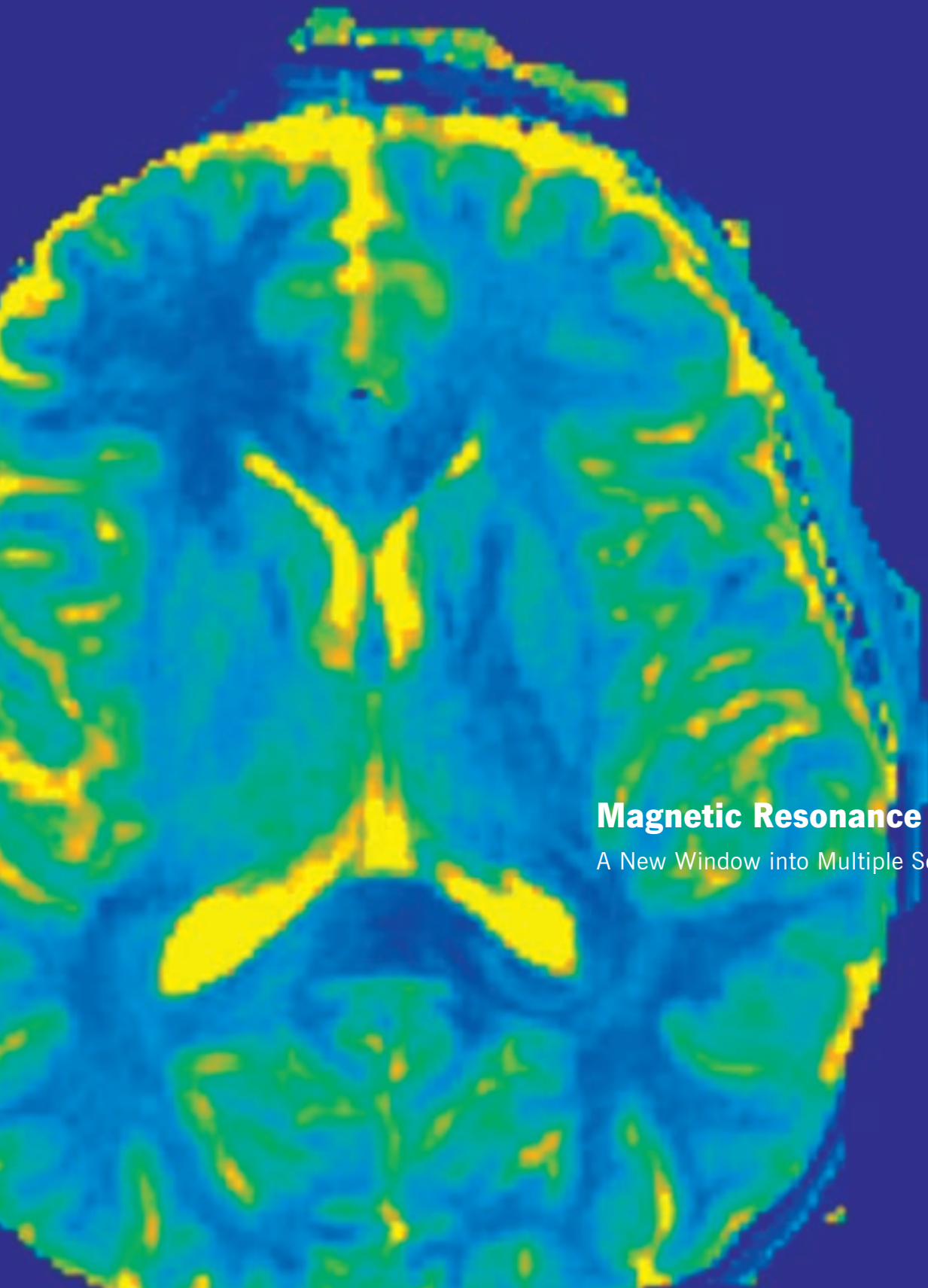
Cleveland Clinic

Neuroscience

# PATHWAYS 2016

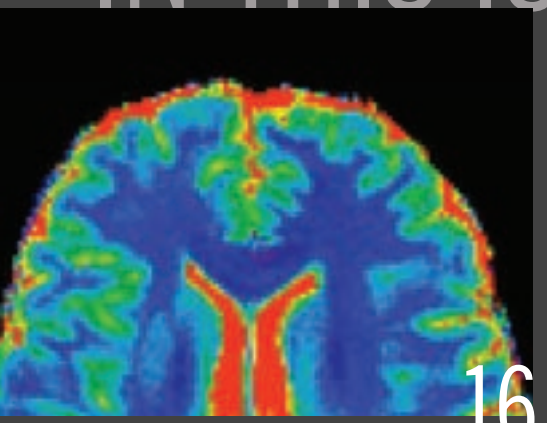
Excellence, Discovery and Innovation



## Magnetic Resonance Fingerprinting

A New Window into Multiple Sclerosis | p. 16

# IN THIS ISSUE



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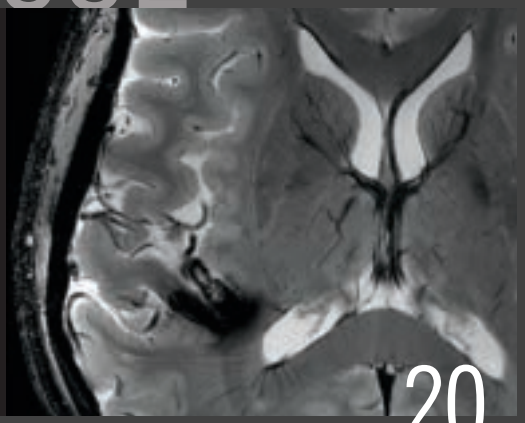

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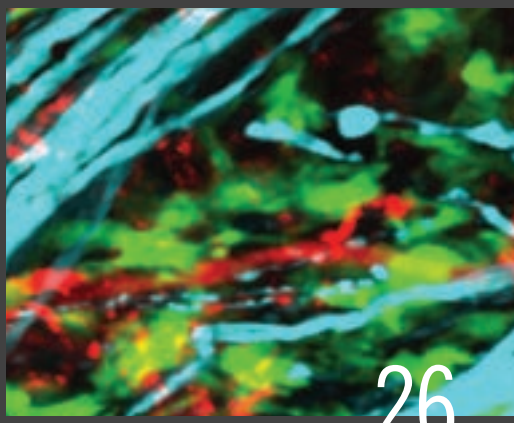

26



**ON THE COVER:** A magnetic resonance fingerprinting (MRF) image of a healthy human brain. To learn how Cleveland Clinic researchers are exploring the utility of MRF to quantify and characterize tissue damage in multiple sclerosis, see the article beginning on page 16.

# DEAR COLLEAGUES,

Cleveland Clinic's Neurological Institute is committed to excellence in patient care, discovery of new treatments for neurological disorders and innovation in healthcare delivery. A testament to our commitment to innovation is the Knowledge Program©. It's been 10 years since the Neurological Institute started using this homegrown tool to collect patient-reported outcomes in a robust, systematic way. This issue of *Neuroscience Pathways* is a validation of our vision in creating the Knowledge Program, as it illustrates how broadly the initiative is now yielding dividends for patient care and research.

Used in conjunction with the electronic medical record, the Knowledge Program is a system enabling collection of patient health status measures at the point of care to inform clinical practice. Patients typically report these measures on wireless tablets just before seeing their provider for a chronic neurological condition. The system allows care to be shaped by real-time monitoring of symptoms and quality-of-life outcomes — often those that matter most to patients.

With such patient-reported outcomes now available from millions of visits, Neurological Institute staff are marshaling these data to improve care for individual patients and yield population-level research insights. At least three examples surface here:

- On page 4, a team from our Center for Behavioral Health reports how Knowledge Program-enabled routine screening for depression in a large sample of youth with epilepsy has helped gauge suicide risk and prevent suicides.
- On page 24, neurologists from our Neuromuscular Center share how systematic collection of patient-reported mental health metrics has enhanced routine care of patients with ALS and made possible the largest single-center study of depression in ALS.
- On page 34, an expert from our Sleep Disorders Center reports on the first study showing consistent improvement in patient-reported outcomes in response to positive airway pressure therapy in a large hypertensive cohort with sleep-disordered breathing.

This ability to scale the Knowledge Program across so many subspecialty areas derives from Cleveland Clinic's distinctive "institutes" model that organizes our neurology, neurosurgery, psychiatry and rehabilitation services into a single structural unit — the Neurological Institute — to maximize opportunities for cross-disciplinary care and collaboration.

As you well know, neurological disorders continue to devastate too many lives. As clinicians, we do all we can, but our reach is limited by the therapies we have. It is abundantly clear that we need to discover new treatments for these disorders. The Neurological Institute is dedicating itself to the discovery and development of new therapies, as demonstrated by our increasing research program and our investments in new recruitments. I would like to highlight the spectacular work (profiled on page 22) of Kenneth Baker, PhD, who was recently recruited in collaboration with Cleveland Clinic Lerner Research Institute. As a translational neuroscientist, Dr. Baker will collaborate with clinicians like me to bring cutting-edge therapies from the lab to the bedside for the first time.

That spirit of collaboration underlies virtually all the research and clinical developments reported in the following pages from across all corners of our diverse institute. I hope you find these updates of interest, and I welcome your input and inquiries.

**Andre Machado, MD, PhD**
Chairman, Cleveland Clinic Neurological Institute | machada@ccf.org

# Screening for Suicidal Behavior Among Youth with Epilepsy: Real-World Data Suggest It Can Save Lives

**By Tatiana Falcone, MD; Migle Staniskyte, BA; and Jane Timmons-Mitchell, PhD**

Is it feasible to do mental health screening during pediatric epilepsy appointments, and can such screening identify patients at risk for suicide?

Those were questions that fueled the development of a depression screening algorithm by specialists in pediatric behavioral health and pediatric epilepsy in Cleveland Clinic's Neurological Institute. We presented findings from the first 400 patients screened with this tool at the 2015 annual meeting of the American Epilepsy Society. Here we summarize those findings and discuss whether integrated mental healthcare and routine screening (every six months) for mood disorders and suicidal ideation can enhance identification referral, determine appropriate treatment and potentially save lives in children and youth with epilepsy (CYE).

## Why Mental Health Matters in Pediatric Epilepsy

Past studies point to increased levels of mental health issues in CYE, including elevated rates of depression, suicidal ideation and attempted suicide. Other studies have reported that there is typically a five-year gap from a patient's first psychiatric symptoms to when he or she receives appropriate treatment.

The 2012 Institute of Medicine report, *Epilepsy Across the Spectrum*,[1] identifies screening for psychiatric comorbidities in patients with epilepsy as a priority. Recognizing that patients with epilepsy often face barriers to obtaining proper treatment for psychiatric comorbidities, the report emphasizes the need for a specific treatment development plan coordinated among all of a patient's care providers.

## An Algorithm for Routine Depression Screening

In light of these issues, several years ago we set out to leverage the Knowledge Program©, a system developed by Cleveland Clinic's Neurological Institute for collecting patient-generated data, to conduct psychiatric screening in Cleveland Clinic's Pediatric Epilepsy Program. Used in conjunction with the Epic electronic health record system, the Knowledge Program enables systematic collection of patient health status measures.

For CYE, screening begins with the Patient Health Questionnaire-2 (PHQ-2) and proceeds according to the algorithm in Figure 1, which we call the Depression Screen Algorithm. Briefly, patients with a PHQ-2 score ≥ 1 take the Center for Epidemiological Studies Depression Scale for Children (CES-DC). Patients with a CES-DC score ≥ 16 proceed to a suicide screen with psychiatry follow-up as detailed in the algorithm.

## Findings from the First 400 Patients

Our analysis of the initial patients (and their families) screened using this algorithm included all eligible CYE seen by Cleveland Clinic's Pediatric Epilepsy Program from 2008 to 2015.[2] A total of 5,303 mental health screenings for 400 CYE were recorded. Each patient was screened at every visit, for an average of approximately 13 screens per patient.

Of the 400 CYE, 106 screened positive for suicidal ideation, yielding a base rate of 26.5 percent. This is higher than that of the overall youth population in Ohio, according to recent Ohio Department of Health statistics on self-reported suicide-related behavior.[3] Those statistics show that, during the prior 12 months, 14 percent of the state's high school students had considered suicide, 9 percent had made a suicide attempt and 4 percent had sustained an injury from a suicide attempt. Thus, our screening findings are consistent with prior evidence that CYE are at higher risk for suicidal thoughts and behavior relative to similar-age youth.

Of the 106 CYE who screened positive, 50.9 percent were male and 49.1 percent were female.

Among these 106 patients, 12 patients were referred to the emergency department (ED), and 13 suicides were prevented. The 13 patients in whom suicide was prevented had the following characteristics:

- 9 female, 4 male
- All Caucasian
- Age range, 9 to 18 years (mean = 15.25; SD = 2.34)
- All reported suicidal ideation. The number of suicide attempts ranged from 0 to 3 per person (mean = 1; SD = 1.05), with a total of 12 suicide attempts.
- Half reported having thoughts of harming others.
- All were taking selective serotonin reuptake inhibitors.
- Nine had been admitted to the pediatric psychiatry inpatient unit (mean = 2.56 admissions; SD = 1.74).
- Overall mean Screen for Child Anxiety Related Disorders score was 47.69 (significant for clinical anxiety).
- Overall mean Children's Depression Inventory score was 88.3 (significant for depression).
- Mean Adverse Childhood Experiences score (for exposure to emotional trauma) was 2.
- Total number of visits to the ED for suicidal ideation or suicide attempts was 41 (mean, 3.1).

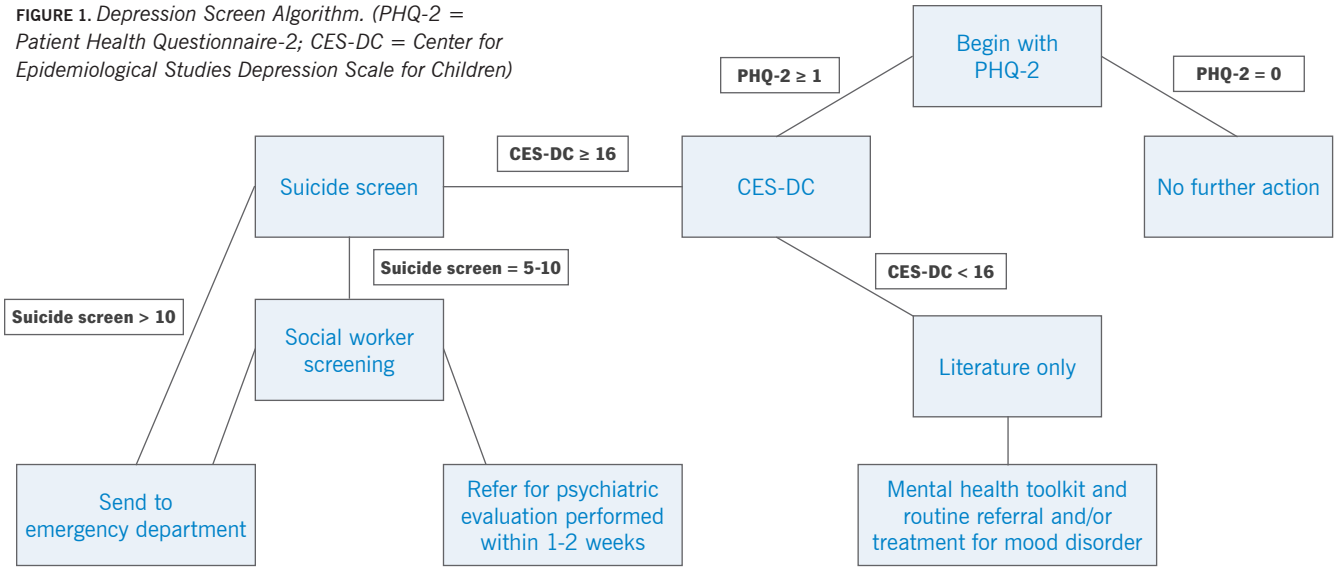


**FIGURE 1.** *Depression Screen Algorithm. (PHQ-2 = Patient Health Questionnaire-2; CES-DC = Center for Epidemiological Studies Depression Scale for Children)*

## The Comorbidities Screen: An Important Step in Enhancing Care

Development of an algorithm that integrates pediatric epilepsy screening with psychiatry follow-up facilitated the routine screening of 400 CYE. Of these patients, 26.5 percent screened positive for suicidal ideation, which, as mentioned, is higher than rates found in other studies of CYE.

As noted in the Institute of Medicine report,[1] development and implementation of a thorough screening process for psychiatric comorbidities in CYE is an important next step in enhancing care. Our Depression Screen Algorithm proved useful in organizing and systematizing the screening process and further applying a proper treatment plan for CYE.

Since 2008, we have used the Impact of Childhood Neurologic Disability Scale and other scales to systematically screen CYE for depression, suicidal ideation and epilepsy issues that could impact quality of life. Screening is done in the 15 minutes before these patients see their epileptologist. Scores are integrated into the chart for viewing during the visit, with results that require further attention (e.g., at-risk status for suicide or a need for further depression screening) flagged with special colors.

We have successfully integrated this Knowledge Program-based screening into the regular appointment workflow in our outpatient epilepsy clinic for CYE and all other patients with epilepsy. Our experience shows that systematic screening of this type is feasible, and we believe these findings show it enhances the quality of care we provide. Indeed, caring for patients with epilepsy goes beyond seizure control, and addressing psychiatric comorbidities should be a priority in the management of all CYE.

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*Dr. Falcone (falcont1@ccf.org; 216.444.7459) is a child and adolescent psychiatrist in the Center for Behavioral Health and Epilepsy Center in Cleveland Clinic's Neurological Institute.*

*Ms. Staniskyte is a research coordinator in the Neurological Institute.*

*Dr. Timmons-Mitchell is a senior research associate with the Begun Center for Violence Prevention Research and Education at the Jack, Joseph and Morton Mandel School of Applied Sciences within Case Western Reserve University (CWRU), Cleveland. She is also an associate clinical professor of psychology at CWRU School of Medicine.*

## KEY POINTS

- Rates of depression and suicidal ideation are elevated in children and youth with epilepsy (CYE), and screening for psychiatric comorbidities in CYE has been identified as a priority by the Institute of Medicine.
- Cleveland Clinic developed an algorithm that integrates depression screening into the appointment workflow in the outpatient pediatric epilepsy clinic to facilitate routine screening for suicide risk in CYE.
- A recent analysis of the first 400 CYE screened with this algorithm found that 26.5 percent of patients screened positive for suicidal ideation and identified 13 cases in which suicide was prevented.

