

NeurosciencesUpdate

Neurologic Surgery and Clinical Neurology News

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Neurological Simulations: The Next Generation

Mayo Clinic routinely uses sophisticated neurological simulations to enhance medical training and patient care. These simulations, covering not just basic procedures but also complex emergency care, incorporate the latest technology, including virtual reality.

“One of the Mayo brothers once said, ‘There is no excuse today to learn on the patient.’ That principle guides our simulation centers,” says William D. Freeman, M.D., a neurologist at Mayo Clinic in Jacksonville, Florida. “Simulations allow trainees — residents, fellows or even

medical students — to practice before they ever touch a patient.”

Mayo Clinic was among the first centers in the United States to develop neurological simulations, which are less common than simulations in other medical specialties. All three Mayo campuses have multidisciplinary simulation centers that engage in neurological activities. Each facility can duplicate multiple settings, including emergency and operating rooms, an intensive care unit, and inpatient and outpatient care rooms.

“People often think of a simulation center as just a place to get CPR training. It’s really much more than that,” says Matthew T. Hoerth, M.D., a neurologist at Mayo Clinic in Phoenix/Scottsdale, Arizona, and co-director of the simulation center there. “Our simulations are geared to accurate and detailed reproductions of real health care experiences.”

Mayo’s simulations utilize life-size high-fidelity patient manikins, trained medical actors and scenarios written by neurologists. Virtual reality headsets allow learners to interact with a “patient” controlled by a computer operator. This technology facilitates critical care simulations that go beyond the basics.

“Since neurologists operate in a primarily non-procedural specialty, our simulations emphasize patient evaluation, recognition of a problem and initial management,” says Sherri A. Braksick, M.D., a neurologist at Mayo Clinic in Rochester, Minnesota. “We develop scenarios to ensure that our trainees are exposed to uncommon but necessary situations, such as a brain death



David W. Dodick, M.D., and Amaal J. Starling, M.D., neurologists at Mayo Clinic in Phoenix/Scottsdale, Arizona, demonstrate the use of a patient manikin in Mayo’s simulation center.



William D. Freeman, M.D.

evaluation. That's a core competency in neurology residency education, but outside of simulation, it's difficult to ensure that all trainees will be exposed to this examination, let alone perform it during residency."

'Our learners are changing'

At Mayo Clinic, some postgraduate year 1 interns practice neurology simulations in May, before starting their residencies in neurology. "Our neurology residents have jumped through a big hoop before they actually see their first patients," Dr. Freeman says.

These experiential activities go beyond pedagogy to provide a higher level of learning appropriate for today. "Our learners are changing," Dr. Hoerth says. "Everyone walks around now with a computer in their pocket. Trainees are very attuned to retrieving information in their own time. Applying that knowledge in the safe environment of the simulation center deepens their understanding and helps them to better retain the information."

Simulation of neurological disease is difficult, as neurological signs can be challenging for actors to portray and manikins typically aren't designed to depict neurological findings. The subspecialty of neurocritical care poses particular challenges, as critical care trainees may have limited exposure to neurological disease. In a study published in the February 2017 issue of *Neurocritical Care*, Mayo Clinic researchers found that a neurological simulation course administered to critical care fellowship trainees improved the trainees' skill and confidence.

Under Mayo's critical care integrated medical practice, neurological simulations are delivered to pulmonary and anesthesia critical care fellows. "The simulation setting is the only way to guarantee that a consultant can directly observe trainee reactions and responses before the trainee sees similar patients, as residents are often the first neurologist to arrive at a patient's bedside," Dr. Braksick says. In a review published in the August 2018 issue of *Seminars in Neurology*, Mayo Clinic critical care neurologists outlined the opportunities for learning that simulations provide.

On the holodeck

Simulations have limitations. "It can be challenging for the manikins and actors to get it right," Dr. Hoerth says. "We can change the way

the manikin appears to breathe or the heart rate. But it's nearly impossible to have a manikin simulate a stroke."

Virtual reality scenarios — a sort of holodeck for trainee physicians — can overcome those limitations. Mayo Clinic already has the capability to perform virtual reality scenarios in which the learner wears a headset and a moderator on a separate computer controls the virtual patient's responses. Now Mayo is working to develop simulations in which the learner interacts directly with the virtual patient, with haptic feedback allowing the trainee to "touch" the patient.

