

# Recommendations for cognitive screening and management in multiple sclerosis care

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## Abstract

**Purpose:** To promote understanding of cognitive impairment in multiple sclerosis (MS), recommend optimal screening, monitoring, and treatment strategies, and address barriers to optimal management.

**Methods:** The National MS Society (“Society”) convened experts in cognitive dysfunction (clinicians, researchers, and lay people with MS) to review the published literature, reach consensus on optimal strategies for screening, monitoring, and treating cognitive changes, and propose strategies to address barriers to optimal care.

**Recommendations:** Based on current evidence, the Society makes the following recommendations, endorsed by the Consortium of Multiple Sclerosis Centers and the International Multiple Sclerosis Cognition Society:

- Increased professional and patient awareness/education about the prevalence, impact, and appropriate management of cognitive symptoms.
- *For adults and children (8+ years of age)* with clinical or magnetic resonance imaging (MRI) evidence of neurologic damage consistent with MS:
  - *As a minimum*, early baseline screening with the Symbol Digit Modalities Test (SDMT) or similarly validated test, *when the patient is clinically stable*;
  - Annual re-assessment *with the same instrument*, or more often as needed to (1) detect acute disease activity; (2) assess for treatment effects (e.g. starting/changing a disease-modifying therapy) or for relapse recovery; (3) evaluate progression of cognitive impairment; and/or (4) screen for new-onset cognitive problems.
- *For adults (18+ years)*: more comprehensive assessment for anyone who tests positive on initial cognitive screening or demonstrates significant cognitive decline, especially if there are concerns about comorbidities or the individual is applying for disability due to cognitive impairment.
- *For children (<18years)*: neuropsychological evaluation for any unexplained change in school functioning (academic or behavioral).
- Remedial interventions/accommodations for adults and children to improve functioning at home, work, or school.

**Keywords:** Multiple sclerosis, cognition, screening, treatment, rehabilitation, remediation, cognitive dysfunction

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## Introduction

Despite all that is known about cognitive impairment in multiple sclerosis (MS) and its impact on individuals with MS and their families, cognitive function is still not openly discussed, routinely assessed, or optimally treated.<sup>1</sup> Ample evidence supports early

and ongoing cognitive assessment and personalized treatment. However, significant barriers stand in the way of individuals with MS and their family members being able to access the care they need in this clinical domain.

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The aims of this paper—which was developed by a multidisciplinary group of clinicians, researchers and people with MS chosen by the National Medical Advisory Committee of the National Multiple Sclerosis Society—are to:

- Promote awareness of, and attention to, cognitive impairment—a common and highly disabling symptom of the disease;
- Describe optimal screening, evaluation, and management of cognitive impairment as supported by the published literature;
- Identify and address barriers that prevent people from getting the cognitive care they need;
- Support the inclusion of cognition as a key component of comprehensive MS care and of lay and professional educational materials.

### Recommendations to address the problem

Only by establishing high standards for the assessment and treatment of cognitive dysfunction is it possible to bring treatment of cognitive dysfunction up to the standards set in other areas of MS care and ensure that people with MS and their families receive adequate care in this critical domain. With this goal in mind, the National Multiple Sclerosis Society recommends the following (See Table 1).

### Background

#### *Etiology and prevalence of cognitive dysfunction*

MS is characterized by inflammatory demyelination and neurodegeneration resulting in damage to both white and gray matter in the central nervous system (CNS). This CNS damage leads to a wide range of symptoms, including changes in cognitive functioning.<sup>5–7</sup>

Cognitive change is common in adults and children with MS. Depending on the sample studied (community vs clinic) and the criteria applied, the prevalence in adults ranges from 34% to 65%<sup>8–10</sup> and is approximately 33% in patients under 18 years of age.<sup>11,12</sup>

Cognitive impairment occurs in all MS phenotypes,<sup>13–15</sup> including clinically isolated syndrome (CIS),<sup>16,17</sup> and has also been demonstrated in radiologically isolated syndrome (RIS).<sup>18</sup> In fact, cognitive impairment appears to predate the appearance of structural abnormalities on magnetic resonance imaging (MRI) and may serve as an early marker of disease activity.<sup>16,19</sup> In a prospective study of cognitive performance prior to the first clinical symptoms of

MS, Cortese et al.<sup>20</sup> found that men in the Norwegian Conscript Service database who later developed MS demonstrated significantly lower intelligent quotient scores than male controls, and those who developed primary progressive MS (PPMS) scored significantly lower than controls up to 20 years prior to their first progressive MS symptoms.