# Immunotherapeutic Approaches to Alzheimer's Disease: How We Got Here and Where Insights Are Leading

**By Jeffrey Cummings, MD, ScD; James Leverenz, MD; and Babak Tousi, MD**

Immunotherapies may transform Alzheimer's disease (AD) therapeutics by harnessing the power of the immune system to rid the brain of toxic proteins. In fact, immunologic approaches to AD are the focus of four active clinical trial programs across the Cleveland Clinic Lou Ruvo Center for Brain Health trial network, which includes Cleveland Clinic sites in Las Vegas, Cleveland, and Weston, Florida. This article outlines the path that's led to current immunotherapeutic approaches to AD and identifies a few remaining hurdles on the road to clinical success.

## Rationale and Initial Setbacks

Immunotherapy refers to treatments that involve immunologic mechanisms to exert disease-modifying effects on the underlying processes leading to cell death (Figure 1). Monoclonal antibodies are typically produced artificially outside the body and infused intravenously on a regular basis. Subcutaneous administration is also being explored. An alternate immunotherapeutic approach is active vaccination, in which the patient is inoculated with an amyloid protein fragment and produces an immunologic response, with the induced response intended to remove the amyloid accumulating in the brain.

The immunotherapeutic approach to AD began in 1999 when immunization with amyloid-beta protein attenuated development of AD-type pathology in transgenic animal models of AD that were engineered to overproduce the amyloid protein. In 2001, a human study of AN1792, an active vaccine against amyloid, was initiated. The study was terminated when 6 percent of enrolled patients developed allergic encephalitis; cross-reactivity of the antigen with normal brain tissues was identified as the likely cause. Autopsy of a small number of enrolled patients found evidence of amyloid removal from the brain but no disease modification.

After this setback, scientists pursued the alternate approach of passive immunotherapy with monoclonal antibodies in an effort to avoid the adverse effects observed with AN1792.

The first passive immunotherapy tested in AD was bapineuzumab, a monoclonal antibody targeting the N-terminal portion of the amyloid-beta protein. The primary outcomes of this trial showed no drug-placebo difference, but a subanalysis appeared to suggest that those who were not carriers of the apolipoprotein e4 allele (*ApoE-4*), a gene known to exert effects in AD, showed positive effects on cognitive testing. A subsequent trial failed to identify any therapeutic benefit in either *ApoE-4* carriers or noncarriers.[1]

A new type of side effect was seen in this trial — the development of amyloid-related imaging abnormalities — that appears to be nearly unique to immunotherapy, represents interruption of the blood-brain barrier, and is usually asymptomatic but has important and permanent stroke-like consequences in some patients.[2] These changes are now routinely monitored with MRI in immunotherapy trials.

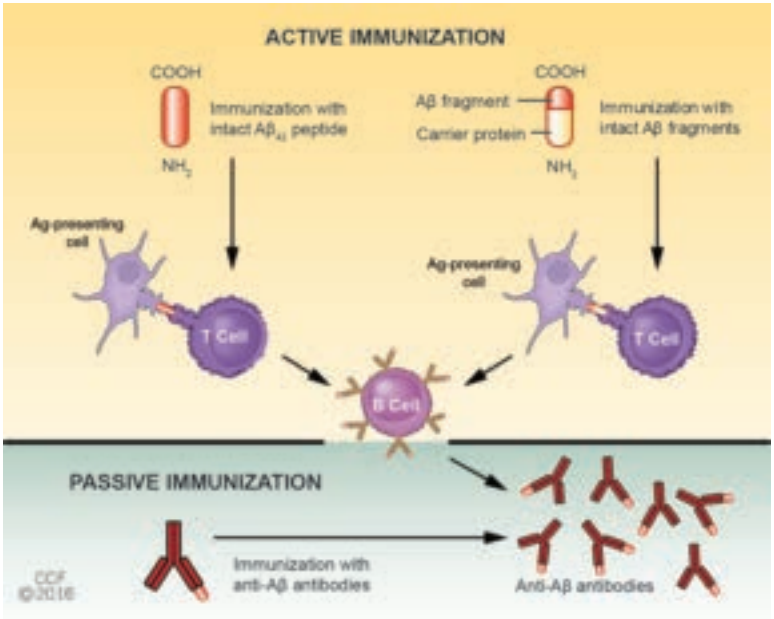


**FIGURE 1.** *The two approaches to immunotherapy in AD.*

## A Proliferation of Candidate Therapies

These early experiences with immunotherapy have served to advance and refine immunologic approaches to AD treatment. The result is 14 types of immunotherapy now in various stages of clinical testing for AD (Table 1) in an attempt to replicate the therapeutic responses observed in animals. Most of these immunotherapies are monoclonal antibodies directed against the amyloid-beta protein, while one (AADvac1) is a vaccine directed against the tau protein, two are polyclonal antibodies and three are active vaccines. Information on the therapeutic effects of the six agents in phase 3 trials will be available within the next few years.

## The Imperative — and Challenge — of Early Intervention

Experience with monoclonal antibodies suggests they may have their greatest effects when given early in the disease course.[3,4] Trials are currently focusing on prodromal AD, before there is any functional deficit, and mild AD dementia.

**Table 1. Immunologic Approaches to AD Treatment in Clinical Trials**

| Drug | Sponsor | Active/Passive | Phase |
|---|---|---|---|
| Aducanumab | Biogen | Anti-amyloid passive monoclonal antibody | 3 |
| Solanezumab | Eli Lilly | Anti-amyloid passive monoclonal antibody | 3 |
| Crenezumab | Roche/Genentech | Anti-amyloid passive monoclonal antibody | 3 |
| Gantenerumab | Roche | Anti-amyloid passive monoclonal antibody | 3 |
| Albumin + immunoglobulin | Grifols | Passive polyclonal antibody | 3 |
| CAD106 | Novartis | Active vaccine | 3 |
| BAN2401 | Eisai/Biogen | Anti-amyloid passive monoclonal antibody | 2 |
| IVIG | Octapharma | Passive polyclonal antibody | 2 |
| UB-311 | United Neuroscience | Anti-amyloid vaccine | 2 |
| AADvac1 | Axon Neuroscience | Anti-tau vaccine | 1 |
| KHK6640 | Kyowa Hakko Kirin Pharma | Anti-amyloid passive monoclonal antibody | 1 |
| Lu AF20513 | Lundbeck/Otsuka | Anti-amyloid vaccine | 1 |
| LY3002813 | Eli Lilly | Anti-amyloid passive monoclonal antibody | 1 |
| MEDI1814 | AstraZeneca | Anti-amyloid passive monoclonal antibody | 1 |

Yet this poses a challenge, as very mildly affected individuals are difficult to enroll in trials since they may not realize their memory deficits are signs of AD. The challenge is heightened by the fact that phase 3 trials tend to be large (> 1,000 patients) and long (18-month double-blind phase followed by an open-label extension). Many individuals with mild memory loss will be excluded when amyloid imaging shows them to be free of amyloid deposits in the brain (the hallmark finding of AD). The "screen fail" rate of these trials can be as high as 75 to 80 percent, and clinical trial sites must screen many patients to enter a few into trials.

Cleveland Clinic Lou Ruvo Center for Brain Health is committed to helping address these enrollment challenges through its active clinical trial programs for four immunotherapies — aducanumab, solanezumab, crenezumab and albumin/immunoglobulin — across its sites in three distinct regions of the U.S. We are hopeful these trials may result in the development of the first successful immunotherapies for AD.

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For a more complete list of references, see the online version of this article at **consultqd.clevelandclinic.org/ADimmuno**.


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*Dr. Cummings (cumminj@ccf.org; 702.483.6031) is Director of Cleveland Clinic Lou Ruvo Center for Brain Health.*

*Dr. Leverenz (leverej@ccf.org; 216.445.4149) is Director of Lou Ruvo Center for Brain Health, Cleveland.*

*Dr. Tousi (batous@ccf.org; 216.444.8602) is Head of the Clinical Trials Program at Lou Ruvo Center for Brain Health, Cleveland.*


## KEY POINTS

- After a decade and a half of lessons from efforts to develop a safe and effective immunologic therapy for AD, 14 immunotherapies are now in clinical trials for AD, with six in phase 3 studies.
- Monoclonal antibodies appear to have their greatest effects when given early in the disease course, so trials are currently focusing on prodromal AD and mild AD dementia.
- Cleveland Clinic has active clinical trial programs for four immunotherapies for AD: aducanumab, solanezumab, crenezumab and albumin/immunoglobulin.

# Immunotherapy and Glioblastoma: Assessing Strategies to Harness the Immune System Across a Range of Clinical Trials

**By Manmeet S. Ahluwalia, MD, and Justin D. Lathia, PhD**

Immunotherapeutic approaches to cancer involve either stimulating the patient's own immune system to work more efficiently to attack cancer cells or giving the patient synthetic immune system proteins to help mount an immune response to enable killing of cancer cells. Immunotherapy's potential utility against brain tumors was initially questioned due to the belief that the CNS was an immune-privileged site, but this belief has since been refuted and there appears to be a dynamic interaction between the peripheral systemic immune system and the CNS.

This is a highly welcome insight, as glioblastoma — the most common primary malignant brain tumor — is still associated with dismal outcomes. Average survival is 15 to 18 months with the traditional treatment paradigms of surgery, chemotherapy and radiation, and less than 10 percent of patients survive more than five years. Recent years have seen considerable excitement around immunotherapeutic approaches in this patient population, and Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center is participating in a multitude of clinical trials assessing a range of these approaches. Those trials are outlined in Table 1 and detailed below.

## Vaccine-Based Approaches

Unlike some cancers, such as melanoma and kidney cancer, glioblastomas are not inherently immunogenic. One of the challenges has been to induce immune responses to glioblastoma.

One such approach uses a peptide-based vaccine to induce an immune response. Survivin is an intracellular protein that regulates cell division and inhibits apoptosis. In the setting of cancer, high-level survivin expression is associated with poor outcomes and high rates of disease recurrence and therapy resistance. These observations prompted development of SurVaxM, a synthetic long peptide mimic vaccine that stimulates an immune response to survivin.

In the wake of a phase 1 study of SurVaxM showing safety and preliminary efficacy in patients with recurrent malignant glioma,[1] a phase 2 study is combining SurVaxM with the oral chemotherapeutic temozolomide in patients with newly diagnosed glioblastoma. Cleveland Clinic and Roswell Park Cancer Institute are recipients of a Roswell Park Alliance Foundation grant to support this study.

Additional vaccine-based immunotherapy approaches in trials here and at other centers include:

- ICT-107, an autologous vaccine that targets six antigens associated with glioblastoma. After a phase 2 study showing benefit from ICT-107 in a select group of patients with glioblastoma, a phase 3 trial is underway in newly diagnosed glioblastoma.
- SL-701, a glioma-associated antigen vaccine in phase 2 testing for use in recurrent glioblastoma.

## Immune Checkpoint Inhibitors

Considerable enthusiasm surrounds the use of immune checkpoint inhibitors in glioblastoma. These agents have demonstrated promising activity in melanoma, lung cancer, head and neck cancer, and kidney and other urothelial cancers. They target molecules/pathways that serve as checks and balances on immune responses, and can enable a patient's T cells to attack cancer cells by releasing the brakes on the immune system.

Two multicenter clinical trials are currently open at Cleveland Clinic investigating the efficacy of one such agent, the anti-PD-1 monoclonal antibody nivolumab, in newly diagnosed glioblastoma patients with either unmethylated $O^6$-methylguanine-DNA-methyltransferase (MGMT) or methylated MGMT.

## Oncolytic Viral Therapies

Oncolytic viral therapeutic-based strategies work on the premise that a modified virus can infect tumors and cause them to self-destruct, thereby facilitating an immune response against the cancer. Viruses being investigated in glioblastoma include poliovirus, genetically engineered poliovirus, the genetically engineered adenovirus known as DNX-2401, measles virus, the retroviral replicating vector Toca 511, and herpes simplex virus.

Of these approaches, the one furthest in development is Toca 511, which expresses the cytosine deaminase gene and selectively delivers the gene to the tumor. It is being studied in combination with Toca FC, a novel formulation of the antifungal drug flucytosine that gets converted to the anticancer drug 5-fluorouracil within infected cancer cells.

A Cleveland Clinic investigator co-directed a newly published phase 1 study that demonstrated significantly improved survival with these therapies in recurrent high-grade glioma relative to an external control.[2] The study also showed excellent tolerability, and a phase 2/3 randomized, controlled study of Toca 511 and Toca FC in subjects undergoing surgery for recurrent glioblastoma/anaplastic astrocytoma is now accruing patients at numerous centers, including Cleveland Clinic.

## Targeting Myeloid-Derived Suppressor Cells

Most current immunotherapeutic approaches target immune interactions rather than immunosuppressive cells themselves, so a direct attack on these immunosuppressive cells would represent an attractive treatment strategy.

Myeloid-derived suppressor cells (MDSCs), a heterogeneous class of immature immunosuppressive cells, accumulate in multiple tumor types and suppress cytotoxic immune cells via cytokine secretion. Cleveland Clinic investigators have demonstrated that patients with

**Table 1. Current Clinical Trials of Immunotherapies for Glioblastoma at Cleveland Clinic**

| Patient Population | Study Phase | Intervention | ClinicalTrials.gov Identifier |
|---|---|---|---|
| Newly diagnosed GBM | 2 | SurVaxM (vaccine) plus temozolomide (chemotherapy) | NCT02455557 |
| Newly diagnosed GBM | 3 | ICT-107 (vaccine) | NCT02546102 |
| Newly diagnosed GBM (unmethylated MGMT) | 3 | Nivolumab (anti-PD-1 monoclonal antibody) | NCT02617589 |
| Newly diagnosed GBM (methylated MGMT) | 2 | Nivolumab (anti-PD-1 monoclonal antibody) | NCT02667587 |
| Recurrent GBM | 2 | SL-701 (vaccine) | NCT02078648 |
| Recurrent GBM/ anaplastic astrocytoma | 2/3 | Toca 511 (viral vector) plus Toca FC (flucytosine, an antifungal) | NCT02414165 |
| Recurrent GBM | 1 | Capecitabine (chemotherapy) plus bevacizumab (angiogenesis inhibitor) | NCT02669173 |

GBM = glioblastoma; MGMT = $O^6$-methylguanine-DNA-methyltransferase

glioblastoma have elevated MDSCs in blood and tumor, and that these MDSCs produce reversible T-cell dysfunction. In a recent paper,[3] we showed that MDSCs localize in tumor regions adjacent to therapeutically resistant tumor cells with stem cell properties (i.e., cancer stem cells). Cancer stem cells produce factors responsible for MDSC function, and targeting these factors can reduce the efficiency of MDSCs.

We also developed an MDSC targeting strategy that relies on low dosing of 5-fluorouracil, a common chemotherapy. In preclinical models, this strategy severely attenuated MDSC numbers and glioblastoma growth while concomitantly increasing cytotoxic T-cell numbers. An ongoing phase 1 trial at Cleveland Clinic is investigating a novel chemotherapeutic strategy targeting MDSC immunosuppression using an alternative dosing schedule of the oral chemotherapeutic capecitabine plus the angiogenesis inhibitor bevacizumab in patients with recurrent glioblastoma. We look forward to sharing results in the coming months and years.

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*Dr. Ahluwalia (ahluwam@ccf.org; 216.444.6145) is Director of the Brain Metastasis Research Program, Associate Director of Clinical Trials and Head of Operations in Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center.*

*Dr. Lathia (lathiaj@ccf.org; 216.445.7475) is Associate Professor in the Department of Cellular and Molecular Medicine in Cleveland Clinic Lerner College of Medicine.*


## KEY POINTS

- Despite initial concerns that the CNS was an immune-privileged site, there appears to be a dynamic interaction between the peripheral systemic immune system and the CNS, fueling enthusiasm for immunotherapeutic strategies against glioblastoma.
- Cleveland Clinic is leading and participating in multicenter clinical trials of various immunotherapeutic approaches to glioblastoma predicated on targeting immune interactions. These include studies of vaccines, immune checkpoint inhibitors and oncolytic viral therapies.
- In addition to these multicenter trials, Cleveland Clinic has launched a single-site phase 1 trial targeting myeloid-derived suppressor cells with a novel chemotherapeutic regimen in patients with recurrent glioblastoma to investigate the strategy of direct attack on immunosuppressive cells.

# Cleveland Clinic Telestroke Network at Year 5: Lessons Learned in Sustaining Remote Stroke Consultation Services

**By M. Shazam Hussain, MD, and Dana Collins, MBA**

In 2015, stroke neurologists with the Cleveland Clinic Telestroke Network (CCTN) provided remote consultation services to more than 1,000 patients in 15 healthcare facilities in Ohio, Pennsylvania and Florida. We achieved an intravenous tissue plasminogen activator (IV tPA) utilization rate of 16 percent, well above the national average of 3 to 5 percent and nearing the approximately 20 percent achieved by highly specialized centers.

One of the primary reasons for the ongoing success of the CCTN is that it's a dedicated service line, with stroke neurologists on call 24/7. This level of support for acute stroke patients ensures a rapid response to partner hospitals, which helps improve outcomes. In 2015, the average time from when a CCTN neurologist was paged for a consultation until the physician called back the hospital was one minute.

Nationwide, there are only four neurologists per 100,000 U.S. residents (*Neurology*. 2013;81:479-486), which makes the need for telestroke services critical. However, implementing and sustaining a telestroke program can be demanding. At Cleveland Clinic, we have tripled our partner hospitals since 2014 and learned some lessons along the way that could benefit other healthcare systems offering telestroke services.

## CLEVELAND CLINIC TELESTROKE NETWORK (CCTN) BY THE NUMBERS

| | |
|---|---|
| 2011 | Year launched |
| 15 | Number of hospitals/EDs served |
| 1,041 | Number of telestroke consultations in 2015 |
| 1 | Average time (in minutes) for attending stroke neurologist to respond to a CCTN page |
| 16 | Percentage utilization of IV tPA among CCTN facilities (vs. 3 to 5 percent national average) |

### Inception and Scope of the CCTN

Launched in 2011, the CCTN is a homegrown program employing a "hub and spoke" model: Our Joint Commission-certified Comprehensive Stroke Center on Cleveland Clinic's main campus serves as the hub, partnering with "spoke" facilities (within and outside the Cleveland Clinic health system) that lack round-the-clock stroke specialist support. The network is enabled with a mobile, two-way videoconferencing system and a dedicated link between our partner hospitals' imaging systems and our main campus to facilitate patient assessment and treatment decision support.

