreement on the management of two common spinal conditions: 69 percent disagreement for recurrent lumbar disk herniations and 75 percent for lower back pain.[1,2]

The reasons for variation are many — including differences in surgeons' experience and training, differences in use of pre- and postoperative resources, and a slew of patient-specific factors — but the bottom line remains that variations in care for common conditions generally undercut the quality of care while driving up its cost.[3]

While the spine care community has a wealth of knowledge in the medical literature, it is impossible for practicing physicians or surgeons to reconcile in real time all the data that will ultimately determine the most efficacious and cost-effective treatment for a particular patient.

Enter artificial intelligence

Contrast this with AI. By analyzing millions of discrete data points housed in electronic medical records and financial databases, AI can complete in milliseconds — and with greater precision — what the human mind accomplishes in hours or days.

Based on past and repeated performance, AI has the capacity to render with high probability the best decisions on surgery or nonoperative treatments for optimal patient outcomes within a given cost and reimbursement model. AI also can suggest, if necessary, an alternative provider in the same healthcare system who would likely perform better on a particular patient.

The implications for clinical practice are staggering. An AI platform would be the first legitimate clinical decision-making tool in spine medicine, delivering on the value equation while serving as a resource for improving physician performance and promoting appropriate, efficient care in this era of healthcare financial uncertainty.

An AI-driven platform of this kind, designed to seamlessly support the surgeon in patient selection and choice of treatment approach, is under development at Cleveland Clinic. By collecting extensive historical data on spine patients in a database and analyzing them, we are identifying many important and previously unrecognized variables that are collectively contributing to optimal patient outcomes. The basic architecture of the model is outlined in Figure 1.

Intriguing results from an early analysis

An early glimpse of the platform's possibilities comes from an analysis we presented at the 2018 annual meeting of the Congress of Neurological Surgeons.[4] We retrospectively reviewed the cases of all patients who underwent lumbar laminectomy at Cleveland Clinic hospitals from 2007 through 2017. Approximately 3,300 of these patients qualified for inclusion in the study because they had sufficient data for analysis of the following outcomes of interest: functional outcome as assessed by EQ-5D™, visual analog scale scores for back pain/right leg pain/left leg pain, depression as assessed by the Patient Health Questionnaire-9, the Pain Disability Questionnaire score, readmissions, venous thromboembolism incidence, treatment costs and reimbursements.

We fed data on more than 120 variables from across this 3,300-patient cohort into our AI platform. Variables included aspects of patient demographics, comorbidities, medications, laboratory test results and functional data, as well as variables related to surgeon quality. Python

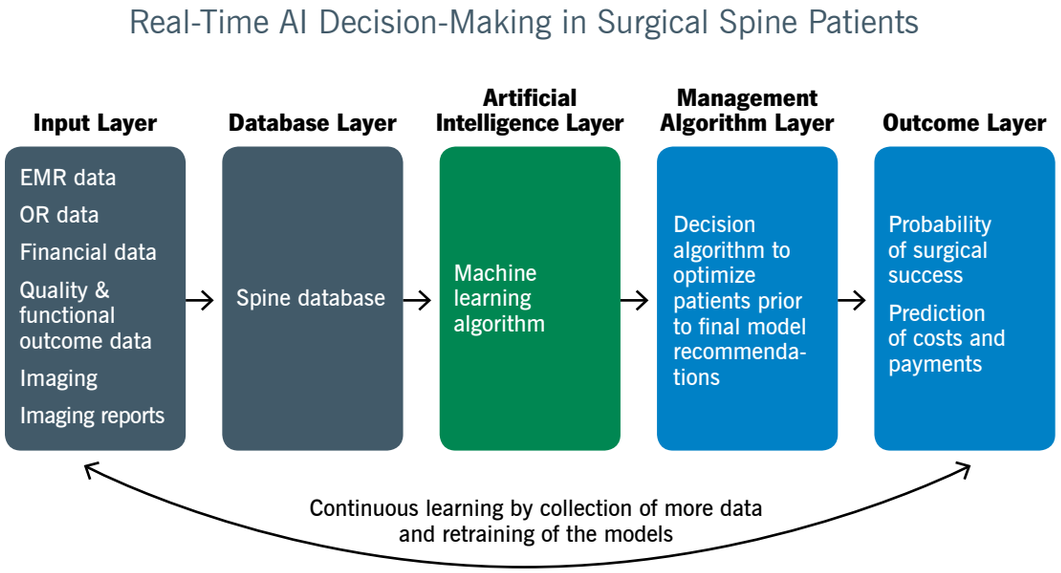

FIGURE 1. *Schematic showing the five sequential layers of the project architecture. The model eventually "feeds" itself, enabling continuous machine learning.*

software was used for data analysis, and TensorFlow™, Keras, XGBoost and scikit-learn were used for machine-learning model creation.

Of the 3,300 patients in the study, approximately 50 percent had success, defined as improvements meeting the threshold of "minimal clinically important differences" in the abovementioned healthcare metrics. The AI system predicted that the success rate would have increased to at least 75 percent — i.e., a relative improvement of 50 percent — if the actual clinical decision-making around surgical candidates, procedures and individual surgical operators had been supplemented with AI guidance. An additional simulated cost analysis demonstrated cost savings of up to $25,000 per case with AI-supplemented decision-making versus standard care without AI support.

Data from the analysis revealed some associations between variables that we would not have otherwise expected, such as between lab test values and indirect compliance measures and outcomes. This has important implications for the setting of targets for modifiable variables used to determine a patient's appropriateness for surgery.

Next steps

We have embedded elements of the AI platform into the electronic medical record and daily provider routines via predictive displays and prompts. We look forward to reporting more on our experience with implementation of the platform — in additional areas of spine care — in the months and years ahead.

This early experience with our AI platform encourages us that this system — when coupled with human expertise and personal, high-touch caregiving — can improve patient outcomes in spine care while reducing costs. AI in spine care has great potential to promote standardization of practice around high-quality care as well as more standardized resource utilization. It also promises more logical and successful strategies for managing large patient populations with more predictable outcomes and expenditures — in other words, the enhanced healthcare value that everyone is seeking.

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INDIVIDUALIZED CARE IN THE NEUROINTENSIVE CARE UNIT: THE EMERGING ROLE OF MULTIMODAL MONITORING

By Christopher R. Newey, DO; Pravin George, DO; and Joao Gomes, MD

Multimodal monitoring (MMM) in the neurointensive care unit — i.e., the continuous, simultaneous evaluation of cerebral and systemic function using different modalities in a single patient — is increasingly utilized in patients with devastating neurologic injuries. The practice is recognized as an "extension of the clinical exam and cognitive skill set of the clinician" and has been advocated as "an important feature of neurocritical care."[1]

The goal of MMM is to detect early neurological/physiological changes (i.e., secondary brain injury) before irreversible damage takes place.[1,2] This early detection may lead to improved outcomes in brain-injured patients.[1,2] The rapid growth of MMM in recent years, reflected in Figure 1, likely stems from its value in the following:[1]

- Detecting early neurological worsening before irreversible brain damage develops
- Individualizing patient care decisions
- Guiding patient management
- Monitoring physiologic response to therapy and avoiding adverse effects
- Enhancing clinicians' understanding of the pathophysiology of complex disorders
- Aiding the design and implementation of management protocols
- Improving neurological outcome and quality of life in survivors of severe brain injury
- Informing development of new, mechanistically oriented therapies where treatments are lacking or empiric in nature

The challenge of integrating multiple monitoring inputs

Secondary brain injuries are classified as cellular injury cascades and/or secondary brain insults.[2] Ischemia — causing excitotoxicity, intracellular calcium influx and free radical membrane damage — is an example of a cellular injury cascade.[2] Secondary brain insults are events not tolerated by the injured brain that lead to further injury. Examples of secondary brain insults include hypoxia, hypotension, hypoglycemia, fever, altered cell metabolism and seizures.[2]

Multiple modalities, both invasive and noninvasive, are used to monitor for secondary brain injuries, including transcranial Doppler (TCD), continuous electroencephalography, computerized quantitative and qualitative pupil assessment (pupillometry), intracranial pressure (ICP) monitoring, brain tissue oxygen tension monitoring, cerebral microdialysis (particularly lactate:pyruvate concentration ratio) and cerebral blood flow measurement. Unfortunately, each of these modalities is monitored on its own proprietary platform and requires manual documentation in the electronic medical record, making real-time assessment and interpretation of large amounts of data challenging.

The quest for relevant real-time data display

Even though high-resolution data acquisition systems have been developed, our group at Cleveland Clinic firmly believes that optimal data integration and display are lacking. To that end, we have submitted a proposal for internal institutional funding to develop an intuitive interface with bedside clinicians in mind that will display relevant pieces of data in real time with the objective of minimizing alarm and data overload.

