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Preclinical Alzheimer's Disease

In May 2011, three consensus groups organized by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) published a new set of diagnostic guidelines for Alzheimer's diseases (ADs)—the first revision since 1984. In those intervening 27 years, findings about the prevalence of AD and its clinical-pathophysiologic relationships have refined and altered the

medical field's concept of the disease.

AD is now recognized as a complex disease for which a single therapeutic target may not be sufficient. Longitudinal studies of age-related neurologic and cognitive changes have confirmed a marked temporal lag between the initiation of neuropathologic characteristics and symptom appearance. In response, the

new guidelines divide AD into three phases: a *dementia phase*, in which clinical symptoms are present; a *symptomatic, predementia phase*, in which mild cognitive impairment (MCI) consistent with AD is present; and an *asymptomatic preclinical phase*, intended as a platform from which to develop primary prevention therapies.

"Amyloid deposition appears to begin as early as 20 years prior to symptom development," explains David S. Knopman, MD. Dr Knopman, along with his Mayo colleagues Clifford R. Jack Jr, MD, and Ronald C. Petersen, MD, PhD, was a member of the NIA-AA consensus group that developed the guidelines. For the first time, the guidelines include biomarkers—such as fMRI, FDG-PET, amyloid imaging, and cerebrospinal fluid analysis—specifically for the MCI and preclinical phases.

Preclinical guidelines are intended to identify people

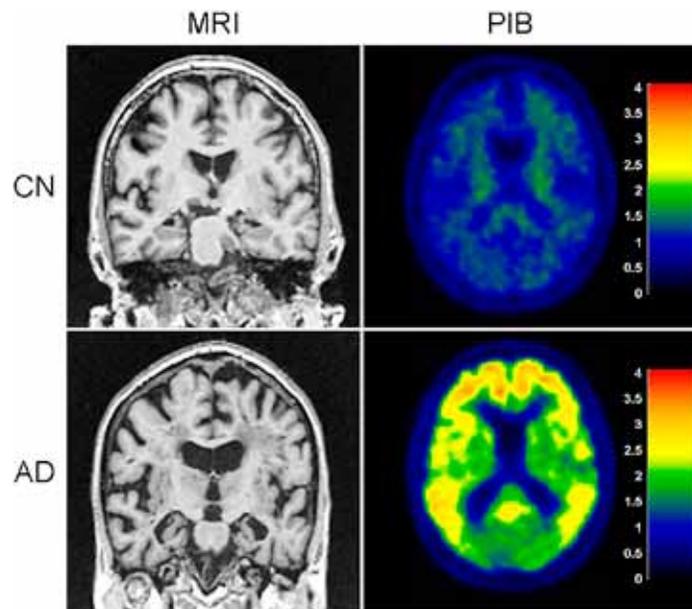


Figure. Brain imaging. MRI scans (left column) and PET scans with amyloid imaging using ^{11}C Carbon Pittsburgh compound B (PIB) (right column) provide complementary information. Top panel, the MRI and PIB PET scans from a person who is cognitively normal (CN); bottom panel, the MRI and PIB PET scans from a person with dementia due to Alzheimer's disease (AD). The generalized brain volume loss and the hippocampal atrophy are evident in the AD MRI scan compared to the CN scan. On the AD PIB PET scan, a dramatic increase in signal intensity can be seen in the frontal and parietal lobes due to retention of the ^{11}C - PIB bound to fibrillar amyloid compared to the CN PIB PET scan, which shows negligible retention of the tracer in the white matter.



David S. Knopman, MD



Clifford R. Jack Jr, MD, and Ronald C. Petersen, MD, PhD



Neill R. Graff-Radford, MD



Steven G. Younkin, MD, PhD

who are asymptomatic for AD but have biomarker risk. Given the less-than-hoped-for effect of symptomatic therapies and the fact that cerebral amyloidosis begins before symptoms appear, researchers hope that a clear definition of preclinical AD will aid in the development of preventive therapies. As of 2012, however, detection of preclinical AD is strictly a research initiative.