When patients identified with stroke arrive at the emergency department (ED) of a partner facility, emergency physicians perform a rapid assessment, order a CT scan and then call the CCTN. Within minutes, a CCTN stroke neurologist is working remotely with the ED staff. Together they check vital signs, perform an examination, review results of the CT scan and make treatment decisions.

Since its inception, the CCTN has grown to serve 15 hospitals or freestanding EDs that do not have stroke specialists. This includes eight within the Cleveland Clinic health system as well as seven external facilities — one in Ohio, five in Pennsylvania and one in Florida. Figure 1 shows how two participating hospitals saw IV tPA delivery rates improve following implementation of telestroke services.

### Keeping Patients in Their Communities

Participating in a telestroke program offers several benefits to these 15 facilities, including access to a multidisciplinary team of stroke experts who can help determine the appropriateness of IV tPA administration, intra-arterial thrombolysis, mechanical revascularization and other treatment options.

But the greatest benefit may be that patients often are able to remain in their local hospitals, closer to family and local physicians. We work closely with our partner hospitals, making sure that neurologists and other healthcare staff understand our decision-making and can seamlessly pick up care of the patient the next day and beyond. Only the most severe stroke patients are transferred to Cleveland Clinic's main campus, which has two neurological ICUs and full neurointerventional and neurosurgical capabilities.

### Three Prongs of an Effective Telestroke Program

Success of a telestroke program often hinges on three key areas: technology, resources and training. During the five years the CCTN has been in operation, we have gained the following insights in these areas:

- **Technology:** A telestroke program requires software, high-quality videoconferencing capabilities, a pan-tilt-zoom camera at partnering facilities, CT image transfer capabilities, and fast, secure transmission systems. We have opted for a high-end system to help safeguard against glitches and downtime. A program's service line is only as good as its software and real-time transmission capabilities allow.
- **Resources:** Telestroke programs run the risk of physician burnout, as they require an immediate response, which can create a higher level of burden on neurologists over time. It's imperative to have a fairly large pool of stroke experts who rotate shifts. The CCTN comprises 15 stroke neurologists, with one primary telestroke physician and a backup physician on call around the clock.
- **Training:** When the CCTN partners with a new participating hospital or ED, our program manager facilitates training of the new site's entire ED staff to do patient assessments with Cleveland Clinic stroke experts. Topics include components of the NIH Stroke Scale (NIHSS) neurologic exam that require nurse assistance and important reminders related to telemedicine, such as to interact with the physician via the camera. In the past year, the CCTN has begun recommending that two nurses be present in the assessment room at participating facilities — one to interact with the physician, the other to work on the NIHSS exam.

### The Future of the Telestroke Network

As a natural extension of the CCTN, Cleveland Clinic launched one of the nation's first mobile stroke treatment units in 2014. We also plan to further expand the number of participating CCTN facilities, continually research best-in-class telestroke technology and investigate the use of telemedicine for situations beyond acute stroke, with the ultimate goal of reaching patients faster and improving outcomes.

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*Dr. Hussain (hussais4@ccf.org; 216.445.1383) is Head of the Cleveland Clinic Stroke Program and Interim Director of Cleveland Clinic's Cerebrovascular Center.*

*Ms. Collins (collind3@ccf.org; 216.445.4176) is Telestroke Program Manager and Department Manager in the Cerebrovascular Center.*

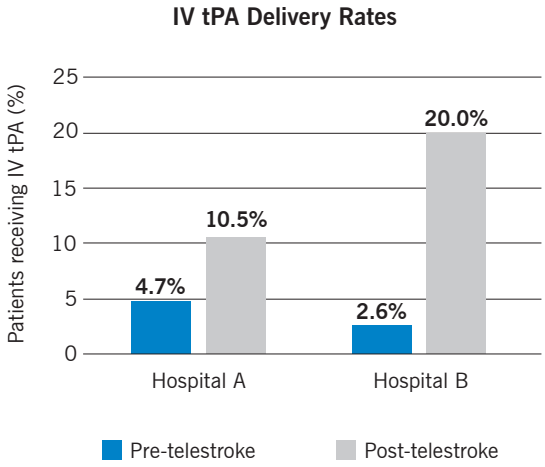


**FIGURE 1.** *Delivery rates of IV tPA to patients with acute ischemic stroke at two participating CCTN hospitals during 12-month periods before and after initiation of telestroke services in 2014.*

## KEY POINTS

- With only four neurologists per 100,000 U.S. residents, the need for telestroke services is critical, yet implementing and sustaining a telestroke program can be daunting.
- The Cleveland Clinic Telestroke Network provides remote consultation services out of Cleveland Clinic's main campus for patients with acute stroke at 15 facilities in Ohio, Pennsylvania and Florida, achieving an IV tPA utilization rate of 16 percent, well above the national average.
- Success of a telestroke program hinges on high-quality software and real-time transmission capabilities; adequate bench strength in stroke neurologist staffing; and a commitment to comprehensive training of all new participating network facilities.

# The Trust: Taking a Multidisciplinary Approach to Brain Health in Former NFL Players

**By Jay Alberts, PhD; James Leverenz, MD; and Nancy Foldvary-Schaefer, DO, MS**

When the NFL Players Association launched The Trust collaboration with a handful of leading medical centers in 2013, it promised to be a clear win-win. On one end, former NFL players would benefit from the chance to undergo a comprehensive brain-body health evaluation to help understand the brain health path they appear to be on, gaining either reassurance or the opportunity for early interventions if indicated. At the other end, brain health specialists at Cleveland Clinic and the other participating institutions would gain an unmatched opportunity to learn from a population with a singular long-term neurocognitive and functional risk profile stemming from the repeated head impacts that can characterize pro football careers.

Now, three years into The Trust initiative, Cleveland Clinic is the program's highest-volume collaborating center (see sidebar). Our experience to date has shown that the collaboration's potential is most fully realized with a broadly multidisciplinary approach that goes beyond neurocognitive function to encompass wellness as holistically as possible. This article outlines the role of two subspecialty centers within Cleveland Clinic's Neurological Institute — the Lou Ruvo Center for Brain Health and the Sleep Disorders Center — that are working closely with Cleveland Clinic's Concussion Center to help bring that approach to bear for participants in The Trust.

## The Player Assessment in Brief

Under Cleveland Clinic's protocol, former NFL players undergo an initial assessment at any of four sites (see sidebar) — three Cleveland Clinic sites, located in diverse parts of the country, or Hoag Health Network in Southern California, which serves as an affiliate of Cleveland Clinic for this program.

The two-day assessment starts with a comprehensive medical exam that includes determining the player's injury history, any functional symptoms and any personal concerns such as depression or the transition to retirement from pro sports. That's followed by brain MRIs, neurological examination, cognitive evaluation, psychiatric evaluation, neuropsychological testing, sleep disorders screening, and assessments of postural stability and motor and cognitive function (the latter done using the Cleveland Clinic Concussion App). Non-neurological evaluations and interventions (e.g., wellness screening, nutrition counseling, life skills consultation) round out the assessment.

> Our preliminary experience suggests a high prevalence of previously unidentified sleep apnea in former NFL players, with objective testing confirming sleep apnea for the majority of players with positive self-assessments.

Former players are then given a report of findings and recommendations, along with a personalized plan of action including subspecialty referral facilitation in their home community, if indicated. The aim is to provide a comprehensive and objective neurological assessment to identify any neurological dysfunction and give each player a sense of whether his cognitive status appears to be normal for his age — and, if not, what further monitoring or interventions are recommended.

## The Role of Specialized Neurocognitive Assessment

At Cleveland Clinic, former players' neurocognitive assessment goes beyond evaluation by general neurologists and concussion specialists to include visits with each of four members of a subspecialist team:

- **A behavioral neurologist**, who reviews the brain MRIs and performs a focused neurological evaluation addressing cognitive change as well as any other neurological symptoms or complaints
- **A psychiatrist**, who performs a focused psychiatric evaluation with special attention to mood and adjustment issues
- **A neuropsychologist**, who administers a several-hour battery of neuropsychological tests of memory and other cognitive abilities
- **A health psychologist**, who assesses for long-standing conditions that may impact long-term brain health

At each location, the same team sees former players on a regular basis (about one player per week). The behavioral neurologists have deep experience in mild cognitive impairment and chronic traumatic encephalopathy, which they bring to bear in evaluating abnormal findings or providing reassurance about the absence of signs of permanent damage from repeated head trauma.

## Giving Sleep Its Due

Chronic sleep deprivation and sleep apnea have been associated with increased risk for various forms of heart disease and metabolic disorders as well as mental health disorders, substance abuse and cognitive impairment.

In view of these associations, participants in The Trust who are evaluated at Cleveland Clinic are given self-assessments for insomnia and sleep apnea. Those with high signals for clinically relevant

## THE TRUST: NUMBERS OF NOTE

**4** U.S. medical centers participating in The Trust

**4** Cleveland Clinic sites/affiliates evaluating former players for The Trust (Cleveland; Las Vegas; Weston, Florida; Southern California)

**>400** NFL players evaluated by Cleveland Clinic to date

problems are offered further testing and treatment. Sleep studies are performed at home or in a hotel to record breathing in sleep for the diagnosis of sleep apnea. Players then meet with a Sleep Disorders Center specialist in person or via telemedicine-enabled virtual visits to review results, initiate therapy and monitor progress over time.

Our preliminary experience suggests a high prevalence of previously unidentified sleep apnea in this population, with objective testing confirming sleep apnea for the majority of former players with positive self-assessments. Most players are surprised to learn that they stop breathing in their sleep and are eager to initiate therapy. Others have had high levels of insomnia and opt to complete a web-based cognitive behavioral therapy program for insomnia, called Go! to Sleep℠, developed by specialists in Cleveland Clinic's Wellness Institute and Sleep Disorders Center. For those with severe insomnia or who are not interested in the online approach, virtual visits with a behavioral sleep medicine expert are available.

These evolving efforts around sleep health make several key contributions to Cleveland Clinic's execution of The Trust collaboration:

- Adding an important wellness component
- Providing an opportunity for intervention with the potential for near-term clinical benefits
- Offering a clearer window into a participant's "true" neurocognitive picture — i.e., after any effects of sleep disorders are identified and treated

### Drawing on Relevant Research When Possible

While The Trust collaboration currently remains strictly a clinical project, many of the multidisciplinary experts involved in The Trust at Cleveland Clinic play key roles in similar initiatives with an explicit research focus, such as the large ongoing Professional Fighters Brain Health Study and related investigations in athletes. Insights from these studies will inform our counseling of participants in The Trust.

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*Dr. Alberts (albertj@ccf.org; 216.445.3222) is Director of Cleveland Clinic's Concussion Center and Neurological Institute Vice Chair for Health Technology Enablement.*

*Dr. Leverenz (leverej@ccf.org; 216.445.4149) is Director of Cleveland Clinic Lou Ruvo Center for Brain Health, Cleveland.*

*Dr. Foldvary-Schaefer (foldvan@ccf.org; 216.445.2990) is Director of the Sleep Disorders Center.*

## KEY POINTS

- Cleveland Clinic has assessed over 400 former pro football players to date as part of its participation in The Trust collaboration with the NFL Players Association.
- Participants in The Trust undergo a comprehensive assessment of their neurological and general health to characterize their neurocognitive health status and recommend potential interventions, if needed.
- Distinctive aspects of Cleveland Clinic's protocol for The Trust include (1) an intensive neurocognitive assessment by a behavioral neurologist, a psychiatrist, a neuropsychologist and a health psychologist; and (2) screening for sleep disorders followed by sleep studies for those with positive self-assessments, plus specialized treatment as indicated.

# Cortico-Cortical Evoked Potentials: A Novel Application Promises to Advance Mapping of Brain Connectivity

**By Dileep R. Nair, MD, and John C. Mosher, PhD**

The need to map the human brain is now a widely recognized priority — even at the world's highest levels of power. Indeed, the importance of this quest is underscored by the NIH's Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative laid out by President Barack Obama in 2013. The initiative's aim is to help researchers uncover the mysteries of various brain disorders by facilitating a more dynamic understanding of brain function.

Cleveland Clinic's Epilepsy Center is pleased to be contributing to those efforts through an NIH-funded brain mapping project that uses the invasive monitoring technique known as cortico-cortical evoked potentials in a novel way. This article outlines the rationale behind that project and looks ahead to its potential clinical payoffs.

## Limits to Traditional Studies of White Matter Connectivity

Current understanding of neuroscience relates mostly to cortical function, i.e., the regions of cortex associated with different functional tasks. This understanding has come from a variety of methods that include studying the impact of neurologic deficits from ischemic lesions, observations on the effect of cortical stimulation on occurrence of observable symptoms, and functional MRI during specific tasks. We have only recently begun to understand how the white matter connections of various brain regions play a role in cognitive tasks.

Much of the knowledge comes from either invasive tracer studies of cadavers or diffuse tractography. Each has its disadvantages, with tracer studies representing anatomic pathways without much information gained on functional relevance, while diffuse tractography yields in vivo information but has difficulty differentiating regions where there is a tortuous or complex crossing of fibers. Studies using resting-state functional MRI have also resulted in additional advances in the understanding of functional brain connectivity.

## What the CCEP Technique Brings to the Table

In 2004, Cleveland Clinic's Epilepsy Center published the first of several articles based on a technique — cortico-cortical evoked potentials (CCEPs) — pioneered by our neurophysiology lab using low-frequency electrical stimulation of electrodes implanted in patients undergoing invasive monitoring for epilepsy surgery. The first two articles published by our group (both in *Brain*) showed how regions of language and motor functions could be mapped using this technique.[1,2]

The CCEP technique is unique and different from the better-known method of standard cortical stimulation, which uses high-frequency direct cortical stimulation (25 to 50 Hz) to observe elicitation of an impairment or production of a behavioral response. In contrast, low-frequency cortical stimulation (1 Hz) is used in CCEP recordings to determine which other brain regions respond by observing a measurable evoked signal in distant or nearby cortical regions (Figure 1). The response, we believe, travels through white matter via cortico-cortical tracts or cortico-thalamo-cortical pathways.

Since those initial publications, our group has published several articles in the peer-reviewed literature reporting studies of various functional and epileptic networks in the human brain. Meanwhile, the CCEP technique has gained acceptance and been adopted by various academic centers in the United States and around the world.

## Next Step: A Single Brain Atlas from Hundreds of Patients

The strength of CCEP research findings to date has attracted an R01 grant from the National Institute of Neurological Disorders and Stroke, with Cleveland Clinic's Epilepsy Center serving as a principal investigative site along with the University of Southern California. The five-year grant is funding a study to develop a brain map of CCEP responses from across hundreds of patients who have undergone epilepsy surgery using the invasive technique of stereoelectroencephalography (SEEG).

The benefits of SEEG are that it minimizes distortion of the brain through placement of depth electrodes. This allows for easy coregistration and thus warping of analogous cortical regions onto a single brain atlas. The clear benefit of this research is that it promises to overcome a major disadvantage of the SEEG technique or any other invasive mapping of the brain, which is a lack of resolution of coverage of different brain regions. Since not all major brain regions are implanted with electrodes in an individual patient, the ability to systematically coregister hundreds of patients onto a single brain atlas will, over time, provide a much clearer picture of the complete and complex interactions of brain regions that can be elicited using CCEP studies.

Current published reports of brain interactions determined by CCEPs have been able to address questions of language organization, motor organization, limbic system connections and epileptic regions within small groups of patients. The objective now is to see how these findings correlate with larger groups of patients with more complete coverage of brain regions and to reveal the dynamic changes that can occur within and across different age groups, epilepsies, mood disorders, stimulation parameters and pathologies. We hope to be able to find noninvasive surrogates, such as in resting-state MRI or resting-state magnetoencephalography, that can identify these cortico-cortical pathways. The study is currently at the point where we are

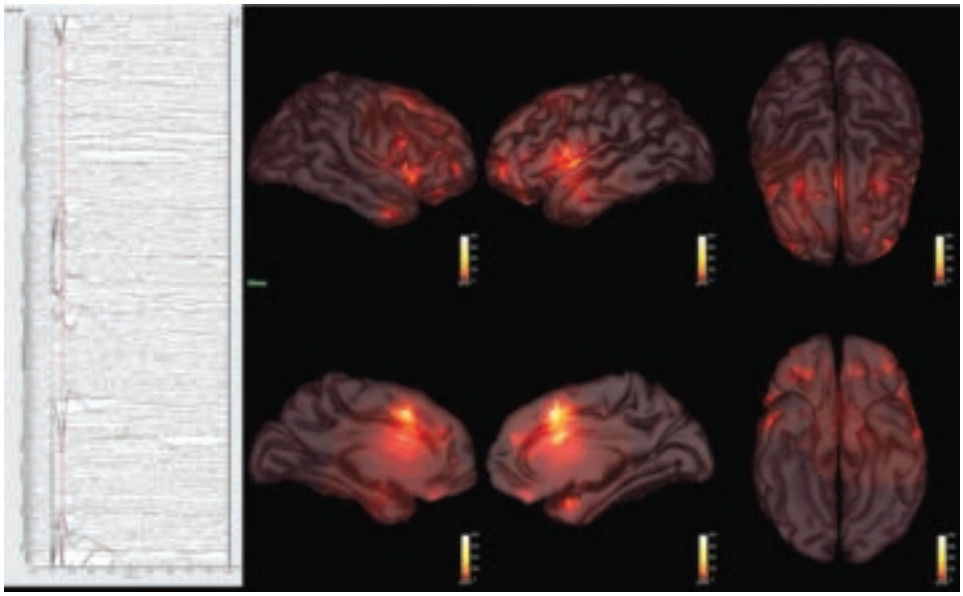

**FIGURE 1.** *A patient's CCEP responses are depicted as waveforms on the left with response estimates depicted by scaled colors (white is strongest) in the MRI scans on the right. Brain currents were estimated using a standard "minimum energy" constraint that restricts the currents to the vicinity of the electrodes to generate a useful estimate of brain dynamics.*

reviewing and processing retrospective data into a common brain atlas and developing new techniques for calculating and displaying connectivity from these data.

