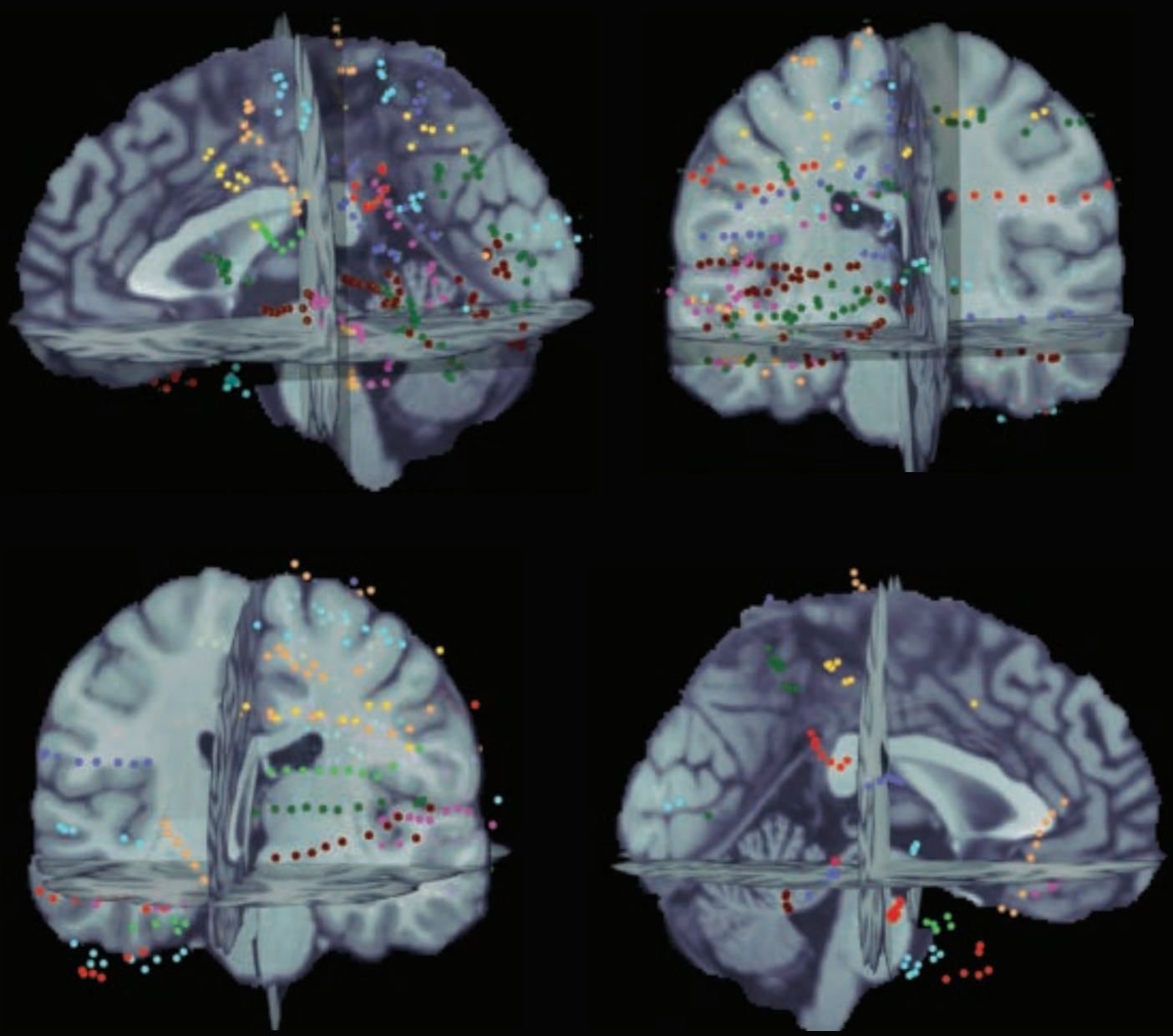
Cleveland Clinic Neurological Institute **Special Report**

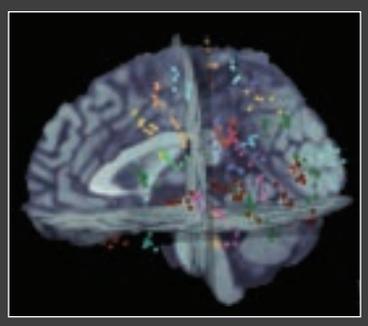


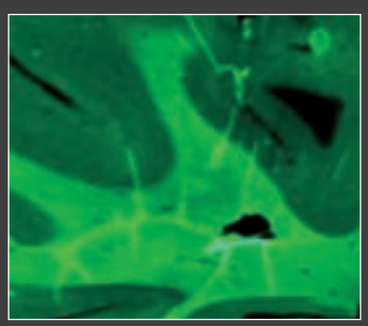
Information-Guided Care: Personalized Brain Mapping in Complex Neurological Disorders

Brain connectivity | Image post-processing | Myelin PET

SPECIAL REPORT

Information-Guided Care: Personalized Brain Mapping in Complex Neurological Disorders





This special report was produced by Cleveland Clinic's Neurological Institute.

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ON THE COVER: *3-D images showing stereoelectroencephalographic contacts from multiple patients with medically intractable focal epilepsy warped to a common atlas of brain connectivity. See related feature starting on page 4.*

Dear Colleagues,

Neurological and neurosurgical care in 2018 has expanded dramatically beyond the neurological examination and core operative procedures that formed the bedrock of practice in our disciplines. As contemporary care evolves, the importance of data that is highly personalized for each individual patient with a neurological condition becomes ever more apparent.

This increasing personalization of care has emerged just as the value of multidisciplinary collaboration has grown more and more evident. At Cleveland Clinic, we recognized this development over a decade ago by embracing an institute-based organizational structure. For individuals with brain and spine conditions, this structure brings together neurologists, neurosurgeons, neuroradiologists and neuroscientists in a Neurological Institute organized around patients' disease-specific diagnostic and management needs rather than traditional departmental groupings. As a result, patients benefit from deeper collaboration across our institute's 14 subspecialty centers.

One area in which these two trends — increasing personalization and multidisciplinary collaboration — intersect with particular power is in what we call "information-guided care." This concept represents a redefinition of neuroscience care that promotes cross-disciplinary collaboration in pursuit of more-personalized diagnosis and less-invasive management of the most challenging cases of various neurological diseases.

Our multidisciplinary teams in the Neurological Institute are at the forefront of this redefinition, which arises from the use of leading-edge imaging technologies, such as state-of-the-art 7T MRI, in innovative ways and combinations. The objective is threefold: to better visualize brain anatomy, enhance understanding of function and provide accurate, noninvasive diagnosis of brain pathology without need for tissue biopsy.

This image-rich special report offers a few snapshots of our efforts at the forefront of information-guided care:

- The first article (page 4) profiles how teams across our institute have been untangling the complex connectivities of the brain in various disorders to create anatomo-functional maps for individual patients to help tailor personalized treatment options.
- The second article (page 16) explores how we are using novel analytic methods and machine learning to enhance the processing of otherwise routine imaging data. These approaches promise more straightforward diagnosis across various neurological conditions, without the need for more-complex and invasive diagnostic methods.
- The final article (page 26) reviews our work on clinical application of a novel PET radiotracer that preferentially binds to molecular components of myelin and provides quantitative imaging of brain white matter integrity beyond what's possible with existing MRI methods. We've started to use it to improve lesion identification in pharmacoresistant epilepsy, with studies in multiple sclerosis, stroke rehabilitation and other conditions planned.

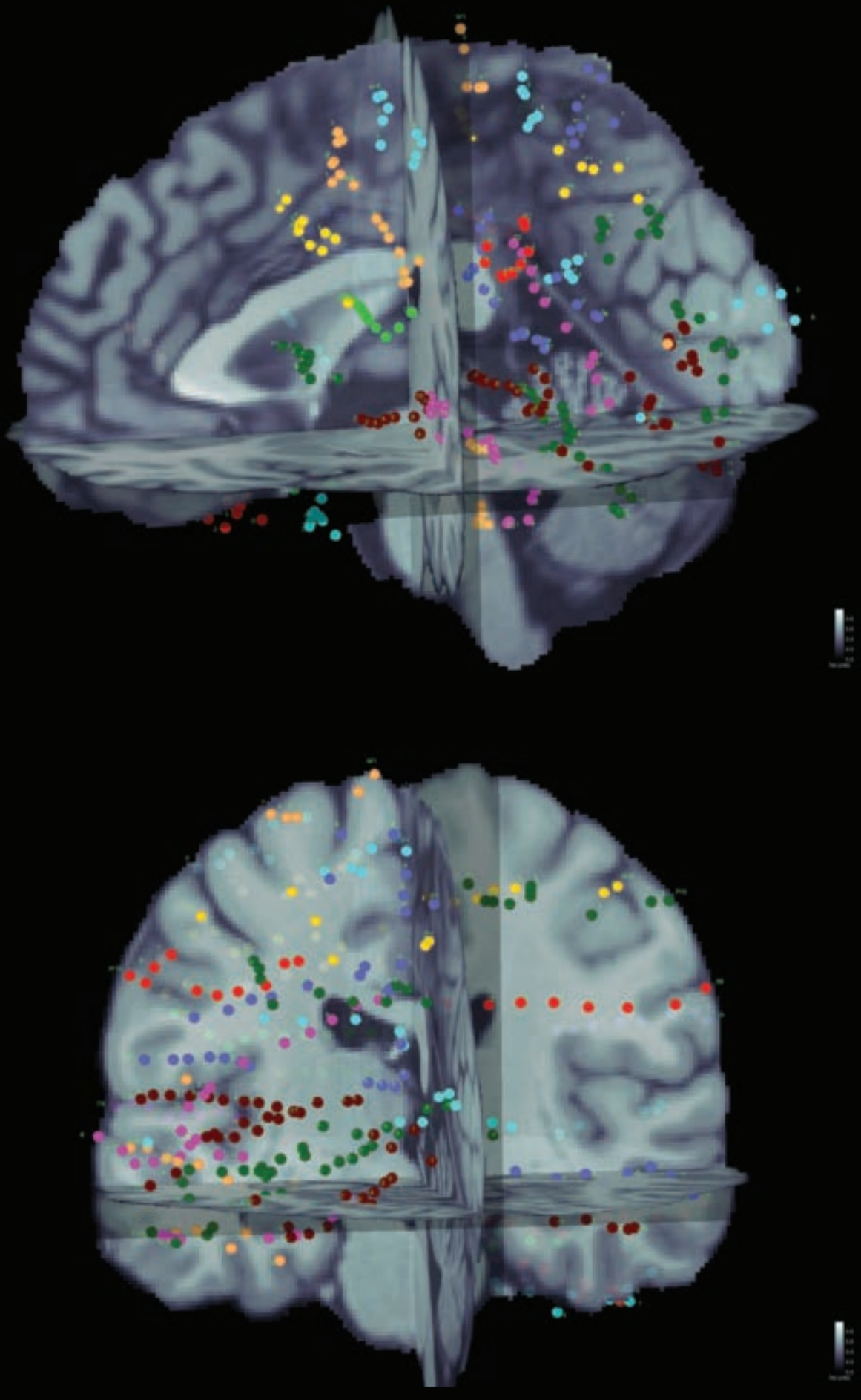
A common theme among all these profiles is that the sum of various advanced imaging techniques can be greater than the individual parts. This is particularly true when their use is informed by cross-disciplinary collaboration.

We believe this information-guided approach to neuroscience care designed and validated by expert multidisciplinary teams will lead to enhanced diagnosis, more-personalized treatment options and improved outcomes for patients with the most complex neurological diseases. We are pleased to share these profiles, and we welcome your input and opportunities for collaboration.

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

Imad Najm, MD | najmi@ccf.org
Director, Epilepsy Center
Vice Chairman, Neurological Institute — Strategy and Development

Robert Fox, MD | foxr@ccf.org
Vice Chairman, Neurological Institute — Research



Mapping Network Connections in the Brain

By Dileep Nair, MD; John Mosher, PhD; Stephen M. Rao, PhD; Balu Krishnan, PhD; Andreas Alexopoulos, MD, MPH; Raghavan Gopalakrishnan, PhD; Andre Machado, MD, PhD; and Stephen E. Jones, MD, PhD

Interlobar and interhemispheric brain network connections are essential for the execution of various brain functions. Dysfunction in some of these networks leads to the expression of various neurological and psychiatric diseases. As a result, mapping these networks in health and disease is essential for the early diagnosis of diseases such as epilepsy, movement disorders and stroke, as well as for the assessment of mechanisms of various therapeutic interventions.

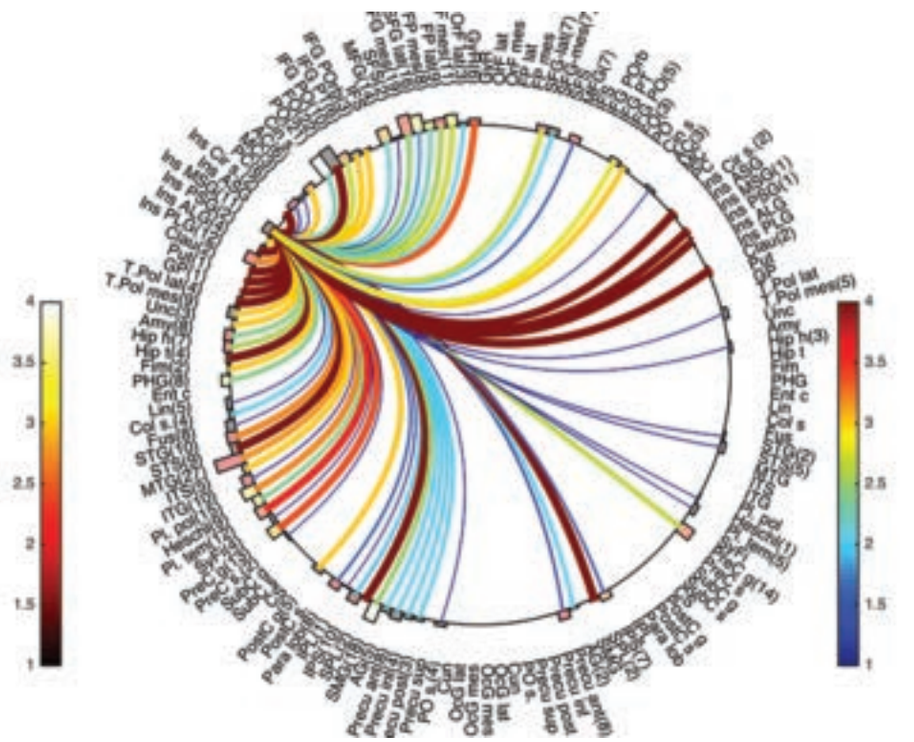
Collaborative research teams from Cleveland Clinic's Neurological Institute and Imaging Institute are making significant strides in creating maps of brain connections using cortico-cortical evoked potentials, resting-state functional MRI (fMRI), diffusion tensor imaging and resting-state magnetoencephalography. Our researchers are also using these same techniques to uncover important mechanisms of some of the most severely disabling neurological conditions, such as pharmacoresistant epilepsy and Huntington's disease, and to inform therapeutic interventions using deep brain stimulation in post-stroke pain syndrome, epilepsy, major depression, obsessive-compulsive disorder, essential tremor and urinary incontinence.