"The idea is that you would go into a virtual reality augmented environment and plug into a scenario. You'd be in that scenario, interacting freely with the virtual environment," Dr. Hoerth says. "We're not there yet. But we're working to line up partnerships that would allow us to incorporate artificial intelligence and voice recognition into these scenario technologies."

Mayo Clinic envisions a future in which a specific learning objective is matched to the simulation modality that can best achieve it. "All simulation modalities have some type of limitation," Dr. Hoerth says. "At least initially, virtual reality won't give us a tactile response. The ability to physically move the patient might work better with live actors who have been trained to simulate tone. But having multiple modalities will allow us to give our learners a very rich experience."

Simulations can also potentially provide data to further improve training and patient care. "We might graph what a learning curve actually looks like, and use that information to improve an individual neurologist's skills," Dr. Freeman says. "Simulation is a great vehicle for change."

For more information

Braksick SA, et al. Neurology education for critical care fellows using high-fidelity simulation. *Neurocritical Care*. 2017;26:96.

Wijdicks EFM, et al. A future for simulation in acute neurology. *Seminars in Neurology*. 2018;38:465.



Matthew T. Hoerth, M.D.



Sherri A. Braksick, M.D.

Post-Traumatic Headache: Clinical Trial Seeks Predictors and Therapies

Mayo Clinic is conducting a major study aimed at identifying mechanisms and predictors of persistent post-traumatic headache attributed to mild traumatic brain injury. With funding from the Department of Defense, the study includes a phase II clinical trial of erenumab for treatment of this type of headache.

“We have a long way to go in truly understanding why two people can have very similar brain injuries, yet one person gets persistent and disabling post-traumatic headache and the other does not,” says Todd J. Schwedt, M.D., a neurologist at Mayo Clinic in Phoenix/Scottsdale, Arizona. “With this large, multifaceted research program, we are trying to find predictors, as well as ways of intervening, so these headaches don’t persist.”

Although post-concussion symptoms often resolve within a few days, persistent symptoms, including headache, can be a debilitating consequence of mild traumatic brain injury. Up to 40% of individuals who develop acute post-traumatic headache will experience persistent headache, defined as continuing for more than three months after injury.

“Persistent post-traumatic headache can be quite disabling,” Dr. Schwedt says. “A lot of patients have continuous headache pain with superimposed exacerbations. Many have symptoms resembling migraine, such as light sensitivity, sound sensitivity, nausea, and worsening of symptoms with routine physical and mental activities.”

Mayo Clinic’s study includes investigations of animal models of post-traumatic headache as well as human studies of potential blood biomarkers, structural and functional brain imaging, and neurophysiological testing. “We will investigate how a person with post-traumatic headache processes visual and painful stimuli, giving us insights into post-traumatic headache pathophysiology,” Dr. Schwedt says.

Participants in the clinical trial portion of the study will be randomized to receive a placebo or erenumab, a calcitonin gene-related peptide (CGRP) receptor monoclonal antibody. That randomization will occur when a participant has experienced post-traumatic headache for 35 to 56 days.

Dr. Schwedt notes that optimal timing for therapeutic intervention will need further study. “The outcomes might be different, depending on when intervention occurs,” he says. “There are several potential time points for intervention — an acute period within the first few days of a head injury, a subacute period of a few days to a couple of months after injury, and a chronic period when headaches have already been present for several months. Clinical trials are needed that include therapeutic interventions during each of these time points.”

Elucidating headache subtypes

Mayo Clinic is at the forefront of efforts to stratify patients’ risk of post-traumatic headache and to find targeted therapies. Directed by Dr. Schwedt, the Neuroimaging of Headache Disorders Laboratory has identified aberrations in brain structure and function that are related to post-traumatic headache due to concussion. “Although brain-imaging studies after concussion are typically considered normal when they are performed for clinical reasons, when we look more closely in our research studies, we often find subtle abnormalities in brain structure and function,” Dr. Schwedt says.



Todd J. Schwedt, M.D.