### Insights May Be Broadly Applicable

If we can understand brain connectivity in a more complete fashion, we stand to gain considerable insights that may extend beyond epilepsy and apply to a host of other neurological conditions, including autism, traumatic brain injury, Alzheimer's disease and various mood disorders.

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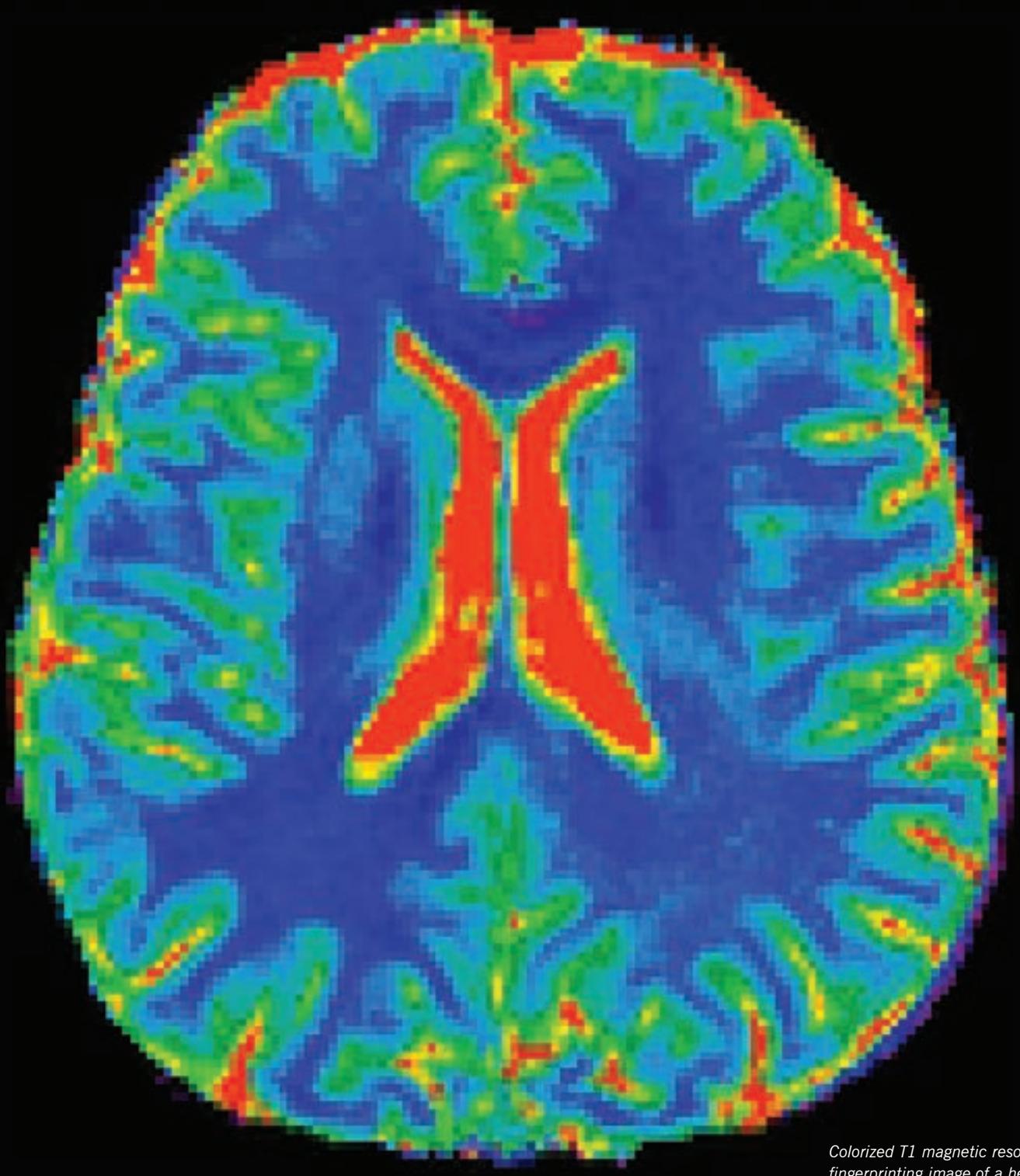
*Dr. Nair (naird@ccf.org; 216.444.2560) is Section Head of Adult Epilepsy in Cleveland Clinic's Epilepsy Center.*

*Dr. Mosher (mosherj@ccf.org; 216.444.3379) is a research scientist in Cleveland Clinic's Epilepsy Center.*


## KEY POINTS

- Cortico-cortical evoked potentials (CCEPs) is an accepted invasive monitoring technique that effectively identifies and quantifies response to low-frequency cortical stimulation in other brain regions.
- Cleveland Clinic's Epilepsy Center is a principal investigative site for an NIH-funded research study designed to develop a brain map of CCEP responses from across hundreds of patients who have undergone epilepsy surgery using SEEG.
- This research aims to elucidate the complex interactions of brain regions that can be elicited using CCEP studies. Its ultimate goal is to find noninvasive strategies to identify the cortico-cortical pathways underlying the pathophysiology of intractable epilepsy and perhaps other neurological conditions.



*Colorized T1 magnetic resonance fingerprinting image of a healthy human brain at 3T.*

COVER STORY

# Magnetic Resonance Fingerprinting: A New Window into Multiple Sclerosis

**By Daniel Ontaneda, MD, MSc; Kunio Nakamura, PhD; and Mark Griswold, PhD**

Although conventional MRI is an adequate tool for measuring focal inflammatory lesions in multiple sclerosis (MS), there is currently no validated method for specifically measuring demyelination and neurodegeneration in MS. One of the most important obstacles to developing therapies for progressive MS — and a significant unmet need in MS management — is the lack of specificity of conventional MRI to varying types and severities of tissue pathology in MS.

To that end, Cleveland Clinic's Mellen Center for Multiple Sclerosis Treatment and Research has collaborated with Case Western Reserve University in the application of a revolutionary technology known as magnetic resonance fingerprinting (MRF) to quantitatively assess brain changes in MS. We recently reported findings from the first study applying MRF in patients with MS. After a brief review of MRF, this article shares findings from that study and next steps in our group's exploration of this technology's compelling potential in MS care.

## Essentials of MRF Technology

MRF has emerged as an alternative imaging method for successfully addressing problems associated with conventional and advanced imaging modalities.[1] It enables the noninvasive quantification of multiple properties of tissue simultaneously through a novel approach to data acquisition, post-processing and visualization.[2] Instead of acquiring data by serial implementation of different sequences, MRF uses a randomized acquisition with varying values for image parameters:

- Flip angle (FA)
- Repetition time (TR)
- Echo time (TE)
- Inversion time (TI)

Data acquisition is conducted with a highly undersampled variable-density spiral k-space trajectory. The result of the acquisition is a set of time-resolved images in which the time course for each pixel reflects its underlying tissue properties. A dictionary is created by simulating the signal time courses that could appear in the data based on the pulse sequence used and ranges of T1 and T2 based on physiological limits. Each pixel is matched to find the dictionary entry that most resembles its characteristics, resulting in a map of the tissue properties for each pixel. This pattern-recognition approach of data analysis makes MRF a robust quantitative imaging technique with high tolerance to motion or artifacts.

## Advantages of MRF

Unlike with other imaging methods, the data processing in MRF is specialized to provide direct quantitative estimates of tissue properties of interest. MRF increases the sensitivity, specificity and efficiency of an MR study and thus may lead to new diagnostic testing methodologies. MRF may provide potential biomarkers for disease progression in MS as well as quantitative metrics of drug efficacy. In particular, MRF may be sensitive to molecular-level changes in myelin and neural tissue states.

The new technology offers advantages over conventional MRI in a variety of areas:

- **Quantitation.** Whereas conventional MRI is a nonquantitative method in which tissue abnormality is based on a signal intensity map, MRF holds the advantage of providing fully quantitative multimetric MRI properties with minimal post-processing.
- **Subvoxel characterization.** In conventional MRI, each voxel of tissue is actually an average of the tissue properties being sampled. By permitting subvoxel characterization of brain tissue, MRF overcomes this problem by enabling detection of multiple tissue properties from a single voxel.
- **Reproducibility.** Quantitative data produced with MRF is reproducible across various scanner setups, coils, hardware types and magnet properties.
- **Robustness to motion.** MRF acquisition is robust to motion error, whereas conventional MRI is significantly distorted by head movements. Motion is a significant problem when imaging MS patients with more severe disability.
- **Speed of acquisition.** Whole-brain acquisition for MRF takes approximately five minutes — a significant improvement over conventional MRI, which for multimodal acquisition takes more than 30 minutes. This means that T1, T2 and proton-density images can be obtained simultaneously with a single acquisition.

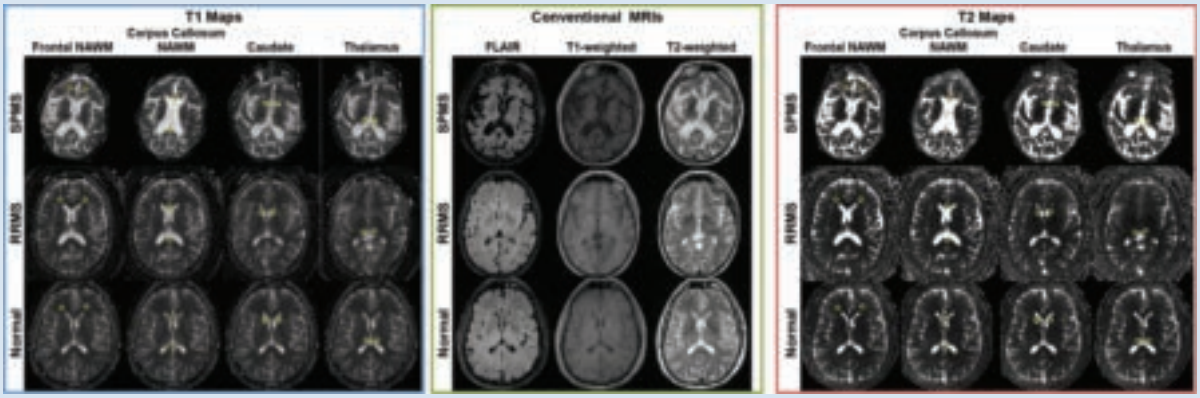



**FIGURE 1.** *MRF-based T1 maps (left panel), conventional MRIs (middle panel) and MRF-based T2 maps (right panel) from patients with secondary progressive MS (SPMS, top row), patients with relapsing-remitting MS (RRMS, middle row) and healthy controls (bottom row).*

## First Experience with MRF in MS

At the 2016 annual meetings of the American Academy of Neurology and the International Society for Magnetic Resonance in Medicine, our research team presented results from the first MRF application in patients with MS.[3] We conducted a cross-sectional study to examine whether MRF detects differences in normal-appearing white matter (NAWM) and normal-appearing gray matter (NAGM) between MS subjects and healthy controls as well as differences in lesions between patients with relapsing-remitting (RR) and secondary progressive (SP) MS (Figure 1). We also sought to understand the clinical relevance of MRF by measuring correlations of MRF findings with clinical disability.

The study's 55 subjects consisted of the following:

- 11 healthy controls
- 5 patients with clinically isolated syndrome
- 23 patients with RRMS
- 16 patients with SPMS

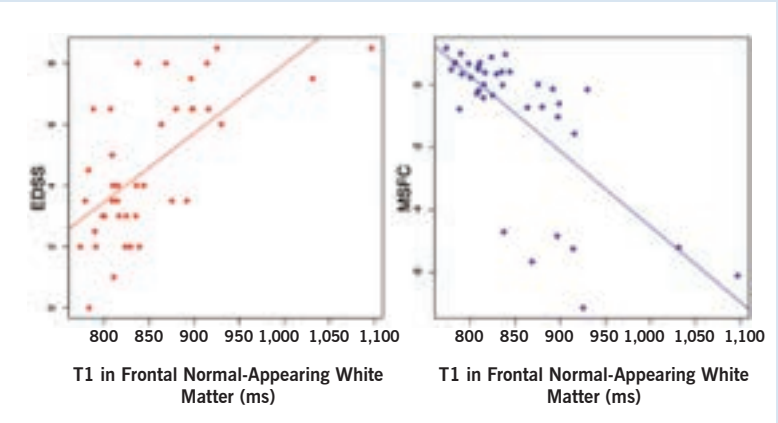



**FIGURE 2.** *Scatter plots showing correlation of T1 values in frontal normal-appearing white matter with Expanded Disability Status Scale (EDSS) score and MS Functional Composite (MSFC) score. Spearman rank correlations were 0.612 for the EDSS and –0.697 for the MSFC.*

All subjects had been followed for 12 years in a longitudinal study and were scanned at 3T (Trio™, Siemens) under written informed consent in keeping with an IRB-approved protocol. Subjects were scanned with a fast imaging with steady-state precession (FISP)-based MRF sequence. Data were reconstructed and processed offline in MATLAB (The Mathworks). A dictionary with 47,049 elements (T1 range, 20-5,000 ms; T2 range, 10-500 ms) was used for pattern matching to generate quantitative T1, T2 and spin density maps.

The study's key results included the following:

- Between healthy controls and the MS groups, T1 values in the thalamus and caudate were significantly different (both $P < .01$).
- Between patients with RRMS and those with SPMS, T1 values in frontal NAWM were significantly different, as were T1 and T2 values in T2 lesions (all $P \leq .001$).
- T1 values in frontal NAWM showed the highest correlation with both the Expanded Disability Status Scale (EDSS) and the MS Functional Composite (MSFC) scores (absolute Spearman rank correlation > 0.61), as detailed in Figure 2.
- T1 and T2 values in T2 lesions also correlated with MSFC score (Spearman rank correlation = –0.697 and –0.582, $P < .001$).

Our findings show that MRF provides simultaneously acquired and intrinsically registered maps of multiple relaxation parameters. In agreement with previous T1-mapping techniques, we also found increased T1 in normal-appearing structures. T2 was increased in certain normal-appearing regions, similar to prior evidence that showed changes in NAWM but not in deep gray matter structures.

In addition to demonstrating differences between healthy controls and patients with MS, MRF distinguished the clinical course of disease even in this small sample. This indicates a high sensitivity for detecting underlying nonlesional changes in MS and suggests that MRF may provide a window into disease pathophysiology. Significant correlations with the MSFC and EDSS scores likewise suggest that MRF measures capture a clinically meaningful change in normal-appearing tissue.

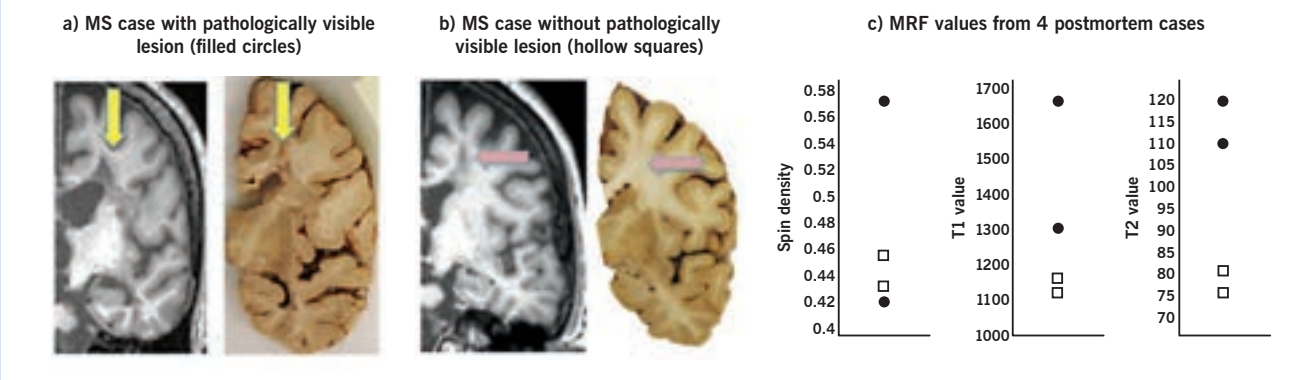



**FIGURE 3.** *Preliminary findings from postmortem brains of two MS subjects with macroscopically visible white matter plaques (a) and two MS subjects without such plaques (b). The plots (c) show the median value within T1 hypointense lesions from MRF imaging in these four brains. Each marker indicates a measurement from a single brain, with filled circles indicating MS subjects with pathologically visible plaques and hollow squares indicating MS subjects without visible plaques.*

## MRF and Pathology

We also have examined potential correlations between MRF and pathology findings through Cleveland Clinic's MS postmortem program using imaging followed by rapid autopsy.

In this preliminary study (data in preparation for presentation), we imaged four MS cadavers on a 3T Trio scanner using conventional MRI and MRF. On conventional FLAIR MRI, all cases had T2 hyperintense and T1 hypointense lesions. When the brain and spinal cord were removed after scanning, macroscopic evaluation of fixed brain slices revealed that two brains contained no white matter plaques and two brains had white matter lesions. We processed the MRI and MRF data as described for lesional analysis, segmented T2 and T1 lesions, and obtained median MRF-based spin density, T1 and T2 values for each brain. The median values in the two groups showed an interesting trend in T1 and T2 values in T1 lesions (Figure 3).

In view of these findings, quantitative MRF seems to hold promise for differentiating T1 lesions into pathologically identified lesions.

## Next Steps

We are now conducting a longitudinal study using MRF measures focusing on the thalamus in MS. This study will help determine the sensitivity of MRF over time and provide improved image resolution. MRF for use at 7T scanning is now under development as well. We also hope to implement an MRF sequence, known as MRF exchange (MRF-X), that takes chemical exchange effects into account and could have significant sensitivity to myelin content.[4]

MRF represents a significant advance in imaging. In MS we expect to identify a marker of disease that can be used as a diagnostic test and as a biomarker of disease severity. Several features — fast acquisition, low variability between scanners and robustness to motion — make MRF an ideal potential outcome measure in phase 2 clinical trials.