Currently, only a small number of centers have integrated MMM into routine patient care, and high-level research on its application has been scarce. Nonetheless, an ongoing phase 3 multicenter randomized trial is evaluating the impact of monitoring both brain tissue oxygenation and ICP versus monitoring ICP alone, building on an earlier phase 2 trial.[3] Similarly, a phase 2 international feasibility study (NCT02982122) is targeting optimal cerebral perfusion pressure in patients with severe brain injuries, with safety and the significance of physiological effects being explored as secondary end points.

Current and emerging efforts at Cleveland Clinic

Cleveland Clinic is now in the process of acquiring TCD-based software (ICM+, Cambridge Enterprise Ltd., Cambridge, UK) that allows for various assessments of cerebrovascular autoregulation and noninvasive ICP monitoring. Along with this, we are developing protocols for routine monitoring of patients with advanced liver failure and encephalopathy in whom invasive probes may be prohibitive. Likewise, we will soon explore cerebral autoregulation in hypertensive patients with spontaneous intracerebral hemorrhage to help determine an individualized optimal blood pressure range, in order to minimize the risk of hematoma expansion while reducing the risk of ischemic stroke associated with a drop in blood pressure. This would represent the first individualized paradigm for management of these brain-injured patients, in contrast to reliance on a one-size-fits-all approach.

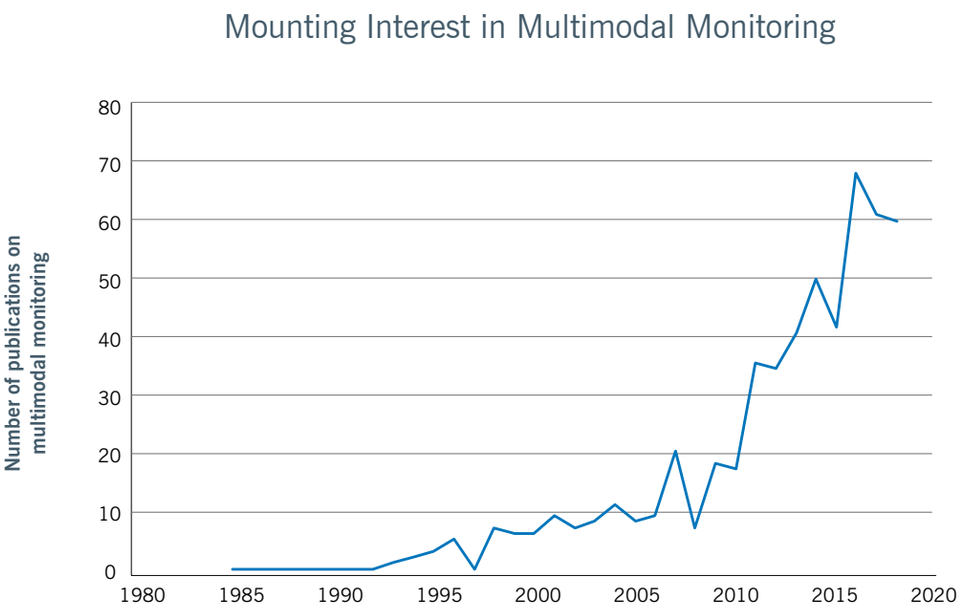

FIGURE 1. *Growth in publications on multimodal monitoring by year, based on a literature search of multimodal monitoring.*

We also recently formed a multidisciplinary MMM committee consisting of members with expertise in the various monitoring modalities used in the neurointensive care unit. This committee recently conceived an algorithm to facilitate triage of patients to various levels of MMM based on injury severity and anticipated risk of secondary injury.

Additionally, treatment algorithms for the various monitoring modalities have been created to guide patient care based on available literature. These algorithms will be continuously reviewed and adjusted as needed based on our experience and growing evidence generated by our research and that of others. Use of MMM to systematically identify and manage patients is expected to not only improve our patient care but also expand innovation and research.

A role for big data?

Finally, we are exploring a collaboration with Microsoft that would allow us to use its computing power, expertise and algorithms to help analyze our large data set and identify clinically relevant patterns and associations that may lead to improved patient outcomes and higher-quality care delivery. Such a collaboration would place Cleveland Clinic among the first centers in the world to systematically apply this technology in patient care and would provide a unique opportunity to advance much-needed research in this area. In the near future, we aim to bring together the fields of large data analysis, artificial intelligence, and individualized care and monitoring to improve the outcomes of critically ill neurology and neurosurgery patients.

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ANOTHER FIRST FROM A HISTORIC TRIAL: NOVEL PAIRING OF CEREBELLAR DBS WITH TMS

By Ela Plow, PhD, PT

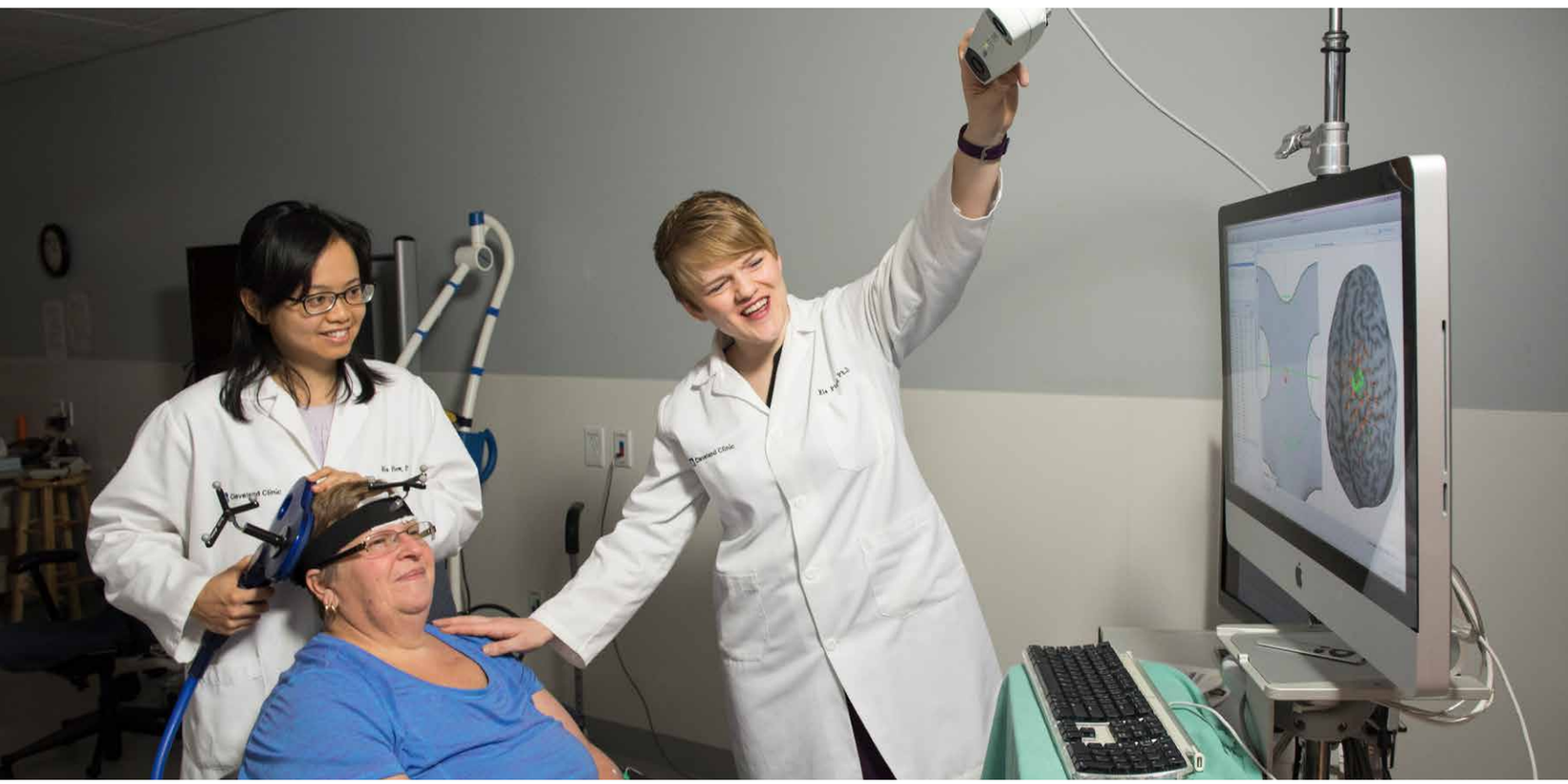
Cleveland Clinic's ongoing EDEN study — Electrical Stimulation of the Dentate Nucleus for Upper Extremity Hemiparesis Due to Ischemic Stroke (NCT02835443) — is notable for being the first-in-human clinical trial of dentate nucleus deep brain stimulation (DBS) for post-stroke rehabilitation (see sidebar). Now the investigation is charting new territory in yet another way — as the first study to combine the use of cerebellar DBS with transcranial magnetic stimulation (TMS). The goal is to study the additive effects of stimulating alternative pathways that facilitate movement in a paretic upper limb.