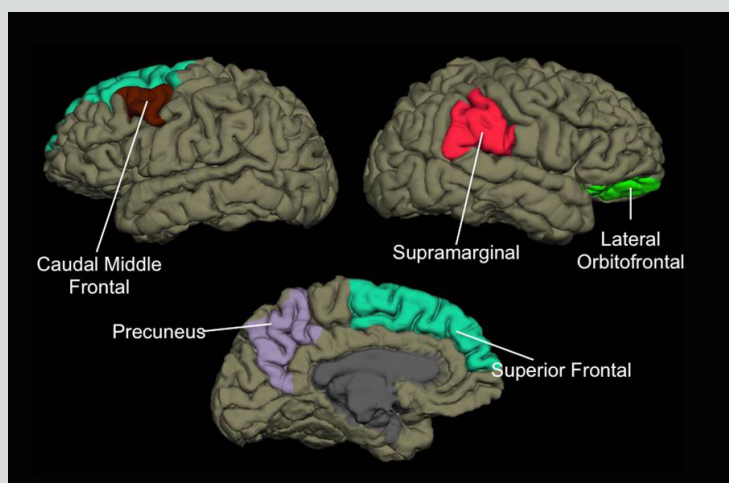


Figure. Illustration shows the brain regions with structural differences when individuals with persistent post-traumatic headache are compared with individuals with migraine. In a study published in the Aug. 22, 2017, edition of *The Journal of Headache and Pain*, Mayo Clinic found that the right lateral orbitofrontal region differed in area, volume and curvature. The left caudal middle frontal, precuneus and gyrus regions differed in cortical thickness. Illustration reprinted with permission from *The Journal of Headache and Pain*.

Many of the laboratory's studies compare symptoms of post-traumatic headache and migraine, as well as brain structure (Figure) and function in the two headache types. "There is a lot of overlap in symptoms between persistent post-traumatic headache and migraine," Dr. Schwedt says. "On imaging, we see what we consider to be meaningful differences both in brain structure and functional connectivity. Although there may be some shared pathophysiology in the two headache types, we believe there is also distinct pathophysiology for post-traumatic headache." Mayo Clinic is committed to continuing studies

of the likely multifactorial pathophysiology of post-traumatic headache. "Our ongoing investigations will ultimately improve our ability to treat patients with this disabling condition and improve our ability to prognosticate outcomes for individuals with post-traumatic headache," Dr. Schwedt says.

For more information

Schwedt TJ, et al. Persistent post-traumatic headache vs. migraine: An MRI study demonstrating differences in brain structure. *The Journal of Headache and Pain*. 2017;18:87.

Epilepsy: The Next Generation of Neurostimulation Therapies



Kai J. Miller, M.D., Ph.D.

Mayo Clinic is committed to providing the least invasive care that will be effective for patients with refractory epilepsy. Treatment options include a range of neurostimulation and ablation techniques, including radiofrequency ablation, as well as laser corpus callosotomy.

"Our goal is to be as minimally invasive as possible, so we can treat the epilepsy while preserving function," says Kai J. Miller, M.D., Ph.D., a neurosurgeon at Mayo Clinic in Rochester, Minnesota. "As technology has advanced, we are now able to ablate sources of seizure with focal laser or electrocautery and avoid an open resection unless absolutely necessary."



Dora Hermes, Ph.D.

Dr. Miller's clinical focus is pediatric neurosurgery, with an emphasis on epilepsy. In conjunction with Dora Hermes, Ph.D., a neurophysiologist at Mayo's campus in Minnesota, he also researches brain signaling and the effects of neurostimulation in adults and children. Based on electrophysiological recordings made intraoperatively and in the epilepsy monitoring unit, the neurostimulation studies help to develop implantation techniques that provide more anatomically characterized recordings.

Mayo Clinic's efforts will aid the creation of the next generation of neurostimulation therapies, aimed not only at placing electrodes more precisely but also disrupting the networks that propagate epileptic activity among brain regions. "We don't yet understand how stimulation affects not just the area we're stimulating but also other brain areas connected to it," Dr. Miller says. "Decoding brain activity will help us localize seizure origin for better placement of electrodes.