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*Dr. Ontaneda (ontaned@ccf.org; 216.444.0151) is a neurologist in Cleveland Clinic's Mellen Center for Multiple Sclerosis Treatment and Research.*

*Dr. Nakamura (nakamuk@ccf.org; 216.444.4789) is a project scientist in the Department of Biomedical Engineering in Cleveland Clinic Lerner Research Institute.*

*Dr. Griswold (mark.griswold@case.edu) is a professor of radiology at Case Western Reserve University School of Medicine, Cleveland.*

## KEY POINTS

- There is currently no validated method for measuring demyelination and neurodegeneration in MS.
- Magnetic resonance fingerprinting (MRF) is a new technology that shows promise as a clinically feasible approach for quantifying and characterizing tissue damage in MS.
- A Cleveland Clinic/Case Western Reserve University research team recently presented the first study of MRF's application in patients with MS and has related investigations underway, including a longitudinal study to determine the sensitivity of MRF over time.

# Brain Lesion Conspicuity at 7T: Defining the Diagnostic Value of High-Field-Strength MRI

**By Stephen E. Jones, MD, PhD**

An advanced 7-tesla (7T) MRI scanner was installed at Cleveland Clinic in 2013 and has now been in active use for more than two years. The principal advantage of 7T MRI over MRI scanning at lower magnetic field strengths is increased signal, which can provide smoother images (higher signal-to-noise ratio), faster scanning and higher resolution. The latter is the factor most likely to expand the future clinical application of 7T MRI.

## Comparative Imaging Studies Underway

In addition to research and development studies, Cleveland Clinic's 7T scanner has been used, with IRB approval, to scan patients with neurological disease for the explicit purpose of comparing lesion conspicuity between 7T images and images obtained previously at lower magnetic field strengths.

To date, 134 patients have undergone this type of comparative imaging, with diseases including epilepsy, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, orbital neoplasm, vasculitis, brain tumors and others. Research is now underway evaluating the clinical utility of 7T MRI for enhancing the diagnosis of epilepsy, with preliminary results showing that 7T images enhance previous findings in nearly half of patients imaged.

## All About Conspicuity

To define 7T's incremental contribution to image quality, 11 members of Cleveland Clinic's neuroradiology staff assessed 80 paired images of various lesions — one at 7T and one at 3T — in a blinded manner. Each image was scored on a 5-point scale for lesion conspicuity (clearly superior, mildly superior, equal, mildly inferior, clearly inferior).

Across the full set of image pairs, the overall assessment of the neuroradiologists was that lesion conspicuity at 7T was mildly superior to lesion conspicuity at 3T, averaged over the large variety of diseases and sequences. Depending on the sequence and disease, many specific examples were considered clearly superior by nearly all neuroradiologists. Figure 1 presents four image pairs as examples.

A conclusion appears to be emerging from these studies that 7T neuroimaging will have a future clinical impact in cases where lesion detail is important and enhanced resolution would aid diagnosis. Typically, 7T imaging does not show lesions invisible at lower field strengths but rather shows visible lesions in greater detail, which can be medically important. While the simple presence of a lesion on a study is significant, so too is the lesion's conspicuity so that a radiologist's eye can detect it.

A conclusion appears to be emerging from these studies that 7T neuroimaging will have a future clinical impact in cases where lesion detail is important and enhanced resolution would aid diagnosis.

## Parallels with Consumer Electronics

On average, 7T imaging enhances lesion conspicuity — and therefore can enhance detection of lesions not previously appreciated. The situation is analogous to how high-definition television has enhanced visualization over conventional TV. Similarly, just as 10 years ago the widespread introduction of 3T MRI enhanced neuroradiological diagnosis compared with 1.5T MRI, our results suggest that 7T MRI is likely to continue this trajectory of diagnostic improvement.

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*Dr. Jones (joness19@ccf.org; 216.444.4454) is Vice Chair for Research and Academic Affairs in Cleveland Clinic's Imaging Institute and holds appointments in the Neurological Institute's Epilepsy Center and Mellen Center for Multiple Sclerosis Treatment and Research.*

## KEY POINTS

- Cleveland Clinic has performed comparative imaging studies at 7T and 3T MRI in over 130 patients to date with a diversity of neurological conditions.
- A formal assessment of lesion conspicuity among 80 pairs of 7T and 3T images by 11 Cleveland Clinic radiologists found the 7T images to be mildly superior to 3T images overall and clearly superior in many cases.
- Neuroimaging at 7T appears to offer potential clinical utility in cases where lesion detail is important and enhanced resolution (beyond that possible with 3T MRI) would aid diagnosis.

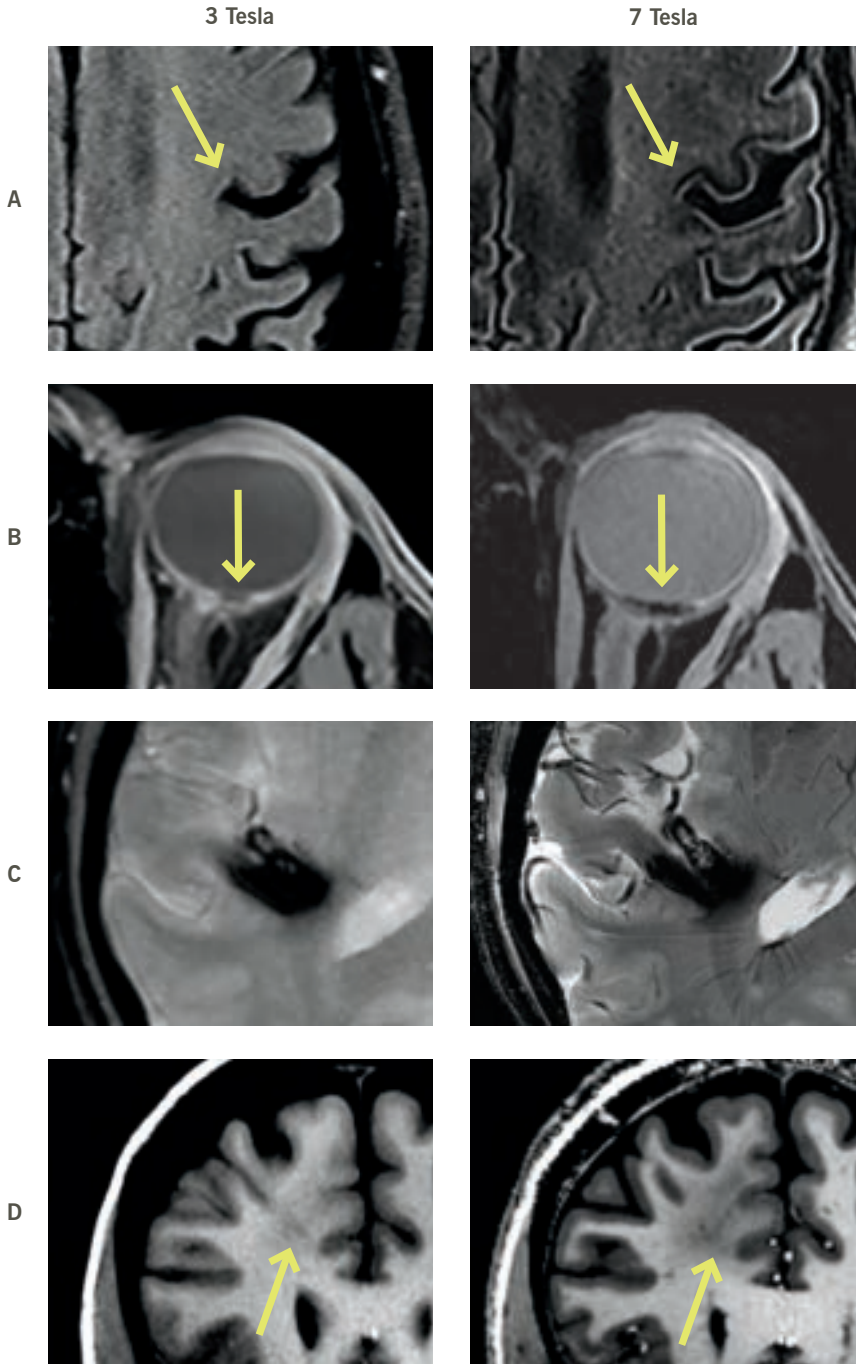


**FIGURE 1.** *Comparative imaging studies at 3T and 7T. (A) Images of a patient with amyotrophic lateral sclerosis in which 7T reveals enhanced signal loss along the motor strip of the precentral gyrus. (B) Images of an orbital melanocytoma of the optic nerve head, with 7T clearly showing the relation of the tumor to the nerve head, an important detail for managing surgical treatment. (C) Images of a large cavernous malformation, with 7T revealing superior details of the lesion with respect to underlying anatomy. (D) Images demonstrating left frontal cortical dysplasia. Note how 7T clearly shows superior delineation of the subcortical lesion.*

# Coordinated Reset DBS: A Promising Approach for Pairing Insight with Efficacy in Neuromodulation

**By Kenneth Baker, PhD**

Deep brain stimulation (DBS) is now a standard treatment for Parkinson's disease (PD), offering hope of significant relief of debilitating motor signs for patients with advanced-stage, medically refractory disease. Current therapy relies on continuous, high-frequency stimulation of the targeted area to achieve motor benefits. However, the targeted subcortical nuclei, including the subthalamic nucleus, includes both motor and nonmotor (i.e., cognitive and behavioral) pathways. Surgical teams and clinical programmers attempt to modulate neural activity along the motor networks while limiting current spread to nonmotor areas to the extent possible.

My colleagues and I are investigating novel approaches to DBS for PD in order to identify new ways to optimize therapy delivery while furthering our understanding of PD pathophysiology and the therapeutic mechanisms of DBS.

## Contemporary DBS: Efficacy Without Insight

The traditional DBS approach involves surgical implantation of a pacemaker-like device to deliver a continuous stream of high-frequency electrical pulses to either the subthalamic nucleus or the internal segment of the globus pallidus — key nodal points in the brain's sensorimotor circuitry. Once in place, the specific parameters (e.g., amplitude) of stimulation are adjusted by a healthcare provider to maximize therapeutic benefit while avoiding stimulation-induced side effects. Once optimized, DBS typically is delivered continuously, 24 hours a day, for the rest of the patient's life.

The physiologic mechanisms of DBS, like the pathophysiology of PD itself, remain a mystery. Theories concerning the latter have evolved from changes in mean firing rate across nodal points in the motor circuit to more recent hypotheses involving pathologically synchronized neural activity within and across those same nodal points. Accordingly, therapeutic benefit is thought to derive from further modulation of that activity, yet a precise mechanistic understanding remains elusive.

## DBS Programming: Balancing the Good and Not So Good

A well-targeted and well-programmed DBS lead typically yields outcomes comparable to the patient's best motor benefit from dopamine replacement therapy — but without the fluctuations inherent to pharmacotherapy.

DBS is not without potential side effects, however, including those arising from slight misplacement of leads (allowing current to spread to brain regions outside the target area) and those thought to arise from current spread to nonmotor areas within the target itself. The latter may be more subtle and include cognitive or affective changes believed to be caused by stimulation interfering with "normal" neural processing. In either case, the effort to avoid such side effects may limit programming to parameters that are suboptimal for treating the patient's motor deficits.

## A Novel Approach to DBS: New Patterns for Old Targets

Using preclinical parkinsonian models, we are investigating a novel DBS paradigm that offers the potential to mitigate the risk of stimulation-induced side effects. The approach, termed *coordinated reset DBS*, was developed using computational modeling techniques by our collaborator, Peter Tass, MD, PhD, in Juelich, Germany.[1] It involves using the multiple contacts of the DBS lead to deliver intermittent, pseudorandomized bursts of brief, low-intensity, spatially distributed pulse trains for the specific purpose of desynchronizing "pathological" neural oscillations (Figure 1).

An advantage of this paradigm is that its effects are achieved using lower individual pulse amplitudes, thus reducing the risk of side effects. Moreover, its desynchronizing effects are hypothesized to endure beyond treatment delivery, perhaps due to plastic changes at the synaptic level, such that intermittent therapy may yield benefit that outlasts stimulation by days or weeks. Such carryover would substantially reduce the overall duty cycle of stimulation, further limiting the potential for stimulation to interfere with cognitive or affective function.

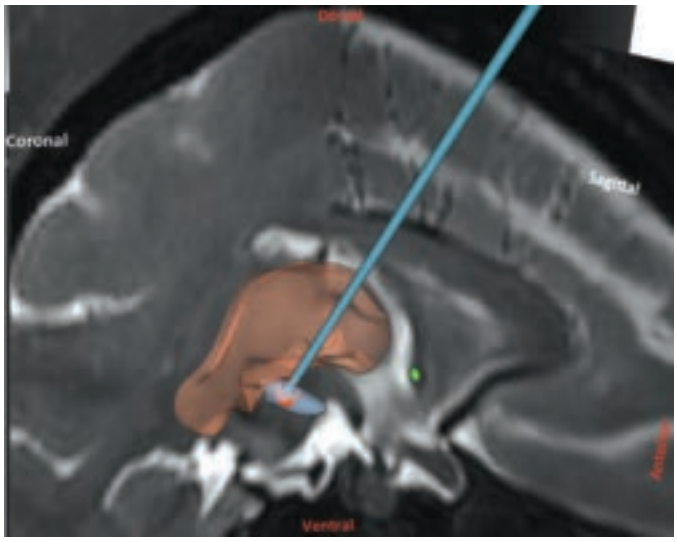


**FIGURE 1.** *Representation of the coordinated reset DBS paradigm in two planes, with a view of how the DBS lead is targeted relative to coronal and sagittal MRIs.*

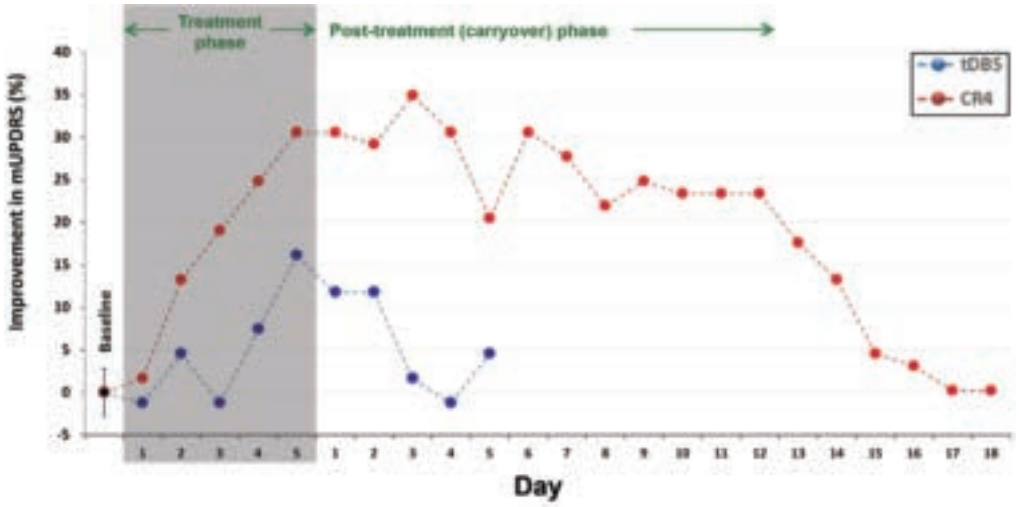


**FIGURE 2.** *Daily percentage changes from baseline in parkinsonian motor severity (mUPDRS) in response to five days of traditional DBS (tDBS; blue) versus coordinated reset DBS (CR4; red). The initial composite rating score was recorded at the beginning of each daily session across the experiment. Each data point represents the OFF DBS rating recorded each morning, including that taken just before stimulation delivery during each day of the five-day treatment phase (shaded gray region). In contrast to traditional DBS, coordinated reset DBS was associated with significant, cumulative improvement in the OFF DBS motor score over the five days of treatment, which persisted for more than a week following cessation of therapy.*

The therapeutic potential of coordinated reset DBS is supported by multiple theoretical models and, more recently, by our own experimental data comparing coordinated reset DBS against traditional DBS of the subthalamic nucleus in terms of the magnitude and time course of their effects on motor performance in a preclinical parkinsonian model.[2] In contrast to the limited carryover effects observed in response to traditional DBS, coordinated reset treatment yielded benefit that accumulated over five days of intermittent treatment (four hours a day) and subsequently persisted for more than one week following therapy cessation (Figure 2).

### What Lies Ahead

In subsequent work, we will further investigate the nature and time course of coordinated reset efficacy to better understand the best way to translate the approach to patients with PD while also characterizing its effects on neural activity across subcortical and cortical motor circuits. Overall, we anticipate that our data will address not only the translational potential of coordinated reset DBS but also the link between changes in neural activity in the motor circuit and motor sign manifestation in PD.

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*Dr. Baker (bakerk6@ccf.org; 216.445.2244) is an assistant staff member in the Department of Neurosciences in Cleveland Clinic Lerner Research Institute.*

## KEY POINTS

- Both the physiologic mechanisms of deep brain stimulation (DBS) and the pathophysiology of Parkinson's disease (PD) remain a mystery.
- Our group is investigating a novel DBS paradigm — coordinated reset DBS — that offers the potential to mitigate the risk of stimulation-induced side effects. Its therapeutic potential is supported by various theoretical models and new data from our group in a preclinical parkinsonian model.
- Our ongoing work aims to realize the translational potential of coordinated reset DBS while also elucidating the link between changes in motor circuit neural activity and motor sign manifestation in PD.

# Self-Reported Depression in ALS: New Insights and Their Implications

**By Nimish J. Thakore, MD, and Erik P. Pioro, MD, PhD**

About half of all patients with amyotrophic lateral sclerosis (ALS) die within roughly three years after onset of weakness, and current treatments prolong survival only marginally. Until a treatment emerges that effectively slows or halts ALS progression, the focus of care is primarily to maximize function, comfort and quality of life.

Despite the fatal nature of ALS, it's a common belief that affected patients tend not to become depressed. To further examine that belief, we recently conducted the largest single-center study of depression in ALS to date that used a validated instrument for depression evaluation. Here we recap the findings of our study, published in *Neurology*[1] in March 2016, and explore their implications for clinical practice and future ALS research.

## Study Design and the Knowledge Program

We sought to examine the prevalence, associations and course of depression, as measured by the validated Patient Health Questionnaire-9 (PHQ-9), among 1,067 patients with ALS evaluated in Cleveland Clinic's Neuromuscular Center over an eight-year period.

All patients had completed the PHQ-9 as part of the Knowledge Program©, a system pioneered by Cleveland Clinic's Neurological Institute in 2006 to electronically capture and store patient-reported outcomes (PROs) entered by patients using wireless tablet devices in waiting rooms.[2] The PROs include generic measures, such as the PHQ-9 for depression and the validated quality-of-life instrument known as EQ-5D, as well as multiple disease-specific metrics. The information gathered via the Knowledge Program is reported to the provider in the electronic medical record to inform clinical care.