Pathophysiologic Model of AD

Findings from the Mayo Clinic Study of Aging (MCSA), a prospective, population-based research program in Rochester, Minnesota, and from the Mayo Clinic Alzheimer's Disease Research Center in Florida helped inform the pathophysiologic model used to generate the preclinical guidelines. Dr Petersen leads the MCSA and also directs the research center with the center's codirectors, Neill R. Graff-Radford, MD, and Steven G. Younkin, MD, PhD. The model, developed by Dr Jack in collaboration with Dr Knopman, Dr Petersen, and others at Mayo Clinic in Minnesota, posits an ordered pattern of progression in AD biomarkers in which amyloid deposition reaches a peak before symptom onset. The amyloid peak is followed by neuronal injury and synaptic degeneration (tau pathology) and the onset of overt symptoms that worsen as neuronal tissue is lost.

Stages of Preclinical AD

The NIA-AA work group identified three stages of preclinical AD. Stage 1 is characterized by asymptomatic amyloidosis. Stage 2 adds evidence of synaptic dysfunction and neurodegeneration. Stage 3 marks the addition of subtle cognitive changes not overtly evident in day-to-day behavior.

Dr Knopman points out that with more than 2,000 study participants, 500 of whom have been tested for AD biomarkers in the MCSA, "Mayo is in a unique position to evaluate the success of NIA-AA criteria in classifying people with normal cognitive function and those with mild cognitive impairment and observing changes over time." A recent Mayo study operationalized the NIA-AA guidelines criteria to test the validity and

frequency of the preclinical stages of AD (Jack et al. *Ann Neurol.* 2012;71[6]:765-75). The investigators' results confirmed the criteria for stages 1 through 3. Two additional categories were needed to classify all of the participants in the study sample. Stage 0 includes cognitively normal (CN) individuals with neither biomarker evidence of AD pathophysiology nor cognitive impairment. The stand-alone category, *suspected non-AD pathophysiology* (SNAP), accounts for individuals with normal amyloid levels but biomarker evidence of neuronal injury consistent with non-AD dementia. The research team was able to classify 97% of the sample and found that 43% were at stage 0, 16% at stage 1, 12% at stage 2, and 3% at stage 3, and 23% were classified as having SNAP. Using the operationalized criteria in a 15-month follow-up study, Dr Knopman and colleagues confirmed the utility of the criteria in predicting progression of cognitive impairment (*Neurology.* 2012;78[20]:1576-82).

Molecular Mechanisms of AD

The risk of AD from the *APOE* ϵ 4 allele is well established. The allele is a gene variant present in 20% of the population and is thought to contribute to amyloidosis. In 1994, Richard J. Caselli, MD, a neurologist at Mayo Clinic in Arizona, began prospective studies of cognitive changes across the lifespan, using longitudinal modeling and in-depth neuropsychological testing. In 2009, grouping study participants as young as 21 years and as old as 97 years by their *APOE* ϵ 4 status and comparing them to noncarriers, Dr Caselli and his colleagues found that memory decline diverged between the groups by age 60 years despite ongoing normal clinical status (*N Engl J Med.* 2009;361[3]:255-63). Their findings helped consolidate the concept of preclinical AD. In that same year, he and Eric M. Reiman, MD, director of the Arizona Alzheimer's Consortium, of which Mayo is a participating member, found that amyloid burden in CN individuals is associated with *APOE* ϵ 4 gene dose. They also found that amyloid deposition is particularly concentrated in the frontal and posterior cingulate-precuneus and in the temporal, parietal, and basal ganglia areas (*PNAS.* 2009;106[16]:6820-5).

At Mayo Clinic in Florida, Dr Younkin, Dr Graff-Radford, Dennis W. Dickson, MD, Nilufer Taner, MD, PhD, and their colleagues are investigating other candidate genes associated with late-onset AD. In 2009, Dr Younkin conducted one of the first genome-wide association studies (GWASs) of AD (Carrasquillo et al. *Nat Genet.* 2009;41[2]:192-8). GWASs are hypothesis-free studies that require many thousands of cases and controls to generate the statistical power needed to find individual and combination gene effects. The study by Dr Younkin and his coinvestigators

has been included in studies by international, consortium-based GWAS groups, in which Mayo Clinic participates. Aside from *APOE* $\epsilon 4$, gene risk can be considered cumulative. Numerous AD-associated genes have been identified and will undergo further validation through in vivo and in vitro functional assessment to determine their impact on risk.

Establishing heritable risk is only one part of the GWAS effort. As Dr Graff-Radford states, "A major goal of molecular genetics is to uncover the mechanism and pathways of disease." For example, genes that contribute to inflammation and oxidative stress appear to be particularly important in neurodegenerative diseases, including AD.

