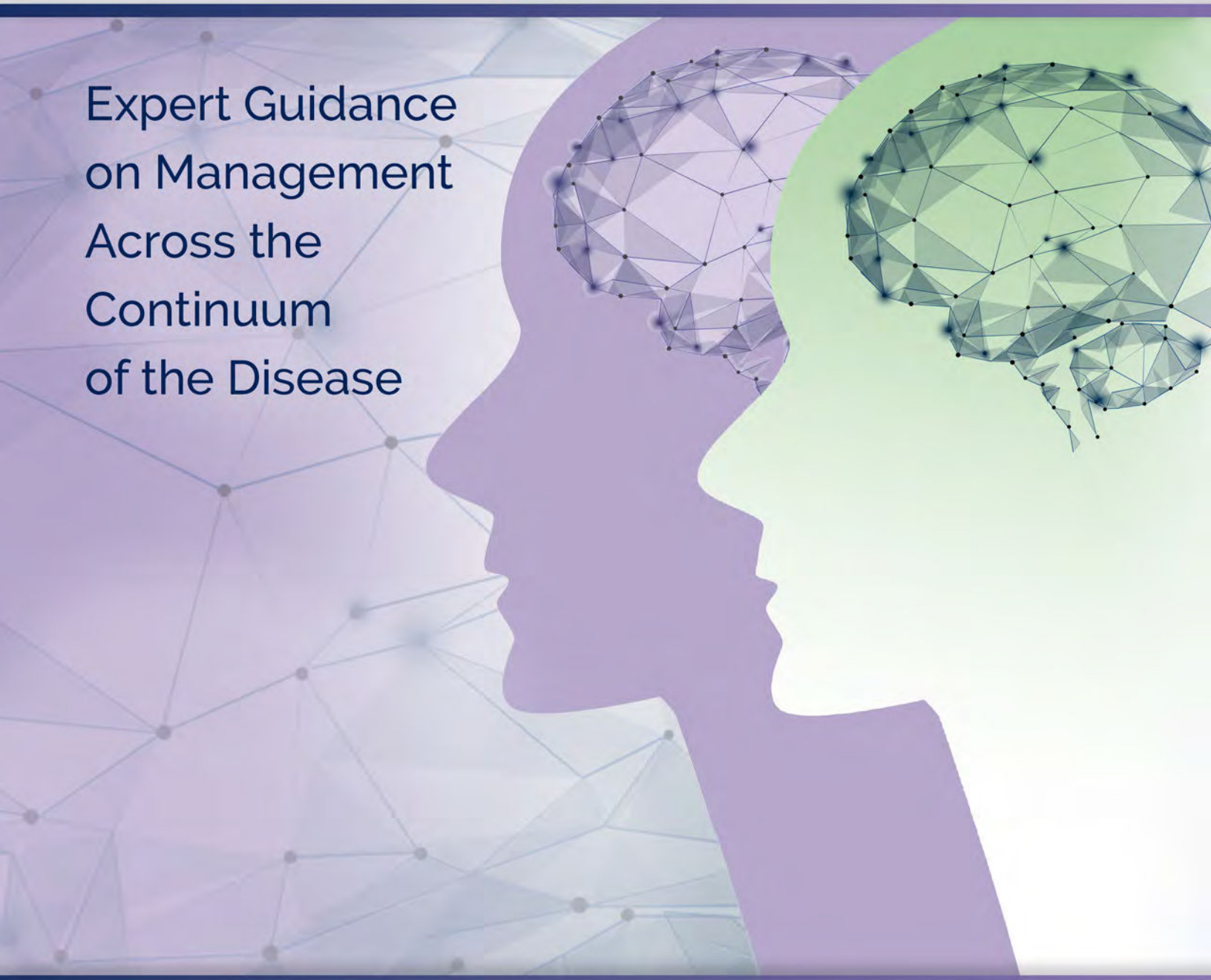
A Consortium of Multiple Sclerosis Centers and Catamount Medical Education Collaboration

UPDATES IN COGNITION AND MULTIPLE SCLEROSIS:

Expert Guidance on Management Across the Continuum of the Disease



THE CONSORTIUM OF MULTIPLE SCLEROSIS CENTERS

CATAMOUNT Medical Education

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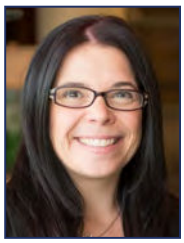

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CE INFORMATION

RELEASE DATE
September 29, 2023

EXPIRATION DATE
September 29, 2024
The estimated time to complete the activity is 90 minutes.

TARGET AUDIENCE
Neurologists, nurse practitioners, PAs, nurses, pharmacists, mental health professionals, and other members of the health care team caring for patients with MS.

LEARNING OBJECTIVES
At the conclusion of this activity, participants should be better able to:

- Discuss the nature and burden of cognitive impairment in patients with MS
- Describe the relationship between cognition and measures of brain volume
- Review current evidence and ongoing needs to understand the effects of disease-modifying therapies on cognitive functioning
- Implement strategies to engage the interdisciplinary team effectively in the assessment and monitoring of changes in cognitive functioning over time in patients living with MS

ACCREDITATION
In support of improving patient care, this activity has been planned and implemented by The Consortium of Multiple Sclerosis Centers (CMSC) and Catamount Medical Education. CMSC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the health care team.

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All other health care professionals completing this course will be issued a statement of participation.

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Speakers Bureau: Biogen; Bristol Myers Squibb; EMD Serono; Novartis Pharmaceuticals Corporation; Roche; Sanofi
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Frederick W. Foley, PhD, has disclosed no relevant financial relationships.

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If you wish to receive acknowledgment for completing this activity, please complete the posttest and activity evaluation at https://www.everythingmultiplesclerosis.com/cognition. Access the site directly or scan the barcode on the back of this publication. Upon successfully completing the posttest with a score of 75% or better and the activity evaluation, your certificate will be made immediately available to you.

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CONTACT INFORMATION

For questions about this activity, please contact Catamount Medical Education at info@catmeded.com.

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MESSAGE FROM **THE CHAIR**

We all know how debilitating a disease multiple sclerosis (MS) can be. Among the many neurologic symptoms involved, cognitive deficits are some of the most common,[1,2] and they affect all aspects of life, including success in school and employment, social relationships, money management, fitness to drive, and the ability to live independently.[3,4]

Despite how pervasive and debilitating cognitive impairments can be for people with MS, they are often not adequately addressed in clinical practice. Reasons for this gap are diverse and include a lack of training in the recognition of subtle signs, lack of awareness of assessment tools and resources, and time constraints. Also, there are no approved medical treatments for MS-related cognitive impairment, leaving many clinicians feeling helpless about how to treat this condition. Moreover the research data about best practices are limited, since historically clinical trials often did not include cognitive endpoints.

So, what lessons can we draw from the evidence that is available? And how can we best educate members of the MS care team about current best practices for assessing and treating cognitive impairment in this population?

On March 10, 2023, a group of leading specialists in the area of MS-related cognition met to discuss current issues in their field: describing the MS cognitive phenotype, reviewing the clinical data, exploring how best to incorporate assessment and treatment in clinical practice, and when to refer to other clinical specialists. This monograph contains a summary of the data presented and captures the discussion that occurred at this roundtable meeting.

It outlines what we know, what we believe, and what we should do, both as researchers and clinicians, to assess, preserve, and enhance the cognitive functioning of people with MS.

Sincerely,

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NATURE AND BURDEN OF COGNITIVE IMPAIRMENT IN MS

WHAT WE KNOW

EPIDEMIOLOGY AND COURSE OVER TIME

Cognitive impairment is a common symptom of MS. Studies have found that up to 70% of people with MS (PwMS) have cognitive deficits, although prevalence varies with the time course and nature of the underlying disease.[1,2] Furthermore, cognitive impairment is more common in certain subpopulations. For example, men have greater MS-related cognitive impairment than women, with greater deficits in verbal memory and encoding.[5] People of color with MS tend to have greater overall disability than White PwMS,[6] including greater cognitive impairment in early MS.[7]

How early in the disease course does cognitive impairment first occur? Some data from studies of patients with radiologically isolated syndrome (RIS) and clinically isolated syndrome (CIS), considered pre-clinical stages to MS, suggest that it may be present even before a diagnosis of MS. Patients with CIS[8] have significantly greater rates of cognitive impairment than the general population. In a study of patients with RIS, although the cognitive abilities of the RIS and control groups were not significantly different, the scores of all 30 patients with RIS were below the overall mean.[9] The only study to directly compare rates of cognitive impairment in patients with RIS and CIS, and healthy controls (n = 28, 25, 22, respectively), found that the RIS and CIS groups performed significantly worse than healthy controls on tests of information processing speed and on 1 measure of executive function (Stroop color-word card test). The RIS and CIS groups performed similarly in all domains studied.[10]

Cognitive impairment increases with age, and over the course of the disease. It is more prevalent in older versus younger PwMS.[11] Multifactorial analysis using disease biomarkers indicates that both neuroinflammatory and neurodegenerative processes contribute to the greater decline at advanced age.[11] A multivariate analysis found that cognitive impairment is significantly associated with advanced age.[12] The cognitive issues facing elder PwMS have not yet been well characterized, and they are not always associated with disease duration. For example, those with late-onset MS (age at onset >41 years) have significantly worse visual memory and working memory than those with adult-onset MS (age at onset <40 years).[13] Also, children with MS are more likely to show impaired information processing than adults with equivalent disease duration.[14] Interestingly, a longitudinal study of adults with pediatric-onset MS found that the development of cognitive impairment was not linear with time; there was cognitive decline at year 2, but improvement at year 5. About half of the patients showed cognitive impairment at year 5, defined as 2 failed tests in a cognitive battery.[15]

CLINICAL PRESENTATION

In PwMS, cognitive impairment can involve any skill or domain; however, certain skills are more likely to be affected: information processing speed, learning and memory, visuospatial processing, word-finding, executive function, and social cognition **(Table 1)**.[1,16,17] There is currently a new effort to move away from the typical cognitive dichotomy of impaired versus intact, and instead define different cognitive phenotypes based on severity and the specific cognitive domains affected.[18,19] Thus far, this work has confirmed varying patterns of deficits among PwMS. More work is needed to further establish these phenotypes and establish unified diagnostic criteria that can be used in both research and the clinic. There is currently a partnership between the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and the International Multiple Sclerosis Cognition Society (IMSCOGS) working to establish such criteria.