This article provides overviews of our efforts in several of these areas.

Cortico-Cortical Evoked Potentials: A Novel Measure of Effective Connectivity that Promises to Advance Brain Mapping

Section authors: Dileep Nair, MD, and John Mosher, PhD

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.[1,2] 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). This technique has now been widely used in several other epilepsy centers across the world after our initial publications.



The CCEP methodology allows in vivo access to direct and indirect interactions across various nodes in the human brain. Our most recent report, published in *Brain* in 2017,[3] shows correlation of these measures with the epileptic networks assessed using ictal single-photon emission computed tomography (SPECT).

Based on the strength of CCEP research findings, our center has received an R01 grant from the National Institute of Neurological Disorders and Stroke. The five-year grant is supporting 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 goal is to create a brain map of connectivity where all the implanted electrodes are nonlinearly coregistered into a single brain template. In this way, greater sampling of regions of brain will become available so that strengths of connections from various nodes of stimulation can be identified, such as those shown in the circle map above (see Figure 1 caption on opposite page).

Our hope is that this information will give us better insight into how to craft more accurate surgical resections in patients with nonlesional medically intractable focal epilepsy if we can uncover the primary epileptic node noninvasively. The overarching goal of this research is to develop a brain atlas of functional connections between various areas of the human brain. This atlas would serve as a guide for mapping physiological and pathological networks involved in focal epilepsies and various neurological and psychiatric diseases.

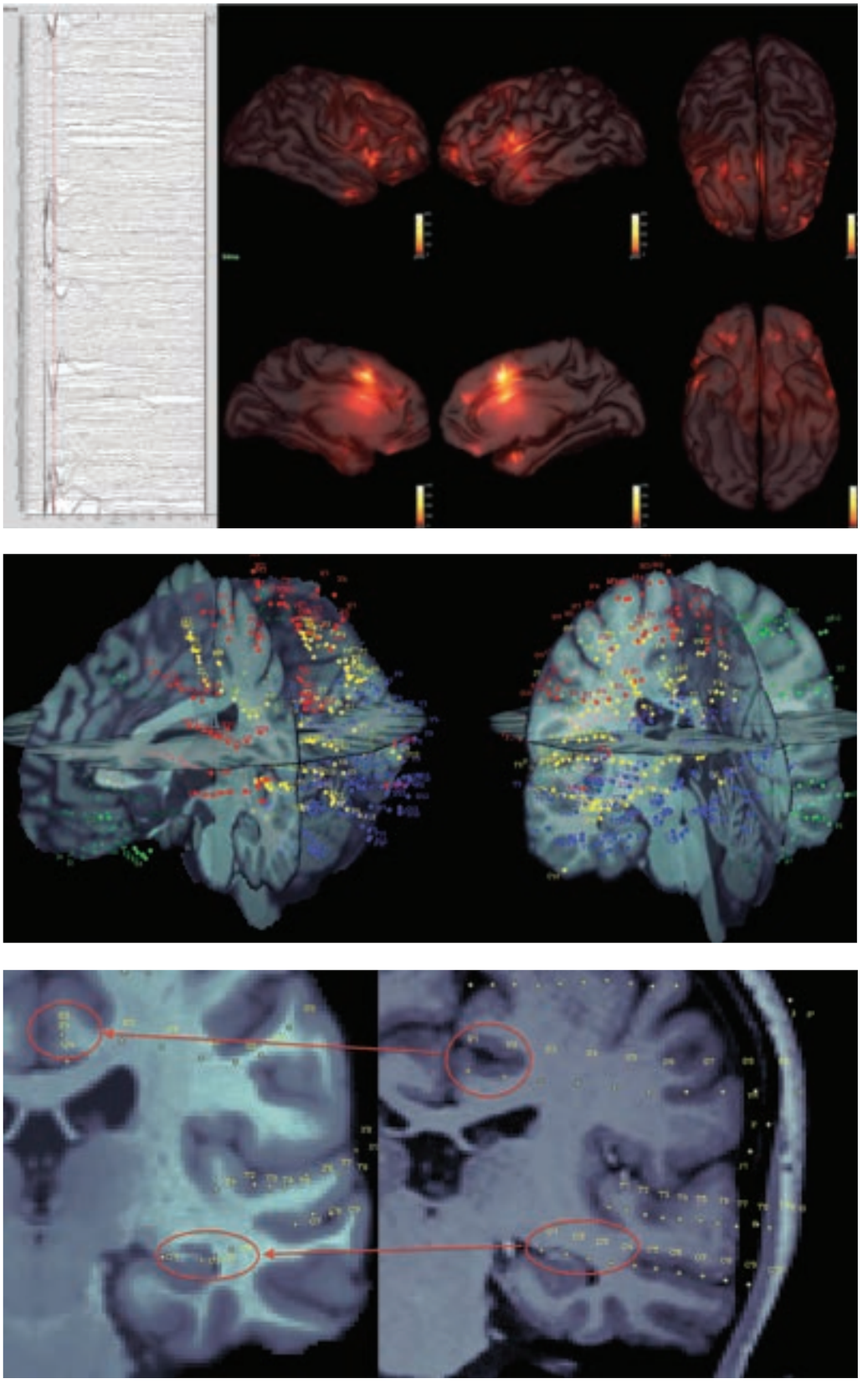


FIGURE 1. ***Top:*** *A patient's CCEP responses are depicted as waveforms on the left with response estimates depicted by scaled colors in the MRI scans on the right. Brain currents were estimated using a "minimum energy" constraint that keeps the currents to a minimum in the vicinity of the electrodes to generate a working estimate for use in studying brain dynamics.* ***Middle:*** *SEEG contacts from four patients (each shown with a different color) warped to a common atlas using open-source Brainstorm software (neuroimage.usc.edu/brainstorm).* ***Bottom:*** *Nonlinear registration of contacts from a patient to the common atlas.* ***Opposite page:*** *Circle map showing example connectivity from one region to other regions of interest for six patients, calculated using RMS of the response at each contact.*

Functional and Structural Connectivity in Prodromal Huntington's Disease

Section author: Stephen M. Rao, PhD

Although formal diagnosis of Huntington's disease (HD) is made at the appearance of unequivocal motor signs, usually between ages 35 and 50, subtle motor, psychiatric and cognitive symptoms can occur decades prior to a manifest diagnosis. This period of time is referred to as prodromal HD (prHD). With the development of treatments that promise to delay the onset or slow progression of HD symptoms, there is a strong need for outcomes that are sensitive to progressive neuronal dysfunction during the prodromal phase to evaluate the efficacy of therapies. Measures of functional (resting-state fMRI) and structural (diffusion MRI) connectivity are of great interest, as they may elucidate the effects of early striatal degeneration and other pathological processes on brain networks.

Our interdisciplinary research team at Cleveland Clinic involves experts in neuropsychology, cognitive neuroscience, neurology, neuroradiology and MR physics and includes collaborations with experts at the University of California San Diego and the University of Iowa. For our studies, we recruited HD at-risk participants (persons with a parent diagnosed with HD) who agreed to undergo genetic testing. Controls are individuals without an expansion in the *HTT* gene (gene-negative). Persons with an expansion in the *HTT* gene (gene-positive) who have not been diagnosed with manifest HD are further classified into low, medium or high prHD groups based on their probability of receiving a diagnosis of manifest HD within five years. This classification, which is a measure of disease burden, is based on a formula that accounts for the person's age and the known inverse relationship between the length of cytosine-adenine-guanine (CAG) repeats in the *HTT* gene and age at diagnosis of manifest HD.

Our initial published work[4] demonstrated that prHD is associated with abnormal interhemispheric interactions among motor areas and disturbances in the functional connectivity of the motor and visual centers. This study cross-correlated the temporal pattern of resting-state fMRI brain activity from a seed region, in this case the left primary motor cortex (M1), with every other region in the brain. In the cuneus and precentral gyrus, an increase in connectivity was observed in the low prHD group, suggesting compensatory changes in brain connectivity at the very earliest stage of the disease process. In contrast, connectivity from left M1 to the right cuneus, postcentral gyrus and precentral gyrus declined in the high prHD participants, a later disease stage event. These results suggest that reduced connectivity in these regions contributes to increased motor symptoms, visuomotor integration problems and deficits in movement control as individuals approach a manifest diagnosis.

In a second study,[5] we used an alternative analysis approach, referred to as the network-based statistic, to examine functional reorganization of whole-brain networks in prHD. Instead of selecting a seed region a priori as in our previous study, we examined patterns of change in functional connectivity by examining cross-correlations among 300 regions throughout the brain. We simultaneously demonstrated a pattern of weakened frontostriatal connections and strengthened frontal-posterior connections as a function of disease burden. These results suggested a reconfiguration of networks, with increased frontal-parietal connections involving long-range pathways involved in attentional processes. These increased connections may enable the prHD person to compensate cognitively for increasingly disrupted network connections between frontal and striatal areas. Importantly, this analysis provided a unique window into brain reorganization that was not related to brain atrophy or motor symptoms.

In our most recent study,[6] we used diffusion tensor imaging (DTI) to examine longitudinal changes in structural connectivity in prHD. DTI measures the integrity of white matter fiber tracts in the brain. We found that

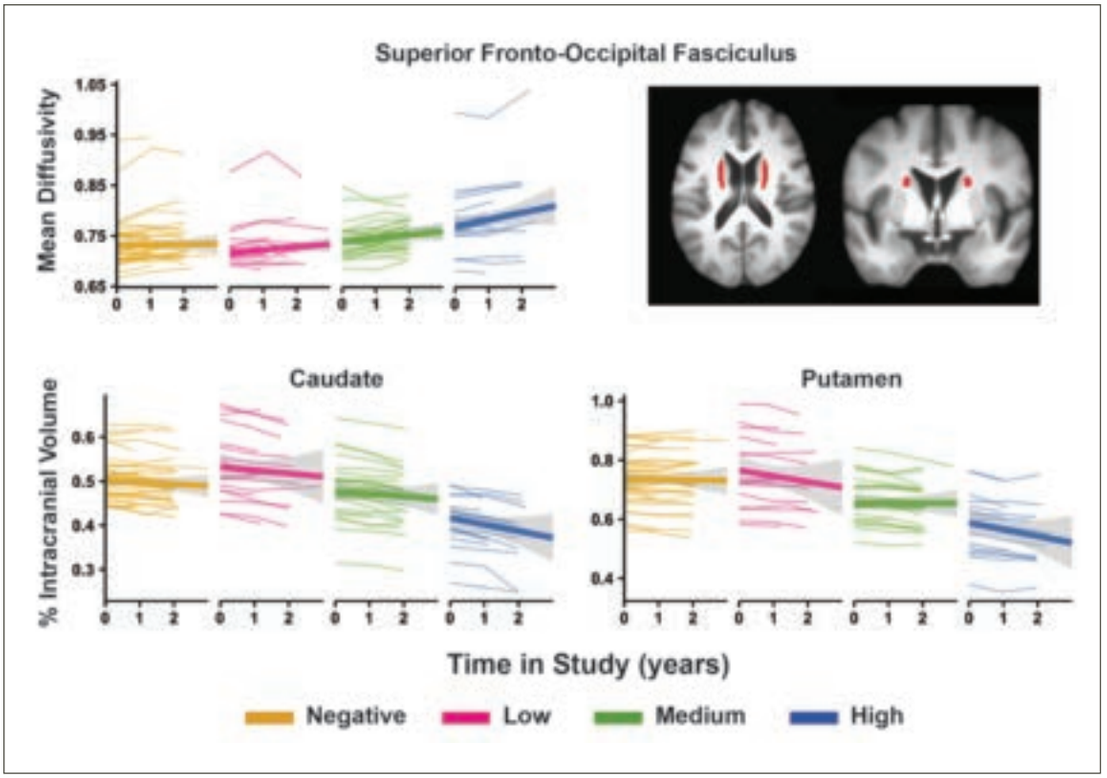


FIGURE 2. *Longitudinal trajectory of change in MRI variables in gene-negative and gene-positive individuals. Graphs display the individual trajectories of change over time for three MRI variables — mean diffusivity for the superior fronto-occipital fasciculus and volumes of the caudate and putamen — that showed a significant group-by-time interaction. The x-axis plots time in study, indexed in years. Graphs show the variability of individual trajectories (thin colored lines) around the group mean trajectory (wide colored lines) for the color-coded participant groups as shown in the key. Adapted, with permission, from Harrington et al,[6] ©2016 International Parkinson and Movement Disorder Society.*

longitudinal changes in diffusivity, measured on an annual basis for two years, were localized to a white matter fiber tract called the superior fronto-occipital fasciculus (Figure 2). These changes were most prominent in individuals closer to a manifest diagnosis. Increases in motor symptoms across time were associated with greater changes in the superior fronto-occipital fasciculus diffusivity over time, in addition to atrophy of basal ganglia (putamen and caudate). These findings provided novel insights into longitudinal changes in different facets of structural brain connectivity in prHD.

Collectively, our results show for the first time a largely disease burden-dependent functional reorganization of functional and structural brain networks in prodromal HD. Both seed- and network-based analytic approaches provided a unique window into brain functional reorganization that was not related to brain atrophy or motor symptoms. Our longitudinal results have charted the course of functional changes to determine the most sensitive imaging biomarkers of disease progression for clinical trials aimed at preventing or slowing progression of the disease during the prodromal HD phase.

Directional Connectivity Analysis of Resting-State MEG Data to Localize Epileptogenic Foci

Section authors: Balu Krishnan, PhD, and Andreas Alexopoulos, MD, MPH

Accurate localization of the epileptogenic focus in patients with intractable epilepsy has a positive impact on the long-term outcome of resective surgery. As part of our continuous effort to improve surgical outcomes, Cleveland Clinic's Epilepsy Center initiated new research to investigate the use of resting-state magnetoencephalography (MEG) data to localize epileptogenic foci.