Cerebrovascular (CV) risk may also contribute to AD risk. Dr Caselli and colleagues recently found, for example, that CV risk plays a role in age-related memory decline in *APOE* $\epsilon 4$ homozygotes (*Neurology*. 2011;76[12]:1078-84). The prevalence of CV-related dementia is thought to be higher in African Americans than in whites, and Dr Graff-Radford and colleagues are comparing amyloid burden between these two populations in an ongoing study.

In addition to participating in consortium-based GWAS studies, Mayo Clinic in Florida is one of 11 institutions participating in the NIH-funded Dominantly Inherited Alzheimer Network (DIAN) study. The goal of DIAN is to discover the molecular mechanisms of a rare form of familial AD, in an effort to decode the pathophysiology of AD and other dementias. As is true of other AD types, in this rare heritable form, amyloidosis can begin to

develop years before symptoms appear.

Toward Preventive Intervention

Although overt AD symptoms are preceded by amyloid deposition, amyloid alone does not interfere greatly in cognitive function. Neurofibrillary tangles (NFT), generated by tau pathology, appear to be the critical biologic requirement for symptomatic AD and other forms of dementia. Some non-AD dementias, such as progressive supranuclear palsy, are characterized by tau pathology in the absence of amyloid deposition. Also of note, there appears to be a mismatch between areas of amyloid burden, such as the frontal lobes and cingulate gyrus, and anatomical areas critical to memory loss, such as the hippocampus and mesial temporal lobe, where NFT first develop and the greatest neuronal death occurs. Even in *APOE* $\epsilon 4$ carriers, memory declines much more quickly and earlier than frontal lobe-mediated function (Caselli et al. *Neurology*. 2011;76[16]:1383-8).

The trigger or triggers for amyloid deposition and the pathophysiologic relationship between amyloidosis and tau pathology are among the important features of AD yet to be uncovered. Across Mayo's three campuses, neuroscientists are collaborating to address these and other potential mechanisms through a coordinated effort in molecular genetics and longitudinal population studies of AD biomarkers and normal and abnormal cognitive function. Defining the features of preclinical AD marks a critical step in moving the field toward the development of preventive therapies.



Richard J. Caselli, MD



Dennis W. Dickson, MD



Nilufer Taner, MD, PhD

Secondary Stroke Prevention: Toward a New Model of Care

Stroke is the leading cause of disability and the fourth leading cause of death in the United States. Although much is known about modifying risk factors to prevent first stroke (primary prevention) or recurrent stroke (secondary prevention), too often a consistent, systematic assessment of stroke risk factors is lacking in clinical practice. This gap between existing evidence and actual practice is especially concerning for patients after first stroke. An estimated 30% of survivors of an initial ischemic stroke have a subsequent stroke within five years, and 18% of subsequent strokes are fatal.

A new model of stroke prevention care developed at Mayo Clinic in Rochester, Minnesota, is showing promising results. In a preliminary study, patients with ischemic stroke were

randomly assigned to two groups—one that followed a physician-directed, nurse-based system of focused preventive care and one that received standard poststroke follow-up care. After one year, 61% of patients in the prevention-based program improved at least one major risk factor, compared with 33% of patients in the usual care program. Patients in the prevention group were also likelier to follow a prescribed diet (50% vs 7%) and maintain an exercise program (83% vs 33%). Although the sample size of 41 patients limits the study's statistical power, its results had sufficient clinical significance for Mayo to bring the model into practice in July 2012.

Mayo's new program of stroke prevention is similar to programs used to manage other



Jody L. Covalt, RN, Kelly D. Flemming, MD, Debra E. Herzig, RN

chronic conditions, such as cardiac disease. Kelly D. Flemming, MD, the Mayo Clinic neurologist who led the study, attributes the success to the program's focus on helping patients commit to lifestyle changes that they themselves have selected. She notes that before being discharged from the hospital, stroke patients typically are given a list of instructions for medication, diet, and exercise. "Our approach is to be more patient centered. Patients are more likely to follow through on changes they are interested in making, as opposed to what the doctor is interested in doing," Dr Flemming says. "Of course, we want our patients to follow through on all recommended lifestyle changes. But if we follow the patient's lead, we are more likely to arrive at that goal."