Table 1. Cognitive Skills Commonly Affected in MS[1,16,17]

Skill	Definition[20]
Information processing speed	Time it takes to perceive a stimulus, select an appropriate reaction, and respond
Working memory	The short-term maintenance and manipulation of information necessary for performing complex cognitive tasks such as learning, reasoning, and comprehension
Episodic memory	The ability to remember personally experienced events associated with a particular time and place
Visual memory	Capacity to remember what has been previously seen in the form of visual images
Verbal memory	Capacity to remember what has been previously heard or read; typically assessed for both rote and contextual-based information
Visuospatial processing	The ability to process information regarding the spatial (relational) aspects of an object in 2 and 3 dimensions
Word finding or verbal fluency	Ability to retrieve a word with which an individual is familiar, as needed. Synonym: word retrieval
Executive function	Higher level cognitive processes such as planning, decision making, problem solving, action sequencing, impulse control, task assignment, initiation, and organization
Social cognition	Ability to perceive, interpret, categorize, and judge one's own social behaviors and those of others

Cognitive impairment is often one of the "invisible" symptoms of MS.[21] Symptom severity differs greatly among individuals and does not necessarily correlate with overall disease severity or Expanded Disability Status Scale (EDSS) scores.[4,22] Because cognitive symptoms can easily go undetected, guidelines recommend routine formal assessment at regular intervals.[3,23]

Cognitive impairment is strongly associated with poorer quality of life (QOL), independent of any physical symptoms.[3,4] It is associated with difficulties with:

Subtle Symptoms

Mild cognitive impairment may not be detected by standard screening tools. Therefore, in addition to routine screening, clinicians should be aware of subtle symptoms suggesting possible cognitive impairment, such as:

- Writing things down during appointments
- Bringing someone with them to visits to help them explain things to the provider or remember what the provider said
- Having trouble providing some of their medical or personal history
- Having trouble following through with plans from past appointments
- Reporting difficulties at work or school in important interpersonal relationships due to cognitive symptoms
- Describing difficulty finding the right words or remembering names
- Changing jobs or other important roles in their lives to something less demanding

- Social participation
- Employment or school
- Mental health
- Fitness to drive
- Money management
- Ability to perform everyday tasks (eg, online shopping[24])
- Medical decision-making and adherence

Children and teenagers with MS-related cognitive impairment are also at greater risk of slowed cognitive development, social problems, and behavioral problems.[3]

Cognitive impairment is often one of the "invisible" symptoms of MS.[21]

ASSOCIATED AND CONFOUNDING CONDITIONS

Individuals with MS may have other health problems or conditions that can cause or contribute to cognitive impairment. Certain conditions, such as comorbid psychiatric disorders,[25] fatigue,[26] and sleep problems[27] are common in PwMS. Fatigue is one of the most common symptoms associated with MS, occurring in up to 78% of patients.[28] It can be either mental or physical, and it increases the risk of comorbidities such as depression.[29] The multidimensional nature of fatigue and other associated symptoms can make them challenging to address.

CLINICAL PEARL

Sleep specialists recommend baseline sleep studies for every MS patient, due to the prevalence of sleep disorders and their strong impact on quality of life and cognition.

Drug and alcohol use present additional confounding conditions. The use of cannabis[30,31] or other medications for symptomatic relief[32,33] is common in PwMS. There are conflicting data on the effect of alcohol use and abuse on the progression of MS; however, the negative effect of alcohol consumption on cognitive function would augment any MS-related cognitive symptoms.[34]

There are also multiple conditions not associated with MS that can alter cognitive function, such as: metabolic issues, effects of concurrent medications, developmental disorders (eg, attention-deficit/hyperactivity disorder [ADHD], learning disorders), traumatic brain injury, autoimmune disorders (eg, lupus, sarcoidosis), central nervous system (CNS) infection (eg, HIV, syphilis), cerebrovascular involvement (eg, stroke, small vessel disease), or another neurodegenerative disease. A comprehensive medical work-up may be necessary to determine the true etiology.

MS-related Cognitive Decline or Another Neurodegenerative Disease?

- Autopsy studies find that Alzheimer's disease occurs in PwMS at the same rate as in the general population.[11]
- Several studies have identified an age-accelerated cognitive decline, relative to disease duration, in PwMS, particularly for information processing speed, attention, executive function, and working and visual memory. In contrast, patients with dementia due to Alzheimer's disease and other neurologic disorders are likely to have deficits in semantic memory and memory storage and retrieval.[11]
- Many clinicians are hesitant to diagnose dementia in PwMS.[11,35] Clinicians may also attribute all cognitive symptoms to MS. Furthermore, in younger PwMS, a diagnosis of dementia is particularly stigmatizing, with potential limitations in driving and the ability to consent in legal and medical affairs.[11]
- Not having a diagnosis of dementia can prevent an individual from receiving services, such as adult day care or caregiver hours.[35]
- A neuropsychological evaluation may be helpful in cases of significant cognitive impairment in PwMS.

DISCUSSION

BURDEN OF COGNITIVE IMPAIRMENT

Sarah Morrow: Our patients are living longer, and with current treatment they are living longer with less physical disability. Now we are doing them a disservice by not focusing on cognitive disability.

Laura Hancock: I have a handful of people in clinic who have really aggressive cognitive symptoms. We are sending some people for PET scans because their cognitive presentation is a little atypical. We need more research in this area to help us determine whether some cases of aggressive cognitive symptoms are outliers versus Alzheimer's disease or another neurodegenerative disease.

Jeffrey Wilken: Some cognitive domains are difficult to measure with standard cognitive evaluations, like social awareness, impulsivity, and other aspects of executive functioning. Some things you pick up only from talking to a person.

Ann Yeh: It points to the limitations of our testing methodology, right? Maybe in the future there will be AI-related ways of evaluating cognition, even mapping of language. Perhaps through wearable devices.

PATIENT PERCEPTION AND COGNITIVE ASSESSMENT

Sarah Morrow: The literature says that patients may have no insight into their cognitive decline, but when you actually talk to patients in clinic, they know there's something going on. They may say "I'm not doing my job as well as I could" or "My kids are reminding me to pick them up from hockey or to sign permission slips." We need to explore this disconnect in future research.

Jeffrey Wilken: Sometimes people don't have the vocabulary for it. So when asked "Do you have any cognitive issues?" they say "No." Or they may say "My memory is shot." If you ask them to be specific, they may say "I can't remember words." Remembering conversations and other events is not an issue. Therefore, it is really a problem with word-finding rather than memory. They just don't have the exact terminology.

Sarah Morrow: I am a big proponent of trying to educate health care practitioners, especially neurologists, about how cognition presents in PwMS. Just because they are carrying on a conversation doesn't mean there is no dysfunction.

Ann Yeh: Even with patients with advanced Alzheimer's you may not see an issue unless you ask the right questions.

Marie Moore: Without screening, cognitive issues are particularly easy to miss with patients who are strong socially. I also find that patients often attribute cognitive changes to aging, despite being quite young.

Jeffrey Wilken: Often a family member or friend will cover for a patient with cognitive impairment, even sometimes during clinical interviews. If we had accurate assessments, we would probably find that a lot more patients with MS are cognitively impaired.

Laura Hancock: I think you're right. We can't find things we're not testing for. But it's not practical to give an 8-hour battery to every research subject, and the short screening tools are not comprehensive enough. Part of the reason we miss word-finding is because language tests are not a standard part of these assessments.

Sarah Morrow: In our clinic we get baseline testing on everyone. Sometimes, patients will say they are not doing as well as before. When we retest them, they may still have normal scores, but decreases from baseline in certain measures. For them, that is real cognitive impairment. They might not technically meet the criteria for cognitively impaired, but they're actually losing cognitive function.

Ann Yeh: Isn't it better to think about things on a continuum rather than saying, bam, your score is 14 rather than 15 now, so you're impaired?

Jeffrey Wilken: Especially when you have very highly intelligent people who come into your office. They know they're not functioning the way they should be, even if they score in the normal range.

Patty Bobryk: This has real ramifications for treatment and insurance reimbursement. How do you justify that you're treating cognition when you don't have data to support that they're impaired?

Ann Yeh: The scales are designed to talk about cutoffs. But that's not always what's significant to the person. Can we make new definitions of what counts as clinically significant? How do we make those definitions?

Laura Hancock: Using a person's estimated premorbid skill is one of the ways we can help determine if a change has occurred. But this is not a perfect method. If we could obtain baseline evaluations on everyone, that would help but it is not always feasible.

Sarah Morrow: There is some work going on in defining what is meaningful change, rather than what is a minimum threshold. Previous work showed that a decrease of 4 points on the SDMT (Symbol Digit Modalities Test) was clinically meaningful. Two research groups argue that it's a change of more than 8 points on the SDMT.[36,37] It may also depend on where you start from. If you are very high functioning and you drop by 4 points, that's probably meaningful for you. Whereas if you start at a level below normal, then only dropping 2 points might be problematic for you.

SOCIAL LIMITATIONS AND CARETAKER BURDEN

Jeffrey Wilken: We focus so much on employment, but when you talk about day-to-day problems, patients describe things that stop them from socializing. They can't follow if 3 people talk at the same time, or they feel less intelligent because they can't remember things. So they limit their social circles. This is such an important point.

Laura Hancock: I agree. Absolutely. I think that's in some ways the most devastating consequence of these cognitive symptoms for many people. "I can't serve on the PTA anymore, and that was something I really enjoyed." Or "I can't manage my finances like I used to" or whatever it might be. These are frustrating changes and limitations for our patients, but our current rehabilitation strategies don't always boost these kinds of skills.

Jeffrey Wilken: And that starts a depression cycle. They withdraw, and depression, if it wasn't already there, kicks in. If it was already there, then it's worse.

Marie Moore: And you see a lot of marriages break down. Then they don't have the support of a partner. Oftentimes they have loss of insurance benefits. This really spirals quickly for a lot of patients.

Jeffrey Wilken: The impact on family can't be stressed enough. One of the reasons why divorce rates are so high is that the patient feels they've lost a partner. Nobody educates the partner without MS about what's truly happening. I'm a consultant for an online MS support community, and I'm seeing this all the time. There are some questions like, "What do I do? My spouse thinks I'm lazy." Has anybody educated this family?

Patty Bobryk: This speaks to us being able to make appropriate referrals, because providing this information is just not enough.

Sarah Morrow: Invisible symptoms are a big part of the burden and they're invisible, so it's harder for spouses and family members to understand. It's also harder for the patient to identify it. So how do we refer our patients appropriately if we don't even realize that some issues might stem from their MS?

Marie Moore: And many areas don't have access to specialists such as psychologists, MS trained physical therapists (PTs), or occupational therapists (OTs).

Ann Yeh: Absolutely. And it speaks to the importance of involving families in the rehabilitation process. Incorporating families reduces family stress and helps to support people who are dealing with that feeling of being a caregiver to someone who is different than the person they married.

Marie Moore: The earlier that the family can be involved, the better, before the frustration has built up. That means starting family education very early in the disease process.

Sarah Morrow: That's where the pediatric model is. You have the family involved from day 1. Whereas for most adult patients, family members rarely come unless they don't want to drive themselves, right?

Marie Moore: And I only have 30 minutes for office visits. I'm not going to have a chance to have an in-depth conversation with the family, even though I do try to involve them.

Laura Hancock: There are organizations that make videos for loved ones of PwMS to explain more about the disease.

Marie Moore: It would be great to have a resource that patients and families could go to after their 30-minute appointment to review the information. Perhaps even something a little bit more interactive than a video.