Progressive decline in cognitive functioning has been documented in some, but not all, longitudinal studies over short durations (1–3 years),<sup>21</sup> and while controlled studies are lacking, there is strong consensus that cognition declines in patients over longer (10–20 years) periods of time.<sup>22,23</sup> Overall, the prevalence and severity of cognitive impairment appears greatest in secondary progressive MS (SPMS) and PPMS patients.<sup>13,24</sup> In a 10-year follow-up of cognitive functioning in patients with MS, degree of physical disability, progressive disease course, and increasing age predicted the extent of cognitive decline, and limitations in a person's work and social activities were correlated with degree of cognitive decline independent of the person's level of physical disability.<sup>22</sup> However, not all individuals with MS experience cognitive impairment and not all of those with impairment progress significantly. Adults with early cognitive impairment tend to show greater decline.<sup>22,25,26</sup> MRI predictors of cognitive outcomes over 7 years included diffuse brain damage and progressive central brain atrophy during the first 2 years after diagnosis.<sup>27</sup>

Some, but not all, longitudinal studies of cognition in pediatric MS demonstrate worsening over time.<sup>11</sup> Younger age at onset may be a risk factor for pediatric MS-associated cognitive problems.

#### *Cognitive symptoms and their impact on functioning and quality of life*

Information processing and memory are the most commonly affected cognitive domains in MS.<sup>2,5</sup> Other cognitive symptoms include deficits in complex attention, executive functioning, verbal fluency, visuospatial perception<sup>5,10,28</sup> and social cognition.<sup>29,30</sup>

Slowed information processing speed is the hallmark cognitive deficit in MS,<sup>2,5,24,31,32</sup> with processing deficits found in newly diagnosed relapsing-remitting (RRMS) patients,<sup>32</sup> as well as CIS<sup>16,18</sup> and RIS.<sup>18</sup> Processing speed is a foundation for higher-level cognitive processes—which means that slowed processing impacts downstream domains.<sup>31</sup> For example, significant variance in new learning can be attributed to processing speed.<sup>33</sup> Similarly, in one study, after

**Table 1.** Recommendations for education, assessment, treatment, and access.

Education and awareness
<ul style="list-style-type: none"> <li>• Individuals diagnosed with MS and their family members need information about common cognitive changes and their impact on activities, participation, and relationships.</li> <li>• Clinicians who treat people with MS need information about common cognitive changes and their impact on daily activities, medical decision-making, and adherence.</li> <li>• Clinicians need information about referral resources in the community for assessment and treatment.</li> <li>• Patients and their providers need to be aware of the high prevalence of cognitive symptoms, the importance of discussing cognition on a routine basis, and the need for early and ongoing assessment to identify and address problems.</li> </ul>
Assessment and management
<ul style="list-style-type: none"> <li>• <i>Baseline cognitive screening with the Symbol Digit Modalities Test (SDMT)</i><sup>2</sup> or other validated screening tool (Table 3), <i>as a minimum</i>, is recommended as an integral component of disease monitoring: <ul style="list-style-type: none"> <li>○ For all adults and children 8 years or older diagnosed with MS;</li> <li>○ For those adults who have experienced a first clinical event or have evidence on magnetic resonance imaging (MRI) of asymptomatic white matter lesions that are consistent with MS (radiologically isolated syndrome), or evidence of early gray matter damage;</li> <li>○ For any patient who reports changes in cognitive functioning at home or work, poor performance reviews, or whose family members or care providers express concern, whether or not the individual has screened positive on the SDMT or other validated measure.</li> </ul> </li> <li>• Annual re-assessment <i>with the same instrument</i>, or more often as needed, is recommended for all adults and children 8 years or older with MS.</li> <li>• <i>Depression screening at least yearly</i> with the Beck Depression Inventory—Fast Screen<sup>3</sup> or the Hospital Anxiety and Depression Scale<sup>4</sup> for adults, or an age-appropriate screening tool for children, is recommended to identify mood changes that may be impacting cognition.</li> <li>• Routine monitoring is recommended for academic and behavioral changes for all children.</li> <li>• A more comprehensive neuropsychological assessment (including assessment of mood) is recommended: <ul style="list-style-type: none"> <li>○ For any adult who initially screens positive for cognitive deficits or whose yearly screening demonstrates a clinically significant drop in functioning from a previous assessment. Clinical significance can be assessed in a variety of ways, for example, a 4-point change or reduction of 10% on SDMT, or change in 0.5 standard deviations, or using Reliable Change Indices.<sup>2</sup></li> <li>○ For any adult, with or without a positive screen, who reports problems at work or poor performance reviews;</li> <li>○ For any child under age 18 years whose academic or behavioral functioning declines significantly for unexplained reasons, in collaboration with the school;</li> <li>○ For any individual who is applying for private disability, Social Security Disability Insurance (SSDI), or Supplemental Security Income (SSI) because of cognitive problems, whether or not she or he has screened positive on the SDMT or other validated measure;</li> <li>○ For any individual who wants or needs cognitive remediation, including compensatory tools and strategies to help manage existing deficits.</li> </ul> </li> <li>• <i>Remedial interventions</i> by appropriately trained professionals are recommended to address objectively-measured deficits in attention, processing speed, memory and learning, and performance of everyday functional tasks.</li> </ul>
Access
<ul style="list-style-type: none"> <li>• Access to adequate screening, assessment, and remediation is essential due to the prevalence of cognitive deficits in the MS population—even in the earliest stages of the disease—and their impact on employment, activities of daily living, relationships, and communication.</li> <li>• Steps are required to obviate barriers to adequate diagnosis and management of cognitive deficits, including: <ul style="list-style-type: none"> <li>○ Insufficient knowledge about MS-related cognitive dysfunction on the part of people with MS, family members, healthcare providers or school personnel;</li> <li>○ Stigma associated with cognitive changes;</li> <li>○ Insufficient numbers of adequately trained clinicians to offer screening, assessment or remediation;</li> <li>○ Insufficient financial resources.</li> </ul> </li> </ul>
MS: multiple sclerosis.