MEG offers a direct measurement of whole-brain neuronal activity while preserving high spatial and temporal resolutions. Traditional MEG-based analyses in epilepsy have relied on source modeling of epileptiform activity. The study pioneered by our neurophysiology team relies on noninvasive localization of the epileptic focus based on analysis of resting-state directional connectivity of the epileptic brain (in this case, resting state means that no epileptiform discharges are necessary) using advanced signal processing of MEG data. This approach is based on the premise that the epileptic focus has increased information exchange with neighboring neural structures during the resting state.[7,8]

Our pilot study on the use of resting-state MEG data for localization of epileptogenic foci was funded by an American Epilepsy Society Young Investigator Award. The study analyzes resting-state MEG recordings from 22 consecutive patients with medically refractory epilepsy who underwent resective surgery and have been seizure-free for at least one year. In this study, information transfer between different brain regions was estimated using techniques from Granger causality. Graph theoretical centrality measures were used to identify important nodes of the connected network, and an asymmetry index was employed to quantify the degree of bilateral asymmetry in graph theoretical measures. Concordance with the epileptogenic zone was evaluated by comparing the regions of high asymmetry with those of the resection cavity. Connectivity-based investigation was able to identify the epileptogenic zone in 16 of the 22 patients, including eight in whom localization was not possible via traditional MEG analysis due to the absence of an adequate number of interictal abnormalities.

Figure 3 shows the net information exchange into (panel A) and out of (panel B) insular cortex across 22 patients. Panel C shows findings from a patient who underwent right temporal lobectomy. A high asymmetry index in network centrality can be seen in the left mesial temporal lobe. Panel D presents an example of where a high asymmetry index in network centrality was observed in the right middle frontal gyrus and the left lingual area (not shown). This patient underwent resection of the right middle frontal gyrus and has been seizure-free.

Our results provide evidence that noninvasive resting-state data carry important information on epilepsy pathophysiology and should guide therapeutic targeting to improve care. The connectivity-based technique has conceptual advantages over traditional point-based models in that it doesn't rely on the presence or absence of epileptiform abnormalities during MEG acquisition. This critical advantage can contribute to the yield of MEG studies by providing solutions to MEG-negative cases (i.e., those with an absence of epileptic events).

Traditionally, whole-brain functional connectivity analysis has been performed using fMRI. fMRI studies rely on measurement of hemodynamic changes, which fluctuate at a slower time scale relative to neural activity. The superior temporal resolution of MEG can be useful in estimating directional connectivity measures from the neural activity. Resting-state MEG analyses can thus be used to investigate brain networks, paving the way for applications that go beyond epilepsy to address the role of networks in other neurological diseases (e.g., dementias), cognitive conditions (e.g., autism) and psychiatric conditions (e.g., schizophrenia, depression, anxiety).

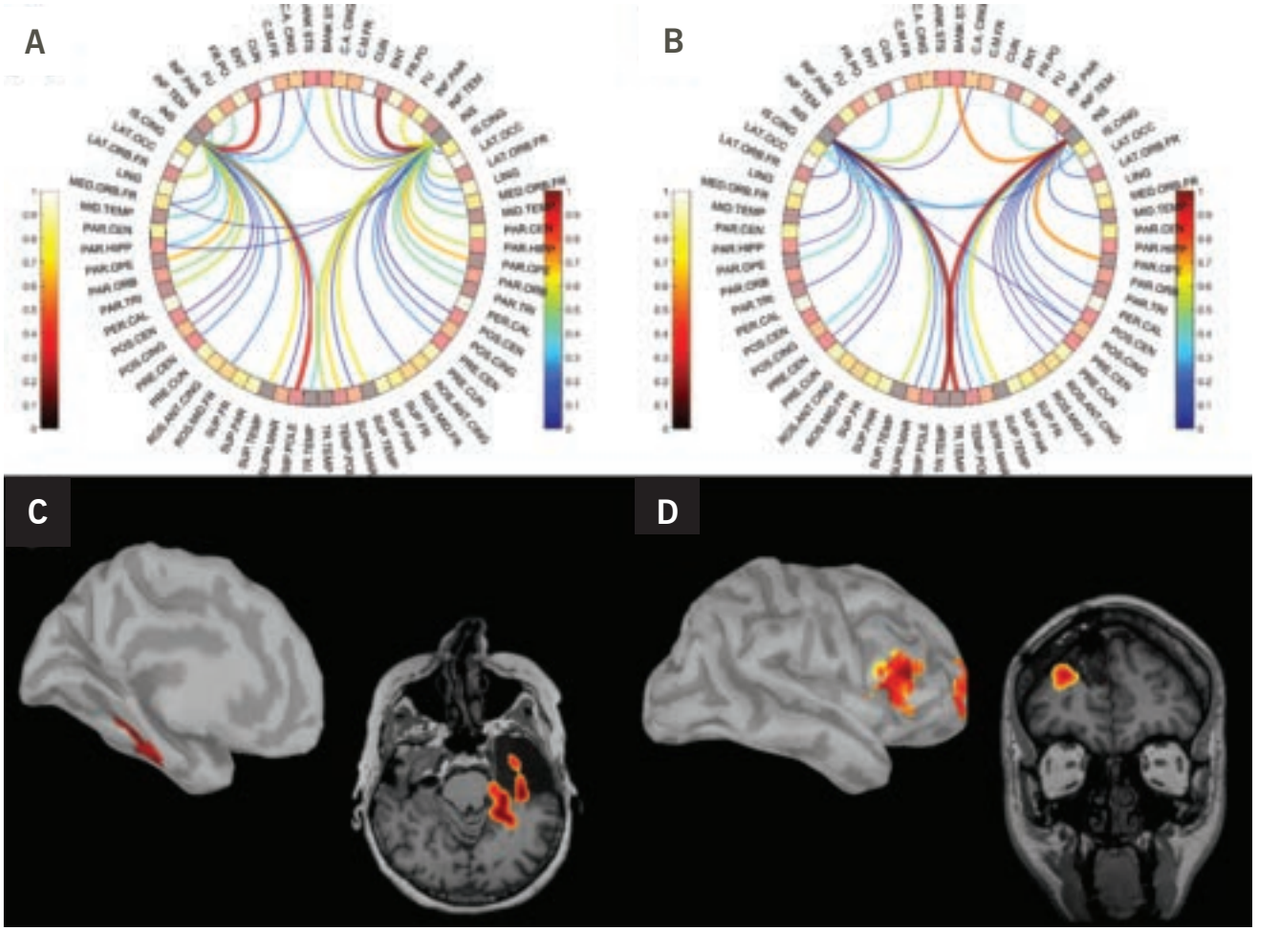


FIGURE 3. *Average information exchange map for insular cortex across 22 patients. Panel A shows net information exchange to insula from other cortical regions, whereas panel B shows net information exchange from insula to other cortical regions. Panels C and D present illustrative examples of results of focus localization using resting-state connectivity analysis rendered of patients' individual cortex and postoperative MRI. Panel C shows a case of temporal lobe epilepsy in which high connectivity was observed in the left hippocampal formation. The patient underwent left temporal lobectomy. Panel D shows a case of frontal lobe epilepsy in which high connectivity was observed in the left lingual (not shown) and right middle frontal gyrus. The patient underwent resection of the right middle frontal gyrus and has been seizure-free. See text for more detail.*

Deep Brain Stimulation of the Ventral Striatal Area for Post-Stroke Pain Syndrome: A Magnetoencephalography Study

Section authors: Raghavan Gopalakrishnan, PhD, and Andre Machado, MD, PhD

Post-stroke pain syndrome (PSPS) is an intractable disorder characterized by unrelenting chronic pain and hemiparesis. While traditional analgesia-based therapeutic approaches (e.g., opioids) have largely failed, integrative approaches targeting affective-cognitive spheres have started to show promise.

Recently, a Cleveland Clinic team demonstrated that deep brain stimulation (DBS) of the ventral striatal area (Figure 4), a key node in the networks that modulate emotion, significantly improved the affective sphere of pain and quality of life in patients with PSPS.[9] We subsequently examined whether this observed clinical improvement was reflected in the electrophysiological correlates and whether they could serve as objective biomarkers of affective pain response.

To test this hypothesis, we recorded neural substrates of pain anticipation using MEG, a neuroimaging modality that records magnetic fields produced by neural currents with millisecond precision, in 10 patients with PSPS. Recordings were made preoperatively and postoperatively in the "DBS off" and "DBS on" states. Visual countdown cues (numbered 3, 2 and 1, as shown in triangles in Figure 5) evoked anticipation as patients awaited a painful stimulus (PS) or nonpainful stimulus (NPS) to their nonaffected or affected extremity (in separate paradigms). Whole-brain event-related responses, a series of fluctuations in neural currents evoked by anticipatory cues, were examined. The responses have specific functional relevance and are labeled using a system with the pattern P1, N1, P2, N2, etc., as shown in Figure 5, depending on the timing and polarity relative to cue onset.

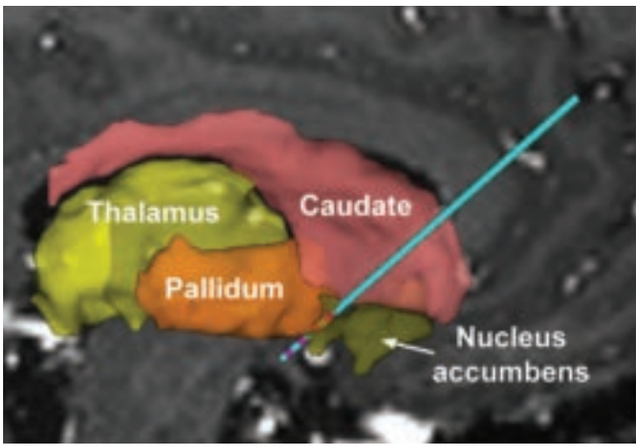


FIGURE 4. *Electrode trajectory and implant location for DBS of the ventral striatum/anterior limb of internal capsule for treatment of post-stroke pain syndrome.*

Preoperatively, NPS anticipation was remarkably similar to PS anticipation (as shown in the left portion of the top panel of Figure 5), possibly due to loss of salience in a network saturated by pain experience. Postoperatively, DBS significantly modulated the early N1 during NPS anticipation, consistent with networks involving restoration of salience and discrimination capacity (top panel of Figure 5, middle and right). Additionally, DBS suppressed the posterior P2 (aberrant anticipatory anxiety) while enhancing the anterior N1 (cognitive and emotional regulation) in treatment responders (Figure 5, bottom panel).

We conclude that DBS-induced changes in event-related components reflect treatment effects and could serve as biomarkers for treatment efficacy.

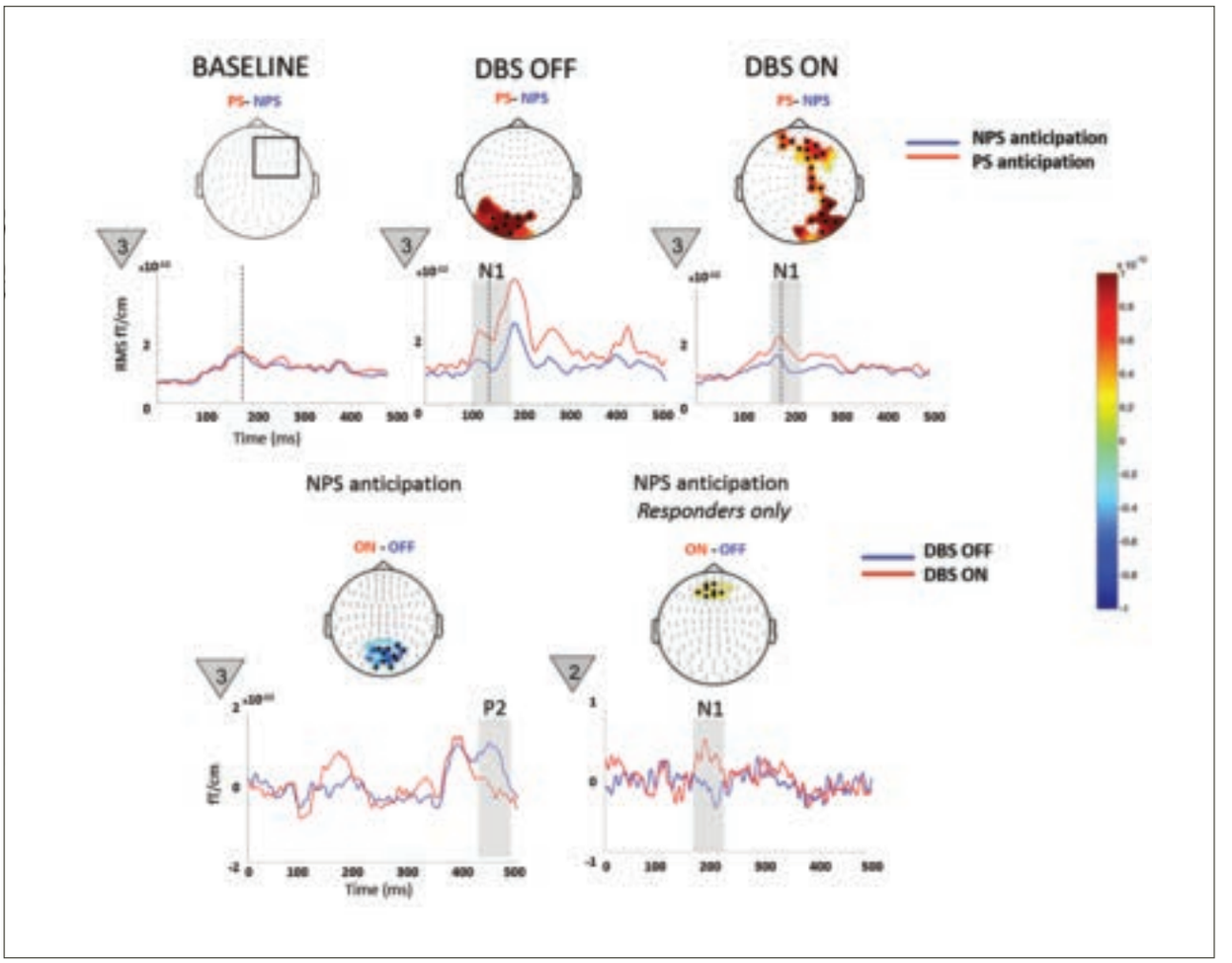


FIGURE 5. *Magnetoencephalographic neural substrate recordings of pain anticipation in 10 patients with post-stroke pain syndrome before and after deep brain stimulation (DBS). See text for details.*

Advanced Connectivity Measures Using Simultaneous Electrode Stimulation and fMRI

Section author: Stephen E. Jones, MD, PhD

To date, the imaging techniques most applicable to neurological disease have been structural, as they can superbly delineate diseased regions of the brain. While MRI has been the workhorse method for the past 25 years, some diseases are often inconspicuous on structural MRI. This has spurred considerable interest in more recent MRI techniques developed to examine brain *function*, rather than *structure*, which in turn is closely related to imaging brain connectivity.