Laura Hancock: I agree. We are trying to give the patients too much information in 1 office visit. If we can direct them to a website with a library of videos, they can digest it at their own speed.

Jeffrey Wilken: How do we get people to use those videos?

Ann Yeh: Exactly. Without a specific plan, through a very strong support network, perhaps with counselors or coaches, I don't think it will happen. How do we advocate to make that happen? Some of the work we have done with teens relates to this. When trying to encourage behavioral change, like exercising more, we found that you can't just give them an app. We have a coaching system set up for behavior change. Is that not something we could study for family involvement? We can think creatively about early implementation strategies, such as coaching intervention, before it's too late.

Marie Moore: I like the coaching term; it has positive connotations for the patient, as opposed to a therapist. Also, sometimes there's too much information up front. Patients are just trying to acclimate to the fact that they have this diagnosis, and now you're telling them their family's going to fall apart because of cognition problems? How do you address this in a gentle way, as the patient is ready? There's a lot of nuance there.

CLINICAL PEARL

Families should be included as much as possible from the very beginning, and educated about what to expect. PwMS and their families should also be provided with educational materials, and, ideally, a support network that they can access outside of office visits.

MEDICAL TRAINING

Jeffrey Wilken: Information about cognition needs to be included in the early medical training of MS specialists. Educating the family early and letting them know what to expect regarding both physical and cognitive changes

is important. New specialists need a lot more training in cognition, in general. Cognition is not such a priority for them, because there is no FDA-approved cognitive medication for MS, and no FDA-approved cognitive endpoint in clinical trials.

> *"Information about cognition needs to be included in the early medical training of MS specialists. Educating the family early and letting them know what to expect regarding both physical and cognitive changes is important. New specialists need a lot more training in cognition, in general."*

Sarah Morrow: We want to help clinicians know what kind of questions to ask. But they also have to follow up on the responses and not just look at the scores. The answers don't necessarily indicate cognition. For example, if a patient is having trouble at work, it could be cognition, but it could also be bladder problems and frequent bathroom breaks, and they were getting reprimanded for not finishing.

Marie Moore: The clinician may feel "Why bring up something that I can't treat?"

Sarah Morrow: Right. But even though there's no treatment, there is a lot you can do. Sometimes I feel like half the time in my clinic I'm just telling them they're not stupid and they're not going crazy. That in itself is a "treatment".

ASSOCIATED AND CONFOUNDING FACTORS

Psychiatric disorders, fatigue, and sleep problems

Laura Hancock: These are confounding factors, but some of them are also caused by the disease itself. And knowing the etiology can be important clinically. An individual can develop depression as an emotional reaction to the disease of MS and the changes it brought about in their lives. Individuals can also develop depression as a neuropsychiatric manifestation of MS, largely driven by disease activity. It is also important to note the interrelatedness of a lot of these confounding factors, including sleep disorders and fatigue.

Jeffrey Wilken: If you're depressed, you're not going be thinking as well. If you're anxious, you're not going to be thinking as well. If you treat anxiety or depression or bipolar disorder, you can get a person who's thinking better, and they may never have had any cognitive problems. Even if they do have cognitive problems from their MS, they will be less severe. Fatigue and sleep problems have a similar effect.

Ann Yeh: Another way to phrase it is the bidirectionality of the condition. It is sometimes hard to know which is driving which.

Jeffrey Wilken: Sleep disorders sometimes get overlooked, and the clinician just treats fatigue. Whereas if you focused on sleep, you could treat it more naturally and the fatigue might improve.

Sarah Morrow: They might not sleep because of the neuropathic pain or their anxiety or bladder problems. So let's treat those.

Medication

Sarah Morrow: Let's talk about the side effects of medication. I did a study that showed that PwMS who took anticholinergic medications for bladder control had lower cognitive scores.[38]

Jeffrey Wilken: Do you see it clinically? Do patients notice this? Do you hear about it?

Sarah Morrow: I'm not finding they complain about it, but when I tell them that it is a possible side effect, then it's something they think about. If they notice trouble, or we notice any changes in cognition, we take them off the drug.

Marie Moore: Our patients are often prescribed sedating medications for symptom management, and they have no idea what they're taking or why they're taking it. When they develop fatigue and other issues, it's a great opportunity to attempt reducing or eliminating medications as tolerated.

Jeffrey Wilken: Another thing to consider with this though, is everybody's different. People react completely differently to drugs like gabapentin and benzodiazepines.

Marie Moore: Even within the same individual, a person's toleration to a medication can change with aging.

Ann Yeh: It's medication inertia. And you're probably not the physician who initially prescribed it. You have to go through the list and say, "What can we get rid of?"

Marie Moore: It takes a lot of time, and a lot of buy-in, which can take multiple visits.

Jeffrey Wilken: I also think patients are afraid to confront the doctor and ask, "Why am I on this?" They know the doc's busy and they don't want to make waves.

Sarah Morrow: At a palliative MS care clinic I work in, one of the things that we get the best feedback on is addressing polypharmacy. The patients really appreciate this.

Cannabis/Marijuana

Jeffrey Wilken: Marijuana is the toughest of these confounding factors, in a lot of ways. Let's just talk about medical marijuana. Everybody has different opinions on that. I don't know what to tell my patients about this. Who am I to tell somebody not to take something to help with their pain or insomnia or anxiety? But there are plenty of people for whom marijuana has a negative effect on their thinking. And there are also issues with motivation. If you're not as motivated, maybe you're not working, and it's harder to take the necessary steps that will help with cognition and help your mood. It's great that it doesn't kill your liver, like alcohol. And if it isn't smoked, it isn't hurting your lungs either. But it's almost being treated by some as a harmless panacea. There is a risk-benefit ratio that is very individual. If you're not

working anymore and you have help around the house and marijuana is helping your pain and your anxiety, then maybe it's the right thing for you. But if you're working at a high-level job, while using gummies every day, that might not be the best idea, cognitively.

Laura Hancock: One study by Anthony Feinstein tracked regular marijuana users who then stopped, and their cognitive skills gradually improved over time as the THC levels tapered.[39] There's evidence that it helps with spasticity and anxiety, and for some people it may help them fall asleep. But there's another side to the coin, and that's the cognitive consequence.

Sarah Morrow: But Feinstein also found that none of the subjects thought their cognition was better and all of them went back on marijuana after.[39]

Ann Yeh: Perhaps they perceived their social functioning to improve with marijuana, which may have been important to them.

Sarah Morrow: The key is to have these conversations so that they are making informed decisions.

Alcohol

Jeffrey Wilken: With alcohol, I tell my patients that it not only affects you while you're drinking. The next day it also can affect you because your sleep might not be as good or you could have hangover effects. And there's the potential for rebound anxiety. And all the negative health implications, which could affect cognition too.

Marie Moore: I think alcohol's a much bigger problem than we really pay attention to, or are discussing in clinic. It's so socially acceptable and it seems like a reward for so many people to have a drink or 2 at the end of the day. But that 1 drink can be a problem.

WHAT WE BELIEVE

- Cognitive impairment occurs early and often
- It impacts all aspects of life
- The distribution is not binary – there is a continuum with multiple phenotypes, rather than normal versus impaired
- Polypharmacy and other confounding factors need to be addressed

WHAT WE SHOULD BE DOING

As researchers

- Conducting more research, especially with older patients and non-White populations
- Focusing on implementation—how can this be used in clinical practice?
- Developing and implementing screening tools
- Advocating to have more information about cognition and cognitive assessment early in medical education

As clinicians

- Performing routine cognitive assessments
- Determining effects of other medications on cognition
- Educating patients and families early and often
  - Encouraging patients to bring a family member
  - Creative use of technology to involve patients/family members
- Referring patients for early assessment and/or rehabilitation

COGNITIVE ASSESSMENT IN CLINICAL TRIALS

WHAT WE KNOW

RELATIONSHIPS BETWEEN COGNITION AND MRI METRICS

In the past 2 decades, research into the relationship between cognition and MRI metrics in MS has shifted our thinking from "How do white matter lesions affect cognition?" to "What is the role of brain atrophy and regional gray matter loss?" MRI studies have established a correlation between lesions and cognitive impairment. In a study by Rossi et al, lesion maps showed a less diffuse distribution of lesions with cognitively impaired versus cognitively preserved PwMS, with lesions in the impaired patients concentrated in the corpus callosum, impeding communication between gray matter regions.[40] Furthermore, this study, along with other early studies, found that lesions did not fully correlate with or account for cognitive decline in PwMS.

Researchers began to consider ways to measure damage other than lesions that may contribute to cognitive impairment. One of the primary ways to measure has been volumetric analysis. Several different studies link whole brain volume loss and cognitive decline in PwMS. One review[41] described correlations between whole brain volume loss not only with worsening of SDMT scores, but also with decrements on several other measures of cognitive functioning. Other studies have shown whole brain volume, as measured by brain parenchymal fraction (BPF) to be associated with a decline in memory functioning in PwMS.[42,43] Similarly, a study by Deloire et al found that BPF in the first 2 years was a primary predictor of impaired processing speed at 7 years.[44]

Researchers have also investigated which specific brain regions show the greatest deficits. Benedict et al, 2004, studied the correlation between a variety of MRI measurements and neuropsychological performance, in both PwMS and healthy controls.[42,45] Third ventricle width had the strongest correlation, although intra- and inter-observer variability limited its use as a clinical tool. Since that time, multiple studies of regional brain volume changes have found a strong correlation in third ventricle and thalamic loss with cognitive decline (as well as fatigue, motor deficits, and other issues) in PwMS, compared with healthy controls.[46-48] Thalamic atrophy correlates with slowed processing speed,[46] as well as verbal fluency, verbal memory, and executive function.[48] The results of these studies suggest that regional brain matter loss is a stronger predictor of cognitive decline than loss of whole brain volume.

An emerging hypothesis that encompasses these findings is that of network collapse. This hypothesis proposes that specific patterns of structural disconnection lead to less efficient wiring of the network underlying cognition, and after a critical threshold is crossed, the network "collapses", leading to clinical progression.[49] This view is supported by the observation that brain atrophy in cognitively impaired PwMS often occurs in heavily connected brain regions, or hubs, such as the thalamus or corpus callosum.

SUBPOPULATION VARIANCE

The data on regional atrophy vary among specific subpopulations. An anatomic study found that Black and White Americans with MS have different patterns of brain volume loss, despite similar T2 lesion volumes.[50] Black patients had greater overall cortical thinning, and greater loss in temporal, parietal, and occipital lobes, as well as the precentral and postcentral gyrus. In contrast, thalamic volume loss was significantly greater in the White patients than the Black patients. In both groups, worse disability was associated with lower total thalamic volume percentage. EDSS scores were lower in the Black group. Similarly, an fMRI study found that male PwMS had significantly lower cognitive performance, as well as significantly less gray matter volume and greater impairment in functional connectivity in regions associated with visuospatial processing, relative to healthy controls. In contrast, these parameters were not significantly different for the female patient and control groups.[51] These studies indicate the need for a more complete understanding of gender- and race-based differences in PwMS at the neuroanatomic level.