The Mayo Clinic study included patients with ischemic stroke or transient ischemic attack of presumed atherosclerotic origin and at least one major uncontrolled risk factor (eg, hypertension, diabetes, smoking, dyslipidemia). Patients were excluded from the study if their National Institutes of Health Stroke Scale score exceeded 7 or they had life expectancy of less than one year due to other medical comorbidities.

Nurses trained in stroke risk factors and motivational interviewing met individually with patients randomly assigned to the prevention group before they were discharged from the Saint Marys Hospital inpatient stroke center or outpatient stroke clinic. The nurses followed algorithms for each risk factor and developed action plans for the patients individually. The interviews lasted about an hour and were followed by a 15-minute visit with the neurologist. The patients were examined in person at six weeks, six months, and one year after baseline and received phone calls at three and nine months. They also received a dietary consultation from a registered

dietitian and an exercise prescription from an exercise physiologist. Patients randomly assigned to the usual care group received an initial risk factor assessment and a scheduled follow-up appointment at one year, as well as follow-up by specialists in primary care or neurology, or both, as recommended.

At one year, both groups were reassessed for modifiable risk factors, medication adherence (patient interview), and vascular events (patient interview with verification through medical records). Modifiable risk factors included measurable characteristics (eg, fasting lipids and glucose, blood pressure, weight and body mass index, homocysteine), as well as subjective items (eg, food frequency questionnaire, physical activity self-report, alcohol and tobacco self-report). Physical assessment and laboratory studies performed at baseline were repeated.

To illustrate the program's beneficial effects, Dr Flemming cites the example of a patient in the prevention group who had seven risk factors for stroke, including smoking, heavy drinking, diabetes mellitus, hypertension, and high cholesterol level. After motivational interviewing with the nurse and a follow-up conversation with Dr Flemming, the patient agreed to stop smoking and drinking and to take a daily aspirin but was reluctant to do more. At his six-week follow-up appointment, the patient had stopped smoking and drinking.

"I asked him if there was something else he wanted to work on, and he agreed to start taking a cholesterol medication," Dr Flemming says. "Had I pushed him about that while he was in the hospital, he might never have started that medication. Some people can change five things at once, but other people need a little time to fit changes into their lifestyle."

The researchers intend to expand the screening to include medical complications of stroke, such as cardiac arrhythmia, depression, and pneumonia. "In the first year after stroke, most people aren't rehospitalized for stroke. They're rehospitalized for these other medical problems," Dr Flemming says.

She notes that motivational interviewing is unlikely to be helpful in severely cognitively disabled patients. Although patients of any age are candidates for the program, the Mayo model is aimed particularly at younger patients who face

years of being at risk of a recurrent stroke. For such patients, ongoing education and positive rapport with a clinician can promote compliance with medication and lifestyle changes. "Anecdotally, we found that patients appreciated a contact person who was approachable and well known to them and who spoke with them on a regular basis," Dr Flemming says. "This new model appears to be a better way to approach patients and to let them be involved in their care."

Movement Disorders Laboratory: Diagnosing and Treating Complex Dystonias

Movement disorders such as tremor, dystonia, and Parkinson's disease are among the most common neurologic conditions. For patients, movement disorders can result in considerable disability. Hand and arm tremor can impair eating, handwriting, and grooming. Vocal tremor can hinder communication, resulting in social withdrawal. For the physician, precise diagnosis can be difficult because of the broad array of related movement disorders.

Mayo Clinic's Movement Disorders Laboratory in Rochester, Minnesota, is one of the few centers in the United States that offers a wide range of analytic techniques capable of aiding in the classification of these conditions. Among the techniques used are tremor frequency analysis, quantitative brain wave analysis, dystonia mapping studies, and movement pattern analysis. The core assessment tool is comprised of simultaneous EEG, EMG, and video recordings taken while the patient exhibits abnormal movements.

"Most EMG laboratories focus on disorders of the peripheral nervous system. But our laboratory also uses these techniques to diagnose problems of the central nervous system," explains Joseph Y. Matsumoto, MD, a neurologist in Mayo's Movement Disorders Subspecialty Group and the director of the Movement Disorders Laboratory.

A typical diagnostic test lasts 20 to 45 minutes in the Movement Disorders Laboratory. Surface EMG is used to monitor muscle activity. For some conditions, such as myoclonus, EEG helps to determine the locus of abnormal movement in the CNS. Computer analysis of the recordings has advantages for diagnostic specificity. "For example, we can generally identify the precise type of tremor a patient has," Dr Matsumoto says.