The combination of DBS with TMS is unique because DBS is a "pacemaking" technique involving surgical implantation of a stimulator, whereas TMS is a nonsurgical technique that modulates brain activity through delivery of a series of magnetically induced pulses of current. Although pairing these techniques is generally fraught with artifacts, noise and data corruption, our group has achieved success in applying these techniques together in real time.

As detailed at *consultqd.clevelandclinic.org/dbs4stroke*, lead investigators Andre Machado, MD, PhD, and Kenneth Baker, PhD, have designed the trial to test DBS of the dentatothalamocortical pathways originating from the cerebellum, a site remote from the target area of TMS, which is used to target the motor cortices. My lab's contribution has been to build filtering strategies to extract valid TMS data during application of DBS.

Thus, while a handful of teams around the world have successfully paired DBS with TMS, our group is the first to pair cerebellar DBS with TMS. The implications of employing this study paradigm are substantial:

- First, this study design gives us, for the first time, the ability to evaluate mechanisms tested so far only in animals. Preclinical work led by Drs. Machado and Baker has repeatedly shown that cerebellar DBS can facilitate the lesioned motor cortices in the



stroke brain. By studying the effect of cerebellar DBS on motor cortical excitability using TMS, we are creating the first opportunity to replicate in humans findings witnessed only in animal studies.

- In a broader sense, combining cerebellar DBS with TMS opens up possibilities for the field of neuroscience. One example is the prospect of new insights into the effects of TMS on cerebellar functioning. These effects have remained elusive, in part because cerebellar nuclei are deep and cannot easily be investigated using TMS and also because of technical challenges of delivering TMS during functional neuroimaging. Our paradigm, which allows application of TMS to the motor cortices with simultaneous recordings from externalized cerebellar DBS leads, offers the first opportunity to monitor real-time effects of TMS on the deep cerebellar nuclei.
- In the same vein, combining TMS and cerebellar DBS can be temporally synchronized to maximize opportunities for plasticity. One can envision that timing TMS and DBS pulses in a tight interstimulus synchrony may generate additive effects on residual pathways to the paretic upper limb — effects exceeding those generated separately with each technique.

We look forward to reporting our findings from this unprecedented pairing of TMS with cerebellar DBS in the months and years ahead.

Dr. Plow (plowe2@ccf.org) is assistant staff in Cleveland Clinic's Department of Biomedical Engineering with appointments in the Center for Neurological Restoration and the Department of Physical Medicine and Rehabilitation.

Updates on the EDEN Trial of DBS for Stroke Rehabilitation

The above work pairing cerebellar DBS with TMS for hemiparesis following stroke is just one aspect of Cleveland Clinic's broader EDEN clinical trial of dentate nucleus DBS for post-stroke rehabilitation. This first-in-human study was featured in this publication last year (see *consultqd.clevelandclinic.org/dbs4stroke*), and it continued throughout 2018, with six stroke patients having been implanted with DBS devices to date.

The aspect of the study involving TMS receives support from a $5 million UH3 grant from the National Institutes of Health's (NIH) Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative, which was announced in 2016.

This support was augmented in 2018 with an additional NIH award, a $2.5 million R01 grant, to Cleveland Clinic investigators to fund continuation of their preclinical research to better elucidate the mechanistic aspects of DBS for stroke recovery in animal models of stroke.

"The experiments funded by this new award will help support successful human translation of this promising novel treatment while also systematically examining its mechanistic underpinnings," says neurosurgeon Andre Machado, MD, PhD, Chair of Cleveland Clinic's Neurological Institute and co-primary investigator on the new grant.

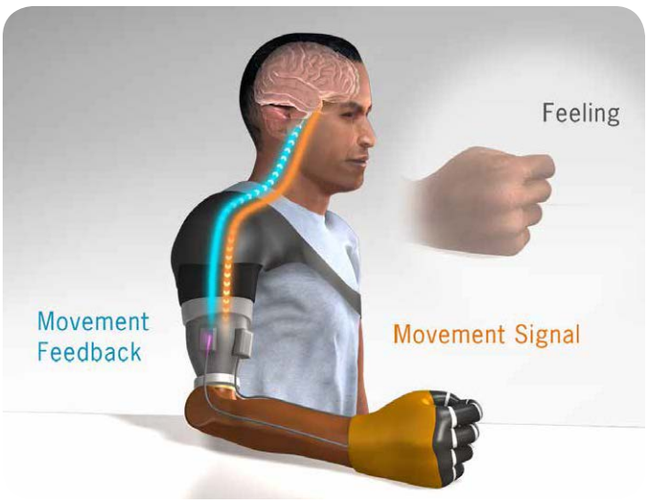
"Our working hypothesis is that low-frequency dentate nucleus DBS augments excitatory dentatothalamocortical output and, in the process, increases cerebral cortical excitability, facilitating functional reorganization in perilesional cortical areas and further supporting motor recovery," adds co-primary investigator Ken Baker, PhD, of the Department of Neurosciences.

The experiments are specifically designed to determine the following:

- How the anatomical extent and distribution of the ischemic core influences DBS treatment efficacy and carryover of benefits
- How movement-related, synchronized oscillatory activity across deep cerebellar nuclei and neocortex may change following a stroke and as a result of DBS — and whether such activity could function as a control signal in a paired-associative treatment paradigm
- Whether age at the time of stroke affects the efficacy of DBS
- Anatomical and functional mechanisms underlying any enhancement of motor recovery by DBS

MORE 2018 RESEARCH AND CLINICAL ACTIVITIES

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

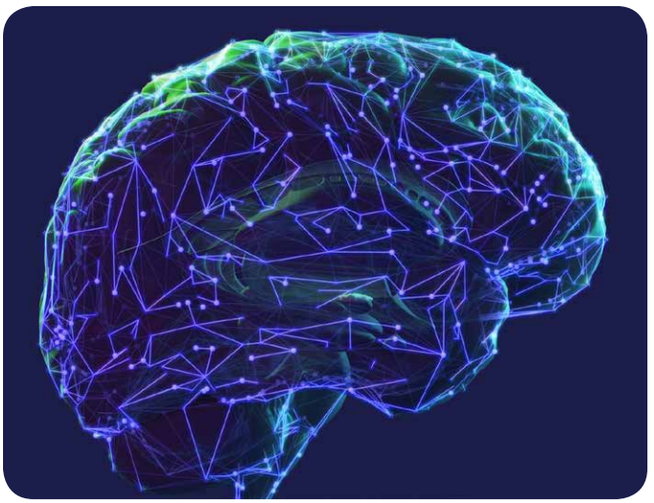


First Demonstration of Illusory Movement Perception with Prostheses in Amputees

A newly developed computerized system has for the first time allowed amputees to effortlessly conduct complex motor tasks in real time using a prosthetic hand while perceiving that their missing hand is carrying out the action. The approach and results of experiments on six above-the-elbow amputees were described by a Cleveland Clinic-led research team in *Science Translational Medicine* in March.

The work provides a critical new element that could lead to fully integrated and efficient prosthesis control, says lead investigator Paul Marasco, PhD, of Cleveland Clinic's Department of Biomedical Engineering. "Combining kinesthetic, cutaneous and motor systems could result in an integrated prosthetic limb that's intuitively controlled and provides a natural perception of complex movement," he notes.

The system developed by Dr. Marasco's team creates an illusory perception that the amputee's missing hand is acting by vibrating a muscle containing the nerves that would be used for natural control. Motor and sensory nerves no longer used due to the amputation are surgically redirected to muscles higher in the arm or chest, where they reinnervate the host muscle. Using a wearable vibration unit and a 22-sensor data glove on the remaining hand, the subject simulates what's perceived to be occurring in the missing hand. A virtual reality prosthetic system is created from the data to integrate movement sensations into control of the hand. "Our experiments show that the brain interprets the signals from the system very effectively," says Dr. Marasco. More at **consultqd.clevelandclinic.org/marasco**.



First Multisite Parkinson's Disease Center of Excellence Designation

In July, the Parkinson's Foundation named Cleveland Clinic a Parkinson's Disease Center of Excellence, a designation given to leading Parkinson's disease (PD) treatment and research institutions. The recognition makes the health system the first Center of Excellence to receive a multisite designation, covering four Cleveland Clinic locations — the main campus in Cleveland plus satellite clinics in Las Vegas, Nevada; Weston, Florida; and Abu Dhabi in the United Arab Emirates.

"The evaluating team from the Parkinson's Foundation noted that they were impressed by how well the care at our main center in Cleveland is integrated with care at our other facilities," says Hubert Fernandez, MD, Director of the Center for Neurological Restoration. Other points of distinction cited by the evaluators were the volume and depth of deep brain stimulation offerings, innovative clinical approaches such as telemedicine-enabled "virtual visits," and the program's comprehensive integration of patient-reported outcomes into the electronic medical record. The Center of Excellence designation enables Cleveland Clinic to contribute to the Parkinson's Outcomes Project, the largest international clinical study of PD. More at **consultqd.clevelandclinic.org/pdcoe**.