It can also open up new mechanisms. We'd like to be able to implant devices that record brain activity continuously, decode it and stimulate the brain in such a way that, over time, an epilepsy network becomes less effective at producing seizures. We will help patients to actually recover. That's the home run."

Achieving concordance

Definitive epilepsy therapy is facilitated by concordance between a patient's imaging and electrophysiological testing. Much of the research done by Dr. Miller and Dr. Hermes involves looking for new ways to achieve that concordance.

"We want to understand the underlying neuronal activity that drives a functional MRI signal," Dr. Hermes says. "That type of biomarker will help us localize and treat disease."

Mayo Clinic's 7-tesla MRI, which helps to define structures that might not be visible at lower resolution, is a key resource. Computational models and simulations of neuronal population activities are also important components of this work. "Since we can never measure every single neuron, we have to make a model of the underlying neuronal activity in order to understand the signaling and to predict brain activity," Dr. Hermes says.

As described in the Nov. 8, 2019, edition of *eLife*, her research team developed a model that predicts from visual input the type of signals produced in the visual cortex of an individual without epilepsy. "We are now trying to translate those findings into predictions of atypical brain activity," Dr. Hermes says.

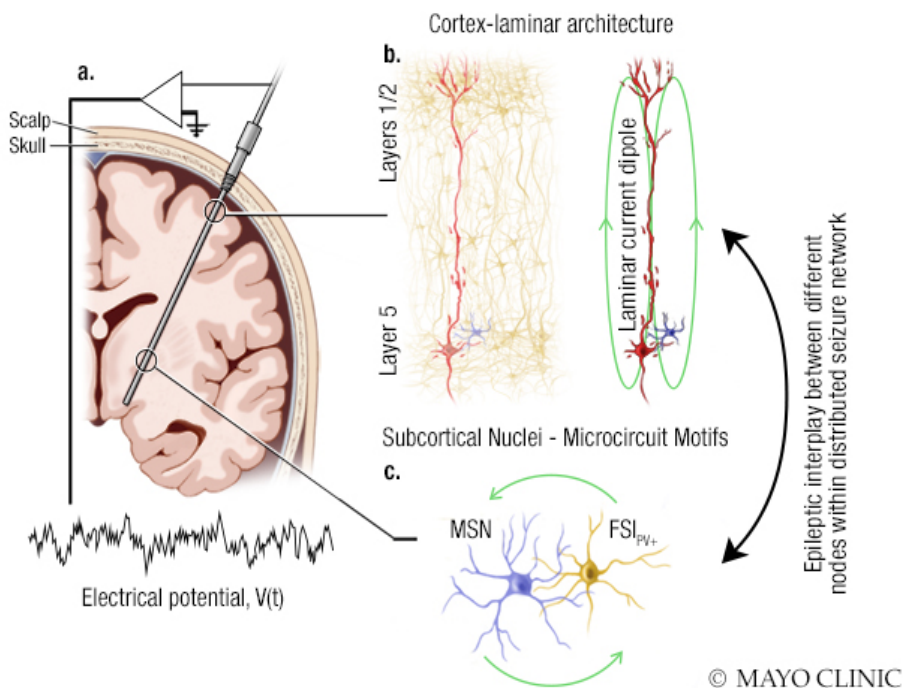


Figure. Illustration shows the system used by Mayo Clinic researchers to study the epilepsy-related interplay between different nodes within a single seizure network. A. A stereoelectroencephalography probe is implanted in the brain to monitor electrical activity. The electrical potential is recorded from several electrodes on this probe. B. Some electrodes record the field potential generated by a cortical circuit, which has a laminar structure. Cortical field potentials are strongly driven by the current dipoles generated by large pyramidal neurons. C. Other electrodes record the field potentials generated by the neuronal circuits in subcortical regions, medium spiny neurons (MSN) and parvalbumin positive (PV+) fast spiking interneurons (FSI).

The researchers have also found that the same visual input that induces narrow band gamma oscillations around 50 hertz can also induce seizures in patients with pattern-sensitive epilepsy. “We think that the same circuitry involved in these oscillations might be changed in patients with photosensitive epilepsy,” Dr. Hermes says. “Ultimately, this information can help us influence these networks to reduce brain excitability in patients.”