The experience and expertise of Mayo's movement specialists extend to rare movement disorders, such as orthostatic tremor and stiff-man syndrome (SMS), also known as *stiff-person syndrome*. (Women comprised two-thirds of

patients who received a diagnosis of this rare disorder at Mayo over the period from 1984 through December 2008.)

SMS, identified by Mayo Clinic in 1956, is characterized by chronic rigidity and spasms in the muscles of the limbs and trunk. Patients frequently have painful spasms and falls, as well as fixed spinal deformities from long-term rigidity. Some patients have respiratory impairment from chest wall spasms.

SMS is distinguishable by hyperexcitability of spinal motor neurons. Mayo's Movement Disorders Laboratory uses multichannel surface EMG, concentric needle studies of the lumbar paraspinal muscles, and electrical and acoustic stimulation of the nerves to evaluate startle reflexes in suspected cases of SMS. "SMS is often mistaken for a psychogenic disorder," Dr Matsumoto says. "But electrophysiological findings consistent with brainstem and spinal hyperexcitability can help confirm the clinical suspicion in many cases."

Diagnostic testing in the Movement Disorders Laboratory can also guide treatment. For example, multichannel EMG needle mapping studies can pinpoint areas of activity that cause spasmodic torticollis. Precise localization can then help physicians choose sites for injecting botulinum toxin and can identify patients who might benefit from surgical treatment.

Mayo also has a large practice in treating spasmodic dysphonia and jaw and orofacial dystonias with botulinum toxin. Movement disorders neurologists, ear-nose-throat surgeons, and speech pathologists share a close collaboration in caring for patients who receive these complex injections.

"Movement disorders, particularly in rare conditions, can be very difficult to diagnose and treat," Dr Matsumoto notes. "Our lab's expertise lies in clarifying a difficult diagnosis, as well as providing botulinum toxin treatment in common and rare conditions."



Joseph Y. Matsumoto, MD

Advancing Parkinson's Disease Research Through the National Brain and Tissue Resource



Charles H. Adler, MD, PhD

What are the earliest biomarkers for Parkinson's disease (PD), and when do subclinical changes in movement, cognition, sleep, sense of smell, and other signs of PD begin? These questions serve as the focus of PD research conducted by Charles H. Adler, MD, PhD, a neurologist and movement disorders specialist at Mayo Clinic in Arizona. They are particularly important questions because, as Dr Adler notes, in PD, "By the time of clinical diagnosis, we know that anywhere from 60% to 80% of a patient's dopamine-producing neurons have degenerated."

One of the best ways to address early detection is to investigate the relationship between postmortem pathology and behavioral and biologic markers in a population sample studied longitudinally. In 2011, the National Institutes of Health awarded an \$8 million, five-year grant to Banner Sun Health Research Institute (BSHRI) and Mayo Clinic in Arizona to support the National Brain and Tissue Resource for Parkinson's Disease and Related Disorders. This brain and tissue bank is a unique resource and the largest of its kind with more than 1,300 autopsy cases, of which more than 100 are PD, and a continuously maintained enrollment of 1,000 living participants, of whom more than 100 have a diagnosis of PD. Equally important, the research team can draw on the long-term clinical study of individuals enrolled in the

brain and tissue donation program.

Thomas G. Beach, MD, PhD, from BSHRI is the principal investigator and will direct the neuropathology aspects of the project. Dr Adler will direct the clinical aspects. The two physicians also serve as co-principal investigators of the Arizona Parkinson's Disease Consortium, funded by the state of Arizona and The Michael J. Fox Foundation for Parkinson's Research. Their work has led to improved PD classification and advances in risk prediction and understanding of the pathogenesis of PD.

A major focus in the group's investigation is the progression from normal cognition to mild cognitive impairment and dementia. In addition to annual physical examinations and biomarker tests, Dr Adler conducts in-depth testing of cognition, as well as measures of olfaction, autonomic function, and sleep disorders, in healthy control subjects and patients with PD enrolled in the program.

Discussing the importance of the PD brain and tissue resource, Dr Adler says, "Advances made in the diagnosis and treatment of Parkinson's disease have come mainly from pathologic and neurochemical samples at autopsy. The creation of a bank for cerebrospinal fluid, brain, and other organ tissue in individuals studied over time represents a significant step in moving the field toward better treatments and an eventual cure."