4 Number of sites recognized in Cleveland Clinic's PD Center of Excellence designation:

Cleveland | Las Vegas, Nevada
Weston, Florida | Abu Dhabi

Amyloid Reversal in Mouse Model Boosts BACE1 Inhibitors' Prospects in Humans

Depleting the BACE1 enzyme in middle-aged mice with a murine form of Alzheimer's disease (AD) fully reverses formation of brain amyloid plaques and improves the animals' cognitive function, reported researchers from Cleveland Clinic's Department of Neurosciences in the *Journal of Experimental Medicine* in February. Their study found that genetic engineering to reduce BACE1 levels not only halted formation of amyloid plaques but actually reversed existing plaques. Additional AD hallmarks, such as microglial cell activation and formation of abnormal neuronal processes, also were reversed, and BACE1 reductions were associated with improved learning and memory in the mice.

The findings, which represent the first observation of a marked reversal of amyloid depletion in an AD mouse model, suggest the potential to treat AD in humans without unwanted toxicity. They give renewed support to the prospects of the BACE1 inhibitor class of experimental drugs for AD in humans, several of which have failed in clinical trials, perhaps because of use too late in the course of AD. "Ongoing human trials of BACE1 inhibitors address various stages of AD, including presymptomatic stages," notes James Leverenz, MD, Director of Cleveland Clinic Lou Ruvo Center for Brain Health in Cleveland. "We're hopeful these results in mice may translate to the human disease." More at **consultqd.clevelandclinic.org/bace1**.

22% Growth in Neurological Institute research program funding over the past 5 years

Achieving Zero RFIs in Comprehensive Stroke Center Survey

Certification as a Comprehensive Stroke Center (CSC) is the highest accreditation offered by The Joint Commission. Recertification is granted if an institution receives a positive evaluation following a biennial two-day site survey in which evaluators typically identify several "Requirements for Improvement" (RFIs), or deficiencies to be addressed to maintain CSC status. Achieving zero RFIs during a CSC recertification survey is highly unusual, but that's what Cleveland Clinic's Cerebrovascular Center did in its recertification survey in April. Cleveland Clinic Stroke Program Director Andrew Russman, DO, attributes the zero RFI achievement to several factors:

- Buy-in from all stakeholders regarding the importance of CSC recertification, expressed via a detailed charter that key stakeholders signed
- Devotion of adequate resources, including hiring and supporting a program manager dedicated to meeting recertification requirements
- Continuous performance monitoring and open sharing of performance data with all stakeholders
- Gap analyses conducted by multiple teams that scrutinize performance data, find gaps to be closed, and develop and execute new protocols to address them
- Periodic outside consultation to augment internal performance reviews

"One Joint Commission evaluator said we seemed to have our system hardwired to ensure meeting CSC expectations for all standards of care," Dr. Russman says. "I think that notion of hardwiring a culture of improvement represents the key to success." More at **consultqd.clevelandclinic.org/zerorfi**.

Teasing Out Sleep Disorders' Role in Neurological Diseases

One-third of neurological outpatients are at high risk for obstructive sleep apnea (OSA), and one-quarter have significant insomnia symptoms. So finds a retrospective analysis of 19,052 adults seen for initial outpatient visits at Cleveland Clinic centers for psychiatry, brain tumor, movement disorders, cerebrovascular disease and epilepsy over an 18-month period. "These associations are of interest because there's a vast body of literature showing that untreated sleep disorders are associated with worse disease-specific outcomes," says Nancy Foldvary, DO, MS, Director of Cleveland Clinic's Sleep Disorders Center. She served as senior investigator for the analysis, which was presented in April at the American Academy of Neurology's annual meeting. The study was conducted with Cleveland Clinic's Knowledge Program platform, which collects patient-reported health status measures at every visit for seamless integration into the electronic medical record.

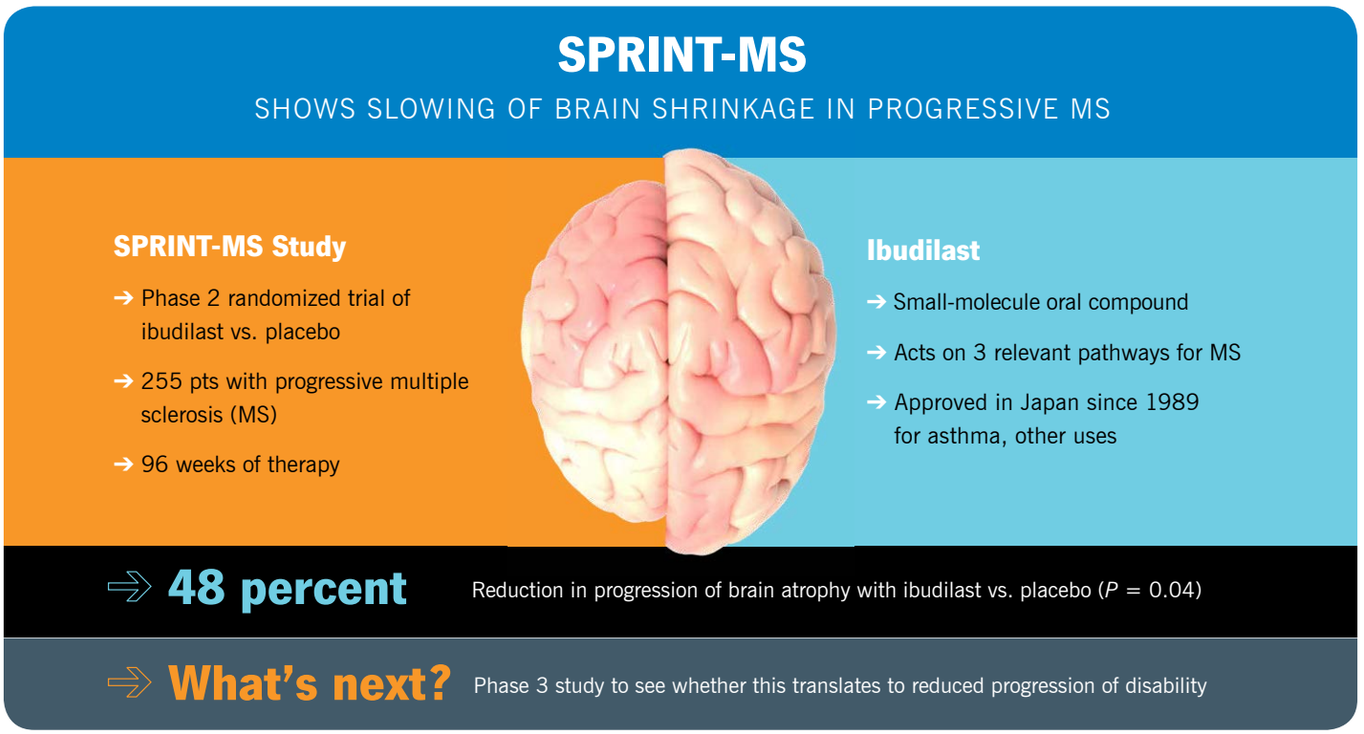
Dr. Foldvary's team is now analyzing similar outpatient data from other centers in Cleveland Clinic's Neurological Institute. After publishing earlier findings that treating OSA with continuous positive

airway pressure led to better seizure control in patients with epilepsy, Dr. Foldvary hopes to launch a study to see if similar benefits can be achieved in additional neurological populations. "Sleep impacts numerous neurological conditions, and treating sleep disorders may have trickle-down effects on the management of many of them," she says. More at **consultqd.clevelandclinic.org/sleepdisorders**.

Marked Slowing of Brain Atrophy Demonstrated in Progressive MS

The investigational drug ibudilast slowed progression of brain atrophy in patients with progressive multiple sclerosis (MS) by nearly half relative to placebo, according to results of the phase 2 SPRINT-MS study published in the *New England Journal of Medicine* in August. 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 in 2017 became the first FDA-approved therapy for progressive MS. "The SPRINT-MS results are very encouraging," says Cleveland Clinic neurologist Robert Fox, MD, lead author and principal investigator of the 28-center trial.

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. "Our hope is that ibudilast's benefit in slowing brain volume loss will translate to slowed progression of physical disabilities in patients with progressive MS," notes Dr. Fox. More at **consultqd.clevelandclinic.org/sprintms**.



Source: Fox et al., *N Engl J Med*. 2018;379:846-855.