Understanding the interactions among nodes in a seizure network (Figure) can potentially facilitate neurostimulation treatments that modify a patient’s disease, ultimately obviating the need for an implanted device. “That’s not something we’ll accomplish in five years — but maybe in 10 years,” Dr. Miller says.

As the practices of neurostimulator placement and stereotactic laser ablation evolve, optimal targeting will require standardized outcome measures that compare electrode lead or laser source with postprocedural changes in seizure frequency.

Targeting is currently prescribed for general anatomical structures. Dr. Miller led a team that developed a stereotactic coordinate system based on landmarks of the mesial temporal lobe. As described in the January 2019 edition of *Journal of Neurosurgery*, the researchers created an open-source software package to test the system.

The overarching goal of Mayo Clinic’s neurostimulation research is to translate innovations into patient care. “The collaborative structure of Mayo Clinic means that physicians see the potential impact of research for patients,” Dr. Hermes says. “At Mayo, there is a route for innovations to become standard clinical practice.”

For more information

Hermes D, et al. An image-computable model for the stimulus selectivity of gamma oscillations. *eLife*. 2019;8:e47035.

Miller KJ, et al. A novel mesial temporal stereotactic coordinate system. *Journal of Neurosurgery*. 2019;130:67.

Robot-Assisted Brain Surgery: Innovating To Improve Patient Care



Alfredo Quinones-Hinojosa, M.D.

Alfredo Quinones-Hinojosa, M.D., chair of Neurosurgery at Mayo Clinic in Jacksonville, Florida, discusses Mayo's efforts to develop robotics technology for performing brain surgery. Mayo Clinic is committed to cutting-edge research and development that improve patient care through innovative technology in the Biotechnology and Innovation Research Neuroscience (B.R.A.I.N.) Laboratory.

What role does Mayo Clinic envision robotics playing in the future of brain surgery?

Robotics is a Mayo Clinic priority. Just as robotics technology is used to perform abdominal surgery, in the near future it will most likely be used to perform minimally invasive brain surgery. Mayo Clinic is developing the relationships and the technologies to enable us to perform robot-assisted surgery in the brain.

Robots will allow us to venture deep into the brain through very small incisions, park a robot at the skull base and remove a tumor. Instead of using an extensive, skull base approach in which large incisions are used with large portions of bone removal to minimize brain retraction, we will be able to bring our equipment to the relevant space through tiny holes in the skull.

For example, when treating a medial sphenoid wing meningioma, it is possible that future robotic technology will allow us to make only a small incision right above the eye and a small keyhole in the bone near the ear. We could then approach the tumor through tiny ports placed in those incisions and be able to disconnect the tumor from nerves and blood vessels.

What are the challenges involved in using robot-assisted surgery in the brain?

The biggest challenge right now is the fact that our equipment is difficult to maneuver through small spaces. We need to be able to precisely

locate arteries and nerves in the brain, but current navigation systems aren't 100% equipped to do this. As a result, the accuracy of intraoperative visualization and manipulation of tissue is suboptimal.

What efforts are underway at Mayo Clinic to develop the technology that will enable robot-assisted brain surgery?

To develop the tools for robot-assisted brain surgery, we first need highly realistic models of the human brain — just as animal models of disease are needed to study treatments in patients. Deceased donors are often used to study human anatomy. But in this case, technological development must utilize a model of the brain that begins to bleed when you touch it, has cerebrospinal fluid and allows the conduction of current so we can stimulate the brain model.



Figure. Alfredo Quinones-Hinojosa, M.D., chair of Neurosurgery at Mayo Clinic in Jacksonville, Florida, evaluates the tactual perception of a highly realistic 3D printed model of the human brain.

Mayo Clinic has created the special B.R.A.I.N. Laboratory that is working to create dynamic 3D-printed models of the human brain (Figure). These models will not only have an accurate feel and consistency but will also "bleed," reproduce injury and conduct energy on a scale that duplicates nerves in the brain. These dynamic factors allow us to tell if we are risking injury to the brain, and possibly could predict patient recovery after minimally invasive treatment techniques.

We expect to develop this model within the next three years.