CLINICAL APPLICATION OF VOLUMETRIC ANALYSIS

There are very few commercially available programs to assist with quantitative volumetric analysis in the clinic. The ones that do exist often are only available in certain clinics, and it costs additional money to have the analyses done. In addition, it often is the case that the software works only with a certain type of MRI machine. Finally, whereas the correlations between research-based volume measures and cognition tend to be relatively strong in clinical studies, this is not always the case with clinic-based, commercially available volumetric analysis software.[52]

NeuroQuant is one of the best known commercially available volumetric analysis softwares. The overall brain report provides volume measurements for 9 brain structures, including the whole brain, white and gray matter, lateral ventricle, thalamus, third ventricle, and hippocampus.[53] LesionQuant is a product of the same company, CorTech, and is designed to evaluate lesions and atrophy in PwMS, comparing volumes of brain to norms established by NeuroQuant.[52] In a clinical study, the number and volume of lesions reported by LesionQuant were comparable to reports from neuroradiologists; in contrast, there was only agreement on atrophy between the neuroradiologist and LesionQuant in 50% of the patients (6 of 12).[52] Additional research is necessary regarding the validity of NeuroQuant and LesionQuant in PwMS.

Due to limited access to MRI in clinical practice, and limited availability of automated software validated in MS, the

MAGNIMS–CMSC–NAIMS (Magnetic Resonance Imaging in Multiple Sclerosis–Consortium of Multiple Sclerosis Centers–North American Imaging in Multiple Sclerosis Cooperative) guidelines do not recommend routine use of quantitative MRI techniques and brain volumetric measurements as diagnostic markers.[54]

DISEASE-MODIFYING THERAPIES

Disease-modifying therapies (DMTs) have been associated with cognitive benefits, relative to placebo, presumably through relapse prevention and mitigation of lesion development.[4] The data are from phase 3 trials which focused on safety and efficacy in slowing disease progression and were not optimally designed to detect changes in cognition. The changes observed have been modest and inconclusive.[4] These findings are summarized in **Table 2**.

Table 2. Key Significant Clinical Findings Regarding the Impact of Disease-Modifying Therapies on Cognition in Patients With MS

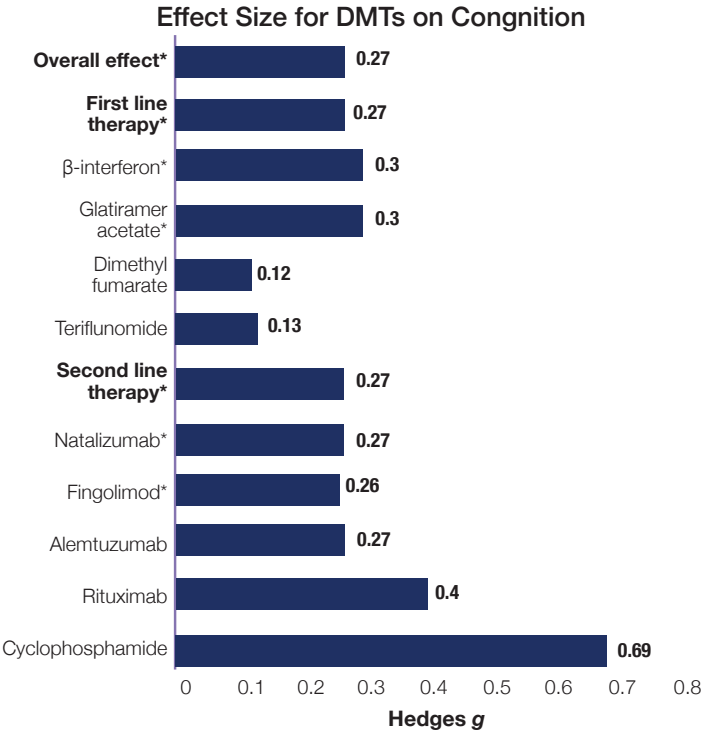
Therapy	Key Significant Clinical Findings	Reference
Interferon β-1a	Decreased impairment (relative to placebo) • Comprehensive and Brief Neuropsychological Battery composite scores • Processing rate – PASAT	Fischer et al, 2000[55]
Natalizumab	Less likely to experience cognitive worsening than placebo group over 2 years (defined as 0.5 SD decrease on the PASAT-3, confirmed for 12 weeks)	Weinstock-Guttman et al, 2012[56]
Fingolimod	• Long-term improvements in PASAT score (relative to placebo) • Baseline PASAT-3 scores predictive of time to first confirmed relapse, time to confirmed disability worsening, freedom from Gd+ lesions and new T2 lesions, brain atrophy and disease activity status at month 24	Langdon et al, 2021[57]
Ozanimod	• More likely to lead to clinically meaningful improvement in SDMT score (≥4 points), relative to interferon β-1a group, at 12 months • Slower rate of whole brain volume loss over 12 months than interferon β-1a among participants who showed clinically meaningful SDMT improvement at month 12	DeLuca et al, 2021[58]
Siponimod	Better SDMT scores • Less likely to have ≥4-point sustained ↓SDMT • More likely to have ≥4-point sustained ↑SDMT	Benedict et al, 2021[59]

PASAT, Paced Auditory Serial Addition Test; SD, standard deviation; SDMT, Symbol Digit Modalities Test.

It is likely that the cognitive benefits of DMTs come from having fewer relapses and fewer new or enlarging lesions. There is, however, little direct evidence for this. The fingolimod and ozanimod randomized, controlled trials (RCTs) were the only 2 that included these data. In the fingolimod RCT, baseline PASAT-3 scores correlated with absence of new gadolinium-enhancing (Gd+) lesions, new T2 lesions, longer time to relapse, and decreased brain atrophy **(Table 2)**.[57] In the ozanimod RCT, there was a slower rate of whole brain volume loss over 12 months in the ozanimod group than the interferon β-1a group among participants who showed clinically meaningful SDMT improvement (≥4-point) at month 12, but not in those with ≥4-point declines **(Table 2)**.[58]

A meta-analysis addressed the impact of various first and second line DMTs on information processing speed in patients with relapsing-remitting multiple sclerosis (RRMS). As shown in **Figure 1**, first and second line DMTs, overall, were associated with similarly improved cognitive performances at follow-up. Effect size, in general, was small to moderate, and it is unknown how much of that is practice effect versus treatment effect. There was no statistically significant difference between first/second line therapies nor between any single DMT and interferon β-1a.[60] These results suggest that in addition to probably helping the physical component and the MRI component of MS, it is likely that DMTs help preserve cognition. Although this has not been fully established, the evidence supports early treatment initiation to prevent cognitive deterioration.

Figure 1. Mean effect sizes of disease modifying therapies (DMTs) on information processing speed in patients with relapsing-remitting MS[60]



DMTs, disease-modifying therapies.
*$P \leq 0.05$.

DISCUSSION

APPLYING MRI FINDINGS IN CLINICAL PRACTICE

Jeffrey Wilken: We're talking about what can be done in the clinic. I don't know if neurologists are going to get accurate results about volume change unless the radiologist specializes in MS. How often is that the case in a radiology center? The neurologists that I know who are MS specialists are looking at the films themselves. Even then, it's hard to figure out what looks like shrinkage versus not. Did the person just move? Was it a different angle? It would be a big change in clinical practice to have the MRIs read by MS specialists.

Marie Moore: I think the closest we come to a clinically meaningful application of the volumetric analysis data is the Benedict 2004 paper describing changes in third ventricle width.

Jeffrey Wilken: It's hard to get newer studies because people already kind of know the answers. They're not going to redo that paper.

Laura Hancock: Is that something that could be done in the clinic or is that something that needs special software?

Marie Moore: You need special software or someone who's going to manually do it.

"A major development is the shift towards understanding and quantifying gray matter loss in the CNS. We used to think about MS purely as a white matter disease and people only focused on white matter lesions for that reason."

Ann Yeh: People just don't have the time in clinic to do measurements. A major development is the shift towards understanding and quantifying gray matter loss in the CNS. We used to think about MS purely as a white matter disease and people only focused on white matter lesions for that reason.

The development of technologies that allowed us to actually look at cortical thickness and at deep gray matter involvement has led to understanding the importance in looking at gray matter, the development of white matter tracts and things like that. Things that are not clinically accessible. What we're looking at when we look at MRIs clinically is: is the disease active or not? And is there any broad evidence for atrophy? But we don't have the tools that really tie it with cognition or that even predict cognition.

There are commercial technologies available now like NeuroQuant, which people are starting to use. But there are challenges. The challenges will probably decrease through time with greater sophistication and more data being put into models. But right now, those tools are not readily available to make the connection between structural change and functional impairment. That's a future direction – determining how these tools might be employed in real life and whether there is a strong link with cognitive metrics. That's where the money is.

Jeffrey Wilken: NeuroQuant findings do not always correlate with neuropsych testing. It focuses on the size of brain regions, but not changes in cells. I couldn't find anything in the literature showing validation in MS.

STANDARDIZATION ACROSS IMAGING CENTERS

Marie Moore: Standardization is a problem. We get patients from so many places; patients are more mobile than ever. They're bringing films from everywhere.

Sarah Morrow: We are trying to educate centers to use the CMSC guidelines. We fax the CMSC MRI guidelines with every MRI request protocol.

Laura Hancock: In our clinics, people who come from far away want to get their MRI done near home. We encourage them to get their MRIs done at the same place each time, to minimize inter-scanner variability.

Ann Yeh: One of the things for the future is to find ways to actually identify the variability between machines.

CLINICAL PEARL

MRI standardization is important in detecting changes over time. Neurologists should encourage PwMS to get their scans done at the same location each time. If possible, MS centers should educate imaging centers about CMSC protocols for MRI standards.

DISCUSSION OF CLINICAL TRIAL DESIGN

Sarah Morrow: Cognitive data from DMT clinical trials are limited. However, interest in capturing that data has increased. The ENLIGHTEN trial, a current ozanimod study, is focused on cognition.

Jeffrey Wilken: Drug studies often use EDSS scores as cut-offs for enrollment in cognitive trials, rather than cognitive metrics.

Ann Yeh: The duration of follow-up is so variable. This could explain some of the differences across studies.

Sarah Morrow: The fingolimod study was 36 months follow-up and that was the longest one. The rest were mostly just 2 years. So, it's still 3 years total, not that long.

Sarah Morrow: Without having a control group, we don't know how much is really from the drug. But I think even just identifying cognitive preservation is important. We're seeing not as many people going down in cognition, and this tells us something's happening.

STANDARDIZATION OF COGNITIVE METRICS FOR CLINICAL TRIALS

Jeffrey Wilken: It would be nice if there were some agreed-upon cognitive measures for clinical trials. Then we could have 1 very large study, using an established cohort as a control for all the rest of the studies. It would be nice if we had some uniformity.

Sarah Morrow: We have some Canadian guidelines published by Lisa Walker's group that are quite good.[61] And I think Lauren Strober is trying to do exactly what you're talking about. So maybe it'll be available.