Helping Lead the Charge in Lewy Body Dementia Trials

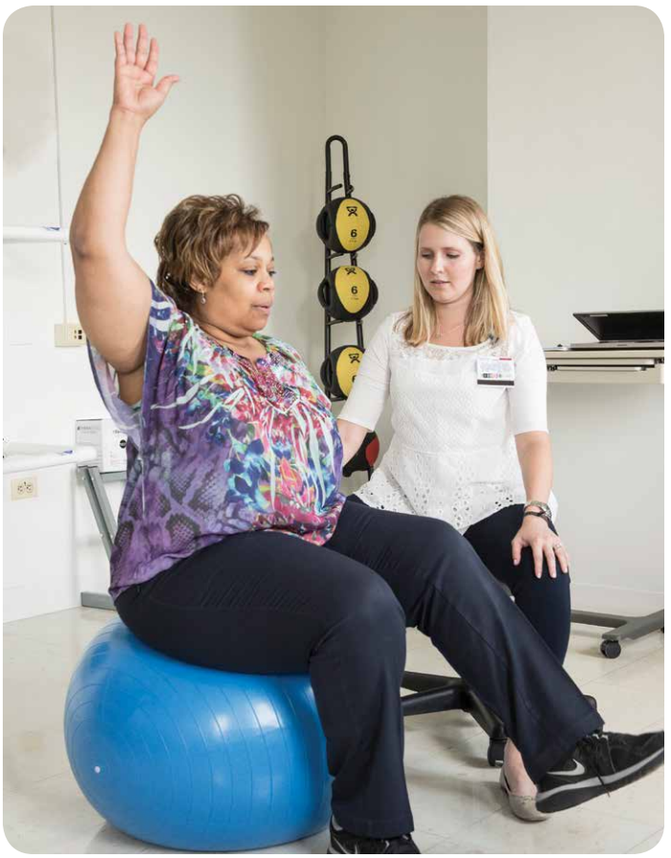
Cleveland Clinic is among 24 U.S. academic medical centers participating in the new Research Centers of Excellence (RCOE) partnership launched in April by the Lewy Body Dementia Association. The RCOE program provides a coordinated research resource to support expanded efforts to conduct clinical trials related to Lewy body dementia (LBD) and offer expert clinical care. Creation of the program was prompted by a desire to coordinate the study of sufficient numbers of correctly diagnosed patients with LBD to shed more light on the condition, which is notoriously difficult to diagnose.

"The RCOE program creates a network of sites ready for rapid implementation of new treatment trials, thus accelerating development of treatments for this devastating disease," says neurologist James Leverenz, MD, who serves as principal investigator for the Cleveland Clinic RCOE site and directs the NIH-funded multicenter Dementia with Lewy Bodies Consortium. Cleveland Clinic will build on its leadership in this realm by hosting the International Lewy Body Dementia Conference in 2019 (see back cover for details). More at **consultqd.clevelandclinic.org/lewyrcoe**.

Finding Success with Biopsychosocial Strategies for Chronic Back Pain

A novel rehabilitation program for chronic low back pain combining physical therapy (PT) with cognitive behavioral therapy (CBT) and pain neuroscience education significantly improves participants' quality of life across multiple metrics. So reported Cleveland Clinic psychologist Sarah Rispinto, PhD, in a study presentation at the annual meeting of the American Academy of Pain Medicine in May. The program, known as Back on TREK, yielded clinically significant changes in validated measures of social role satisfaction, pain interference in daily life, perceived disability, fatigue and overall physical health. It also improved depression and anxiety in nearly half of the retrospective study's 116 participants, all of whom had chronic low back pain for at least three months.

Patients attend the 12-week program for at least three hours a week for a mix of individual and group PT sessions plus behavioral medicine group sessions involving instruction on pain neuroscience and CBT techniques. "Participants generally come to understand that pain is a biopsychosocial phenomenon and they can learn ways to self-manage it," says Dr. Rispinto. "We hope to raise the profile of biopsychosocial approaches like this as first-line interventions for chronic back pain." Ongoing research is comparing the program's effectiveness to that of standard PT care and gauging its effect on opioid use and healthcare utilization over the long term. More at **consultqd.clevelandclinic.org/backstudy**.



Directing Large Trial of New Disease-Modifying Therapy for Parkinson Disease

The pharmacologic armamentarium for Parkinson disease (PD) currently contains no disease-modifying therapies, but the international SPARK trial aims to ultimately change that. The phase 2 trial — which launched in January with Cleveland Clinic neurologist Hubert Fernandez, MD, as co-principal investigator for North America — is testing a recombinant human monoclonal antibody, BIIB054, that binds to aggregated alpha-synuclein and prevents it from spreading in the brain, where it contributes to PD progression. "SPARK is evaluating the most promising compound yet developed to fight early-stage PD," says Dr. Fernandez. "Unlike existing therapies, BIIB054 has been shown to target the underlying cause and may slow disease progression."

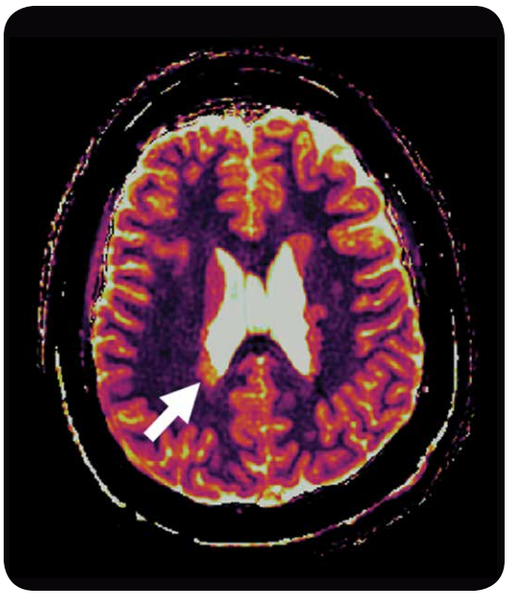
The trial will recruit more than 300 patients with early PD for randomization to monthly intravenous infusions of one of three doses of BIIB054 or placebo for 18 months. Safety, pharmacokinetics and pharmacodynamics will be evaluated, with study completion expected by June 2022. "If findings are favorable, we will be promptly planning for a large phase 3 study," notes Dr. Fernandez. More at **consultqd.clevelandclinic.org/spark**.

Finding a Role for Ultra-Early Thrombolysis in Emergent Large Vessel Occlusion

For patients with emergent large vessel occlusion (ELVO), ultra-early treatment with intravenous tissue plasminogen activator (IV tPA) increases rates of recanalization and improves clinical outcomes, according to a retrospective Cleveland Clinic study presented in January at the International Stroke Conference. The study is the first to look at ultra-early thrombolysis — within 60 minutes of symptom onset, the "golden hour" — specifically in the setting of ELVO. Among 158 patients who received IV tPA for ELVO strokes at Cleveland Clinic, several key outcomes were significantly improved in those who received IV thrombolysis within 60 minutes versus those who received it later: rates of recanalization (28 percent vs. 7 percent), early neurological improvement (seen in 72 percent vs. 41 percent) and good neurological outcomes at 90 days (achieved by 52 percent vs. 26 percent).

"Our data suggest that if we're really quick in getting these patients to medical attention and administering tPA, treatment can be highly effective," says senior investigator M. Shazam Hussain, MD, Director of Cleveland Clinic's Cerebrovascular Center. "Initiating treatment within the first hour is very difficult, but we've seen that new approaches, like the use of our mobile stroke treatment unit, can enable treatment of a much larger number of patients during that golden hour." More at **consultqd.clevelandclinic.org/elvo**.

Novel Brain MRI Techniques Improve Epilepsy Surgery Evaluation



About 30 percent of patients with medically intractable seizures who undergo evaluation for epilepsy surgery have a conventional MRI showing no abnormality. Researchers with Cleveland Clinic's Epilepsy Center are working to improve MRI's sensitivity to subtle epileptic pathologies, and they reported progress on two fronts at the American Epilepsy Society's annual meeting in December.

Intriguing pilot data on the use of magnetic resonance fingerprinting (MRF) in 15 patients undergoing presurgical evaluation showed that MRF revealed clinically relevant information on epileptic lesions not appreciable on conventional MRI in four patients, enabling successful surgical resection.

Two additional studies focused on the incremental utility of computer-assisted post-processing of clinical MRIs. One analysis focused on nine patients with epilepsy from the cingulate cortex. In six of these nine patients, MRI post-processing detected abnormalities that were not adequately localized by noninvasive testing (EEG, PET, ictal SPECT and MEG) but were confirmed on intracranial EEG. The other analysis involved eight patients with epilepsy from the orbitofrontal cortex. In seven of the eight patients, MRI post-processing showed a subtle abnormality in the orbitofrontal region. "These data suggest that MRI post-processing should be incorporated into the surgical evaluation for challenging patient populations, to better guide intracranial EEG implantation and/or resection," says staff scientist Irene Wang, PhD, who presented all three studies. More at **consultqd.clevelandclinic.org/aes2018**.