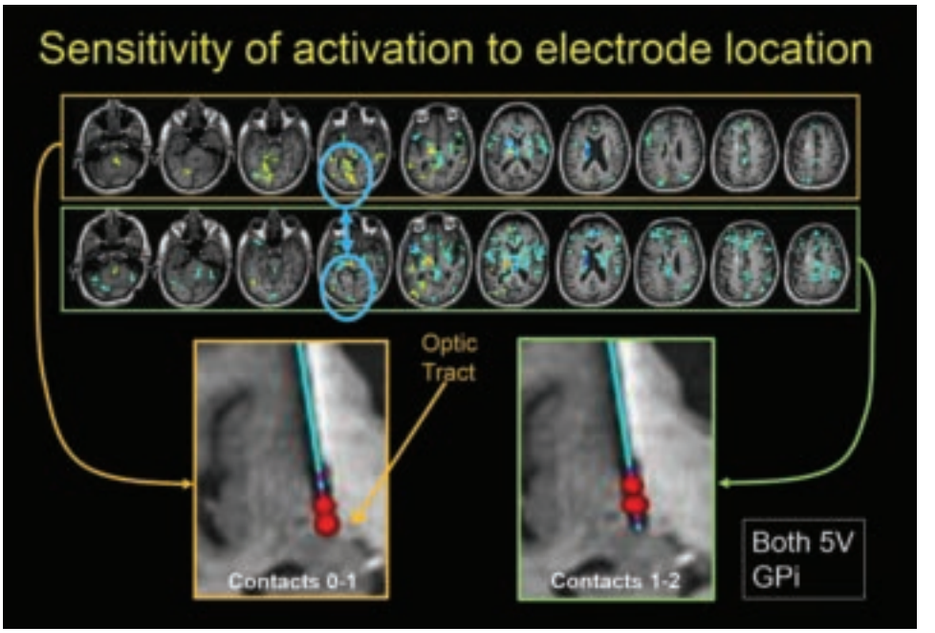


FIGURE 6. *The top row of images shows BOLD activation maps resulting from stimulation of electrode contacts in the globus pallidus interna (GPi) regions. This stimulation, depicted in the large image on the lower left, is specifically a bipolar stimulation between contacts 0 and 1, where the red spheres indicate predicted regions depolarized by electrical current. Yellow-green shading indicates regions with increased BOLD activation with electrical stimulation, whereas blue regions show decreased activation with electrical stimulation. The second row of brain maps shows the results when the location of the stimulation electrodes is slightly changed, now in the adjacent contact pair 1-2. While the two rows of brain maps show activation in many brain regions, there are some notable differences, such as the right-sided visual areas of the occipital lobes, as indicated within the blue circles (fourth images in each row). This is likely due to proximity of the activation at contacts 0-1 to the optic tracts, as indicated by the arrow.*

Close collaboration between Cleveland Clinic's Imaging Institute and Neurological Institute has enabled demonstration of a new technique to image brain connectivity featuring simultaneous DBS electrode stimulation and fMRI performed at 1.5T in patients with movement disorders under general anesthesia. Robust blood-oxygen-level-dependent (BOLD) activation can be easily elicited at voltages greater than 4V. The patterns of BOLD activation include both proximal and distal brain regions, with high spatial sensitivity, and these patterns also reflect clinical efficacy.

The technique of simultaneous electrical stimulation of the brain and BOLD fMRI is generally applicable to any neurological disease that can be treated with electrical stimulation. To date, this has included epilepsy, major depression, obsessive-compulsive disorder, essential tremor and urinary incontinence. For these experiments, patients were scanned in a 1.5T intraoperative MRI scanner during DBS electrode implantation under general anesthesia. After anatomically guided implantation,

a BOLD-sensitive echo planar imaging sequence was acquired during stimulation of the electrodes in a block design of 30 seconds on/off. Stimulation parameters were 2, 5 and 8V across bipolar contacts at 130 Hz. Up to four DBS-fMRI sequences were obtained during the imaging session, each with variations of stimulation parameters such as voltages, contacts and duration.

To date, seven patients have been studied and there have been no adverse reactions. Various stimulation parameters were explored, generally showing robust BOLD activation with voltages greater than 5V. BOLD activation included brain regions both proximal and distal to the electrodes, with patterns reflecting motor circuits, and the patterns were very sensitive to lead location. Figure 6 presents example findings.

This technique of simultaneous DBS electrode stimulation and fMRI offers a possible alternative for patients desiring DBS implantation while under general anesthesia as well as functional location of electrodes to maximize clinical response and minimize side effects. This technique could easily be generalized to any functional localization electrodes during implantation.

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Dr. Nair (naird@ccf.org) is Section Head of Adult Epilepsy in the Epilepsy Center. **Dr. Mosher** (mosherj@ccf.org) is a research scientist in the Epilepsy Center. **Dr. Rao** (raos2@ccf.org) holds the Ralph and Luci Schey Endowed Chair in Cleveland Clinic Lou Ruvo Center for Brain Health, Cleveland. **Dr. Krishnan** (krishnb@ccf.org) is a research scientist in the Epilepsy Center. **Dr. Alexopoulos** (alexopa@ccf.org) is a staff physician in the Epilepsy Center. **Dr. Gopalakrishnan** (gopalar@ccf.org) is Principal Research Engineer in the Center for Neurological Restoration. **Dr. Machado** (machada@ccf.org) is Chairman of the Neurological Institute. **Dr. Jones** (joness19@ccf.org) is Vice Chair for Research and Academic Affairs in the Imaging Institute and holds multiple appointments in the Neurological Institute.

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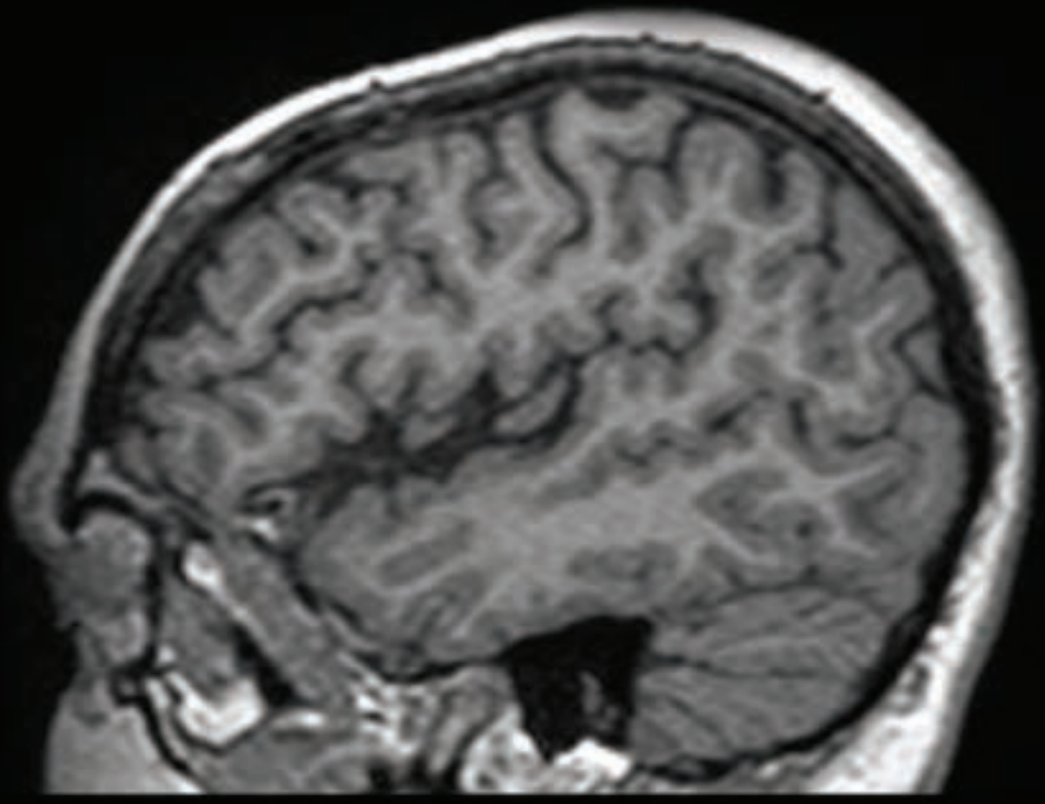
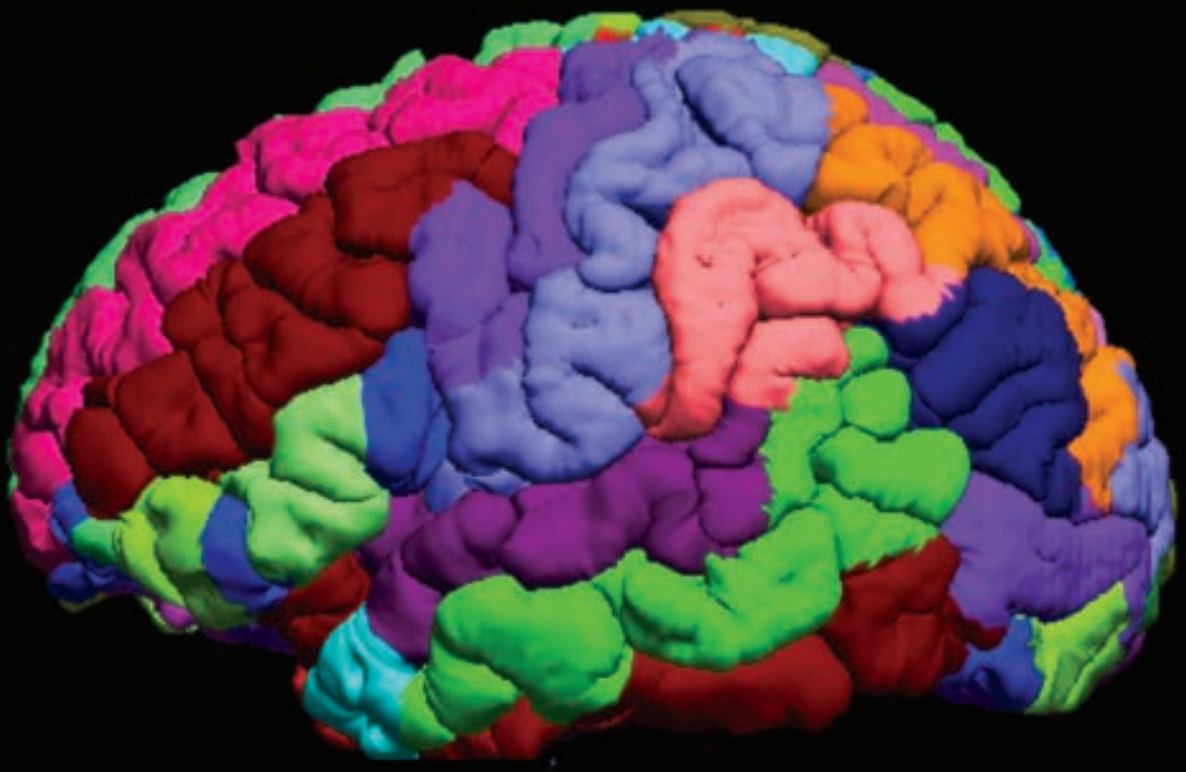




Making the Most of MRI:

From Morphometric and Volumetric Analyses to Post-Processing Informed by Machine Learning

By Z. Irene Wang, PhD; Kunio Nakamura, PhD; and James B. Leverenz, MD

New and emerging uses of magnetic resonance imaging (MRI) processing techniques are enabling an understanding of brain pathology across neurological diseases that we couldn't imagine a few decades ago. And these novel techniques — which include computer-assisted morphometric assessment, volumetric analysis and image post-processing guided by machine learning — are making more-personalized care possible with minimal invasiveness.

This update focuses on how Cleveland Clinic Neurological Institute researchers and clinicians are using these techniques in major therapeutic areas such as epilepsy, multiple sclerosis (MS) and neurodegenerative diseases.

Computer-Assisted Morphometric Assessment of MRI Findings

Interpretation of MRI data can be markedly improved by computer-assisted methods designed to pull out information not easily seen by visual analysis. At Cleveland Clinic's Epilepsy Center, scientists and clinicians are spearheading efforts to use computer-assisted morphometric assessment of MRIs to improve noninvasive epilepsy localization in clinical practice. This strategy offers a novel field of analysis that goes beyond expert visual inspection of the MRI and allows for rater-independent imaging correlates to be generated for each individual patient.

The new technology has already made an impact on many patients with epilepsy evaluated at Cleveland Clinic, particularly those whose MRIs were negative by conventional visual analysis. These "MRI-negative" or "nonlesional" patients, approximately 40 percent of the total epilepsy surgery population, typically require expensive and invasive intracranial electroencephalography (EEG) to identify the epileptogenic zone.