Ann Yeh: There are efforts now to try to use registry cohorts. I think that some money should be put into that. So much money has been spent on building different cohorts and enrolling healthy controls. It is a shame to see the effort being wasted—these data should be used across multiple studies.

"There are efforts now to try to use registry cohorts. I think that some money should be put into that. So much money has been spent on building different cohorts and enrolling healthy controls. It is a shame to see the effort being wasted—these data should be used across multiple studies."

WHAT WE BELIEVE

- Brain volume loss, especially in the thalamus and third ventricle, is a better predictor of cognitive impairment than lesion volume and number
- The available data regarding the impact of DMTs on cognitive decline or preservation are limited, due to clinical trial design, duration of follow-up, and practice effect
- DMTs would be expected to affect cognition, at least indirectly, through decreasing relapses and atrophy, including regional atrophy
  - Higher-efficacy DMTs are probably more effective in slowing cognitive decline, as well
  - Earlier use may provide earlier protection

WHAT WE SHOULD BE DOING

For researchers

- Using commercially available technologies and validating in MS
- Matching up structural changes with functional abnormalities
- Disseminating CMSC MRI guidelines
- Agreeing upon norms and reference populations to use as controls
- Conducting future studies to establish the impact of DMTs on cognitive impairment

For clinicians

- Using CMSC MRI guidelines
- Looking at brain atrophy as well as lesions
- If using NeuroQuant, being aware that it is not validated in MS
- Using/optimizing DMTs; although the effect has not been well demonstrated in clinical trials, there may be an indirect benefit by decreasing relapse rate and brain atrophy

ASSESSMENT AND MONITORING OF COGNITIVE IMPAIRMENT IN CLINICAL PRACTICE

WHAT WE KNOW

Clinical guidelines recommend cognitive assessment for ALL adults and children 8 years or older diagnosed with MS phenotypes, including CIS and RIS, followed by reassessments with the same instrument.[3,23]

Despite the effect of cognitive impairment in PwMS, cognitive assessment is underutilized in clinical practice.[62] Clinical guidelines recommend cognitive assessment for ALL adults and children 8 years or older diagnosed with MS phenotypes, including CIS and RIS, followed by reassessments with the same instrument.[3,23] Although the National MS Society recommends annual reassessment, the Canadian MS Working Group recommends evaluation every 2-3 years, if clinically stable, to minimize practice effect.[3,23] Additional screening should be performed following MS relapses and/or recovery or following any observed academic or behavioral changes in children. Objective measurements are necessary to accurately evaluate cognition and identify changes over time or following relapses and/or recovery. Furthermore, a study has shown that cognitive impairment often goes unrecognized by physicians in the absence of formal assessment.[63]

Early and ongoing cognitive screening help identify those at risk for income or job loss, driving restrictions or accommodations, or difficulty with self-care, treatment adherence, and medical decision-making.[3] When using screening tools, it is important to account for ways that factors such as mood, fatigue, sleep, pain, certain medications, polypharmacy, and smoked cannabis may impact the subjective reporting and objective assessment of cognition.[3]

CLINICAL PEARL

Cognitive testing may not be appropriate for somebody who has recently received corticosteroids for a relapse. Other medications that could affect performance should be considered.

ASSESSMENT TOOLS

Several assessments tools appropriate for clinical practice are available. Key features of these different tools are summarized in **Table 3**.

Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT) is considered the simplest and best rapid screening tool for adults in clinical practice and is also validated for children 8 years and older.[3,23] It takes less than 5 minutes, with high sensitivity and reliability.[23] SDMT is included in 2 other more extensive batteries used to assess information processing speed: the Brief International Repeatable Neuropsychological Battery (BRNB) and the Brief Cognitive Assessment in Multiple Sclerosis (BICAMS).[3] SDMT is sensitive to changes in mental status during and following clinical relapses, including relapses identified by cognitive change and/or changes on EDSS.[64-66] SDMT is a proprietary tool, with associated fees.[3] The Multiple Sclerosis Outcome Assessments Consortium recommends SDMT as a cognitive outcome measure in clinical trials.[67] SDMT is traditionally administered orally or on paper, although unsupervised digital administrations have also been validated, including a smartphone app.[68,69]

The Symbol Digit Modalities Test (SDMT) is considered the simplest and best rapid screening tool for adults in clinical practice and is also validated for children 8 years and older.[3,23]

Many aspects of SDMT have been proven superior to other assessments. It is superior to the PASAT, with greater association with: disease progression as measured by MRI, less of a ceiling effect; smaller practice effect; and greater correlation with physical measures such as the EDSS and the Timed 25-Foot Walk Test (T25FW), and with the physical component score of health-related quality of life (HRQOL).[67] SDMT also has greater mean effect size than other common cognitive assessment tools. A limitation of the SDMT is that it only assesses processing speed.

NIH Toolbox

Cognition is 1 of the 4 domains in the digital NIH Toolbox (NIH-TB) for the Assessment of Neurological and Behavioral Function. (The others are motor function, sensation, and emotion.)[70] All domain measures were intended to be easily accessible, usable with individuals from 3 to 85 years of age, and not to exceed 30 minutes in duration. These subdomains were the ones identified as most important for health, success in school and work, and independence in daily functioning.[70] The NIH-TB is convenient to administer in clinical practice as a tablet app.

The cognitive subdomains screened for are executive function, episodic memory, language, processing speed, working memory, and attention. It includes a battery of assessments, although the clinician can choose to administer individual components.

The validity of NIH-TB has been studied in PwMS, and results suggest its validity for processing speed, working memory, and episodic memory is comparable to that of gold standard assessments such as corresponding sections of the Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV), Minimal Assessment of Cognitive Function in MS (MACFIMS), SDMT, and PASAT.[71]

The Brief International Cognitive Assessment for MS

The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) is a brief, 15-minute assessment that includes SDMT, California Verbal Learning Test (CVLT), and the Brief Visuospatial Memory Test-R (BVMT-R). Like SDMT, it is proprietary with associated fees. In a clinical trial, BICAMS detected cognitive impairment to a comparable degree as a more comprehensive neuropsychological battery—the Brief Repeatable Battery (BRB). BICAMS is a validated measure of cognition in PwMS,[72] including pediatric patients.[73] A version of BICAMS for the iPad has also been validated.[74]

Paced Auditory Serial Addition Test

PASAT is a component of the MS Functional Composite (MSFC). It assesses information processing speed and attentional processing, as well as calculation ability.[75]

PASAT's psychometric properties demonstrate high levels of internal consistency and test-retest reliability in MS.[76] A limitation of PASAT in clinical practice is the anxiety it causes patients. Other limitations include the negative effects of increasing age and decreasing IQ and a high practice effect. Once patients are familiar with the format, they become more proficient, and improved scores can mask any real changes in cognitive ability. Multiple aspects of PASAT have shown to be inferior to SDMT.[67]

Minimal Assessment of Cognitive Function in MS

MACFIMS is a 90-minute battery of 7 tests, including PASAT, SDMT, CVLT-II, BVMT-R, Controlled Oral Word Association Test, Judgment of Line Orientation Test, and Delis-Kaplan Executive Function System Sorting Test. These tests, combined, assess processing speed, working memory, learning and memory, executive functioning, visuospatial processing, and word retrieval. The individual components are proprietary with associated fees.[2]

The validity of MACFIMS has been established in a clinical trial, and all tests showed impairment in the MS group, relative to healthy controls. MACFIMS' accuracy was sufficient to distinguish relapsing-remitting from secondary progressive courses. It also discriminated disabled from employed patients, with the tests emphasizing verbal memory and executive function most predictive of vocational status.[2] However, its 90-minute duration makes MACFIMS inconvenient for routine screening in clinical practice.

MS Neuropsychological Screening Questionnaire

The MS Neuropsychological Screening Questionnaire (MSNQ) is a 5-minute, self-reported measure that includes both a patient and informant component. The patient MSNQ form correlated strongly with measures of depression but not cognitive function, whereas the informant form correlated with the patient's cognitive performance. Therefore, patient self-reports may be exaggerated in depressed patients or reduced in patients with severe cognitive impairment.[45] MSNQ is proprietary, with associated fees.

CogEval Processing Speed Test of the MS Performance Test

Computerized assessment batteries, like CogEval Processing Speed Test (PST) of the MS Performance Test (MSPT), offer several advantages—precise measurement of response time, alternate forms to reduce the practice effect, easier administration, and instant scoring. However, they may not be appropriate for individuals with limited arm and hand dexterity.[77]

The MSPT is a digital assessment with 4 neuroperformance tests, designed to closely resemble the Multiple Sclerosis Functional Composite (MSFC).[78] The 4 tests assess cognition, upper extremity motor function, lower extremity motor function, and vision, and they are available as a free iPad app **(Figure 2)**. The cognitive test is the CogEval PST that is adapted from the SDMT. A clinical study found that CogEval PST has excellent test-retest reliability and is highly correlated with SDMT, although slightly more sensitive than SDMT in discriminating MS from healthy control groups.[79] CogEval PST is self-administered, and performance is comparable whether or not a technician is present.[79]

Computerized cognitive assessment batteries: Neurotrax, the Automated Neuropsychological Assessment Metrics

The computerized cognitive assessment batteries, Neurotrax and the Automated Neuropsychological Assessment Metrics (ANAM), have both been evaluated in the MS population.[77,80] Neurotrax is a commercially available battery that is used frequently in clinical practice. The full battery takes 45 minutes to complete, although individual components can be accessed separately. It includes tests for processing speed, working memory, episodic memory, attention, executive functions, visual spatial processing, verbal skill, and motor skill.[80] Neurotrax components have demonstrated validity and reliability in clinical studies and were more sensitive in detecting impaired executive function and prolonged response times than traditional batteries.[80,81] ANAM is a multicomponent battery developed by the US Department of Defense. It assesses information processing speed, motor response time and coordination, working memory, calculation ability, problem solving, visual reasoning, attention, and letter recognition.[77]

Figure 2. An iPad Air® with attachments used in the MSPT

The left panel shows the grid overlay in the kickstand position used for all modules except the manual dexterity test. The right panel shows aluminum pegs inserted into the grid overlay for the manual dexterity test. A Bluetooth remote is used for the walking test.[82] https://creativecommons.org/licenses/by-nc/4.0/

Table 3. Cognitive Assessment Tools for MS

Assessment	Cognitive Domains	Time (min)	Fee	Print Version	Computer-based Version
SDMT[3,23, 68, 69]	Processing speed	5	☑	☑	☑
NIH-TB Cognition[70]	Executive function, episodic memory, language, processing speed, working memory, attention	30	☑ low cost		☑
BICAMS[72,74]	Processing speed, verbal memory, visuospatial memory	15	☑	☑	☑
PASAT[75]	Attentional processing and information processing speed; calculation ability	5 (Version 3s)	☑	☑	
MACFIMS[2]	Processing speed, working memory, learning and memory, executive functioning, visuospatial processing, and word retrieval	90	☑	☑	
MSNQ[45]	Wide range of cognitive domains; depression	5	☑	☑	
MSPT Processing Speed Test[78]	Processing speed	5			☑
Neurotrax[80]	Processing speed, working memory, episodic memory, attention, executive functions, visual spatial processing, verbal skill, and motor skill	45	☑		☑
ANAM[77]	Information processing speed, motor response time and coordination, working memory, calculation ability, problem solving, visual reasoning, attention, and letter recognition	30	☑		☑

ANAM, Automated Neuropsychological Assessment Metrics; BICAMS, Brief International Cognitive Assessment for MS; MACFIMS, Minimal Assessment of Cognitive Function in MS; MSNQ, MS Neuropsychological Screening Questionnaire; MSPT, MS Performance Test; NIH-TB, National Institutes of Health Toolbox; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digits Modalities Test.