Exploring the Promise of an Immunotherapy Vaccine for Glioblastoma

The immunotherapy vaccine SurVaxM is safe and appears to improve survival in patients with newly diagnosed glioblastoma compared with matched historical controls receiving standard therapy. So concludes a multicenter phase 2 trial of the vaccine led by Cleveland Clinic. SurVaxM stimulates the immune system to kill tumor cells that contain survivin, a protein that helps cancer cells resist conventional treatments.

The single-arm trial included 63 patients with newly diagnosed glioblastoma who had undergone surgical resection, chemotherapy and radiation. Patients received four priming doses of SurVaxM with montanide and sargramostim every two weeks, after which they received adjuvant temozolomide therapy and maintenance SurVaxM every 12 weeks until progression. Progression-free survival at six months was 96.7 percent, and overall survival at 12 months was 94.2 percent. "These results are encouraging," says Cleveland Clinic neuro-oncologist Manmeet Ahluwalia, MD, who served as lead investigator and presented the results at the Society for NeuroOncology meeting in November. "Overall survival at 12 months with traditional treatment is about 60 to 65 percent." Particularly notable, he adds, is that patients with poor prognostic factors — unmethylated MGMT and higher survivin levels — appeared to have better survival than would be expected. The next step is a randomized phase 2 trial of SurVaxM. More at **consultqd.clevelandclinic.org/survaxm**.

6 Clicks Functional Measurement Tool Keeps Gaining Ground

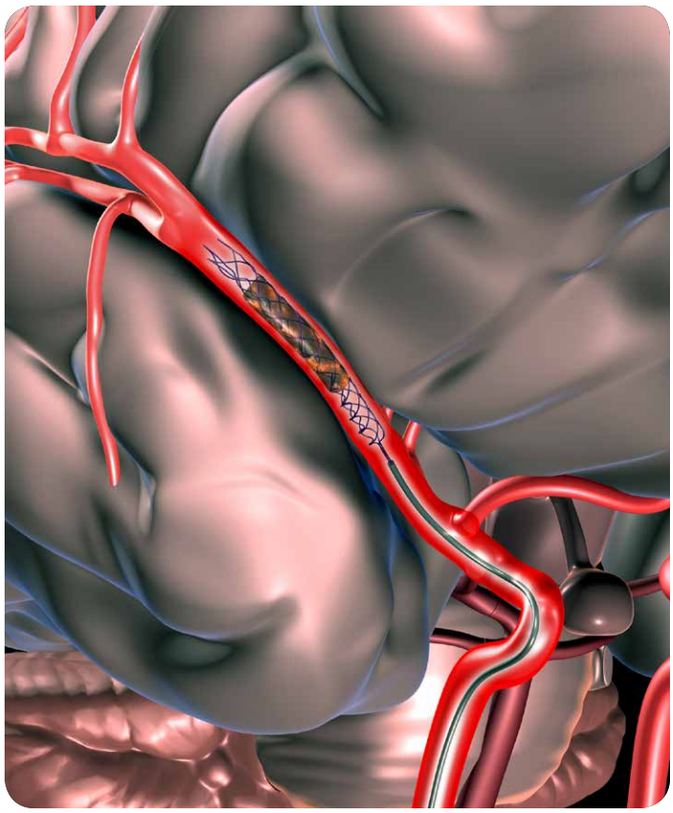
Cleveland Clinic's 6 Clicks functional measurement tool continued to expand in nationwide use and clinical impact in 2018, as detailed in the callout statistics on the right. The validated tool, designed as a short form of the AM-PAC™ instrument developed by Boston University, was created by Cleveland Clinic's Department of Physical Medicine and Rehabilitation several years ago to provide a reliable but minimally burdensome method of quickly assessing patients' mobility and self-care abilities in the acute care hospital. Its utility for determining appropriate referrals for physical and occupational therapy, guiding discharge recommendations and optimizing allocation of therapy resources has made it a hit among acute care hospitals across the U.S. More at **consultqd.clevelandclinic.org/6clicks**.

>1,000

Number of hospitals/health systems that have licensed 6 Clicks to date

~75%

Reduction in precertification therapy visits over a 12-month pilot study of Cleveland Clinic's "Floor to SNF" initiative allowing prompt discharge from hospital to skilled nursing facility without a precertification visit if the patient meets a 6 Clicks score threshold



Assessing Mechanical Thrombectomy in Mild Stroke

Are patients with minor stroke symptoms and intracranial large vessel occlusions appropriate candidates for mechanical thrombectomy? This largely neglected question is now getting attention from a pilot study at Cleveland Clinic. Guidelines now recommend mechanical thrombectomy and/or tissue plasminogen activator to remove vessel occlusions, but they don't address patients with mild stroke symptoms, who generally have not been represented in studies of stroke therapies.

That's the backdrop for the recently launched prospective MISTWAVE registry, whose main goal is to assess the safety of mechanical thrombectomy for removal of large vessel occlusions in patients with mild stroke symptoms. Cleveland Clinic is now enrolling patients in this single-arm pilot study in which up to 20 enrollees will receive best medical therapy plus endovascular mechanical thrombectomy. Lead investigator Gabor Toth, MD, presented findings from the first three enrollees at the annual meeting of the Society of NeuroInterventional Surgery in July. "We've been able to open vessels and restore blood flow in all three patients, who have had no complications and largely returned to neurological baseline by follow-up a few weeks after their event," he says. The pilot study may soon expand to additional centers. More at **consultqd.clevelandclinic.org/mistwave**.

Leading Efforts to Give Mitochondrial Disease Its Due

2018 witnessed the latest of mounting efforts to standardize care for mitochondrial disease with the formation of the Mitochondrial Care Network. The network, the first of its kind, formally aligns U.S. clinicians who care for individuals with mitochondrial disease in order to define and implement best practices and optimize care. As one of 19 initial mitochondrial medicine centers in the network, Cleveland Clinic is taking part in the effort's pilot phase to define the network's scope and priorities in advance of eventual expansion. Designation as a mitochondrial medicine center indicates that a program is capable of providing comprehensive and multidisciplinary care for individuals with mitochondrial disease.

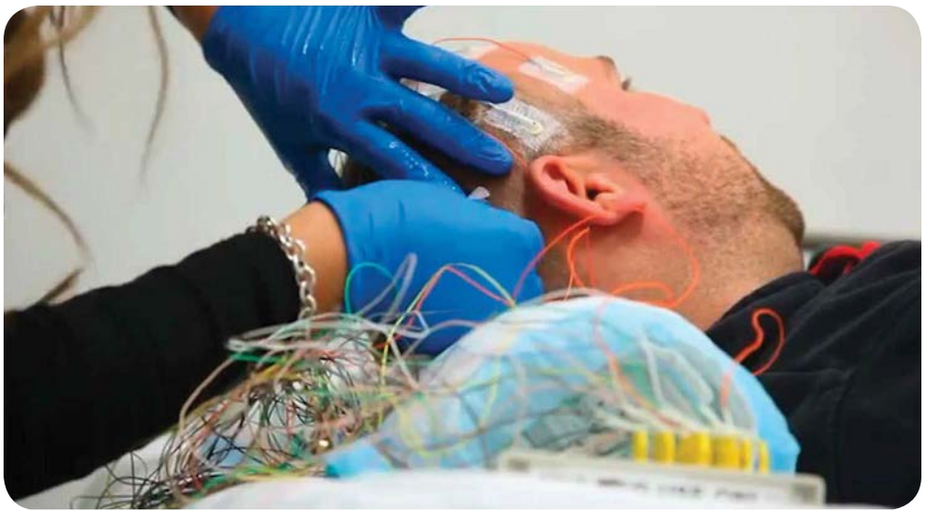
"Mitochondrial medicine has evolved significantly in the past decade," says pediatric neurologist Sumit Parikh, MD, Director of Cleveland Clinic's Mitochondrial Medicine Center and medical co-chair of the Mitochondrial Care Network. "Over 1,500 genes have been identified as being involved in mitochondrial function, with at least 290 linked to human disease. Related advances in genome sequencing have enabled development of updated diagnostic criteria in recent years — an effort led by Cleveland Clinic. Formation of the Mitochondrial Care Network should build on efforts to standardize care that began with development of clinical guidelines for mitochondrial medicine a few years ago — another effort led by Cleveland Clinic." More at **consultqd.clevelandclinic.org/mitonetwork**.

Serendipitous Discovery Leads to First Study of an Alpha-1 Agonist's Cognitive Effects

A team in Cleveland Clinic's Lerner Research Institute was studying a novel alpha-1 agonist they had synthesized to protect against cardiac ischemia when serendipity struck: They discovered that it had significant benefits on cognition, learning and memory in mice. That finding resulted in the lead investigator, molecular cardiology researcher Dianne Perez, PhD, being named the 2018 Alzheimer's Drug Discovery Foundation-Harrington Discovery Institute Scholar. The honor comes with up to $600,000 in project funding, which Dr. Perez is using to further evaluate the cognitive effects of the alpha-1 agonist, which her team has dubbed "compound 3."