That is very ambitious. But our

B.R.A.I.N. team — led by myself, Aaron C. Damon, assistant professor of medical education, and William (Bill) E. Clifton III, M.D., Neurosurgery — thinks it's doable.

Why is Mayo Clinic committed to pursuing robotics in neurosurgery?

At Mayo Clinic, we encourage innovation that meets the needs of patients. When we identify a problem and a need, we support the innovation and research that will bring about a solution. We are very systematic in this approach because it has been part of our Mayo culture from the beginning.

Research Highlights in Neurology and Neurosurgery

Elucidating the Structural Diversity of Tauopathies

Tau aggregation into insoluble filaments is the defining pathological hallmark of tauopathies. However, it is not known what controls the formation of structures into disease-specific tauopathies. Structural studies have failed to pinpoint changes associated with an individual tauopathy, likely due to the methods used to evaluate tau filaments. With collaborators from Columbia University and Emory School of Medicine, Mayo Clinic researchers used a new method combining cryo-electron microscopy and mass spectrometry proteomics. Applying that method to human tissue samples from the Mayo Clinic Brain Bank, the researchers identified post-translational modifications as playing an important role in mediating the distinct structures of tau fibrils in corticobasal degeneration and Alzheimer's disease. Comparisons of the structures of post-translationally modified tau filaments in the two neurodegenerative conditions showed many common structural elements as well as both shared and distinct post-translational modifications. Although the beta strand-forming motifs in the two diseases are highly similar, their misfolding and self-assembly into fibrils are radically different. The researchers propose a structure-based model in which cross-talk between post-translational modifications influences tau filament structure and behavior, contributing to the structural diversity of tauopathy strains. The researchers further propose that their approach of combining cryo-electron microscopy and mass spectrometry-based proteomics form a methodological blueprint to fully decipher the role of post-translational modifications in neurodegeneration. (Arakhamia T, et al. Posttranslational modifications mediate the structural diversity of tauopathy strains. *Cell*. 2020;180:633.)

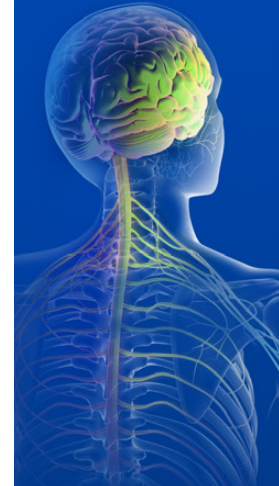
Favorable Long-Term Outcomes in Pediatric AVM Interventions

Intervention is critical in maximizing outcomes of pediatric arteriovenous malformations (AVMs). Although short-term functional outcomes following intervention have been established as favorable, long-term outcomes haven't been thoroughly studied. Mayo Clinic researchers have found that favorable functional outlooks for pediatric AVM patients can persist for many years after initial intervention. The researchers identified 14 pertinent studies describing outcomes for 699 pediatric AVM patients, with a median 75% presenting with hemorrhage. The use of surgery, embolization and radiosurgery were reported by 12 (86%), 14 (100%) and 10 (71%) studies respectively. By a median study follow-up time of 4.1 years, a favorable functional outcome was estimated to occur in 87% of patients across all 14 studies. Hemorrhagic versus nonhemorrhagic presentations didn't statistically differ in the incidence of this long-term outcome. Although formal protocols don't yet exist for pediatric AVM intervention, the metadata suggest that intervention of any type can lead to favorable long-term functional outcomes for most patients. The researchers further suggest that the risk of long-term functional deficit shouldn't be the sole factor in deciding whether to pursue intervention. (Lu VM, et al. Long-term functional outcome after intervention for pediatric intracranial arteriovenous malformations: A systematic review and meta-analysis. *Clinical Neurology and Neurosurgery*. 2020;191:105707.)