Several years ago, our Epilepsy Center research group published a study indicating that the main pathology in nonlesional epilepsy is focal cortical dysplasia (FCD).[1] These lesions are usually characterized by subtle MRI features and can be difficult to identify by visual analysis of 3T MRI scans. Our group performed well-designed studies to validate the usefulness of a voxel-based morphometric analysis program (MAP) for detection of subtle FCD.[2,3] Reliable performance has been seen on MRI scans with different field strengths (1.5T/3T) and from different scanners (Siemens, Philips and GE). In

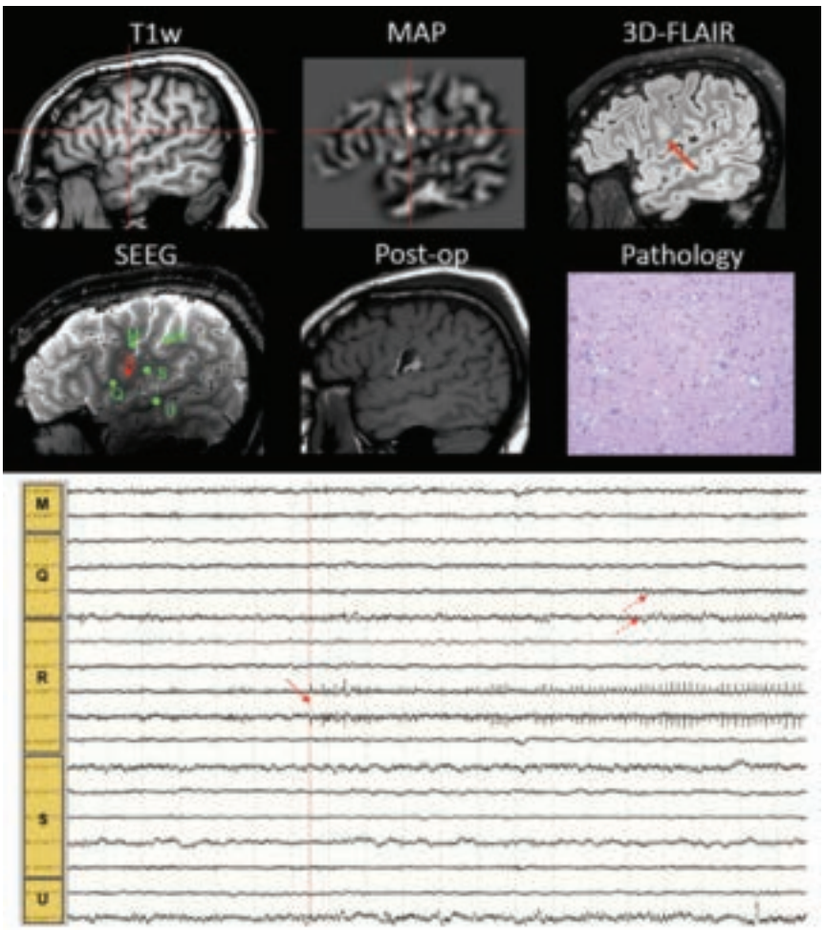


FIGURE 1. *Images from an illustrative case in which computer-assisted morphometric assessment (MAP) of MRI provided essential information. A subtle lesion was detected by MRI post-processing using the MAP method in the depth of the central sulcus (top row of images). This finding was missed on multiple previous MRI scans and only became apparent based on MAP-guided analysis of the MRI. The first image in the second row shows the ictal onset location from invasive evaluation using SEEG (onset electrodes marked with red; other electrodes marked with green). A typical seizure captured during the invasive monitoring is shown in the bottom panel. Seizure onset at R5-8 is marked by the red arrow; dashed arrows denote the quick spread to Q7-10. Ictal onset was in the exact location of the detected subtle abnormality. The postoperative MRI in the second row of images shows complete resection of the abnormality. Pathological examination showed type IIb focal cortical dysplasia in the surgical specimen, characterized by balloon cells (lower right panel; HE stain, ×200).*

a retrospective study of a cohort of 150 MRI-negative surgical patients,[3] MAP-guided MRI interpretation showed positive findings in 43 percent, and complete resection of the MAP-positive region correlated positively with seizure-free outcome. The false-positive rate was 2 percent in a group of 52 healthy controls.

Figure 1 presents images from a 37-year-old right-handed man evaluated for surgery for drug-refractory focal epilepsy. Seizure semiology suggested a perisylvian/opercular onset of unclear laterality. During three previous video-EEG monitoring evaluations, no interictal spikes were captured, and ictal events were lateralized only to the right hemisphere. This patient had several previous MRIs that were reported as normal. Other noninvasive modalities did not provide additional localization. MRI post-processing using MAP showed a subtle lesion represented by gray-white blurring in the ventral aspect of the depth of the right central sulcus, which was concordant with the seizure semiology. This finding prompted a very focal design of stereoelectroencephalographic (SEEG) electrode implantation, which confirmed the epileptogenicity of the subtle lesion. The patient became seizure-free after focal resection, which was confirmed to contain the lesion.

Our published studies provided validation of the morphometric analysis methods, which enabled us to integrate them in the routine presurgical evaluation of patients with MRI-negative medically intractable epilepsies at Cleveland Clinic's Epilepsy Center. With minimal extra cost and no additional tests or risks to the patient, this process has shed light on many difficult cases like the one profiled in Figure 1.

Moreover, the MAP method is now being applied to 7T MRI. Figure 2 shows images from a patient with histopathologically confirmed FCD type IIb whose 3T MRI was previously interpreted as normal but in whom 7T MRI revealed a transmantle abnormality in the right frontal lobe. The presence and extent of the abnormality in the cortical mantle was further illustrated by MAP: The 7T MAP results showed markedly enhanced visualization of blurring in the gray-white boundary radially connecting the cortex to the ventricle, whereas the 3T MAP results also highlighted the region but only showed the component adjacent to the cortex. These findings strongly suggest that higher field strength combined with MRI morphometric analysis can assist in delineation of epileptogenic pathologies.

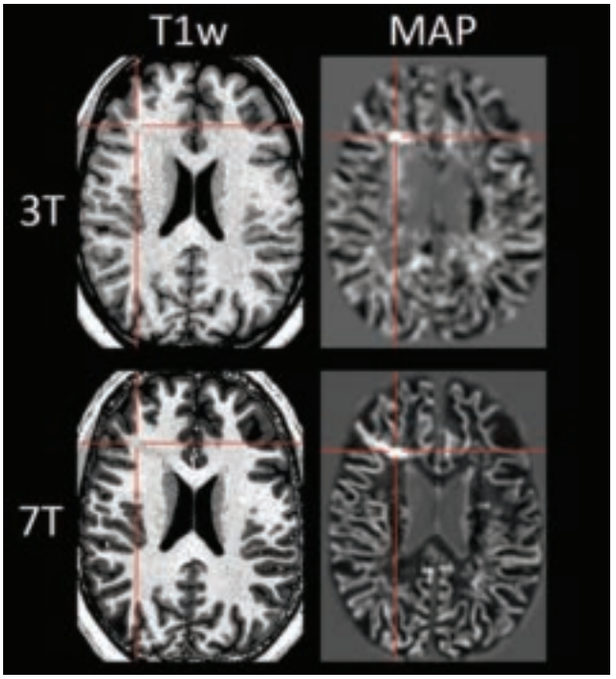


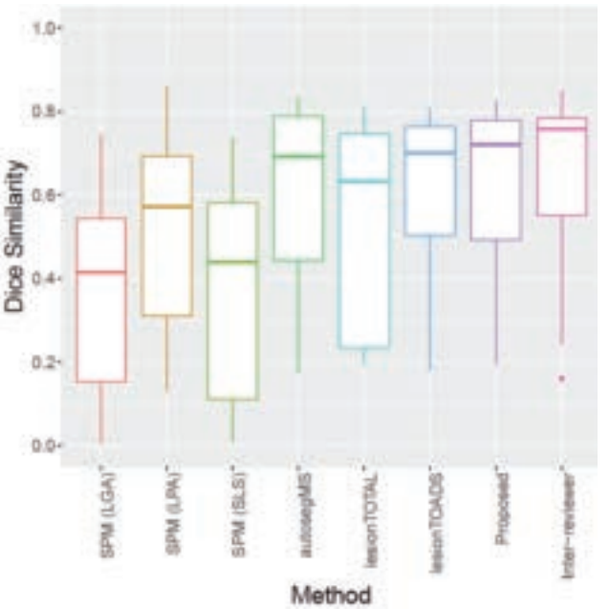
FIGURE 2. *Comparison of the application of MAP to 3T and 7T MRIs in a patient with histopathologically confirmed FCD type IIb. The top row shows a 3T T1w sequence followed by a MAP gray-white junction feature map showing the subtle FCD lesion with a voxel size of 1 mm^3. The bottom row shows a 7T T1w sequence followed by a MAP gray-white junction feature map highlighting the same lesion with a voxel size of 0.5 mm^3.*

Machine Learning Integrated with MRI Post-Processing

The advent of artificial intelligence and machine learning is revolutionizing the way large volumes of patient data are interpreted. Scientists in Cleveland Clinic's Neurological Institute are devoting substantial efforts to using machine-learning algorithms to inform the way pathological substrates are being detected and delineated.

Multiple Sclerosis

One innovative application of machine learning is for quantification of MS lesion loads from clinical imaging studies. Researchers with Cleveland Clinic's Lerner Research Institute and Mellen Center for Multiple Sclerosis have analyzed MRIs acquired on clinical scanners using a Random Forest algorithm, which improves overall segmentation accuracy over other methods when compared with consensus segmentation from multiple reviewers (Figure 3). Notably, the algorithm is able to analyze MRIs from various clinical protocols and from different MRI models, including field strengths of 1T, 1.5T and 3T, as well as from various scanner manufacturers (Figure 4). When compared with the clinical reads by neuroradiologists, the automatic lesion volumes showed good associations between severity categories and visually confirmed the lesion probability maps based on the categories (Figure 5). These findings highlight the usefulness of machine-learning techniques and suggest a potential to change routine practice.



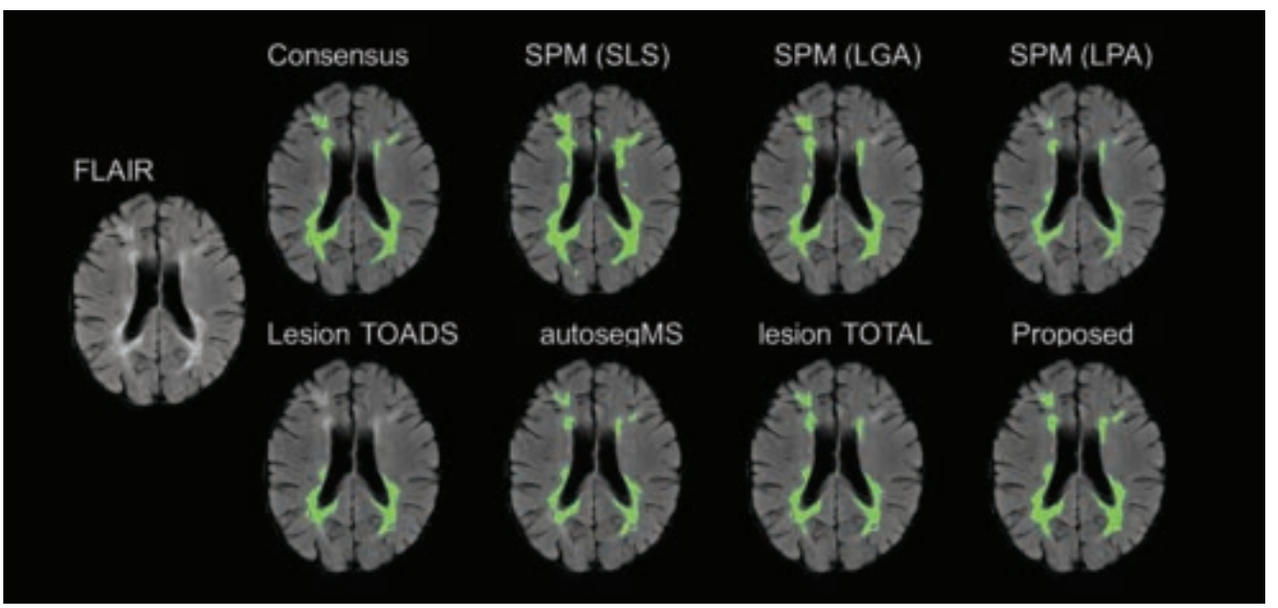


FIGURE 3. ***Top panel:*** *Box plots of Dice similarity measures from various MS lesion segmentation methods. The Dice ranges from 0 to 1, with 0 being no overlap and 1 being perfect overlap. Our proposed machine-learning method (second plot from the right) showed the highest mean Dice measure. Although far from achieving perfect overlap, our method is approaching the range of inter-reviewer variability (rightmost plot).* ***Bottom panel:*** *Example of visual comparison of lesion segmentation methods.*

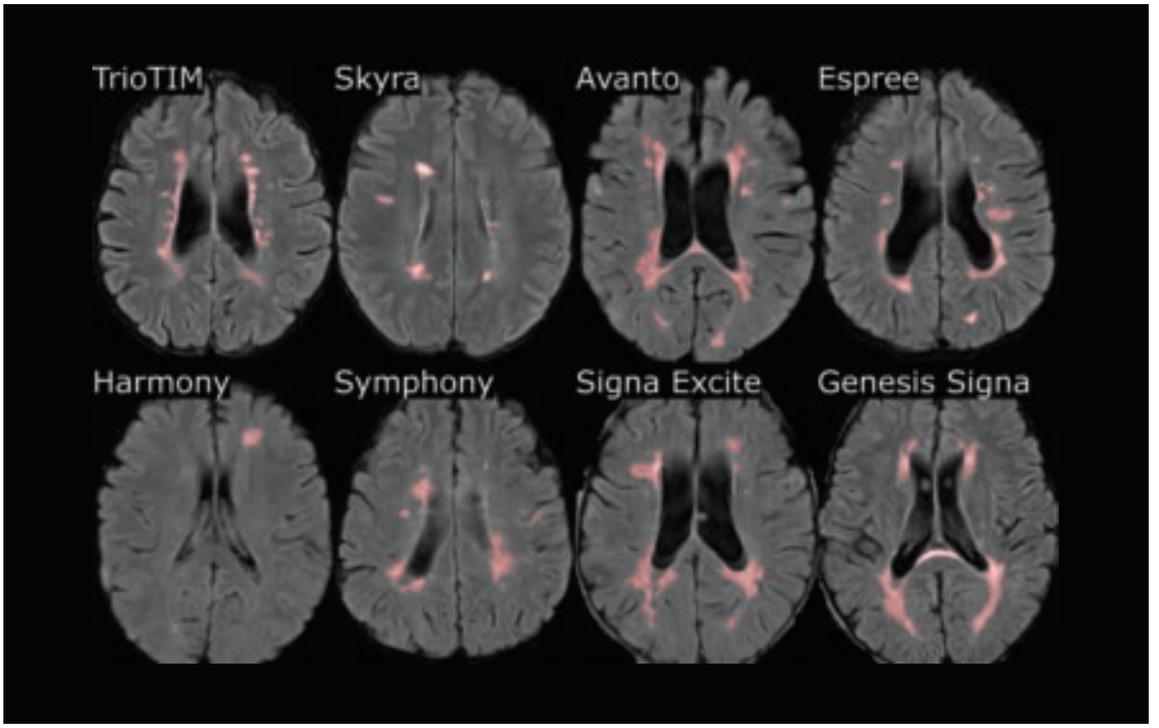


FIGURE 4. *T2 lesion segmentation from eight different scanner models showing the applicability in various clinical MS protocols.*