Development of compound 3 is the result of nearly three decades of work by Dr. Perez, who designed the agent to exhibit effects of other alpha-1 agonists without those agents' traditional harmful elevations in blood pressure. As an agonist-like compound and allosteric modulator, it favors norepinephrine binding in the brain and amplifies cAMP signaling rather than epinephrine binding and calcium signaling throughout the peripheral nervous system. Initial mouse studies found that animals treated with compound 3 showed enhanced learning and memory as well as increased neurogenesis and synaptic plasticity, leading to the hypothesis that it could be used to treat Alzheimer's disease (AD). After ongoing testing in a preclinical model of AD, Dr. Perez plans to optimize compound 3 before pursuing clinical trials in people with or at risk for AD. More at **consultqd.clevelandclinic.org/compound3**.

Pinpointing Optimal cEEG Monitoring in the Critically Ill



Among critically ill patients undergoing continuous EEG (cEEG) monitoring, the factors most predictive of seizure risk are mental status, the primary etiology for cEEG monitoring and epileptiform patterns. So finds the largest study to date of consecutive critically ill patients monitored with cEEG. The study, reported by Cleveland Clinic researchers in the *Journal of Clinical Neurophysiology* in April, concludes that these factors may help guide targeting of cEEG monitoring in the face of resource limitations. "Acute seizures in critically ill patients have been associated with worse clinical outcomes, but because clinical suspicion isn't always correct, well-targeted cEEG monitoring is increasingly important," says lead author Christopher Newey, DO, MS, of Cleveland Clinic's Cerebrovascular Center and Epilepsy Center.

His team's study of 1,123 patients over a 24-month period showed that, when present, seizures were detected within 24 hours of the start of cEEG monitoring in 92 percent of cases. The question of optimal duration of cEEG monitoring was the focus of a separate study presented by Dr. Newey's colleague, Stephen Hantus, MD, at the 2018 annual meeting of the American Academy of Neurology. "Our next step is to determine whether patient acuity predisposes to seizure risk among the critically ill," says Dr. Hantus. "The ultimate goal is to create an algorithm to identify patients at higher seizure risk prior to cEEG and a separate algorithm to determine patients' daily seizure risk based on EEG data." More at **consultqd.clevelandclinic.org/ceeg**.

New-Onset Seizures During Hospitalization: Making the Case for Follow-Up Clinics

A clinic dedicated to systematic follow-up of patients with new-onset seizures during hospitalization enables critical monitoring of epilepsy development and assessment of medication needs. So concluded epileptologist Vineet Punia, MD, in two presentations at the American Epilepsy Society's 2018 annual meeting in December. He detailed Cleveland Clinic's first year of experience with the Post-Acute Symptomatic Seizure (PASS) clinic, a novel outpatient care model for patients newly identified with seizures during hospitalization. Half of the patients seen at the epileptologist-staffed clinic needed their antiepileptic drugs (AEDs) either reduced, increased or switched.

Candidates for a post-discharge PASS clinic appointment are inpatients with no history of epilepsy who undergo continuous EEG monitoring and are discharged on an AED. "With increasing use of continuous EEG during hospitalization, more patients with no previous diagnosis of epilepsy are being discharged on AEDs," explains Dr. Punia. "They need monitoring by an epileptologist to check if their medications are appropriate over the longer term, but they're often lost to follow-up. More clinics like this will improve care and enhance collaborative research." More at **consultqd.clevelandclinic.org/passclinic**.

Setting the Stage for Sleep Science Innovations

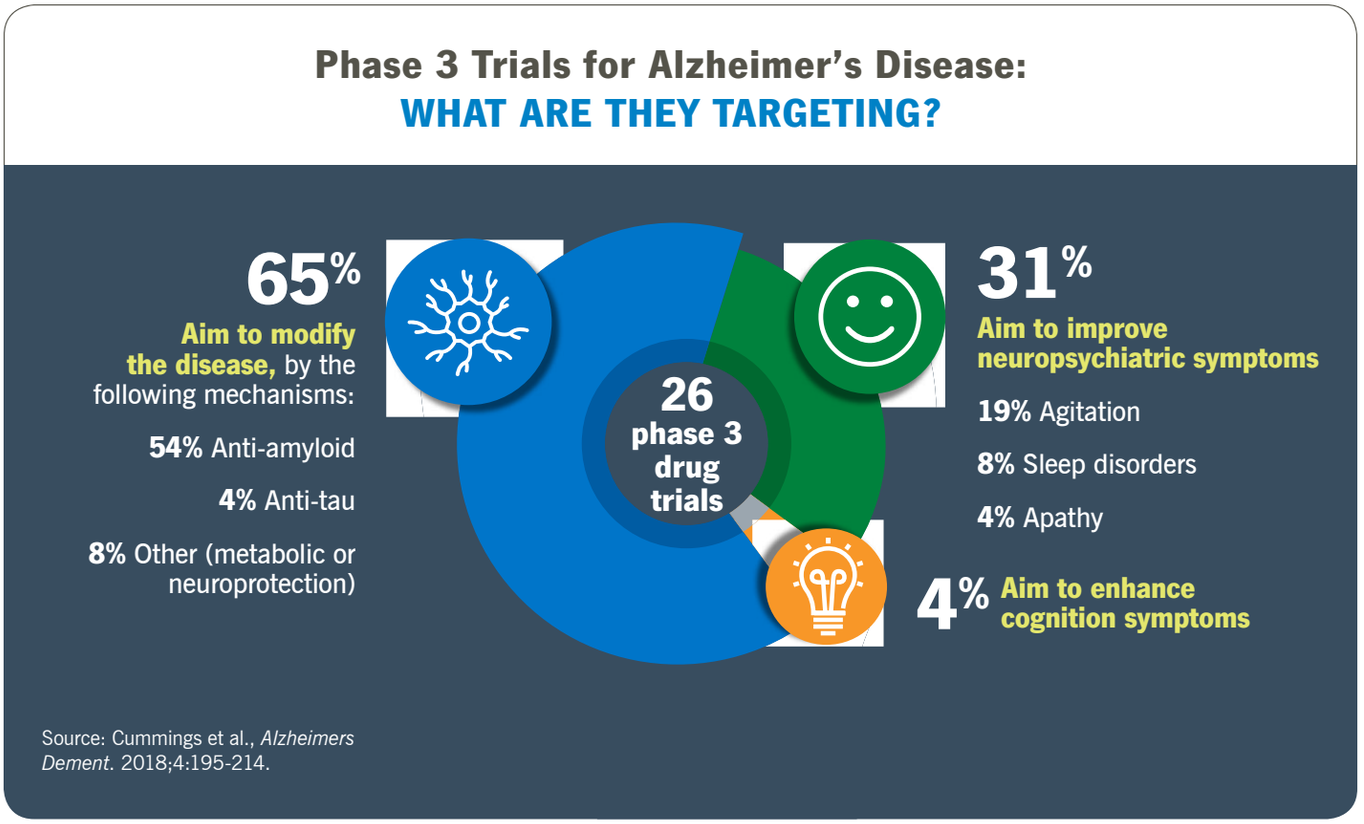
Cleveland Clinic sleep research teams led by Reena Mehra, MD, MS, received two funding awards in 2018 that promise to advance sleep science. The Clinical Translational Science Collaborative/National Center for Advancing Translational Sciences announced it will fund a Cleveland Clinic pilot study that aims to characterize the influence of obstructive sleep apnea on QT prolongation in long QT syndrome and other cardiac electrophysiologic biomarkers of sudden cardiac death.

Separately, a philanthropy-enabled Cleveland Clinic seed funding award will help establish a multimodal neurocardiorespiratory sleep biophysiologic repository to leverage more than 100,000 sleep studies performed by Cleveland Clinic's Sleep Disorders Center over approximately the past 10 years. "The result will be a first-of-kind multimodal sleep physiologic signal registry of clinic-based sleep and cardiorespiratory data," says Dr. Mehra, Research Director in the Sleep Disorders Center. "Data generated will set the stage for identifying sleep physiologic signal forecasters of negative health consequences over time, provide a platform to develop and apply novel advanced and innovative signal processing analyses and inform priority outcomes in clinical trials." More at **consultqd.clevelandclinic.org/sleepscience**.

Gauging the State of Alzheimer's Drug Development

Cleveland Clinic's third annual analysis of Alzheimer's disease (AD) drug development — published by *Alzheimer's & Dementia: Translational Research & Clinical Interventions* in May — shows that progress continues to be disappointingly slow. But the report also finds that researchers are studying a variety of new drug targets and testing agents earlier in the disease course. Moreover, 63 percent of the 112 investigational agents in the AD drug pipeline are aimed at disease modification rather than symptomatic improvement. The graphic below breaks down the pipeline's 26 late-stage (phase 3) trials by targeted mechanism.