## Key Findings on Depression Prevalence and Associations in ALS

As reported in detail in our *Neurology* paper,[1] we found that about one-third of the 1,067 ALS patients were at least moderately depressed at initial assessment, and approximately 5 percent were severely depressed. Overall, depression was substantially more prevalent in patients with ALS than in the general population.

Patients with more severe ALS and prominent respiratory symptoms were the most depressed. Not unexpectedly, depression was associated with poorer quality of life. However, severity of depression did not increase with time despite worsening weakness (Figure 1).

## Key Findings on Depression's Effect on Survival

Next we examined predictors of mortality using dates of death ascertained in 499 patients. Interestingly, we found a robust deleterious effect of depression after adjusting for other predictors of survival including age, gender, bulbar onset, prominent respiratory symptoms, disease severity (as measured by the revised ALS Functional Rating Scale), rate of progression and body weight. Median survival from onset of ALS was 11 months shorter in depressed patients than in their nondepressed counterparts (Figure 2), and univariate proportional hazards modeling showed that each 1-point increase in a patient's initial PHQ-9 score (indicating greater depression severity) increased the risk of death during follow-up by 4.4 percent. There have been few prior reports of depression affecting survival in ALS, and all have studied much smaller cohorts.[3]

## Implications for Both Clinical Care and Research

These findings reinforce the importance of recognizing depression in patients with ALS and then treating it aggressively. Although we could not determine in our study whether survival improved in ALS after depression was treated, it is certainly reasonable to offer such treatment, if only to improve quality of life and help patients cope better as their disease progresses.

Additionally, the results of this study may influence the design of future ALS therapeutic trials so that the effect of depression is taken into account. For a number of proposed therapies for ALS, initial positive findings from registry studies (using historical controls) have proved to be at odds with negative results from subsequent randomized controlled trials,[4] and it is possible that depression played a role in those discordant outcomes.

## Why Does Depression Affect Survival?

Depression negatively affects survival in many chronic diseases, and our study adds ALS to the list. ALS is believed to be different, however, because it is characterized by severe and inexorable physical deterioration leading to death. The mechanism mediating this effect of depression on survival in ALS is unknown and demands further study. Possibilities include poorer general health, poorer adherence to treatment and even biological mechanisms. An obvious question for future studies is whether aggressive treatment of depression in ALS would extend survival.

## Value and Power of the Knowledge Program

PROs captured by the Knowledge Program and reported to providers during clinical encounters add a rich quantitative dimension to other available information. Although some may question the incremental value of such extra information in routine clinical care, our results demonstrate the tremendous prognostic importance of such PROs and prove the transformative value of the Knowledge Program in caring for individual patients. This study also showcases this tool's value as a low-burden means of electronic capture and assembly of PROs to address clinically and scientifically meaningful questions.

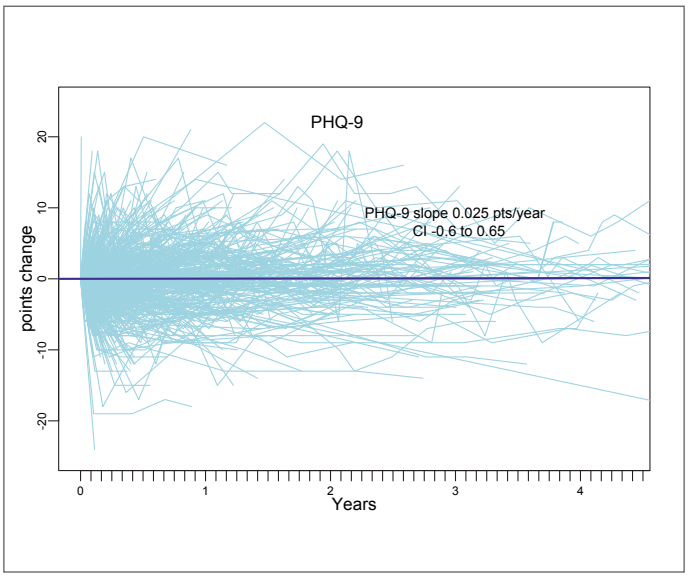


**FIGURE 1.** *Plots of ALS patients' individual trajectories of serially measured PHQ-9 scores showed no overall worsening of depression over time.*
(Reprinted, with permission, from Thakore and Pioro.[1] © 2016 American Academy of Neurology.)

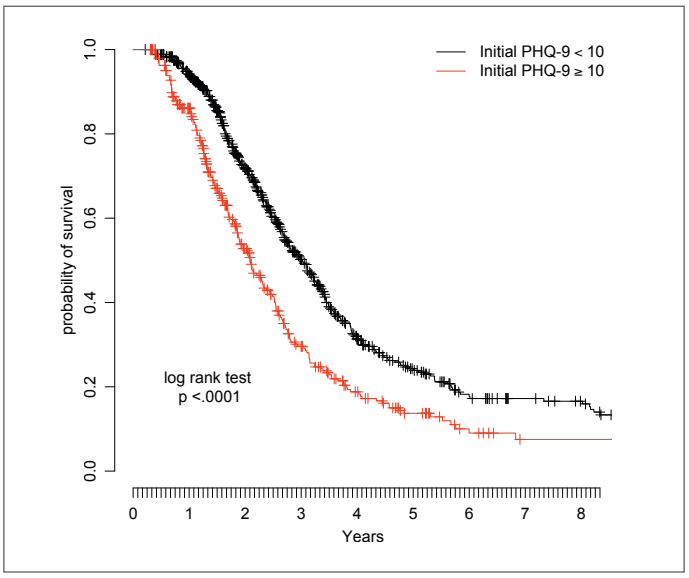


**FIGURE 2.** *Kaplan-Meier curves showing significantly shorter survival among patients with ALS who were at least moderately depressed (PHQ-9 score ≥ 10) versus those who were not depressed (PHQ-9 score < 10).*
(Reprinted, with permission, from Thakore and Pioro.[1] © 2016 American Academy of Neurology.)


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*Dr. Thakore (thakorn@ccf.org; 440.312.6100) is a neurologist in Cleveland Clinic's Neuromuscular Center and Center for Regional Neurosciences.*

*Dr. Pioro (pioroe@ccf.org; 216.445.2988) is the Barry Winovich Endowed Chair in ALS Research and Director of the Section of ALS and Related Disorders in the Neuromuscular Center.*


## KEY POINTS

- In the largest reported single-center study of depression in ALS using a validated instrument, we found that depression is more prevalent in this population than is typically perceived.
- We found that depression has detrimental effects on survival and quality of life in ALS, underscoring the importance of its identification and treatment in this population.
- Our findings demonstrate the potential for patient-reported outcomes to enhance routine clinical care.

# Imaging Microglia in Living Mice Reveals Unexpected Roles for the Brain's Guardians

**By Dimitrios Davalos, PhD**

Microglia are the resident immune cells of the brain and spinal cord that form the first line of defense when the CNS or the blood-brain barrier (BBB) is compromised. Microglia can be protective when they contain injuries and remove dead cells or pathogens — or damaging when their activation exacerbates pathologies.

Historically, microglia were mostly studied in the context of CNS disease, but over the past decade microglia have been continuously linked with new functions that are essential for normal brain function, like sculpting neuronal networks during development and possibly even regulating neuronal plasticity in the adult brain. The advent of cutting-edge imaging technologies and novel genetic tools to detail and manipulate microglial behavior in living animal models promises an even more exciting future for microglial research.

## Early Insights Prompt Rethinking of 'Resting' Microglia, Reveal Novel Protective Roles

In the physiological brain, microglia were previously thought to be sessile and were hence termed *resting* microglia. When we imaged microglia in the living mouse brain for the first time, we found that they continuously survey the CNS by extending and retracting their fine processes on a time scale of seconds (Figure 1).[1] This unexpected finding inspired numerous studies aimed at understanding the mechanisms and the significance of this novel microglial function for neuronal plasticity, function and dysfunction.

We also found that microglia have an impressive ability to detect small injuries in the brain and contain them with their processes within only a few minutes (Figure 1). Moreover, we identified that adenosine triphosphate (ATP), a molecule that gives energy to every living cell, can function as a danger signal that makes microglia aware of injury in their vicinity. When cells in the brain are physically injured, they spill ATP in the surrounding tissue. Since ATP is normally not present in the extracellular space, it is immediately detected by astrocytes in the vicinity of the injury, and the astrocytes release more ATP locally, which guides microglial processes to find and contain brain damage.[1]

These unexpected findings introduced a new category of microglial responses that are much faster than their previously known inflammatory activation. The findings also established a new paradigm for studying microglia in physiology and after injury, by combining two-photon microscopy with laser- or mechanically induced injury and micropharmacology in the living brain, in real time.

## Blood Protein Activates Microglia to Drive Formation of Perivascular Inflammatory Lesions

More recently, we studied microglial responses following BBB disruption using the animal model of multiple sclerosis (MS), experimental autoimmune encephalomyelitis (EAE). We identified microglia as the first cells to show signs of activation by clustering around blood vessels. By performing repetitive in vivo imaging in the same mice, we found that perivascular clustering of microglia starts before disease onset and continues throughout the course of EAE (Figure 2).[2]

Also, by imaging microglia and axons in real time, we found that axons undergo severe morphological alterations within microglial clusters that often result in axonal fragmentation and uptake by microglia (Figure 2).[2] These microglial clusters form at sites of BBB disruption where the blood protein fibrinogen leaks out of blood vessels and is converted to insoluble fibrin. Fibrin is the end product of the coagulation cascade and is extensively deposited in EAE and MS lesions. By combining pharmacological or genetic inhibition approaches with correlated histology of spinal cord areas previously imaged in vivo, we found that fibrin(ogen) binding to the integrin receptor CD11b/CD18 (also known as Mac-1, $\alpha M\beta 2$ or complement receptor 3 [C3R]) is required for microglial clustering and axonal damage.[2] Moreover, by showing that, upon extravasation, fibrinogen induces reactive oxygen species release by microglia, we identified a link between BBB disruption, microglial activation and axonal damage, the main culprit in neuroinflammatory disease.

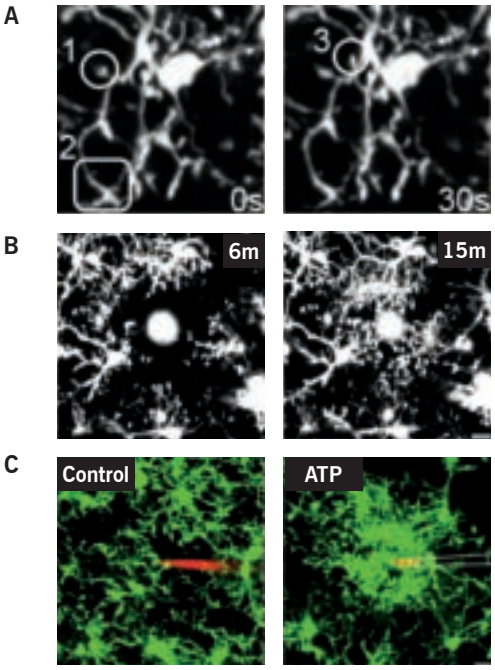


**FIGURE 1.** *Microglia perform tissue surveillance by constantly extending and retracting processes (A, circles), rapidly responding to localized brain injury (B) in an ATP-dependent manner (C).* (Adapted from Davalos et al.[1] in *Nature Neuroscience*.)

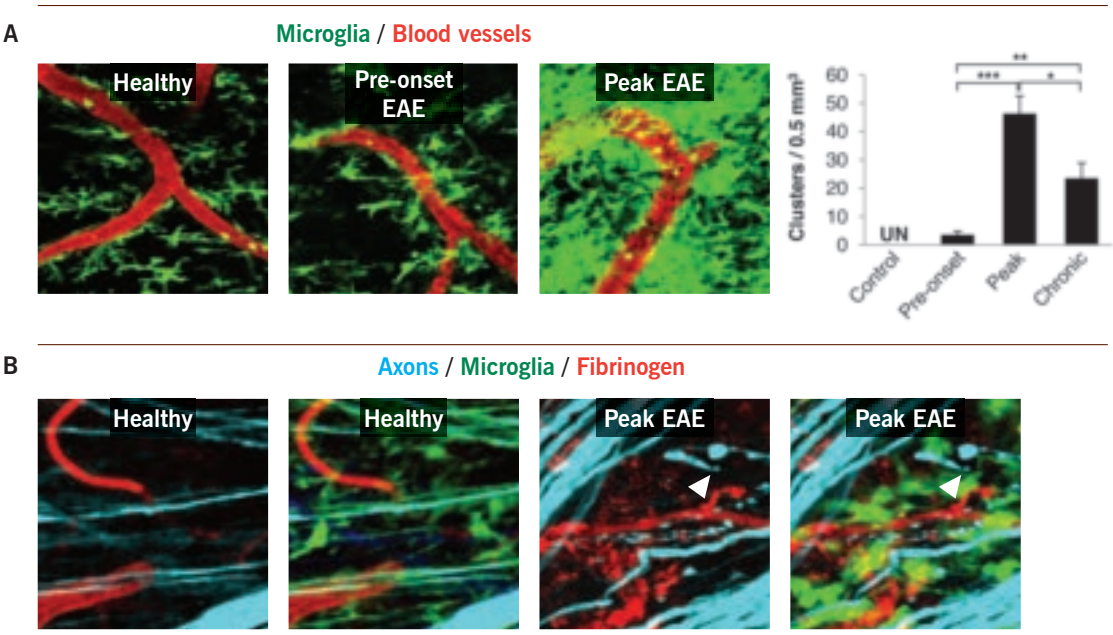


**FIGURE 2.** *(A) Microglia (green) cluster around blood vessels (red) throughout experimental autoimmune encephalomyelitis (EAE), starting before disease onset. (B) Clusters form in perivascular areas with fibrin deposition. Axonal damage (cyan), including bending, swelling and fragmentation (arrowhead), occurs only within such fibrin-rich areas (red) with microglial clusters.* (Adapted from Davalos et al.[2] in *Nature Communications*.)

## New Lab Studies Mechanisms of Microglia's Protective and Damaging Functions in Stroke and MS

At our newly established lab in the Department of Neurosciences in Cleveland Clinic's Lerner Research Institute, we are pursuing two main projects designed to characterize the cellular responses and molecular pathways involved with microglial-neuronal and microglial-vascular interactions in the healthy CNS and in the context of neurological disease.

We use novel genetic tools to perform microglia-specific pathway manipulation in combination with in vivo imaging in models of neuroinflammation to decipher how microglia and peripheral immune cells might be involved with processes regulating BBB integrity and neuronal damage. We are also investigating the sequence of events and the molecular pathways that drive microglial responses in the ischemic brain. In particular, we study the real-time responses of microglia, in relation to vascular and neuronal disruption during and after ischemic injury, by longitudinal in vivo imaging. Also, by using genetic models to manipulate fibrinogen, we aim to decipher the molecular links between vascular rupture or ischemic insult and microglial responses, especially in relation to neuronal degeneration after stroke.

Our in vivo imaging studies have the potential to provide target validation for the activating effects of blood proteins and other danger signals on microglia. These studies should prove instrumental for the initiation of drug discovery efforts and for development of screening and validation assays for novel therapeutic targets for diseases with BBB disruption, such as MS and stroke.

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*Dr. Davalos (davalod@ccf.org; 216.444.7690) is an assistant staff member in the Department of Neurosciences in Cleveland Clinic Lerner Research Institute.*

## KEY POINTS

- The advent of novel imaging technologies and genetic tools to detail and manipulate microglial behavior in living animal models has significantly advanced microglial research over the past decade.
- Key insights include the discovery that (1) microglia continuously survey the healthy CNS and can rapidly contain localized brain injuries; and (2) in neuroinflammatory disease, fibrinogen leaking from disrupted blood vessels activates microglia and contributes to axonal damage and formation of new inflammatory lesions.
- Our new lab at Cleveland Clinic is building on these findings with the aim of characterizing the cellular responses and molecular pathways that alter microglial-neuronal and microglial-vascular interactions in health versus neurological disease.

# Eye Gaze-Based Autism Risk Index Shows Promise as First Objective Tool for Diagnosing Autism

**By Thomas W. Frazier, PhD, and Sumit Parikh, MD**

An old adage holds that the eyes are the window to the soul. But for children with suspected autism spectrum disorder (ASD), new research suggests that the eyes promise to be even more — the key to the first objective and quantitative tool for diagnosing ASD.

Our team at Cleveland Clinic recently developed an objective measure of autism symptom level — named the "autism risk index" (ARI) — based on remote eye gaze tracking to various stimuli. In April 2016, we published a paper in the *Journal of the American Academy of Child and Adolescent Psychiatry* reporting results of initial and replication studies that showed the ARI to have high diagnostic accuracy in differentiating between children with ASD and similar children with non-ASD developmental disorders.[1] These findings suggest that the eye gaze-based ARI could prove to be a useful quantitative and objective measure of risk for ASD in at-risk settings.

This article summarizes the essentials of the ARI and the data supporting it, and then shares plans to further validate the index and scale it for potential widespread clinical use.

## Rationale and Hypothesis

Our efforts to develop the ARI stemmed from the reality that current methods for diagnosing ASD — direct clinical observation, interviews and parent reports — are highly subjective. Spurred by the recognition that abnormal eye gaze and social attention patterns are core features of ASD and by recent studies supporting the potential discriminative value of eye gaze tracking in ASD, we hypothesized that children with ASD gaze longer at nonsocial targets and less at social targets relative to children with non-ASD disorders. So we set out to develop and replicate a measure of ASD symptom level based on eye gaze tracking to social and nonsocial visual stimuli.

We opted to collect eye gaze data using remote eye tracking, a promising technology that avoids the use of the headgear or disruptive monitoring associated with other methods (such as EEG or MRI). Remote eye tracking is unobtrusive and akin to watching TV, with the eye tracker mounted to the frame of a 19-inch LCD monitor that presents visual stimuli to young subjects.

## Study Design

We evaluated two samples of children ages 3 to 8 who had been referred for evaluation by their pediatricians and were later diagnosed, based on clinical consensus, as having either ASD or another (non-ASD) developmental disorder. (Consensus diagnosis was based on multidisciplinary evaluations that included administration of the Autism Diagnostic Observation Schedule [ADOS-2] and the Social Responsiveness Scale [SRS-2].)