COGNITIVE ASSESSMENTS FOR REHABILITATION

Rehabilitation professionals, including occupational therapists (OTs), speech language pathologists (SLPs), rehabilitation psychologists, and neuropsychologists, play an important role in assessing patients' cognitive functioning in daily life. In addition to utilizing the assessment tools described above, they may also include performance-based assessments, depending on the patient's needs. For example, OTs evaluate and treat functional cognition, which encompasses assessment of everyday task performance (eg, self-care, household management, childcare, workplace tasks). Therefore, they specialize in identifying performance-based cognitive impairments. SLPs detect cognitive deficits based on how the individual communicates, interacts, and functions in all environments. There are no rehabilitation assessment batteries specific to, or validated in, the MS population.

REFERRAL FOR NEUROPSYCHOLOGY EVALUATION

Ideally, a neuropsychological evaluation will take place as early in the disease as possible, to establish a cognitive baseline for future comparison. During the course of the illness, a referral for a neuropsychological evaluation could be made for a variety of reasons, such as notable change in screening performance, to evaluate treatment benefit, or to inform treatment decisions.[3] A neuropsychological assessment is valuable for a variety of reasons. It can help determine whether cognitive problems arise from factors independent of MS. A thorough evaluation is also important for characterizing cognitive strengths and weaknesses/deficits for a person with MS-related cognitive impairment, which can be used to guide treatment. For instance, the report can help determine goals in cognitive rehabilitation.

Neuropsychological assessment frequently is required by academic environments and workplaces in order to allow a person to have accommodations as per the Americans with Disabilities Act (ADA) and the Accessible Canada Act (ACA). It is also often required by disability insurance companies and Social Security Disability Insurance for a person to be eligible to receive benefits for cognitive impairment.

Remote Assessment

Remote neuropsychological evaluations are an option for patients in rural areas, where a neuropsychologist may not be available, or in other conditions that make in-person neuropsychological assessment less feasible. It was used a great deal during the COVID-19 pandemic.

Although there are benefits, remote administration presents certain complications. People with reduced computer skills may have trouble using video conferencing or other interfaces. People with physical disabilities sometimes have difficulty using technology. There are also a multitude of things that can go wrong and invalidate the test administration, such as a signal drop. It may be difficult for the patient to see the stimuli or hear the examiner. Assessments involving physical props may not be able to be included.

Preliminary research suggests that there is adequate validity and reliability with respect to certain types of neuropsychology remote assessment in the general population.[83,84] In PwMS, recent studies found a high correspondence between SDMT and CVLT-II scores gathered through remote and in-person testing.[85-88] These assessments are 2 components of BICAMS. Additionally, PwMS and/or clinicians report equal satisfaction with in-person and remote evaluations.[89,90] The existing literature indicates that more research is needed.

DISCUSSION

SCREENING VERSUS ASSESSMENT

Jeffrey Wilken: We need to be clear that SDMT is not a measure of cognition. It's a screening tool that predicts cognitive functioning on a larger battery. I love that we actually have an easy test that the neurologist can use in the office, but I don't think everybody truly understands what it is.

Patty Bobryk: I agree with you 100%. All of these are screening tools and not a full neuropsychological battery. They are options to use in the clinic for monitoring over time.

Laura Hancock: We can't suggest to people that you just use one of these screening tools in your practice without educating yourself as to its limitations, benefits, how performance can be skewed by a practice effect, etc.

ASSESSMENT FREQUENCY

Sarah Morrow: Every 2 to 3 years, unless there is change, reduces the practice effect and the number of assessments. Annually doesn't provide more useful information.

Marie Moore: From my perspective in clinic, it's easier to track annually than going back through charts to find out how long has it been.

DISCUSSION OF INDIVIDUAL SCREENING TOOLS

SDMT

Marie Moore: We need to screen in the most efficient way possible. SDMT is a 90-second test. Unfortunately it's proprietary, which is limiting, although it's inexpensive. For clinicians that don't yet screen routinely, this is an easy place to start.

Ann Yeh: Very practical. I think that's great.

NIH Toolbox

Ann Yeh: The toolbox includes a number of validated cognitive tests with good psychometric properties. It includes the SDMT, the card sort test, and many others. Not everybody uses all the tools. There is a training procedure, with a lot of videos. If you are familiar with what it offers, you can use it for more than just screening. It can provide solid information on different aspects of cognition. If you choose the right tests, it is an inexpensive way to highlight impairment in specific cognitive domains or determine that a person should be referred to a neuropsychologist. One problem, however, is that it is really easy to just to buy it, put it on an iPad, and start using it without doing it in a rigorous manner.

Sarah Morrow: Anything else about that toolbox just since you've had more experience with it?

Ann Yeh: I personally think it's great. It also provides a lot of data, such as percentile ranking, ranking per age, or time lapse scale with previous testing.

Sarah Morrow: So if you're seeing worsening, it indicates something's changed. It may or may not be cognition, but it's a red flag that something's happening.

Jeffrey Wilken: And you pay NIH for the tests?

Ann Yeh: You can do it on the computer or pay NIH an annual fee for the iPad version. It's super convenient. And it's a nominal fee for the amount of work put into it – about $600-$700 a year.

Marie Moore: What is the total time that this takes? It says each domain battery "not to exceed 30 minutes."

Ann Yeh: Whatever you choose. You choose your battery.

BICAMS

Jeffrey Wilken: Many clinicians only use BICAMS for the CVLT and the BVMT-R.

PASAT

Patty Bobryk: Everybody leaves the clinic upset because they feel like they're such a failure at it. We have to consider the impact of that on the information we can glean from this. Certainly for someone who has low math ability, it is not an appropriate test for them.

Jeffrey Wilken: The impact of the practice effect can't be understated. It's worse than for other tests because there is a lot to get used to.

Sarah Morrow: And it has a ceiling effect. You can only get 60.

Laura Hancock: And we don't have norms.

Patty Bobryk: It's being used in research. Is anybody using it in clinic?

Sarah Morrow: I find it a good measure of cognitive fatigue, so I use it for that.

Jeffrey Wilken: I use it in neuropsych batteries when I have a very high functioning person. I want to see about anxiety and fatigue. I have seen a stark reduction in its use in clinical trials. The SDMT is used instead.

MACFIMS

Sarah Morrow: I think 90 minutes is an underestimate. If it's their first time, even for high functioning patients, it's up to 2 hours. And they recommend that you also test for mood and probably for sleep and anxiety and then suddenly the battery is so much bigger.

Patty Bobryk: And yet it's still not a full neuropsych battery test. A clinician isn't going to use this as a screening tool. There's just not enough time in a clinic session to perform a lengthy assessment.

Ann Yeh: You would need an ancillary psychologist or psychiatrist in your clinic.

MSNQ

Ann Yeh: We can't bring things to clinical practice that interfere too much with practice. Perhaps if families are willing to fill it out before people come in, then that includes the family without having to bring them in and does not take up clinic time.

Patty Bobryk: One of the values that I find is that it opens a discussion between the patient and the family about perception. I agree that these forms are something that can be done outside of the clinic. But again, when we talk about the vast number of forms that we might ask a patient to fill out – sleep questionnaire, Modified Fatigue Impact Scale – at some point we have to prioritize what we're giving the patient. And how often do we re-screen on these tools?

Ann Yeh: Agree. There's a high patient burden with these.

Jeffrey Wilken: It is important to note that this screens for perception, not cognition.

CogEval PST

Laura Hancock: It's amazing to see. Patients easily learn how to self-administer it. They put the bluetooth device in their pocket and they do the T25FW and the 9-Hole Peg Test (9HPT) and it's all administered by the iPad.

Marie Moore: We don't have iPads, and I can't foresee us buying them. We need assessments that have hard copies.

Laura Hancock: There are some hospital systems that worry about patient data on this portable device and keeping it secure, even though the network can be secure.

Ann Yeh: Paperless is the direction that the field is going, overall.

Computerized cognitive assessment batteries

Jeffrey Wilken: Neurotrax is useful in MS specialty practices, especially since the patient can complete it in a separate room without an investigator present. ANAM is another well-designed tool. It is a government program designed for the military, so it needs to be purchased from a government contractor.

TELEMEDICINE FOR NEUROPSYCHOLOGICAL EVALUATION

Ann Yeh: Clinical assessment involves context. We can't really understand where the patient is without them in the room.

Jeffrey Wilken: It is a reasonable approach when there's nothing else you can do. We needed to do that at the beginning of COVID. And it is good for somebody in a rural area who has no access to anything else.

Sarah Morrow: It's better than nothing, but it was based on everyone having in-person assessment first.

Laura Hancock: At the beginning of COVID, one of my clinics switched to complete tele-neuropsychology for everyone; there are both benefits and drawbacks. In my other clinics, we often did the clinical intake and the follow-up visit to discuss results via telemedicine, but the testing took place in person. That actually started pre-pandemic, and it's even more important now. It has been really helpful for people with disabilities. With the testing, you have to worry about test security, WiFi dropping, seeing stimuli longer than you're supposed to, and other issues like that. And you still can't do a fully comprehensive evaluation remotely because some tests involve manipulating physical objects.

Jeffrey Wilken: And we don't know for sure how well the tests transfer on a screen.

WHAT WE BELIEVE

- These are mostly screening tests rather than full batteries
  - MACFIMS is more comprehensive than the others, but does not replace a complete neuropsychology evaluation
- They should be administered to all PwMS
  - Early in disease course
  - At regular intervals
  - After any clinical changes or intervention
- SDMT is probably the best
  - NIH Toolbox is also a useful tool
- Allied health professionals—OT, PT, SLP—play an important role in assessing the patient's ability to perform daily tasks and the impact altered cognition may have on their execution
- Computer or tablet-based assessment can be valuable in clinical practice and is the direction of the future

WHAT WE SHOULD BE DOING

- Choosing an initial assessment at the time of diagnosis and doing serial testing to detect any change – SDMT is best suited for this
- Planning for future directions in cognitive assessments
  - Paperless
  - Telemedicine, which increases access and social equity, but has limitations
- Working in collaboration with allied health professionals such as OTs, PTs, and SLPs
- Avoiding the use of assessments that are inappropriate for MS, such as Montreal Cognitive Assessment (MoCA), Mini Mental State Examination (MMSE), or Saint Louis University Mental Status (SLUMS). (These may be used to screen for a suspected dual diagnosis.)