"Cleveland Clinic continues to lead efforts to assess the evolution of new therapies for AD through these annual analyses," says co-author Aaron Ritter, MD, Director of the Clinical Trials Program at Cleveland Clinic Lou Ruvo Center for Brain Health. "We believe it's crucial to drive conversation about our annual findings to foster collaboration and bring public awareness to the need for accelerated drug development." He and his co-authors suggest that optimizing the use of registries can help accelerate clinical trial execution and drug development. More at **consultqd.clevelandclinic.org/pipeline**.



Leadership of a Major New Guideline on DMTs for MS

When the American Academy of Neurology (AAN) issued at its annual meeting in April its first practice guideline on disease-modifying therapies (DMTs) for multiple sclerosis (MS) in 16 years, Cleveland Clinic neurologist Alexander Rae-Grant, MD, led the unveiling. As lead author of the guideline and director of its evidence review process, Dr. Rae-Grant says the document is notable for several reasons. "Our guideline was the result of a transparent and systematic process that stuck closely to the published evidence without significant reliance on expert opinion," he says, noting that the writing group strictly followed National Academy of Medicine recommendations for evidence-based guidelines. Second, an abundance of significant research on DMTs has been published since the last AAN guideline on the topic, in 2002. Third, the writing group incorporated patient preferences into recommendations by drawing on a survey of more than 5,000 patients from a large MS registry. "Shared decision-making is especially important in a disease like MS," Dr. Rae-Grant notes. More at **consultqd.clevelandclinic.org/dmt4ms**.

1st guideline on disease-modifying MS therapies in 16 years

Additional Notable Funded Research Projects Led by Cleveland Clinic Neurological Institute

Project	Source	Funding
Clinical trial comparing ketamine vs. electroconvulsive therapy for treatment-resistant depression	PCORI	$11.8 million
5-year study comparing intensive vs. escalated use of disease-modifying therapy for relapsing-remitting multiple sclerosis	PCORI	$10.6 million
IMMUNE-AD study of the effects of physical activity on risk of Alzheimer's disease in humans and a mouse model	NIA	$8.8 million
First-in-human trial of deep brain stimulation for stroke rehabilitation (see p. 19)	NIH BRAIN grant	$5 million
Clinical trials of lenalidomide for early Alzheimer's disease	NIA and ADDF	$3.9 million (total)
Clinical trial assessing lithium's effects on MRI and blood-based gene expression changes in bipolar II disorder	NIH	$3.7 million
Development of a nomogram to predict individual outcomes of epilepsy surgery	NIH	$3.4 million
Study of laser interstitial thermal therapy for glioblastoma	Monteris	$2.6 million
Study of transcranial magnetic and direct current stimulation for rehabilitation of patients with incomplete cervical spinal cord injury	DOD	$2.5 million
Preclinical research on mechanistic aspects of deep brain stimulation for stroke recovery in animal models of stroke (see p. 19)	NIH	$2.5 million
Development of a brain atlas of cortico-cortical evoked potential responses from epilepsy surgery patients who have undergone stereoelectroencephalography	NINDS	$2.1 million
Study of perceptions of personality in Parkinson disease and its treatment with deep brain stimulation	NIH BRAIN neuroethics grant	$1.6 million

PCORI = Patient-Centered Outcomes Research Institute; NIA = National Institute on Aging; NIH = National Institutes of Health; BRAIN = Brain Research through Advancing Innovative Neurotechnologies; ADDF = Alzheimer's Drug Discovery Foundation; DOD = U.S. Department of Defense; NINDS = National Institute of Neurological Disorders and Stroke

2019 CME FROM THE NEUROLOGICAL INSTITUTE: A PARTIAL CALENDAR

For more on these live CME-accredited events, email tobinm@ccf.org. For the most up-to-date and complete directory of courses, visit **consultqd.clevelandclinic.org/neurocme**.

Advanced Cranial Radiosurgery (Training on the Gamma Knife® Icon™)

JAN. 28-FEB. 1, 2019
APR. 1-5, 2019
MAY 13-17, 2019
JUNE 24-28, 2019
AUG. 19-23, 2019
OCT. 7-11, 2019
DEC. 2-6, 2019
Cleveland Clinic Gamma Knife Center, Cleveland, Ohio

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

All offerings include both introductory and upgrade courses.

Info/registration: **ccfcme.org/radiosurgery19**

12th Annual International Symposium on Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery

FEB. 22-24, 2019
Grand Floridian Resort, Lake Buena Vista, Florida

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

Info/registration: **ccfcme.org/sbrt19**

Cleveland Clinic Brain Mapping Workshop

JUNE 5-8, 2019
InterContinental Hotel & Conference Center, Cleveland, Ohio

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

Info/registration: **ccfcme.org/seeg19**

International Lewy Body Dementia Conference

JUNE 24-26, 2019
Caesars Palace, Las Vegas, Nevada

Director: James Leverenz, MD

Info/registration: **ccfcme.org/ilbdc19**

(see back cover for more information)

Innovations in Cerebrovascular Care 2019

JUNE 27-28, 2019
InterContinental Hotel & Conference Center, Cleveland, Ohio

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

Info/registration: **ccfcme.org/iicc19**

(see back cover for more information)

Mellen Center Update in Multiple Sclerosis

JUNE 28, 2019
InterContinental Hotel & Conference Center, Cleveland, Ohio

Director: Alexander Rae-Grant, MD

Info/registration: **ccfcme.org/ms19**

Cleveland Spine Review

JULY 17-23, 2019
Cleveland Clinic Lutheran Hospital, Cleveland, Ohio

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

Info/registration: **ccfcme.org/spinereview19**

(see back cover for more information)

2019 Neurology Update – A Comprehensive Review for the Clinician

AUG. 2-4, 2019
Ritz-Carlton, Washington, D.C.

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

Info/registration: **ccfcme.org/neuroupdate19**

Cleveland Clinic Neurological Institute Summit 2019: Epilepsy – Focus on Cortical Dysplasia

SEPT. 12-15, 2019
InterContinental Hotel & Conference Center, Cleveland, Ohio

Director: Imad Najm, MD

Info/registration:
ccfcme.org/nisummitepilepsy19

(see back cover for more information)

21st Annual Brain Tumor Update and 10th Annual Symposium on Brain and Spine Metastases

NOV. 2-3, 2019
The Cosmopolitan of Las Vegas, Las Vegas, Nevada

Offered in joint providership with Keck School of Medicine of USC and American Brain Tumor Association

Directors: Gene Barnett, MD; Manmeet Ahluwalia, MD; Pablo Recinos, MD; John Suh, MD; Eric L. Chang, MD; Steven L. Giannotta, MD; Gabriel Zada, MD

Info/registration: **ccfcme.org/brainmets19**

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

Cleveland Clinic

The Cleveland Clinic Foundation
9500 Euclid Ave. / AC311
Cleveland, OH 44195

2019 CME HIGHLIGHTS FROM THE NEUROLOGICAL INSTITUTE

A sampling of our major upcoming live activities. For a fuller slate of Cleveland Clinic's 2019 neuroscience CME offerings, see page 29.

International Lewy Body Dementia Conference

JUNE 24-26, 2019
Caesars Palace, Las Vegas, Nevada

Director: James Leverenz, MD

This three-day forum for research scientists and clinicians will highlight progress in Lewy body dementia research, from diagnosis to imaging, biomarkers, therapeutics and more. Clinical and scientific oral abstract presentations are featured, along with a track for patients and caregivers.

Information/registration: **ccfcme.org/ilbdc19**

Innovations in Cerebrovascular Care 2019

JUNE 27-28, 2019
InterContinental Hotel & Conference Center, Cleveland, Ohio

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

Management of cerebrovascular conditions is advancing rapidly. This meeting helps providers keep up by focusing on how clinical care is being shaped by the field's technological advances. Sessions will highlight multidisciplinary approaches to some of the biggest challenges posed by complex cerebrovascular cases.

Information/registration: **ccfcme.org/iicc19**

Cleveland Spine Review

JULY 17-23, 2019
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 focus on problem-based learning, nonoperative strategies and hands-on education in the cadaver lab. Plus, the legendary social functions can't be beat.

Information/registration: **ccfcme.org/spinereview19**

Neurological Institute Summit 2019: Epilepsy – Focus on Cortical Dysplasia

SEPT. 12-15, 2019
InterContinental Hotel & Conference Center, Cleveland, Ohio

Director: Imad Najm, MD

World leaders in epileptology, epilepsy surgery, imaging, pathology, genetics and pharmacology will meet for a dynamic, comprehensive exploration of advances made in the recognition and management of focal cortical dysplasia in the setting of refractory focal epilepsies. Discussion will also pinpoint challenges and opportunities for management and future research.

Information/registration: **ccfcme.org/nisummitepilepsy19**

These activities have been approved for *AMA PRA Category 1 credit™*.
See page 29 (inside back cover) for more live neuroscience CME in 2019.

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