Figure. Brain slice (left) showing dark-colored substantia nigra (v-shaped area at bottom middle of the brain [right]) superimposed on a microscopic photograph of dopaminergic pigmented substantia nigra neurons stained with an antibody that recognizes tyrosine hydroxylase, the rate-limiting enzyme necessary for the production of dopamine.

Research Highlights in Neurology and Neurologic Surgery



New Method for Predicting the Potential for Organ Donation After Cardiac Death in Neurocritical Patients

Successful donation of organs after cardiac death (DCD) depends on the length of time between withdrawal of life-sustaining treatment (WLST) and the cessation of cardiopulmonary function. The optimal length of time for successful organ donation is 60 minutes; anything longer can compromise organ function. Patients with catastrophic, irreversible brain injury who do not meet the criteria for brain death are the most frequent candidates for DCD, yet approximately half of them sustain life for more than 60 minutes after WLST. Mayo researchers conducted a multicenter, prospective observational study to investigate a new model of prediction to estimate the time from WLST to death in patients with nonsurvivable brain injury (Rabinstein et al. *Lancet Neurol.* 2012;11[5]:414-9). Current protocols involve temporary disconnection from the mechanical ventilator and scoring of the degree of pulmonary and circulatory support. The Mayo team's previous investigations had identified four clinical variables associated with death within 60 minutes of extubation: absent corneal reflex, absent cough reflex, extensor or absent motor response, and increased oxygenation index (pulmonary function). The current study validated the predictive value of this small set of variables in patients with irreversible brain injury. The bedside scoring system, the DCD-N, used in the study is less invasive and labor intensive and is less distressing for grieving families than current protocols. Further studies will help to establish its reliability in patients from whom permission for DCD has been obtained.

Comparison of Imaging Biomarkers Across Study Samples: Implications for Treatment Trial Design and Assessing New Diagnostic Criteria in Alzheimer's Disease

A recent Mayo Clinic study may have implications for designing treatment trials and evaluating the new diagnostic criteria for the various stages of Alzheimer's disease (AD) (Whitwell et al. *Arch Neurol.* 2012;69[5]:614-22). The study compared imaging biomarker results from the Mayo Clinic Study of Aging (MCSA) with those from the Alzheimer Disease Neuroimaging Initiative (ADNI). The MCSA is a population-based study of aging; the ADNI is an observational study initiated to improve methods for clinical trials and biomarker validation in AD. The ADNI study participants are considered a "convenience sample" and come from 59 centers in Canada and the United States that use identical recruitment mechanisms. The researchers found that there were critical differences between the MCSA population-based cohort and the ADNI convenience-sample cohort. The ADNI participants were older, had less education, performed worse on the Mini-Mental State Examination, and were more likely to have a family history of AD than participants in the MCSA study, who were drawn randomly from the general population. Rates of decline in hippocampal volume suggested that ADNI participants may not be representative of the general population. The investigators concluded that sampling bias may occur in convenience samples, such as those studied in the ADNI, in which participants are enlisted through advertising or memory clinics.

Novel Genetic Defect at the Nerve-Muscle Junction Identified in Myasthenic Syndrome

Mayo researchers have discovered a novel genetic defect in the acetylcholine receptor at the nerve-muscle junction that causes disabling muscular weakness known as *myasthenic syndrome* (Shen et al. *J Clin Invest.* 2012;122[7]:2613-21). Treating this syndrome requires an understanding of how the genetically altered protein product, the acetylcholine receptor, is functionally modified. By generating copies of the altered receptor and monitoring the electrical signals generated in response to its activator, the research team identified the unique molecular step that was altered. The discovery impacts treatment and affects the understanding of the acetylcholine receptor, a member of a large gene family of molecules known as *Cys-loop receptors* that mediate cell-to-cell communication throughout the brain and spinal cord. The findings have broad implications for understanding and treating neurologic disease, as well as for advancing the science of synaptic transmission.

To read more about Mayo Clinic neurosciences research and patient care, visit www.mayoclinic.org/medicalprofs.

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Clinical Trials Update

Study of Thymectomy in Acetylcholine Receptor–Positive Myasthenia Gravis: Patients with generalized MG with or without treatment with Mestinon and Prednisone are randomly assigned to receive thymectomy or not and are observed for three years.

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