STRATEGIES AND INTERVENTIONS TO MANAGE IMPAIRMENT

WHAT WE KNOW

RESERVE

Reserve is the difference between the actual and expected disability for a given level of disease burden.[91] Those with more severe disease burden (eg, lesion load, cerebral atrophy) are at increased risk for cognitive impairment, yet correlations between disease burden and cognitive status are relatively modest; many patients with considerable disease burden are not cognitively impaired.[22]

There are 2 hypotheses for the source of this reserve in some PwMS – brain reserve and cognitive reserve. Brain reserve refers to the reserve that results from larger brain size. Patients with larger maximal lifetime brain volume (MLBV), as estimated by intracranial volume, have less cognitive decline relative to disease burden.[91,92] According to the cognitive reserve hypothesis, lifetime intellectual enrichment can also create reserve. This has been confirmed by studying the link between vocabulary and cognitive efficiency over 4.5 years.[92] Vocabulary is used as a metric for lifetime intellectual enrichment because it reflects enriching life activities, such as education, occupation, and reading.

How can this theory of reserve be applied in clinical practice? While brain size and previous intellectual enrichment cannot be changed, in children and younger populations, one can support the introduction of intellectually enriching activities and other beneficial lifestyle factors. Moreover, helping younger individuals develop lifestyle habits that may benefit their outcomes may result in substantial long-term benefits. In all populations, certain "brain maintenance" activities have been identified that may help slow the decline of whatever baseline reserve the patient has.[93] Modifiable factors include DMT, a mentally active lifestyle, management of comorbidities and cardiovascular risk factors, physical activity/exercise, smoking cessation, stress management, nutrition, and sleep.[93,94]

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Clinical data link these factors to disease progression and MRI findings in MS. There are, however, little data available from controlled trials, or trials focused on cognition. More information is needed to better understand mechanisms of action of modifiable factors. Despite the need for further study, currently available data support modifying these risk factors, to the extent possible, to help maintain cognitive reserve in PwMS.[93,94]

Disease-modifying therapy

Disease progression is the most influential factor in depleting reserve. The ability of treatment with DMTs early in the disease course to slow or minimize disease progression is well established; this effectively preserves the neurological reserve. A meta-analysis of 13 RCTs, representing >13,500 patients with RRMS, found that treatment effects on disability progression were correlated with treatment effects both on brain atrophy and active MRI lesions, both in univariate and multivariate analysis.[95]

Mentally active lifestyle

Studies have found that PwMS who engaged in early life cognitive leisure activities, such as reading, writing, producing art, playing music or board games, engaging in hobbies, exhibited better current cognitive status and were able to withstand more severe brain atrophy before/without suffering cognitive impairment.[22,96] Findings were independent of MLBG (maximal lifetime brain growth) and education. One of these studies found that of these cognitive leisure activities in early life, reading and writing predicted normalized hippocampal volume when later diagnosed with MS.

Management of comorbidities and cardiovascular risk factors

The presence of multiple comorbidities or cardiovascular risk factors is associated with an increase in disease progression, lesion burden, and brain atrophy.[93,97] A prospective multicenter cohort study of Canadian MS clinics found that increased relapse rate in RRMS is associated the presence of ≥3 comorbidities, migraine, or hyperlipidemia.[97] Cardiovascular risk factors are also strongly linked to disease progression or brain lesions or atrophy. Even without MS, cardiovascular disease is associated with brain structural abnormalities. In PwMS, one or more cardiovascular risk factors (eg, heart disease, hypertension, smoking, obesity, diabetes) confers increased lesion burden and more advanced brain atrophy.[93] A retrospective analysis from the North American Research Committee (NARCOMS) registry found that those with >1 vascular comorbidity at the time of MS diagnosis had increased risk of ambulatory difficulty. Cholesterol levels also correlate with MRI findings. Elevated total cholesterol is associated with both worsened disability and decreased brain parenchymal fraction, whereas higher high-density lipoprotein cholesterol levels are associated with lower contrast-enhancing lesion volume.[93]

Nutrition

Preliminary data suggest that certain foods correlate with brain health in PwMS. In a longitudinal cohort study of 185 patients with relapsing MS or CIS, participants completed a

detailed food frequency questionnaire.[98] Those whose diets included more of 10 "brain healthy" food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine) had significantly higher thalamic volumes than those who ate less of these foods. Specifically, vegetables (not including green leafy vegetables) were marginally associated with higher thalamic volumes. In contrast, a higher intake of full fat dairy was associated with lower T2 volumes.[98]

Exercise and physical activity

Observational studies have demonstrated associations between brain volumes and fitness or physical activity level in both adults and children with MS. One study found an association between improved cardiovascular fitness and preservation of gray matter volume, as well as preservation of white matter integrity. Preserved gray matter volume and white matter integrity were both associated with better performance on measures of processing speed.[99] In children with MS, strenuous exercise was associated with smaller T2 lesions and lower annualized relapse rates than low activity levels.[100]

Clinical trials have also identified cognitive benefits of exercise in PwMS. In one 24-week RCT, exercise 3x/week was significantly associated with improved processing speed, as well as improved measures of mobility and physical fitness. The exercise group received trainer-led sessions of aerobic, resistance, and balance exercises, whereas the control group participated in stretching and toning.[101] A separate 24-week RCT of aerobic and resistance training 3x/week found that exercise was associated with greater improvement in processing speed, balance, fatigue, and ambulation than the control group, which did not have formal exercise.[102] Furthermore, these benefits persisted during a 24-week wash-out period, suggesting that physical activity has long lasting effects if performed regularly over an extended period of time.

A meta-analysis of 26 studies on the effects of exercise, physical activity, and physical fitness on cognition in persons with MS found conflicting evidence. The impact of exercise and physical activity was positive overall, but there was insufficient well-designed research to definitively conclude that exercise, physical activity, and physical fitness are effective for improving cognition in MS.[103] Of the 26 studies, there was only 1 Class I study, 3 Class II studies, and 6 RCTs. Furthermore, the Class I and II studies had important methodological issues, such as poorly developed exercise interventions or paucity of cognitively-impaired patients.

MEDICATION

Medications for dementia do not help with MS-related cognitive and memory decline. One early study of cholinesterase inhibitors was positive.[104] These findings, however, could not be replicated, and long-term studies show no efficacy for these medications.[105]

Stimulants and other medications for fatigue may be helpful with respect to "mental fatigue" and attention problems in MS, but the results are mixed. Several small studies, with limited data, suggest a benefit for amphetamines[106,107] and methylphenidate.[108,109] Other studies found no benefit of either amphetamine[110] or methylphenidate,[111] relative to placebo. The cognitive benefits may occur indirectly, through their effect on mental fatigue. There is, however, a risk of cardiac and other side effects. Therefore, caution is urged against indiscriminate use of these medications for this purpose.

REHABILITATION

Cognitive rehabilitation is the use of behavioral treatments designed to improve cognitive function and activities of daily living (ADLs). There are 2 categories of cognitive rehabilitation. Restorative cognitive rehabilitation (or cognitive remediation) aims to reinforce, strengthen and reinstate cognitive skills, usually through repetitive exercise, which is frequently computer-based **(Table 4)**. Compensatory cognitive rehabilitation aims to develop strategies to compensate for cognitive impairments. These strategies may be internal (eg, visualization) or external (eg, reminders). Both types of interventions have been studied in MS, targeting individual or multiple cognitive domains.[112] A 2018 meta-analysis and systematic review of the literature on the use of restorative cognitive rehabilitation programs found that most studies provide Class II or III levels of evidence and contain important methodological limitations.[113] Overall, a number of controlled trials showed benefits, with no adverse effects, suggesting that restorative cognitive rehabilitation is an option in clinical practice, for maintaining performance in the areas of attention, learning and memory, and metacognition in PwMS. Further research, however, is necessary to establish cognitive rehabilitation as a practice standard.[113]

Preliminary data show that cognitive rehabilitation may also be a suitable intervention for pediatric MS; in a 3-month pilot study, use of an attention-focused program was associated with improved overall cognitive impairment scores, compared with those who performed non-targeted tasks.[114]

Table 4. Commonly Used Cognitive Rehabilitation Programs			
Program	**Content**	**Controlled-Trial Results**	**Control**
Attention Processing Training[115]	Tasks require focused attention in the presence of distracting stimuli	Significantly improved PASAT scores up to 3 months after training	Nonspecific computerized training
Brain HQ[116,117]	Gamefied program aimed at multiple cognitive domains	Significantly improved composite cognitive scores relative to controls, but results were modest and no significant differences in any individual measure	Nonspecific computer games
COGNI-TRAcK[118]	3 different cognitive tasks, assessing multiple cognitive domains	Significantly improved learning and memory, verbal fluency, attention, concentration, processing speed, and long-term retention (6 months post)	Constant difficulty (in contrast to study group, who received adaptive levels of difficulty)
Kessler Foundation modified Story Memory Technique[119]	Develop a story incorporating items to be remembered and visual imagery	Significantly improved memory, as measured by CVLT learning curve, maintained for 6 months. Associated with fMRI changes in frontal, parietal, precuneus, and parahippocampal regions	Therapist-led sessions
RehaCom[120,121]	Gamefied versions of cognitive tasks, with >30 modules	Significant improvement in attention, response control, processing speed, working memory, visuospatial skills, and verbal/non-verbal executive functions. Improvements in attention were associated with increased activity in the posterior and superior parietal lobes	Nonspecific computerized training

CVLT, California Verbal Learning Test; fMRI, Functional magnetic resonance imaging; PASAT, Paced Auditory Serial Addition Test.

DISCUSSION

COGNITIVE RESERVE

Laura Hancock: The literature hasn't given us the clear results that say, yes, absolutely. It's possible to address cognitive reserve in clinical practice and it's worth doing. I don't know about the pediatric literature though.

Ann Yeh: I think it's the same. The studies aren't long enough. It takes 2 years to see a difference. Short-term studies mostly measure practice effects.

Jeffrey Wilken: We're not even necessarily using the right subjects.

Ann Yeh: And maybe our testing modalities are not sensitive enough.

Sarah Morrow: And then there are other confounding factors. They're going to school, having other experiences, and perhaps creating more networks.

COMORBIDITIES

Sarah Morrow: Cardiovascular comorbidities are often not well managed in PwMS. This actually gives them a worse quality of life overall. When talking about cognition, we have to consider comorbidities that affect quality of life.

NUTRITION

Sarah Morrow: It would be nice to have a tool for helping PwMS make dietary modifications.

Jeffrey Wilken: People get discouraged and they don't even start it.

Sarah Morrow: Fresh food is expensive.

Marie Moore: I use Michael Pollan's advice: "Eat [real] food,

Discussing the Concept of Cognitive Reserve With Patients

You have to be careful how you present this to patients. It could almost sound like you're saying if you didn't start smart, there is no hope.

You can't always predict exactly how a person's cognitive reserve will affect future cognitive weaknesses.