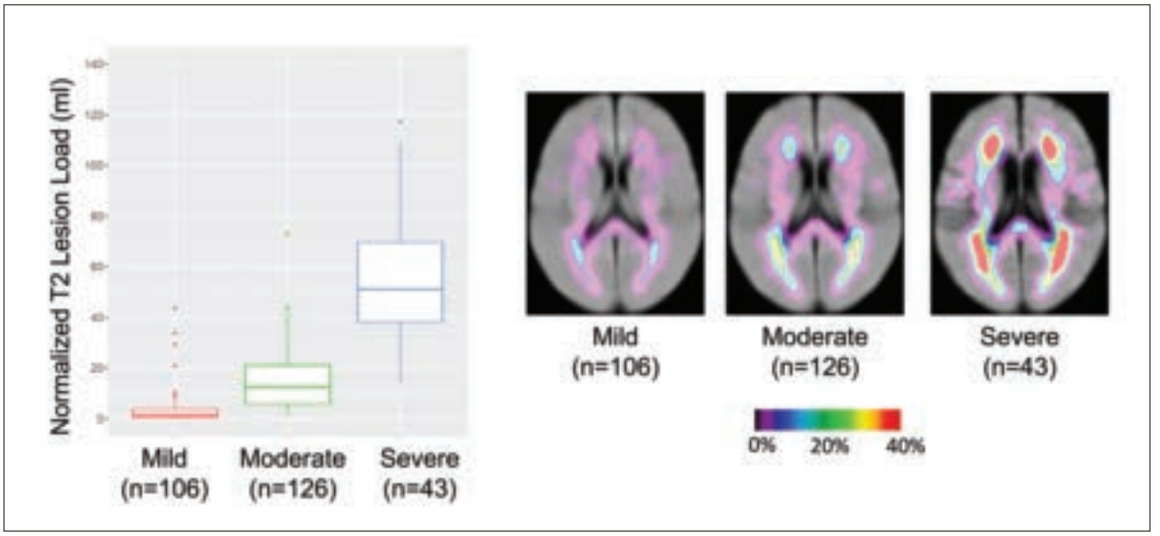


FIGURE 5. ***Left panel:*** *Box plots of normalized T2 MS lesion volume according to clinical reads.* ***Right panel:*** *Average lesion probability map overlaid on average fluid-attenuated inversion recovery (FLAIR) images for each clinical category. The images show increasing lesion probability in periventricular and subcortical areas. Concurrently, an enlargement of the ventricles is seen as clinical severity intensifies from mild to severe.*

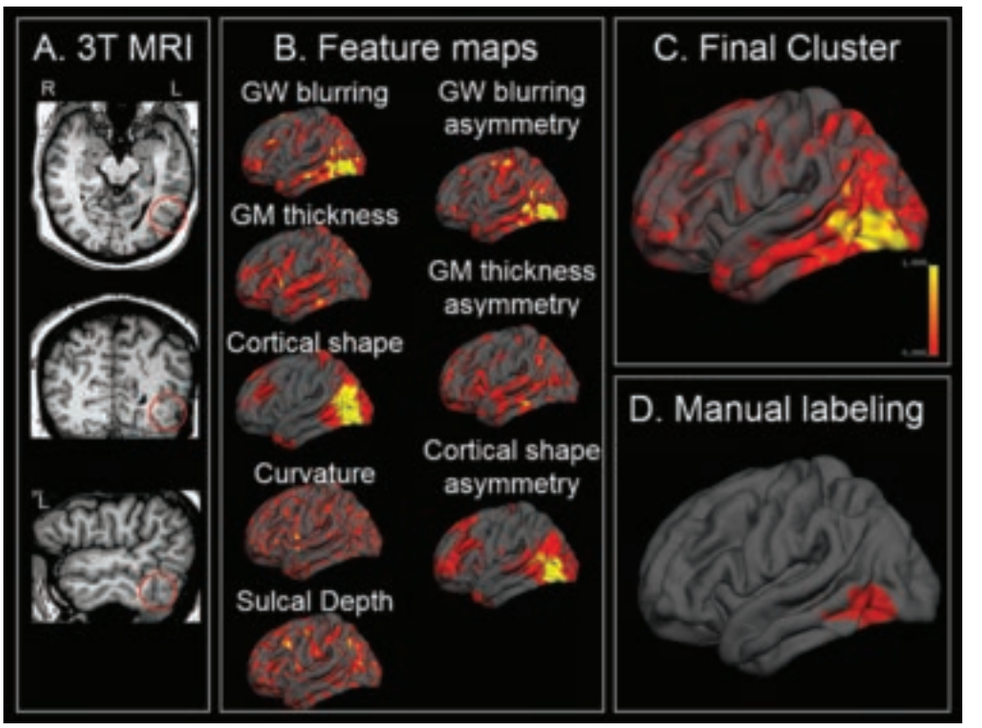


FIGURE 6. *Images illustrating a multivariate surface-based morphometry approach for automated focal cortical dysplasia (FCD) detection. (A) 3T T1w MRI from a patient with histopathologically confirmed type I FCD in the left basal temporal area (circles). (B) Various cortical features generated from the surface-based morphometry approach, which were used as input to a nonlinear neural network classifier. The output cluster with the highest mean probability value (as yielded by the classifier) was considered the final cluster (C). Success of detection was defined by overlap between the final cluster and manual labeling (informed by noninvasive test, SEEG, postoperative MRI and histopathology) (D).*

Epilepsy

Equipped with a large surgical volume, MRI data and pathological confirmation of resected tissue, the Epilepsy Center research group is investigating machine-learning strategies designed to directly correlate MRI with pathological findings.

Figure 6 shows an automated multivariate surface-based morphometry analysis methodology combined with machine learning for automated FCD detection. The analysis was based on measures such as cortical thickness, gray-white matter blurring, sulcal depth and curvature, and cortical shape deformation. Additionally, asymmetry maps were generated to account for inherent left-right differences in each individual brain. These features were used as input to a machine-learning algorithm realized by a nonlinear neural network classifier for automated lesion detection, yielding output of clusters with a high likelihood of abnormality. The current method already showed robust performance on 3T data from different scanners. Figure 6 presents findings from an example patient whose subtle MRI lesion was successfully and automatically recognized by the current method.

Eventually, machine-learning techniques will enable the construction of a well-trained computer algorithm based on retrospectively validated data derived from a large number of patients. Such an algorithm could be used as an independent “consultant” to inform clinical recommendations on a case-by-case basis. This strategy will have lasting impact across the country by markedly improving epilepsy seizure outcomes and increasing the number of patients who can be deemed favorable candidates for potentially curative surgery.

Quantitative MRI Volumetric Analysis

Important MRI characteristics of neurological diseases can be obtained from volumetric analysis of brain MRI. Current technologies allow for volumetric analysis to achieve realistic rendering of the cortical surface in an accurate and prompt manner. Cleveland Clinic's Neurological Institute has been applying this technology across multiple subspecialties, with examples profiled below.

Multiple Sclerosis

One of Cleveland Clinic's long-standing research interests in MS is volumetric brain analysis. Since our first report in 1999 on brain atrophy in MS using brain parenchymal fraction,[4] our center has continued to perform quantitative measurement of whole brain atrophy in both clinical trials and research studies. The method has been applied in more than 20 separate clinical and research studies to date on over 40,000 MRIs collected at Cleveland Clinic and from other centers. We have also developed methods for measuring cortical thinning, i.e., cortical longitudinal atrophy detection algorithm (CLADA),[5] and for measuring gray matter atrophy using pairwise Jacobian integration.[6] These methods are particularly suited for longitudinal studies in that they are designed to detect subtle differences in brain MRIs and quantify the structural change.

More recently, we have studied thalamic atrophy, which occurs early in the course of MS. To this end, we have created a large normative trajectory of thalamic volumes from over 1,500 neurologically normal subjects using publicly available databases to more accurately detect abnormal thalamic volumes[7] (Figure 7).

Brain Health and Neurodegenerative Diseases

Cleveland Clinic Lou Ruvo Center for Brain Health is a three-site program that accommodates more than 14,000 patient visits annually at locations in Cleveland, Ohio; Las Vegas, Nevada; and Weston, Florida. In addition to standard MR imaging, all scans performed by our center can have automated post-imaging volumetric measurements to accurately assess for atrophy and

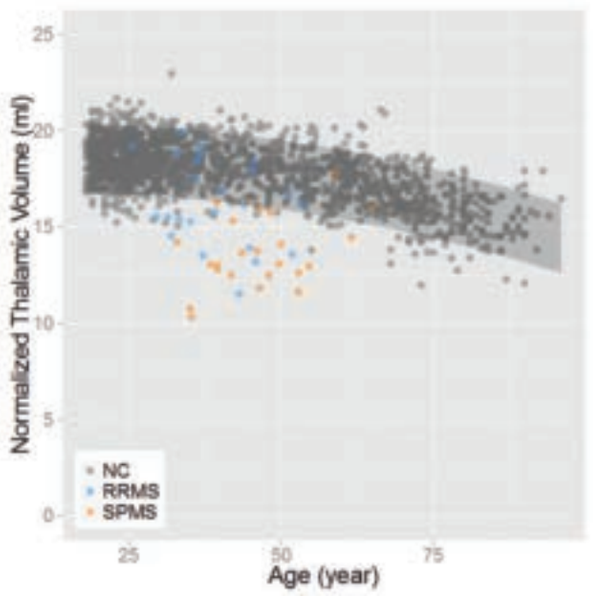


FIGURE 7. *Trajectory of normalized thalamic volumes of 1,552 healthy controls from various publicly available databases and thalamic volumes of patients with MS. Large normative datasets allow more accurate detection of abnormal thalamic volumes. NC = normal controls; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.*

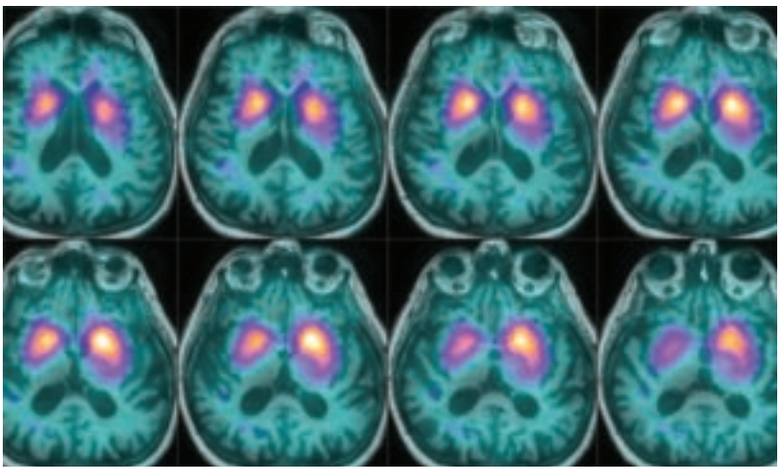


FIGURE 8. *Ioflupane (DaTscan) images of a patient with parkinsonian symptoms, including tremor. The decreased ioflupane tracer uptake on the left side of the scans indicates depletion of dopamine transporters in the striatum, consistent with a neurodegenerative process. Image courtesy of Mykol Larvie, MD, PhD, Cleveland Clinic.*

other characteristics, such as severity of white matter changes. We also employ amyloid imaging, FDG-PET, and both qualitative and quantitative dopamine transporter imaging (DaTscan™ and DaTQUANT™) (Figure 8).

We frequently supplement findings from these advanced imaging modalities with cerebrospinal fluid analysis to confirm atypical Alzheimer's disease (e.g., early onset, atypical clinical syndrome) and to diagnose rare neurological disorders such as paraneoplastic and prion disease. Imaging findings are frequently integrated in many of the 25-plus active clinical trials in the Lou Ruvo Center for Brain Health research program. Distinctive offerings include clinical trials in pre-symptomatic at-risk patients, repurposing of medications, and treatments for non-Alzheimer's dementias such as Lewy body disease.

Epilepsy

At the Epilepsy Center, one recent success with MRI volumetric analysis has been achieved in the diagnosis prediction of patients with epilepsy and Rasmussen's encephalitis (RE).[8] Over the past decade, MRI has become an increasingly important tool in the diagnosis of RE, as well as in assessing disease progression and therapeutic effectiveness. We set out to examine how volumetric measures can help predict RE — i.e., whether the extent of atrophy on MRI can be quantified to predict the probability that a patient with suspected RE truly has RE.

In our study, we included 42 MRI scans from a group of pediatric patients with RE and performed automated MRI volumetric measurements (one example is shown in

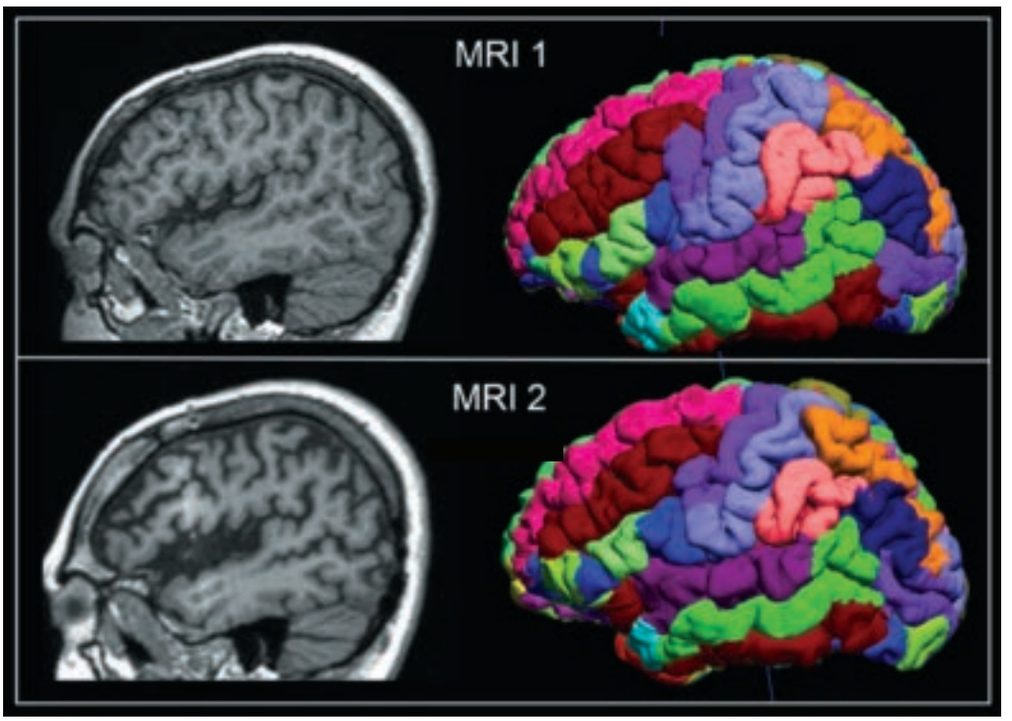


FIGURE 9. *Serial MRIs from a patient with Rasmussen's encephalitis (RE) — taken at age 10 (top row) and age 17 (bottom row) — and the corresponding volumetric analysis results from BrainSuite software (brainsuite.org). The MRI scans in the left column are T1w images that were used as input to the analysis. Automatic segmentation results are shown on the right; different colors denote different brain anatomical regions. Pronounced atrophy can be observed at the perisylvian region. The interhemispheric ratio showed a marked decrease from 0.79 to 0.70 over the course of seven years of disease. Republished with permission of the American Society of Neuroradiology from Wang et al.,*[8] AJNR Am J Neuroradiol. *2016;37:2348-2355, ©2016; permission conveyed through Copyright Clearance Center Inc.*