Blinded researchers conducted the seven-minute evaluations at the LCD monitor, during which the eye tracker recorded how long children looked at prespecified regions of interest (ROIs) as they were presented with literature-based social stimuli (e.g., faces) and nonsocial stimuli (inanimate objects and geometric shapes) (Figure 1). Looking times were recorded for each prespecified ROI and averaged across ROIs to generate a composite risk index (i.e., the ARI). Area-under-the-curve (AUC) analyses evaluated classification accuracy relative to consensus clinical diagnoses for both the initial study (N = 45) and the replication study (N = 34).

## Key Results

In both the initial and replication study samples, the ARI demonstrated high diagnostic accuracy, with AUC values for sensitivity versus specificity as follows:

- Initial sample, AUC = 0.91 (95% CI, 0.81-0.98)
- Replication sample, AUC = 0.85 (95% CI, 0.71-0.96)

The index dramatically outperformed the SRS-2 instrument in diagnostic accuracy and showed a strong correlation with ADOS-2 severity score ($r = 0.58$ and $r = 0.59$ for initial and replication samples; $P < .001$), which is the gold-standard measure of ASD symptom severity.

We concluded that combining eye tracking measurements into a risk index has strong potential clinical value for objectively enhancing ASD diagnosis, grading symptom severity and even gauging symptom changes in response to treatment.

## ADVANTAGES OF THE AUTISM RISK INDEX

- The index promises easier acceptance of an ASD diagnosis by parents wary of relying on clinical impressions alone.
- Remote eye tracking is unobtrusive and well-suited to young children.
- Assessment is rapid, can be largely automated, requires limited technical expertise and does not require ongoing verification of interrater reliability.
- The technology is highly scalable, and hardware costs are likely to be modest.
- The index can be easily used in conjunction with other clinical measures.

### Next Steps: Further Replication, Refinement, Commercialization

Before we can turn our findings into a clinical tool, we need to replicate the approach again in a larger sample. In this next step, we also plan to fine-tune the ARI algorithm to make it more accurate and sensitive to ASD. Our original approach was conservative — i.e., all prespecified ROIs were included, regardless of direction and validity level — and we expect that more sophisticated machine-learning methods can greatly enhance the ARI's accuracy.

After this replication, we will take the final ARI and examine its performance across multiple sites in the U.S. to ensure that it performs as expected. We will also begin collecting data from a larger sample of healthy children to see whether the ARI can be helpful not only for diagnosis but also for screening in general population settings. We will simultaneously be taking steps in the commercialization process to move toward availability of an objective tool that clinicians can purchase and use to inform their judgment.

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*Dr. Frazier (fraziet2@ccf.org; 216.448.6440) is Director of Cleveland Clinic Children's Center for Autism.*

*Dr. Parikh (parikhs@ccf.org; 216.444.1994) is a pediatric neurologist in the Center for Pediatric Neurosciences and Medical Director of Cleveland Clinic's Autism Spectrum Evaluation Team.*

## KEY POINTS

- Cleveland Clinic clinicians and researchers have developed an autism risk index (ARI) based on a composite of measurements of remote eye gaze tracking in response to established social and nonsocial visual stimuli.
- Initial and replication testing of the ARI found it to be highly accurate in distinguishing children with autism spectrum disorder (ASD) from those with non-ASD developmental disorders.
- Although further replication of these findings in larger samples is warranted, the ARI represents a promising new objective tool to supplement clinical observation for ASD symptom assessment and potential measurement of treatment response.

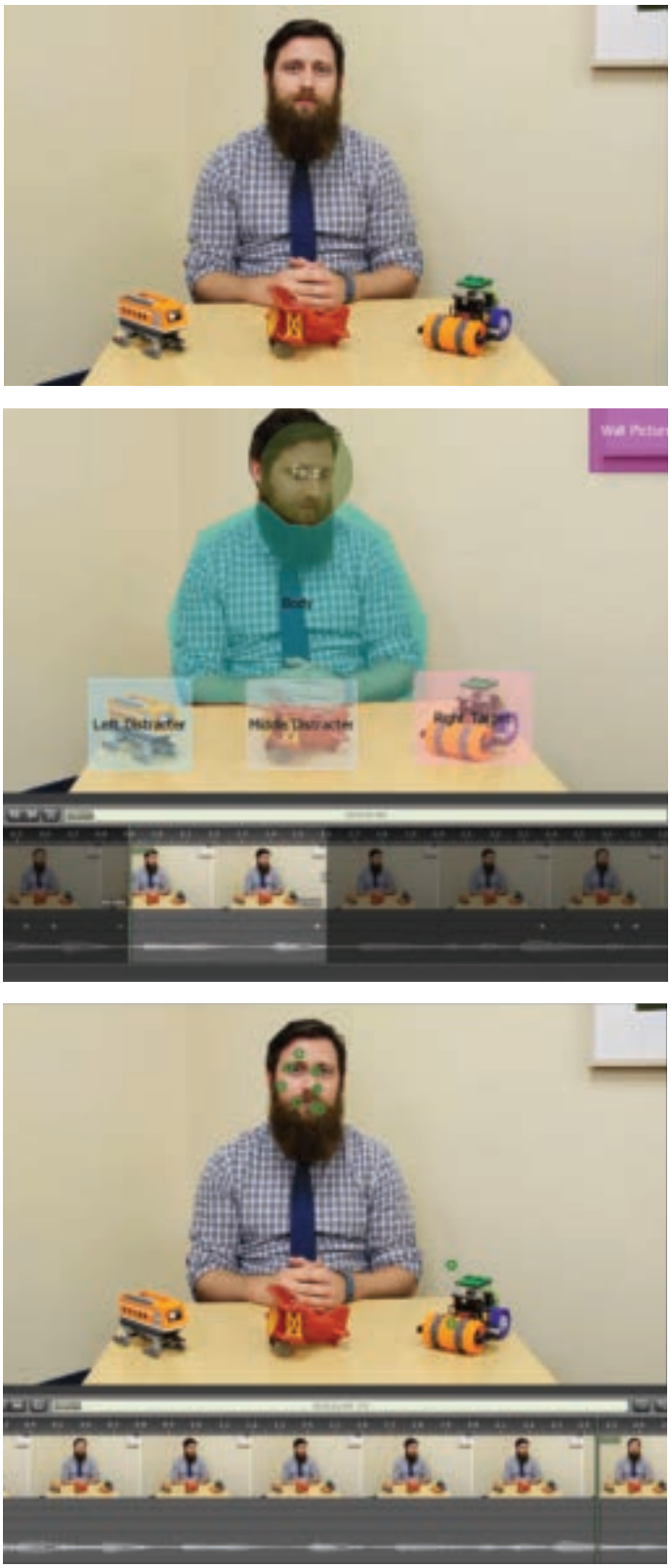

**FIGURE 1.** *Example screenshots of some of the joint attention stimuli used in the replication study. Top image shows the stimulus alone; middle image shows the stimulus with temporal regions of interest designated; bottom image shows attention to the social regions of interest (green circles) in healthy controls.* (Top two images reprinted from Frazier et al.[1] with permission from Elsevier.)

# Using a Precision Medicine Approach to Improve Rehabilitative Care in Stroke

**By Ela Plow, PhD, PT; Yin-Liang Lin, PhD; Kelsey Potter-Baker, PhD; Vishwanath Sankarasubramanian, PhD; David Cunningham, PhD; and Andre Machado, MD, PhD**

One of the most prominent recent initiatives of the National Institutes of Health (NIH) is the Precision Medicine Initiative, launched in 2015. It's founded on the idea that the likelihood and extent of recovery differ among individuals, with individual characteristics dictating how much recovery can be achieved with therapies. Greater emphasis is therefore placed on customizing interventions to individual characteristics.

## Applying Precision Medicine to Post-Stroke Rehabilitation

Our group at Cleveland Clinic has embraced the founding premise of the Precision Medicine Initiative to develop targeted rehabilitative therapies for individuals suffering from stroke. As survival rates after stroke continue to improve, more patients live longer lives facing chronic impairments. One of the most debilitating is weakness of the upper extremity, with up to 70 percent of affected patients experiencing lifelong difficulties in activities of daily living.

Improving the effectiveness of rehabilitation appears to be central to any solution. Pairing additional therapies within the limited time allotted for rehabilitation can supplement benefits without adding to stroke's cost burden. One such promising adjunct involves stimulation of the brain. Delivering electrical stimulation to residual, surviving areas in the lesioned hemisphere is believed to enhance mechanisms of plasticity — i.e., restorative processes that contribute to recovery. Stimulation has become even more popular since the advent of noninvasive techniques applying currents from atop the scalp/skull without requiring surgery.

## Targeting Stimulation for Efficacy Regardless of Severity

Although several hundred studies have claimed that stimulation can dramatically enhance outcomes of the weak upper extremity in stroke survivors, this therapy is not yet accepted for use in outpatient clinics.

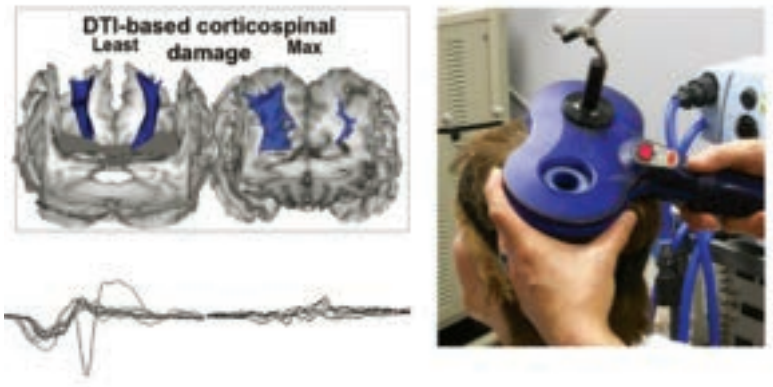


**FIGURE 1.** *Damage in our study was measured using diffusion tensor imaging (DTI) (left), and physiologic condition of pathways was assessed using transcranial magnetic stimulation (right).*

Stimulation-associated improvements vary across individuals. Those who are mildly affected are able to experience substantial outcome gains, but more-disadvantaged patients remain compromised in the use of their paretic upper limb.

Our group's contribution has been to develop targeted brain stimulation techniques that can dramatically enhance rehabilitation outcomes in stroke survivors with minimal as well as serious disability. Our approach to developing targeted or tailored techniques has been unique. Before predicting a priori who should receive which type of stimulation, we have adopted a data-driven, post hoc empirical strategy.

Over the past few years, our findings and those of other groups led us to realize that traditional stimulation fails to affect outcomes because it relies on the potential of residual networks, which are substantially damaged in severely affected patients. These patients cannot rely on residual networks in the lesioned hemisphere and must depend on helpful changes or plasticity occurring in the intact hemisphere. Yet the intact hemisphere can reroute alternate pathways to move the ipsilateral paretic limb. Moreover, the intact hemisphere can influence activity of the lesioned hemisphere via the corpus callosum to enhance its ability to drive movement of the severely affected limb.

Given how patients with minimal damage can exploit the potential for plasticity available within residual networks of the lesioned hemisphere, as well as how patients with severe damage rely on plasticity offered by the intact hemisphere, we've proposed that targeted stimulation in stroke should involve offering traditional stimulation to patients with mild functional disability and stimulation of the alternate, intact hemisphere to those with severe disability.

## New Insights for Stratifying Patients to Stimulation Type

Yet the biggest roadblock is lack of understanding of what constitutes severe disability. At what level of damage and deficit do patients fail to rely on residual areas in the lesioned hemisphere and need to rely on the intact hemisphere? How does one stratify patients for one or the other type of stimulation therapy? Our empirical, data-driven approach has offered the first solution, as indicated by findings presented at the 2015 annual meeting of the Society for Neuroscience.[1,2]

Using a crossover study design, we enrolled stroke patients across the spectrum of severity of upper limb impairment to receive stimulation to traditional targets in the lesioned hemisphere and, on a separate day, stimulation to the intact hemisphere. Ours is the first group to stimulate activity of

the intact hemisphere on the assumption that it serves as a critical resource for recovery in severely disabled patients.

We allotted an adequate gap between sessions so the effects of stimulating one region did not influence effects of stimulating the other. We documented stroke-related damage and impairment at baseline and then measured improvements in patients' ability to move their paretic limb. Damage was measured using diffusion-weighted MRI, which depicts damage to the structure of pathways (Figure 1). The physiologic condition of pathways was assessed using transcranial magnetic stimulation (TMS), which can study conduction of emergent pathways by delivering brief currents to motor areas in the brain. Conduction is indexed on the basis of movement potentials evoked with TMS in muscles of the paretic limb.

Our findings reveal that functional improvements associated with traditional stimulation and stimulation of the intact hemisphere share an inverse relationship. Whereas functional improvements associated with traditional stimulation are reduced with greater degrees of damage and impairment, improvements associated with stimulation of the intact hemisphere increase. Overall, as anticipated, mildly affected patients recovered the most with traditional stimulation while severely affected patients recovered with stimulation of the intact hemisphere.

### First Attempt to Develop Targeted Stimulation for Stroke

The unique aspect of our findings is that we have established that the relationship between improvements associated with alternate forms of stimulation is inverse. We are thus able to identify the intersection, or cutoff level, of damage and impairment at which to stratify candidates for traditional stimulation versus stimulation of the intact hemisphere (Figure 2).

This represents what we believe is the first attempt to develop targeted brain stimulation therapy for stroke. Not only can mildly affected patients achieve gains of greater than 30 percent in upper limb outcomes with traditional stimulation, but for the first time severely affected patients are likewise able to achieve greater than 30 percent gains with stimulation of the intact hemisphere.

In this way, our premise and findings are highly aligned with NIH's Precision Medicine Initiative. By accounting for an individual's damage and impairment following stroke, we can stratify that patient a priori for tailored stimulation so that all types of patients have an equal opportunity for fuller recovery.

*This work has been funded by the NIH, the American Heart Association and the American Stroke Association.*

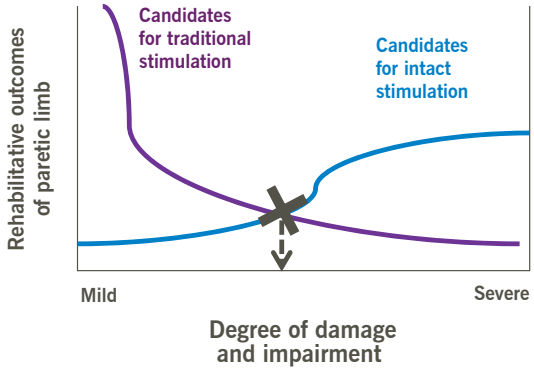


**FIGURE 2.** *Our research establishing the inverse relationship between outcomes associated with alternate forms of stimulation can serve to stratify patients to therapy according to the severity of their functional impairment.*

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*Dr. Plow (plowe2@ccf.org; 216.445.6728) is an assistant staff member in Cleveland Clinic Lerner Research Institute's Department of Biomedical Engineering with an appointment in the Department of Physical Medicine and Rehabilitation.*

*Drs. Lin, Potter-Baker, Sankarasubramanian and Cunningham are postdoctoral fellows in Dr. Plow's lab.*

*Dr. Machado (machada@ccf.org; 216.444.4270) is Chairman of Cleveland Clinic's Neurological Institute and a neurosurgeon with specialty interests in neuromodulation and deep brain stimulation.*

## KEY POINTS

- Traditional electrical stimulation of the brain fails to affect rehabilitative outcomes in stroke patients because it relies on the potential of residual networks, which are substantially damaged in severely affected patients.
- Our group has shown that stimulating activity of the intact hemisphere in severely disabled stroke patients can yield substantial functional outcome gains, supporting our hypothesis that the intact hemisphere serves as a critical resource for recovery in such patients.
- Our study represents the first attempt to develop targeted brain stimulation therapy for stroke. It suggests that patients can be stratified a priori for tailored stimulation to optimize opportunity for recovery.

# Getting Teleneurology Right: Insights from One Center's Early Experience

**By Stephen D. Samples, MD; Kuruvilla John, MD; and Tara Schubert, MS**

As the U.S. geriatric population continues to swell, the nation's neurologist shortage looms ever larger, especially for small and/or rural hospitals that lack full-time neurologist coverage. As a result, increasing numbers of small or remotely located hospitals are looking to large, highly specialized health systems for teleneurology services.

Cleveland Clinic has been offering such services through the Cleveland Clinic Teleneurology Program since early 2015, first for selected Cleveland Clinic regional hospitals without 24/7 neurologist coverage and increasingly to external hospitals. The program uses distance health technology to provide basic neurological services to hospitalized patients with noncritical neurological illnesses. It's distinguished by the fact that it extends beyond the core services of emergency assessment for stroke or limited outpatient triage to include robust, thorough consultations enabling clinical decision-making for a range of neurological conditions.

Teleneurology offers a number of potential benefits, including:

- An efficient way to address neurologist shortages in remote or small practice settings
- Convenience for patients, allowing them to receive care locally when possible, avoiding the hassle, time loss, and expense of travel or transfers
- Superior quality of evaluation over traditional telephone consults, as video capabilities make neurological localization easier, change in mental status more evident and abnormalities (e.g., in gait or reflexes) easier to identify
- Possible healthcare cost savings, as cost reviews show that, for appropriate conditions, many patients can be cared for at smaller hospitals more efficiently and at lower costs than at large centers

This article shares a few insights we have gained in the process of establishing and refining our program, with a focus on how to get things right in four essential aspects of teleneurology care.

## The Right Team

In our model of the teleneurology visit, the patient (perhaps with family members) is present at his or her local hospital or health facility with a specially trained nurse who works at that facility. They are connected via video connection, established through a mobile transmission unit, with a neurologist located remotely at a Cleveland Clinic facility, who directs the visit in collaboration with the nurse.

The neurologist takes the patient's history and actively guides the nurse through a full neurological examination of the patient, with the nurse acting as the "telepresence." The history and exam can be supplemented by imaging studies obtained on-site as needed (and transmitted to the neurologist in real time via the mobile unit or remote connection to the EMR), as most smaller or remote partner hospitals have imaging modalities sufficient for diagnosing teleneurology-appropriate conditions.

Drawing on all these elements (history, nurse-enabled exam, any imaging studies), the neurologist then discusses his or her assessment and plan with the patient via the video connection and also with the referring physician, either via the mobile transmission unit or by telephone.