Ventricular Volume: Clinical Utility for Assessing Current and Future Cognition and Gait

An increase in ventricle size is associated with degenerative brain disease and gait. A clinically relevant measure of ventricle size could facilitate the evaluation of current and future cognition and gait. Mayo Clinic researchers have found that ventricular volume measures are clinically more useful in indicating current and future gait and cognition than is the standard linear ratio of Evans' index. From MRI scans of 1,774 participants in the Mayo Clinic Study of Aging, the researchers calculated various ventricle size measurements: Evans' index (frontal horn width divided by widest width of skull inner table), total ventricular volume, and frontal horn and total ventricular volume as ratios of intracranial volume. Gait was measured by a timed 25-foot walk, and cognition by a composite of psychometric tests. The researchers also evaluated variables associated with the measure of ventricular size, as well as gait and cognition associations with MRI of extraventricular findings seen in normal pressure hydrocephalus — specifically, disproportionate enlargement of subarachnoid space (DESH) and focal sulcal dilations (FSD). Ventricular volume measures had a stronger association with gait and cognition measures than did Evans' index. In decreasing order of strength of association with ventricle size were DESH, FSD, white matter hyperintensity volume ratio, age, male sex, cortical thickness and education. The researchers note that ventricle volume measures can be generated automatically; their inclusion on MRI reports would allow a clinician to be more objective in determining whether a patient's ventricles are enlarged. Information about a patient's ratios of ventricular and frontal horn volumes to total intracranial volume would alert a physician to the patient's likely diminished gait and cognition, and a risk of more rapid decline in the next few years. (Crook JE, et al. Linear vs volume measures of ventricle size: Relation to present and future gait and cognition. *Neurology*. 2020;94:e549.)

To read more about Mayo Clinic neurosciences research and patient care, visit www.MayoClinic.org/medical-professionals.



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Resources

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Clinical trials, CME, Grand Rounds,
scientific videos and online referrals



Education 2021 Neurology and Neurologic Surgery Continuing Medical Education Programs

The current environment presents many challenges. Mayo Clinic's highest priority is patient and staff safety. We are taking every precaution to manage patient safety to the highest standard through universal masking, enhanced safety protocols, robust screening and COVID-19 testing strategies. Mayo Clinic has a long-standing history of helping our community in crisis while maintaining capacity to care for patients who need it most. We will continuously evaluate the circumstances at each of our sites and follow federal and state mandates to protect the safety of our patients, staff and community.

Find resources for providers and answers to questions on referrals and testing for COVID-19 on the Medical Professionals available at www.MayoClinic.org/medical-professionals/neurology-neurosurgery.

2021 COURSES

February

Mayo Clinic Multiple Sclerosis and Autoimmune Neurology Update 2020 — Livestream

Feb. 5-6, 2021

This course provides the latest clinically relevant updates on multiple sclerosis and autoimmune neurology. Mayo Clinic experts discuss evidence-based strategies for practical, multidisciplinary clinical management of patients with these neurological disorders. Attendees learn about latest clinical and laboratory research through didactic lectures, case vignettes, interactive Q&A sessions and open discussions with faculty.

March

Electromyography (EMG), Electroencephalography (EEG), and Neurophysiology in Clinical Practice 2021 — Livestream

March 14-20, 2021

This course offers a review and update of techniques and topics pertaining to the practice of clinical neurophysiology in the evaluation and diagnosis of a variety of neurological disorders. The course focuses on techniques and pitfalls, along with clinical correlation of various neurophysiological tests used for the evaluation of patients with peripheral nerve and neuromuscular disorders, epilepsy, central nervous system disorders and sleep disorders.

April

Mayo Clinic Sleep Medicine Update — Livestream

April 15-17, 2021

This CME course — the first from Mayo Clinic pertaining entirely to sleep medicine — is designed for established providers, new practitioners, physician assistants and nurse practitioners. The faculty mirrors the multidisciplinary approach to the practice of sleep medicine, and draws on the wealth of cases from sleep centers at all three Mayo Clinic campuses. A pre-course session on fundamentals of sleep medicine takes place Thursday, April 15, 2021.

May

7th Annual Neuro and Intensive Care: Review, Workshops and Controversies 2021 — Livestream

May 6-8, 2021

This course is designed for medical providers who care for patients with neurological/neurosurgical emergencies, acute stroke and brain hemorrhage, acute brain injury, coma, and disorders that require hospital, emergency department and intensive care unit (ICU) evaluation and management. The course will provide a mixture of didactic, case-based and evidence-based guideline review and workshops.

Information and registration

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