But patients want to know "What can I do?" I ask them "What do you do with your brain that you enjoy doing? Keep doing that. That's great."

I actually tell my patients to not just do the things they like and that they're good at. I tell them to try different things. "If you're not good at this, don't do it all the time. But you need to do things you're not good at, too."

mostly plants, not too much." It's important to make it simple and accessible. It is a place to start.

EXERCISE/PHYSICAL ACTIVITY

Ann Yeh: Instinctively, we know that there are benefits to exercise. The problem is that the parameters are so variable in studies and maybe not controlled as well as they could be, so the results are heterogeneous.

There is a lot to learn from animal models and the effect of exercise on the hippocampus, and some of the basic science related to pathways that are likely involved in neuroprotection and neuroregeneration. We also need to talk about what we should be testing. It should be memory, right? Maybe we're not testing the right things, or we're not testing people that are impaired enough to show a difference, and we're not doing it for long enough.

Sarah Morrow: Exercise may have mixed results, but earlier we talked about the negative impact of comorbidities, and exercise is good for all those comorbidities. It's good for cardiovascular health, it's good for sleep, it's good for mood. And on top of that, it will probably help their MS health in so many ways.

Ann Yeh: There's no reason not to recommend it.

Jeffrey Wilken: So many of these studies have significant design flaws. It almost makes sense that some of the studies will say exercise doesn't help.

Patty Bobryk: I think the methodological issues are the crux of it.

Jeffrey Wilken: There's work in dementia showing that a mile walk a day can help.

Patty Bobryk: There is research looking at biomarkers and the anti-inflammatory effects of exercise. But it doesn't go a step further to say, what impact does that have on cognition? What does that mean in the big picture? There's a lot more work to be done.

Patty Bobryk: With patients, we might use the term physical activity rather than exercise. Exercise sounds like you're going to the gym, and physical activity can be gardening or dancing or whatever they enjoy.

Laura Hancock: I encourage patients to redefine the word exercise. It empowers them to do things differently.

Marie Moore: You don't have to do it for an hour, you can do it in 5-minute bites—5 minutes here, 5 minutes there.

Jeffrey Wilken: If you're in a wheelchair, maybe you can use little weights. The treatment team certainly can help people with physical limitations design an appropriate exercise regimen.

Ann Yeh: Scientifically, it's moderate to vigorous activity that makes a difference. But people have to build up to that point.

Laura Hancock: Walking around the block is a gateway to being able to do more.

CLINICAL PEARL

For lifestyle changes, such as nutrition and exercise, it is most effective for PwMS to make gradual changes, of their choosing, in order to promote lasting change.

MEDICATION

Jeffrey Wilken: I believe stimulants work for a lot of people. It depends on who the person is and what the actual problem is, so neuropsychological testing could potentially help. Do they truly have an attention problem or is it truly a fatigue problem or is it something else? If it's anxiety, you don't want to prescribe a stimulant. But many of my patients come in and tell me that they benefit. If they don't, then switching to another drug might help.

Sarah Morrow: We're treating their fatigue, and we know fatigue makes MS, cognition, everything worse. You're keeping people employed and improving their quality of life.

Jeffrey Wilken: And stimulants help with mood.

Ann Yeh: It's true in the pediatric world. Secondary effects of ADHD are anxiety and depression.

Jeffrey Wilken: In clinical trials, you have to really choose your subjects the right way and choose the right outcome measures. Anecdotally, we're seeing people functioning better—staying at work or school or functioning better at home.

Sarah Morrow: In Canada we're doing a larger placebo-controlled trial of extended-release amphetamine/dextroamphetamine salts, using 10- and 20-mg doses for cognition in MS. It should be completed in 6 months. That should provide more information.

Ann Yeh: This brings up the issue of personalized medicine. One of the problems with the trial designs of most of the things that we're discussing is that there is variability in people's deficits. You need to pay attention to specific deficits and have a personalized approach.

"You need to pay attention to specific deficits and have a personalized approach."

COGNITIVE REHABILITATION

Patty Bobryk: I worked in a large rehab center and we didn't have access to the computerized tools for cognitive rehab. Cognitive rehab specialists aren't necessarily available for PwMS. We have evidence of benefits, but are clinics

actually administering treatment or facilitating access to these computerized programs?

Laura Hancock: At Johns Hopkins there are several rehabilitation psychologists who do evaluation and treatment, but that's a unique model and it may need to be financially supported by the hospital.

Jeffrey Wilken: We work with a rehab center and direct patients there. I think they're doing more compensatory strategies than restorative. I think RehaCom is something that we could potentially use if they have a little bit more research behind it.

Laura Hancock: We have neurorehabilitation at our hospital, so we refer people there, but they have a wait list. In the meantime, I recommend Brain HQ because patients like it. I think it is $14/month or $96/year. You can do it on a tablet or computer. And there's likely some benefit to self-efficacy, too. People want to feel like they can take control of something.

Jeffrey Wilken: That's much easier than RehaCom, which works best if you have a special attachment for a computer.

Ann Yeh: It's great that we can recommend certain things that are low cost, easy to access, with some evidence for benefit. We did a small pilot study and found that cognitive rehab is a huge burden on the patient because of the amount of time required.

Laura Hancock: Yes, not all patients will have the time to devote to cognitive rehabilitation, whether it's delivered by a computer or in-person.

Ann Yeh: Gamifying the programs makes it less burdensome and more fun. RehaCom is kind of a game. Brain HQ is a game.

Jeffrey Wilken: They're trying to make them more fun. I just don't think it's there yet. RehaCom is as fun as I've seen them, but it's still a little challenging at times.

Laura Hancock: I think Brain HQ is reasonably fun.

Patty Bobryk: There was a higher utilization of those two than traditional cognitive rehab programs.

Jeffrey Wilken: The question I have is, if you use the apps repeatedly and get better at Brain HQ or RehaCom, what does it mean for your daily life? There are some studies that say it correlates with doing better at work, doing better in other areas, but I just don't think we know enough about that yet. You can't just focus on the restorative and leave out the compensatory strategies. Compensatory strategies can help in daily life.

Patty Bobryk: Traditional rehab specialists like PT, OT, and SLP will target restorative techniques but are usually compensatory-based. It may have to do with the length of time we are able to follow them in rehab. We need to provide them with strategies to restore function, if possible, but that is a much longer process. More often, we have to focus on ways to manage their issues most expeditiously and that is usually compensatory approaches.

Jeffrey Wilken: A lot of imaging studies show that computer-based restorative rehab results in changes in neural networks. They're doing something.

Ann Yeh: A colleague has developed something called HippoCamera. People make these videos to help them remember specific events. Then they are tested on them in a fun way. It was designed to improve episodic memory, but it improved their everyday social lives and their confidence, as well. This kind of organic approach can have a bigger social impact on people. I think that's a direction we should go in the future, targeting functional, rather than specific pathways.

Laura Hancock: I sometimes tell patients: it's not going to hurt you. If something's too frustrating, then turn it down a notch or try something different, but the worst thing that could happen is they spent money on it and didn't enjoy it.

Patty Bobryk: I couldn't find any studies on preventive use of these tools in newly diagnosed patients without cognitive impairment.

Ann Yeh: That would be a difficult study to do because of the slow rate of brain atrophy, and the confounding factor of highly efficacious therapy. It's an impossibly hard question to answer.

WHAT WE BELIEVE

- Lifestyle matters
  - Evidence supports the benefit of certain lifestyle changes on cognition in MS, including sleep, nutrition, managing comorbidities
  - For some interventions, such as cognitive rehab, the data are stronger for dementia, but might also be valid in PwMS
- DMTs probably help preserve cognitive reserve, although they may act indirectly
- Exercise is likely beneficial
  - Inconsistent study designs make it difficult to translate research to clinical practice

WHAT WE SHOULD BE DOING

- Encouraging behavioral change
  - Coaching—goal-setting; promoting social support; increasing self-efficacy through success
  - Encouraging patients to focus on incremental change, one step at a time
  - Using repetition and reinforcement
  - Developing ways to encourage and increase physical activity of any kind
    - > Redefine "exercise" for MS patients
  - Empowering patients to do things differently

- Managing overall health and comorbidities

- Referring to other specialists
  - Psychologists to support health-related behavior change
  - Refer to other rehab professionals, such as PT, OT, and SLP, to support goals

KEY TAKE-AWAYS AND RECOMMENDATIONS

- To properly treat, we need to properly evaluate patients
  - Early identification and early intervention are critical
  - Use assessment tools that are easy to implement in clinical practice
    - SDMT most highly recommended
  - Monitor for change at regular intervals and after any clinical changes or interventions
- Encourage lifestyle changes for prevention and treatment, including exercise, nutrition, sleep, and management of comorbidities
  - Provide support for patient-driven plan
  - Set achievable goals and take small steps
  - Involve family support early and frequently
    - Increase their awareness of invisible symptoms and manage expectations
- Refer to other specialists to facilitate interdisciplinary care—eg, neuropsychologists, PTs, OTs, and SLPs
- Advocate to reduce barriers to evaluation and treatment, such as
  - Lack of awareness
  - Financial cutbacks in health care in every area
  - Lack of access to necessary resources
  - Insufficient medical education for physicians early in medical training
  - Inadequate numbers of adequately trained clinicians to perform comprehensive cognitive evaluations and rehabilitation therapy
  - Inadequate treatment options
- Educate patients and families about community resources and support

RESOURCES

GUIDELINES

MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis

Card (can be faxed to imaging center)
https://mscare.sharefile.com/share/view/s16fa7f9d0c214c1cb5bd8f809ac07215

Clinician manual
https://mscare.sharefile.com/share/view/saf504881dcad41afb6c1810db720e78a

A comprehensive literature review of interventions for cognitive impairment in PwMS: KITE | MSBEST: Modules (kite-uhn.com)

PATIENT AND FAMILY SUPPORT

Can Do MS: https://cando-ms.org/

National MS Society: https://www.nationalmssociety.org/

MS Brain Health provides materials for both health care providers and patients to disseminate information and implement recommendations in their report "Brain health: time matters in MS": https://www.msbrainhealth.org/information

ASSESSMENTS

Automated Neuropsychological Assessment Metrics (ANAM): https://vistalifesciences.com/anam-intro

Brief International Cognitive Assessment for MS (BICAMS): bicams.net

CogEval processing speed test (PST): https://apps.apple.com/us/app/cogeval/id1366437045

Minimal Assessment of Cognitive Function in MS (MACFIMS): https://pubmed.ncbi.nlm.nih.gov/12607150/

MS Neuro-psychological Screening Questionnaire (MSNQ): https://pubmed.ncbi.nlm.nih.gov/17503124/Neurotrax: https://www.neurotrax.com/National Institutes of Health Toolbox (NIH-TB): https://www.nihtoolbox.org/

Paced Auditory Serial Addition Test (PASAT): http://www.pasat.us/

Symbol Digit Modalities Test (SDMT): https://www.wpspublish.com/sdmt-symbol-digit-modalities-test

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