This model relies on three critical elements:

- The specialized knowledge and experience of the neurologist
- The clinical information gathered from the neurological examination jointly conducted by the neurologist and the nurse
- The human presence and connection that the nurse provides to the patient

The trained nurses have been crucial to the program's success. By serving as physician extenders, they provide the human factor that patients expect while enabling the service to be economically feasible. Moreover, the experienced neurology clinicians in our program have consistently found the guided neurological examination completed by trained nurses to be sufficient for diagnosis.

## The Right Training

That degree of confidence requires the right approach to nurse training, which begins by enlisting nurses at the partner facility who have had some exposure to neurology — e.g., from experience as ICU nurses or ED nurses who have routinely performed NIH Stroke Scale evaluations.

The training programs for nurses are delivered either one day a week for six weeks or as an intensive 14-hour weekend program, with all neurologists involved in the teleneurology program participating. These programs are usually at the remote hospital and allow the neurologists and nurses to interact as colleagues. Nurses then spend at least two days rotating with participating Cleveland Clinic attending neurologists in a hospital setting. We have found this sufficiently equips nurses with a wide range of skills to perform a guided neurological examination that provides reliable, reproducible information.

## The Right Patients

The sidebar box on the opposite page lists a sampling of neurological complaints and conditions that are commonly evaluated and managed with success via our teleneurology program. Once an accurate diagnosis is reached, it guides the decision whether the patient needs to be transferred to a more specialized hospital for higher-level service.

In many cases, with appropriate diagnosis, there is no need to transfer patients elsewhere.

Of course, certain aspects of neurologic evaluation, such as assessment for subtle findings in muscle tone, do not translate well in teleneurology. And other challenging situations, such as evaluation of brain death, cannot be reliably performed via teleneurology. A good approach is to predefine general guidelines for teleneurology-appropriate conditions and complaints and be open to refinements as experience dictates.

### CONDITIONS AND COMPLAINTS COMMONLY MANAGED BY THE TELENEUROLOGY PROGRAM

- Stroke not eligible for intervention
- Seizure disorders
- Altered mental status
- Headache
- Weakness
- Noncritical follow-up of pre-existing neurological problems (e.g., multiple sclerosis) in the setting of acute medical illness
- New-onset numbness or weakness
- Cranial neuropathy
- Neurological complications of medical illness
- Nontraumatic spine conditions

## The Right Equipment

Telehealth programs require dedicated hardware and robust internet connections. Several HIPAA-compliant hardware solutions are available, with varying levels of expense and support. All devices provide asynchronous connection for video/audio communications. In addition, some provide stethoscopes or other equipment for further evaluation. For teleneurology, the essential requirement is a basic system that transmits video and audio reliably.

The mobile units employed in our program automatically correct for variation in internet connection speed and allow for accurate monitoring of movements. They operate in a wide range of lighting and other variables. Through use of a pan-tilt-zoom video lens, these units enable close observation and facilitate examination. A good system provides sufficient resolution to allow remote examination of the pupil.

## Initial Responses, Mounting Momentum

Patients have responded positively to the teleneurology program, with virtually all rating the service they received at the highest level in surveys. Verbatim patient comments have included “felt like the doctor was in the room” and similar statements. Most consultation requests come from internists, hospitalists, family practitioners and physician extenders. Although referring physicians were initially reluctant to use teleneurology, the number of consults per month dramatically increased after the first few months and continues to grow. Two-thirds of referring physicians who have used the service have rated it as good or excellent.

A host of factors have converged to spur interest in teleneurology, from neurologist shortages to limits in some patients’ travel abilities to changes in reimbursement. Our experience shows that neurological services can be provided efficiently using telemedicine systems, including in smaller or rural hospitals with limited services.

**ACKNOWLEDGMENT**

The authors gratefully acknowledge all the teleneurology program’s participating neurologists and nurses, most notably Sheila Rubin, MD, who developed the curriculum to train nurses in the neurological examination.

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*Dr. Samples (samples1@ccf.org; 216.444.4375) is Vice Chairman for Regional Neurosciences in Cleveland Clinic’s Neurological Institute and Director of the Center for Regional Neurosciences.*

*Dr. John (johnk@ccf.org; 216.444.5563) is Director of Teleneurology in the Center for Regional Neurosciences.*

*Ms. Schubert is the administrator for the Center for Regional Neurosciences.*

## KEY POINTS

- Many factors have converged to spur interest in teleneurology, from neurologist shortages to limits in patients’ travel abilities to changes in reimbursement.
- Cleveland Clinic’s experience over the past couple of years shows that neurological services can be provided efficiently using telemedicine systems, assuming they are focused on the right patients and provided by properly trained teams working with reliable video and audio equipment.

# Patient-Reported Outcomes of Treating Sleep-Disordered Breathing in Hypertensive Patients: Insights from the First Study of Its Kind

**By Harneet K. Walia, MD**

Sleep-disordered breathing (SDB) is highly prevalent and is often accompanied by worsening of a variety of patient-reported outcomes (PROs), including excessive daytime sleepiness, depressive symptoms and fatigue. These symptoms have been shown to demonstrate striking yet complex interrelationships in SDB and hypertension — observations that loom large in view of the high prevalence (estimated from 50 to 85 percent[1,2]) of SDB in patients with hypertension and resistant hypertension.

These symptoms also contribute significantly to SDB's considerable impact on quality of life, which is a key emphasis of recent quality measures developed by the American Academy of Sleep Medicine (AASM) to guide management of obstructive sleep apnea.[3] And since individuals with hypertension appear to have lower quality of life than those without hypertension,[4] coexisting hypertension is germane to quality-of-life considerations as well.

Given the strong association between SDB and hypertension, particularly resistant hypertension, there is a need for greater understanding of PROs in individuals suffering from both conditions. Moreover, patients with and without concomitant hypertension could demonstrate varying subjective changes in response to SDB treatment, the first line of which is usually pressure stenting with continuous positive airway pressure (PAP).

## A Novel Study of PROs After SDB Therapy in the Setting of Hypertension

To explore these issues, Cleveland Clinic researchers retrospectively examined PROs collected from patients with both SDB and hypertension. We postulated that treatment of SDB with PAP would be associated with improvement in PRO measures ranging from sleepiness to depressive symptoms to fatigue, and we aimed to determine any effect modifiers of these relationships.

Electronic medical record (EMR) data were extracted for all adults with outpatient visits in Cleveland Clinic's Sleep Disorders Center from February 2008 to July 2013 who had a confirmed hypertension diagnosis and self-reported use of PAP therapy.

> Statistically significant improvements were observed with PAP therapy across the overall cohort in all three patient-reported outcome measures and were not dependent on resistant hypertension status.

Our study leveraged the Knowledge Program©, a system pioneered by Cleveland Clinic's Neurological Institute to electronically collect disease-based PROs in the patient's EMR at the point of care to make the measures immediately available to providers to inform clinical care. PROs collected in the Sleep Disorders Center include:

- Epworth Sleepiness Scale (ESS) score
- Patient Health Questionnaire-9 (PHQ-9) score for depression
- Fatigue Severity Scale (FSS) score
- Self-reported number of days per week and hours per night of PAP use

Of the 1,000 patients with hypertension and SDB reporting use of PAP who had pre- and post-PAP PRO data, 894 (89 percent) had complete visit data over the course of the study. Among these patients, 130 (15 percent) had resistant hypertension. Compared with patients with nonresistant hypertension, those with resistant hypertension were significantly older, had a higher mean body mass index (BMI) and were significantly more likely to have diabetes and cardiac disease.

## Key Findings: Improvements in PROs Across the Board

Notably, there was no difference in PRO measures between the resistant and nonresistant hypertension groups.

In models fully adjusted for age, sex, race, BMI, median income by zip code, and cardiac and diabetes history, statistically significant improvements ($P < .001$) were observed during the year following PAP therapy initiation in each of the following:

- ESS score (–2.09; 95% CI, –2.37 to –1.82)
- PHQ-9 score (–1.91; 95% CI, –2.25 to –1.56)
- FSS score (–4.06; 95% CI, –4.89 to –3.22)

These improvements were observed in the sample overall and were not dependent on resistant hypertension status.

## Notable Subanalysis Findings

Various subanalyses revealed notable additional findings, including the following:

- Among the 147 patients objectively determined to be adherent to PAP therapy, improvements in all PRO measures (ESS, PHQ-9 and FSS) were more pronounced than in the overall sample.

- Greater improvements in all PROs were observed after PAP therapy in Caucasians compared with African Americans and other races.
- Younger patients had worse scores than older patients on all PROs at baseline ($P < .01$), but the interaction of the effect of PAP therapy and age relative to PROs was statistically significant for ESS ($P = .04$) and PHQ-9 ($P = .0003$) scores, demonstrating greater improvement in younger versus older patients.

### Important Potential Implications Call for Prospective Study

This observational study, recently published in the *Journal of Clinical Sleep Medicine*,[5] provides novel longitudinal documentation of improvement in daytime sleepiness, depressive symptoms and fatigue in patients with SDB and hypertension treated with PAP in a real-world setting. We are aware of no prior study evaluating changes in sleep-related functional outcomes of PAP therapy in a strictly hypertensive cohort containing a sizable sample of patients with resistant hypertension.

As expected, the reported effects were somewhat more robust in patients with the best PAP adherence, and both this and the overall findings provide support for untreated SDB as a potential etiology for the reduced quality of life reported in hypertensive patients.[4]

While this work has implications for population health and aligns with the AASM's call for tracking outcomes in SDB care paths,[3] these findings should be built upon in prospective randomized studies of PROs in response to PAP in patients with SDB and hypertension — ideally with a comparative group of normotensive patients.

Future studies should aim to confirm our findings of similar PRO response in resistant and nonresistant hypertension as well as enhanced response in Caucasians and younger patients, with an eye toward informing SDB treatment guidelines.

The reported effects were somewhat more robust in patients with the best PAP adherence, providing support for untreated sleep-disordered breathing as a potential etiology for reduced quality of life in hypertensive patients.

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*Dr. Walia (waliah@ccf.org; 216.445.5523) is a staff physician in Cleveland Clinic's Sleep Disorders Center and Assistant Professor of Family Medicine in Cleveland Clinic Lerner College of Medicine.*

## KEY POINTS

- Sleep-disordered breathing (SDB) is often accompanied by worsening of patient-reported outcomes (PROs) such as excessive daytime sleepiness, depressive symptoms and fatigue. These symptoms can demonstrate striking yet complex interrelationships in SDB and hypertension.
- A large observational study at Cleveland Clinic has demonstrated consistent improvement of broad PRO domains in response to positive airway pressure (PAP) therapy among patients with SDB and hypertension (including resistant hypertension). Effects were strongest in patients with the best PAP adherence.
- These findings have implications for SDB management at the population level but should be built upon in prospective randomized studies of PROs in response to PAP therapy.

# Clinical and Quality-of-Life Outcomes After Cervical Decompression for Coexisting Parkinson's Disease and Cervical Spondylotic Myelopathy

**By Roy Xiao, BA; Jacob A. Miller, BS; and Ajit A. Krishnaney, MD**

## A Dilemma of Symptom Overlap

Patients with Parkinson's disease (PD) may exhibit symptoms similar to those observed in cervical spondylotic myelopathy (CSM), including ataxia, weakness, and bowel or bladder dysfunction. These similarities present diagnostic and therapeutic challenges when PD and CSM coexist. While CSM is typically treated with surgical decompression (Figure 1), PD requires pharmacologic therapies and is expected to derive little benefit from decompression. This poses a dilemma for both neurologists and spine surgeons treating patients with PD who may have evidence of cervical spondylosis and myelopathy.

Clinical and quality-of-life (QOL) outcomes following cervical decompression in the PD population remain undefined. Defining these outcomes may improve patient management and help avoid unnecessary surgical intervention. To that end, Cleveland Clinic Center for Spine Health clinicians and researchers recently sought to investigate clinical and QOL outcomes following cervical decompression among patients with CSM with and without coexisting PD. We hypothesized that both groups would benefit from surgery but that patients with concomitant PD would experience inferior outcomes.

## Study Design in Brief

We retrospectively identified all patients with coexisting PD and CSM who underwent cervical decompression at Cleveland Clinic between June 2009 and December 2014 and then matched them to controls with CSM alone who underwent cervical decompression over the same period by the same team of spine surgeons. Matching was done on the basis of age, gender, American Society of Anesthesiologists classification, preoperative modified Japanese Orthopaedic Association (mJOA) score and operative parameters.

The primary outcome measure was postoperative improvement in mJOA score at patients' last follow-up visit. The mJOA scale ranges from 0 to 18, with lower scores indicating greater neurological disability. Two points was considered the minimum clinically important difference. Additionally, scores on the Nurick scale were collected to measure ambulatory status, with greater scores indicating greater impairment.

> Although decompression may have a role in alleviating pain-related disability in the PD population, this intervention appears to offer marginal benefit with respect to improving myelopathy and quality of life.

In a secondary QOL analysis, outcomes included QOL improvement as measured by the EuroQol 5 dimensions questionnaire (EQ-5D), the Pain Disability Questionnaire (PDQ) and the Patient Health Questionnaire-9 (PHQ-9). These measures were prospectively collected before and after surgery.

Simple and multivariable linear and logistic regression analyses were used to assess the impact of PD on primary and secondary outcomes.

## Results: PD Attenuates Clinical and QOL Improvements

Fifty-five patients met the study's inclusion criteria: 11 with both PD and CSM and 44 with CSM alone.

We found that symptoms improved postoperatively in both cohorts; however, back pain, radiculopathy and bowel/bladder dysfunction persisted among patients with PD relative to those without PD. Moreover, patients with PD experienced poorer improvement on both the Nurick (0.0 vs. –1.0, $P < .01$) and mJOA (0.9 vs. 2.5, $P < .01$) scales. PD was identified as a significant independent predictor of decreased improvement in patients' functional status.

In the QOL analysis, while the control cohort experienced improvement across all measures examined, PD patients improved in only one (the PDQ). Despite an absence of significant differences between the cohorts in preoperative QOL, patients with PD had poorer QOL at last postoperative follow-up as measured by the EQ-5D (0.526 vs. 0.707 for controls; $P = .01$) and PDQ (80.7 vs. 51.4 for controls; $P = .03$), and a smaller proportion of PD patients achieved the prespecified minimal clinically important difference on the EQ-5D (18 percent vs. 57 percent among controls; $P = .04$). No between-cohort differences in achieving a minimal clinically important difference were observed for the PDQ or PHQ-9.

Multivariable regression analysis identified PD as a significant independent predictor of poorer improvement on the EQ-5D ($\beta = -0.09$; $P < .01$) and of failure to achieve a minimal clinically important difference on the EQ-5D (OR = 0.08; $P < .01$). Results of this QOL analysis were recently published in *The Spine Journal*.[1]

## Bottom Line: Only Selected Cases Appear to Benefit

This study is the first to characterize clinical and QOL outcomes following cervical decompression among patients with concomitant PD and CSM. Matched-pair analysis showed that patients with PD experienced diminished symptomatic and QOL improvement relative to controls.

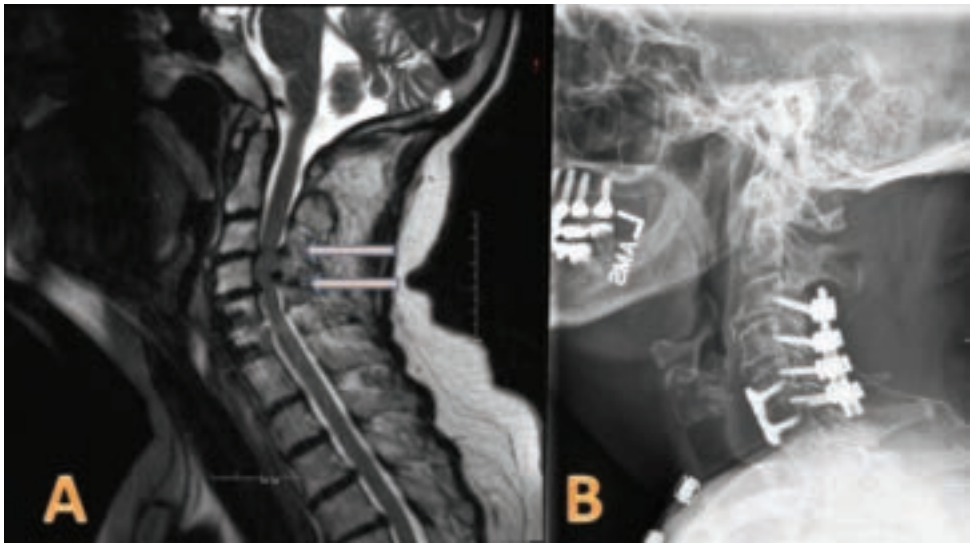


**FIGURE 1.** *(A) Preoperative sagittal T2 MRI of a patient with coexistent cervical spondylotic myelopathy and Parkinson's disease. Note the severe cervical stenosis and cord compression at C3-4 and C4-5 (arrows). (B) Postoperative X-ray after the patient underwent laminectomies at C3 through C5 and extension of her fusion to C3 via a dorsal approach.*

Although decompression may have a role in alleviating pain-related disability in the PD population, this intervention appears to offer marginal benefit with respect to improving myelopathy and overall QOL. It is possible that only selected patients with coexisting PD and CSM respond favorably to cervical decompression. Accordingly, preoperative pharmacologic optimization of PD should precede surgical correction of the spine. Further studies are needed to determine which patients with PD may benefit from surgical intervention for their myelopathy.

## KEY POINTS

- Patients with Parkinson's disease (PD) may exhibit symptoms similar to those observed in cervical spondylotic myelopathy (CSM), presenting diagnostic and therapeutic challenges when the conditions coexist.
- In the first study to characterize clinical and quality-of-life (QOL) outcomes following cervical decompression among patients with CSM with and without PD, we found that patients with PD experienced diminished symptomatic and QOL improvement.
- In patients with coexisting PD and CSM, pharmacologic optimization of PD should precede surgical spine correction. Further studies are needed to determine which subgroups of patients with PD might benefit from surgical intervention for their myelopathy.

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*Mr. Xiao and Mr. Miller are medical students at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University.*

*Dr. Krishnaney (krishna@ccf.org; 216.445.3777) is a neurosurgeon in Cleveland Clinic's Center for Spine Health and Department of Neurological Surgery.*

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Sekar Bhavani, MD
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