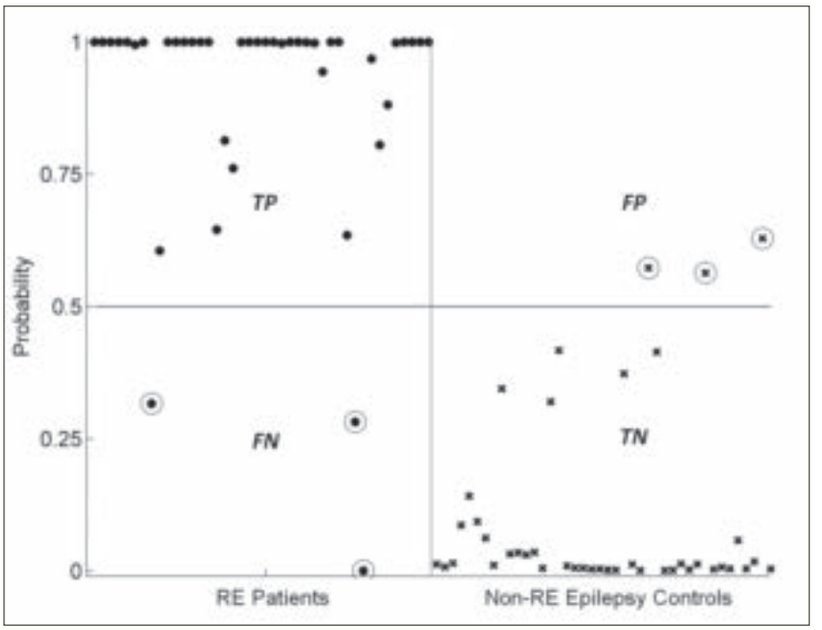


FIGURE 10. *Performance of the classifier constructed using the interhemispheric ratio. Patients with Rasmussen's encephalitis (RE) are denoted with dots, and non-RE epilepsy controls are denoted with crosses. True positives (TP) are patients correctly identified as patients by the classifier. True negatives (TN) are controls correctly identified as controls. False positives (FP) are controls incorrectly identified as patients. False negatives (FN) are patients incorrectly identified as controls. The vast majority of cases were correctly classified (TP and TN). Republished with permission of the American Society of Neuroradiology from Wang et al.,*[8] AJNR Am J Neuroradiol. *2016;37:2348-2355, ©2016; permission conveyed through Copyright Clearance Center Inc.*

Figure 9). Ratios of volumes from the affected hemisphere divided by those from the unaffected hemisphere (such as interhemispheric ratio) were used as input to a logistic regression classifier that was trained to separate patients from controls. Our study showed that automated quantitative volumetric analysis provides accurate separation of RE patients from normal controls and non-RE epilepsy patients (Figure 10) and thus may assist in the diagnosis of RE.

Used in relevant clinical settings, such as initial and follow-up investigations in epilepsy patients with suspected RE, the probability curve that was estimated (see our study[8]) can potentially provide an objective measure to solidify the confidence of an RE diagnosis. Additionally, with the methodology established in this paper, such patients can be studied prospectively by comparing volumetric findings with surgical pathology/biopsy.

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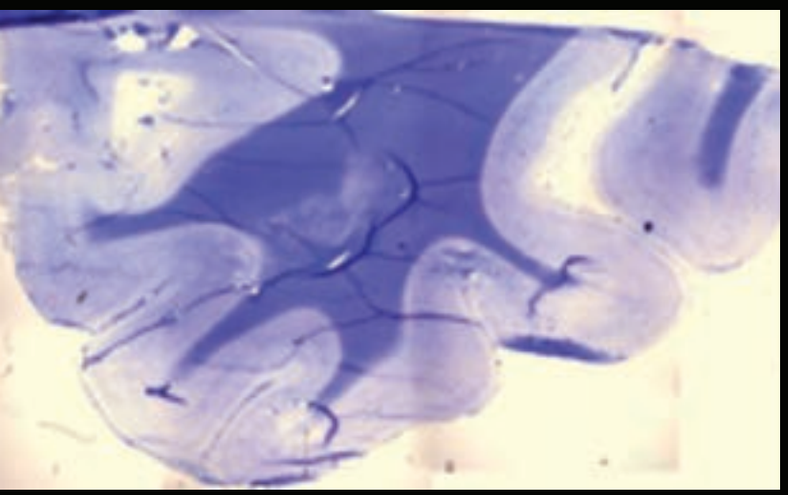
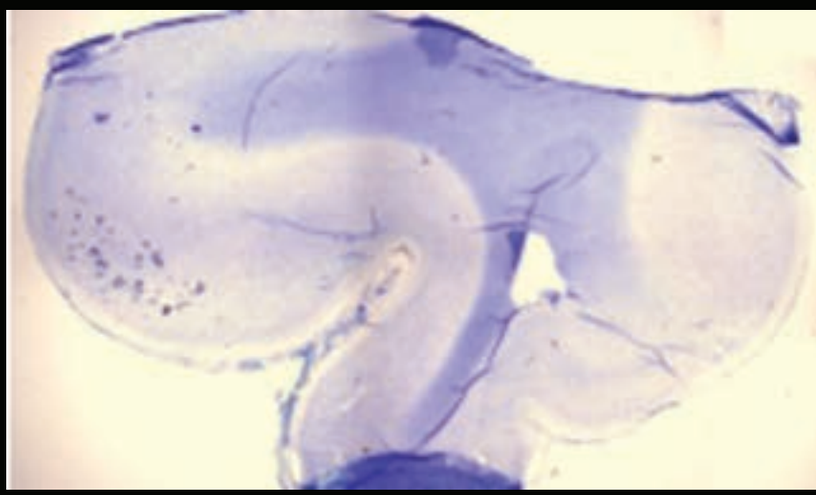
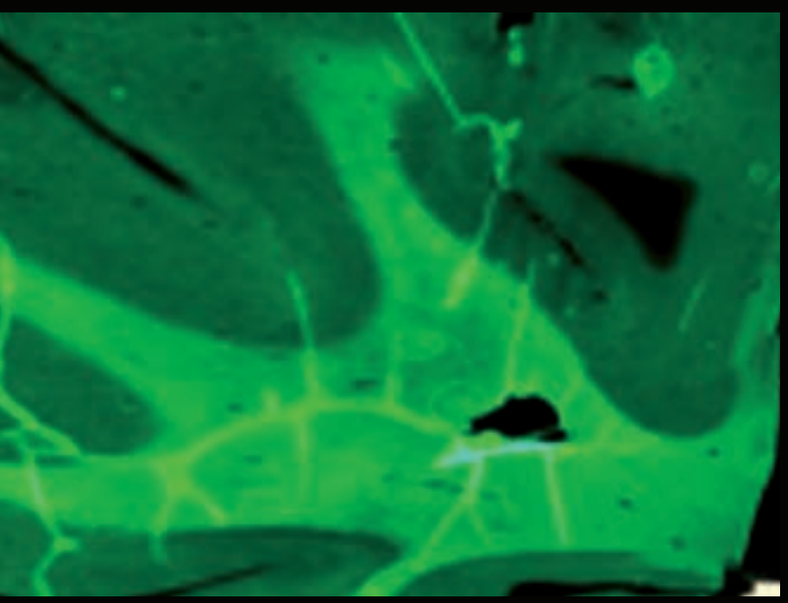
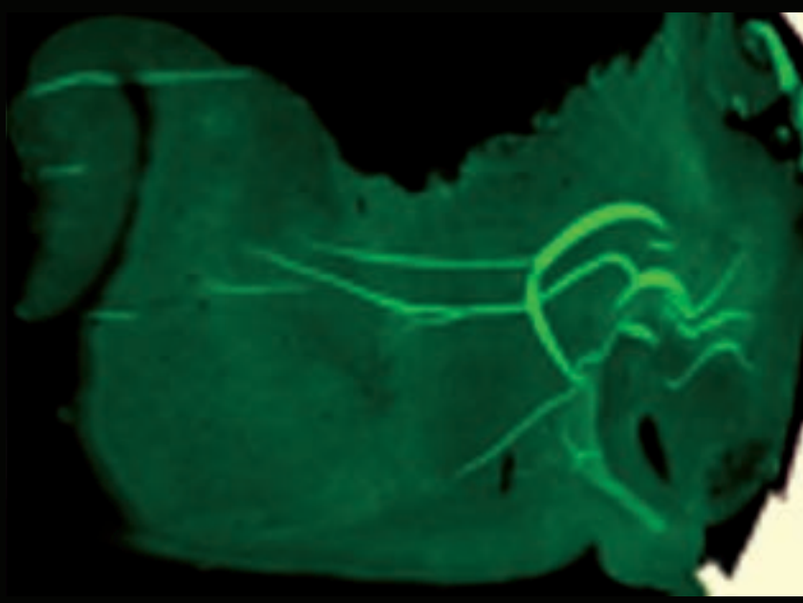
Dr. Wang (wangi2@ccf.org) is a staff scientist in the Epilepsy Center and joint staff in the Department of Biomedical Engineering, Cleveland Clinic Lerner Research Institute. **Dr. Nakamura** (nakamuk@ccf.org) is a project scientist in the Department of Biomedical Engineering. **Dr. Leverenz** (leverej@ccf.org) is Director of Cleveland Clinic Lou Ruvo Center for Brain Health, Cleveland.









Adding a New Dimension to Brain Mapping: Myelin PET

By Mykol Larvie, MD, PhD; Imad Najm, MD; and Yanming Wang, PhD

Positron emission tomography (PET), restricted by nothing less than the cold, hard physical laws governing the decay and detection of positrons, is a highly sensitive and specific imaging modality that is nevertheless limited to spatial resolution on the order of millimeters, typically about 5 mm for a good-quality brain PET scan. For this reason, PET images are necessarily much less structurally detailed compared with, for instance, the extraordinarily high resolution that is now routinely achieved with MRI, and thus appear relatively blurry. Despite this seeming limitation, new PET radiotracers are being developed that provide heretofore unavailable information regarding the smallest possible brain structures — the molecules of which the organ is composed. This ability to evaluate the molecular structure of the brain provides a new approach to mapping brain structure, composition and, ultimately, function.

A multidisciplinary initiative has been launched at Cleveland Clinic to bring to clinical application a PET radiotracer that binds preferentially to the molecular components of myelin, one of the principal components of nerves in the central nervous system (CNS) as well as the peripheral nervous system. This is a new class of imaging agent that has never before been used in humans and represents the first agent of its kind to be brought to clinical application. This compound is known by its chemical name, [*N*-methyl-^{11}C]-4,4'-diaminostilbene (MeDAS), now termed Myelivid. The molecule was developed by a group at Case Western Reserve University in Cleveland, and the translational research program for use in human patients is being led by faculty from Cleveland Clinic's Neurological and Imaging Institutes.

Approaches to Characterizing Myelin in the CNS

Disorders of myelination may reflect an intrinsic defect, most commonly associated with specific genetic conditions characterized as dysmyelinating diseases, as the myelin is abnormally formed when it is initially expressed. Alternatively, myelin that is normally formed in development may be perturbed in acquired myelin disorders known as demyelinating diseases, the best known of which is multiple sclerosis (MS). Additionally, as we have discovered in research related to the development of myelin PET, there is disruption of myelin in many other brain diseases not typically known for their effects on myelin, such as epilepsy, stroke, neurodegenerative disease and possibly neuropsychiatric disease. Consequently, characterization of the state of myelination in the brain provides a fundamental measure of brain integrity.

Conventional approaches to evaluation of white matter in the brain and spinal cord rely on MRI, particularly T1- and T2-weighted images and diffusion imaging. Structural T1- and T2-weighted images are dominated by the water content in white matter, which is a nonspecific parameter that relates only in part to the integrity of myelin. Diffusion imaging can be used to model white matter tracts with techniques known as diffusion tensor imaging (DTI). A limitation of DTI methods is that the diffusion tensor signal arises principally from water within the axons and thus provides limited information regarding myelin integrity. While this area requires further investigation, including myelin PET analysis, there is evidence that substantial myelin deficits may be relatively inapparent by conventional MRI methods.

Development of a Myelin PET Radiotracer

Recognizing the lack of PET radiotracers and limitations of MRI for evaluation of brain white matter, Professor Yanming Wang led a team in the development of a small-molecule radiotracer with selective binding to myelin. To function effectively as a brain imaging agent, the tracer had to meet several stringent molecular design criteria:

- Solubility in plasma
- Ability to cross the blood-brain barrier
- Chemical functional groups that permit labeling with an appropriate radionuclide
- A robust synthetic route to allow manufacturing and distribution in routine clinical practice

The result of this drug discovery effort is the molecule MeDAS,[1] now known as Myelivid (Figure 1).

To assess its translational potential for use in humans, Myelivid underwent extensive preclinical testing.[1,2] This included tests in experimental systems to demonstrate that the molecule specifically detected myelin in normal brain tissue and could sensitively demonstrate abnormal myelin changes as well (Figure 2). Testing was then performed to ensure that the molecule could serve reliably as a radiotracer, which required testing radiolabeled Myelivid in brain tissue specimens (Figure 3). Having established that the molecule is a sensitive and specific radiotracer, extensive testing was done to evaluate its uptake in the intended tissues of the CNS (Figure 4).

Unique Advantages of Myelin PET

Structural brain imaging is currently dominated by MRI, which is capable of revealing brain tissue with extraordinary precision and detail. However, MRI has fundamental limitations that have not been overcome with advances in technique such as diffusion-weighted imaging and DTI. These include the inability to distinguish tissues of different biologic structure if the chemical composition is similar, as well as the qualitative nature of MRI. Myelin PET with Myelivid recognizes specific molecular structures in myelin, and therefore provides sensitive detection of intact myelin, whereas MRI cannot distinguish between the molecular structures but is most sensitive to myelin's water content, which may not accurately reflect the biological integrity of the tissue. Additionally, since PET is based on the detection of radionuclide decay events, Myelivid PET provides an intrinsically quantitative measure of myelin integrity and quantity in the brain, which can be calibrated and used for detecting changes over time in a single patient or for comparing the abundance of myelin in different patients. This enables detection of subtle changes in a patient that may reflect response to therapy, for instance. Additionally, measurement of the absolute quantity of myelin in brain tissue may allow thresholds to be determined for diagnosing specific disease states.

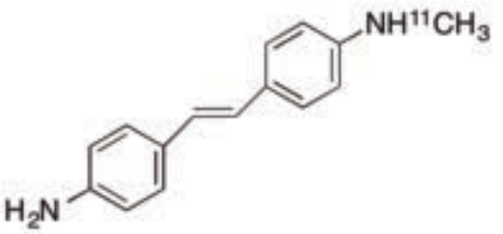


FIGURE 1. *Molecular structure of Myelivid ([N-methyl-^{11}C]-4,4'-diaminostilbene, MeDAS).*

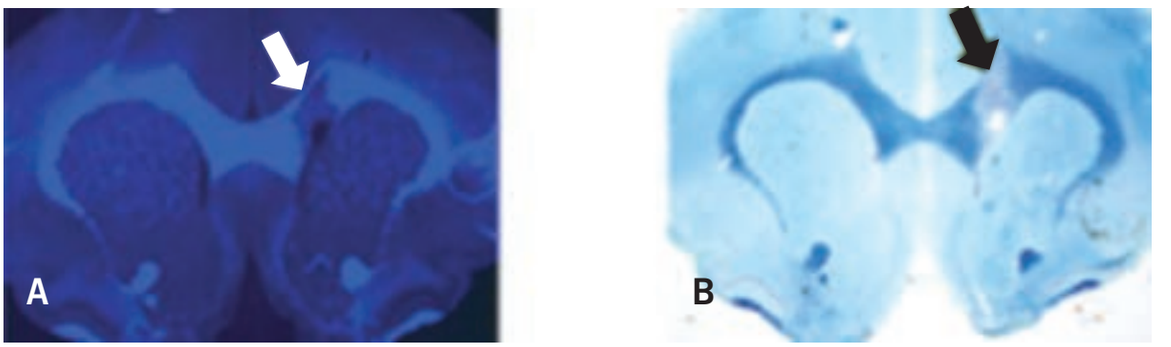


FIGURE 2. *Myelivid stains normal myelin and sensitively detects myelin lesions. Brain tissue specimens from a murine model were stained with Myelivid (A) and Luxol fast blue stain (B) and visualized with fluorescence microscopy (A) and light microscopy (B). The bright signal in panel A is due to intrinsic fluorescence properties of Myelivid. Stains were performed on adjacent slices of brain tissue obtained from the same subject. Arrows indicate the site of a myelin lesion, which is conspicuous due to decreased uptake of Myelivid and Luxol fast blue stain.*

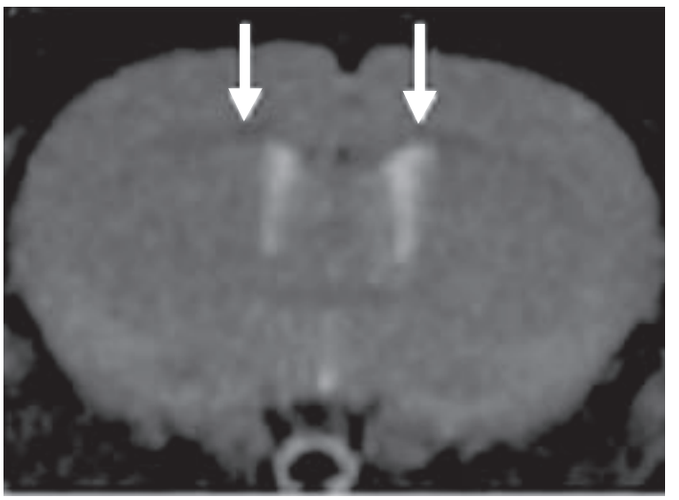


FIGURE 3. *Myelivid is a sensitive radiotracer. Brain tissue from a murine model was stained with radiolabeled Myelivid and detected using autoradiography. Arrows indicate myelin lesions, which show up as bright spots in the autoradiograph due to decreased Myelivid uptake in these areas.*

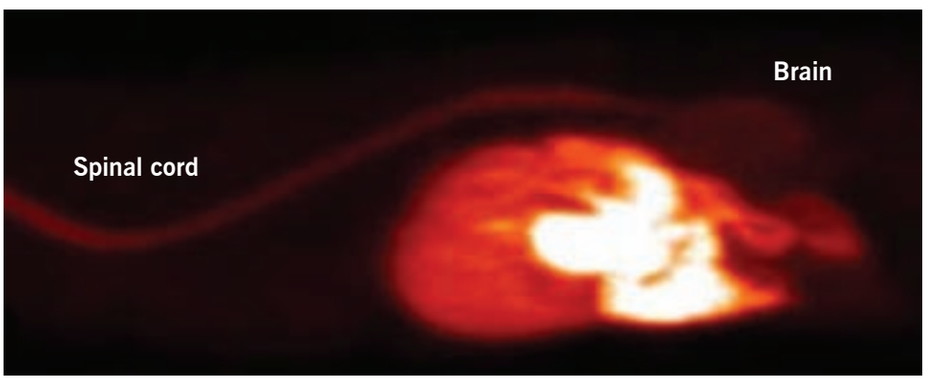


FIGURE 4. *Whole-body PET images using Myelivid radiotracer in a murine model system. The brain and spinal cord are clearly defined here by Myelivid uptake. Additional radiotracer uptake is identified in other parts of the body, reflecting both specific and nonspecific binding.*

An additional advantage of PET imaging is that implanted electronic devices can be safely accommodated in a PET scanner, and metallic hardware generally does not strongly interfere with brain imaging. Consequently, patients with devices such as vagal nerve stimulators or EEG electrodes — commonly used in patients with epilepsy, for instance — can be safely and reliably imaged with Myelivid PET.

Myelivid PET in Epilepsy

One of the major goals of the presurgical evaluation of patients with medically intractable (pharmacoresistant) focal epilepsy is localization of the epileptic focus. This constitutes the most important determinant of seizure freedom following potential surgical resection, particularly in patients with epilepsy due to focal cortical dysplasia (FCD). Despite advancements in MR technology, MRI studies remain negative in almost 25 percent of these patients.

To improve lesion detection in patients with MRI-negative epilepsies, we recently started to use Myelivid on human FCD tissue and in animal models of cortical dysplasia. Our preliminary data show significant and focal changes

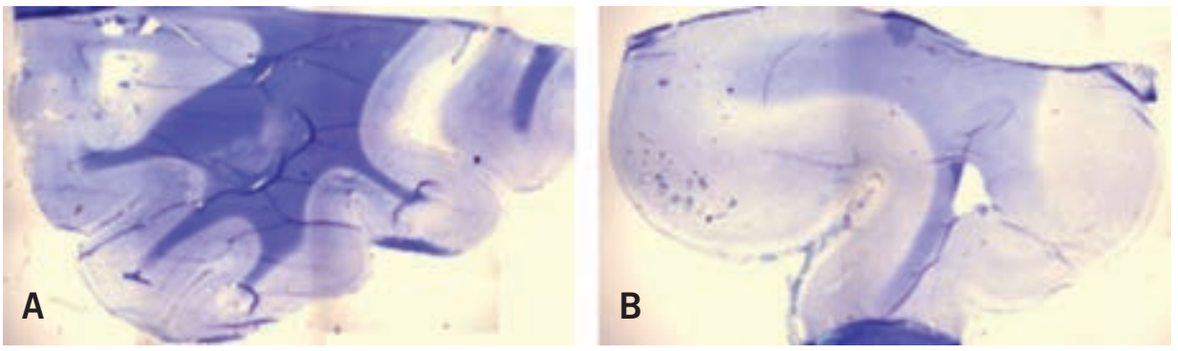


FIGURE 5. *Myelin is substantially depleted in regions of some focal cortical dysplasias. Brain specimens from normal human brain tissue (A) and abnormal human brain tissue in the region of a focal cortical dysplasia (B) were stained with myelin stains Luxol fast blue and cresyl violet acetate and visualized with light microscopy. Normal brain tissue (A) shows strong uptake of stain in white matter compared to cortex, as well as a sharp margin between white matter and gray matter. The abnormal brain tissue (B) shows markedly decreased volume of white matter compared to gray matter, abnormally thickened cortex representing the focal cortical dysplasia, poor definition of the gray matter/white matter boundary and sharply decreased stain uptake within the white matter, reflecting myelin depletion.*

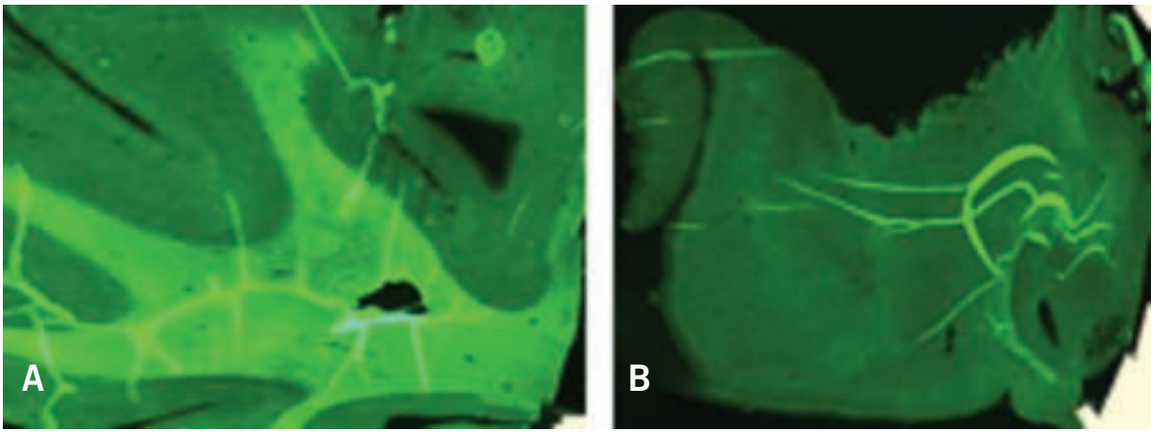


FIGURE 6. *Myelivid detects normal and abnormal myelin in human brain tissue. Brain specimens stained with Myelivid were visualized with fluorescence microscopy. The patterns of normal and abnormal myelin seen in Figure 5 using conventional myelin stains are similarly seen using Myelivid. Normal human brain tissue (A) shows robust Myelivid uptake and a sharp boundary between gray and white matter. Abnormal human brain tissue in the region of a focal cortical dysplasia (B) shows very low-level Myelivid uptake, reflecting markedly depleted myelin, and poor definition of the gray matter/white matter boundary.*

in the imaged myelin in the dysplastic human tissue and the dysplastic animal brains. Figure 5 shows the difference in myelin in normal and abnormal brain tissue using conventional myelin stains, while Figure 6 shows that these differences are similarly depicted with Myelivid staining.

We will continue to study the myelin changes in FCD and possibly other epileptic lesions. As a second step, we will be starting a first-in-human trial to study the usefulness of Myelivid in patients with pharmacoresistant epilepsy undergoing presurgical evaluation at Cleveland Clinic's Epilepsy Center. Our ultimate goal is to use this exciting new imaging method to improve lesion identification and thus provide new opportunities for intervention and optimizing surgical outcomes.

Future Directions with Myelivid PET

Myelivid PET provides a new approach to quantitative imaging of brain microstructural integrity, providing information not available from other PET radiotracers or existing MRI methods. This presents the opportunity for widespread application in neurologic disease, and we expect to give priority to the following areas in our initial clinical trials with Myelivid PET.

Multiple sclerosis. MS is the most common of the demyelinating diseases, and the clinical and research programs of Cleveland Clinic's Mellen Center for Multiple Sclerosis are among the largest in the world. In collaboration with Robert Fox, MD, a Mellen Center neurologist and Vice Chair for Research in the Neurological Institute, we will study Myelivid PET in patients with a variety of MS phenotypes. As MS can affect myelin in multiple CNS compartments, including the brain, spinal cord and optic nerves, we will test Myelivid to determine its ability to detect and characterize demyelinating lesions in all these areas. The quantitative results may be useful for detecting improvement or worsening of disease, and thus may help determine optimal therapy for individual patients. Similarly, Myelivid PET may be useful in the design, development and evaluation of new therapies to treat MS and other demyelinating diseases.

Stroke rehabilitation. Ischemic stroke injures the brain directly through deprivation of oxygen and nutrients and removal of waste from brain tissue. Additionally, brain tissue is damaged indirectly due to disconnection of remote brain areas that continue to receive adequate blood flow but no longer receive synaptic input from the ischemic brain tissue. This injury, known as diaschisis, is mediated by connectivity of white matter tracts and may contribute significantly to the deficits experienced by stroke victims.

Andre Machado, MD, PhD, and Kenneth Baker, PhD, of Cleveland Clinic's Neurological Institute and Lerner Research Institute have pioneered a program of stroke rehabilitation based on cerebellar stimulation[3] in an attempt to reverse the effects of crossed cerebellar diaschisis to aid in recovery from stroke. Myelivid PET will be tested in stroke patients to study the degree of white matter loss following acute infarction and the degree to which white matter recovery correlates with improved function following stroke rehabilitation. This will provide a quantitative metric to permit better evaluation of interventions to improve recovery following stroke, which could sharply accelerate development of new stroke rehabilitation therapies.

Spinal cord injury. Spinal cord injury causes disruption of long, myelinated axons connecting the brain with peripheral nerves. Repair of myelinated spinal cord axons can be sensitively assessed with Myelivid PET[2] and used for the evaluation and development of diagnostic and therapeutic approaches to spinal cord injury.

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Dr. Larvie (larviem@ccf.org) is Director of Functional and Molecular Neuroimaging in Cleveland Clinic's Imaging Institute. **Dr. Najm** (najmi@ccf.org) is Director of the Epilepsy Center in Cleveland Clinic's Neurological Institute. **Dr. Wang** (yxw91@case.edu) is Professor of Radiology, Chemistry and Biomedical Engineering at Case Western Reserve University (CWRU), Cleveland, and Director of the Radiopharmaceutical Program at CWRU.

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The Cleveland Clinic Foundation
9500 Euclid Ave. / AC311
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