**Table 2.** Impact of cognitive deficits on daily functioning and quality of life.

Work, school, activity participation, coping, and quality of life
<ul style="list-style-type: none"> <li>• Cognitive impairment predicts limitations in the workplace and in social settings independent of level of physical disability.<sup>36–39</sup> <ul style="list-style-type: none"> <li>○ Cognitive impairment at diagnosis predicts a change in vocational status seven years later.<sup>40</sup></li> <li>○ In patients with SPMS, corpus callosum atrophy (correlated with cognitive flexibility, processing speed, reaction time and verbal fluency) predicts clinically meaningful cognitive decline and change in vocational status.<sup>41</sup></li> </ul> </li> <li>• People who are cognitively impaired are more likely to be unemployed and to score lower on measures of quality of life.<sup>39,42</sup></li> <li>• Cognitive impairment is related to work problems such as verbal reprimands and the need for extra training in employed MS patients, representing an at-risk condition prior to job loss.<sup>43,44</sup></li> <li>• Slowed information processing is associated with lower income, independent of physical dysfunction.<sup>37</sup></li> <li>• Compared to healthy controls, people with MS perform more poorly on everyday life tasks (e.g. Internet use), as predicted by their performance on cognitive screening tasks.<sup>45</sup></li> <li>• Cognitive impairment in children and teens is associated with lack of age-appropriate cognitive development<sup>46</sup> and academic difficulties, including grade retention, social challenges, depression, and behavior problems.<sup>26,47,48</sup></li> </ul>
Driving
<ul style="list-style-type: none"> <li>• Thalamic brain atrophy predicts number of motor vehicle violations among people with MS compared to healthy controls.<sup>49</sup></li> <li>• Slowed processing speed and impaired visual–spatial memory impair driving ability and safety.<sup>38</sup></li> <li>• Compared with unimpaired MS patients and healthy controls, cognitively impaired MS patients with mild physical disability perform less well on some tests of driving functions<sup>50</sup> and are at higher risk of an accident.<sup>51</sup></li> </ul>
Medical decision-making and adherence
<ul style="list-style-type: none"> <li>• Progressive MS patients with deficits in verbal learning, memory, and verbal fluency perform less well on appreciation, reasoning, and understanding consent standards, suggesting that these individuals are less able to make informed decisions about their treatment.<sup>52</sup></li> <li>• Cognitive deficits are associated with poor adherence to treatments.<sup>53</sup></li> </ul>
Money management
<ul style="list-style-type: none"> <li>• Compared with healthy controls and cognitively intact MS patients, cognitively impaired people with MS have significantly reduced money management skills.<sup>54,55</sup></li> </ul>
Impact on caregivers
<ul style="list-style-type: none"> <li>• Caregivers of people with MS experience high levels of distress and a reduced quality of life related to their partners' cognitive impairment and psychiatric symptoms, beyond that related to their physical symptoms.<sup>56</sup></li> <li>• Slowed information processing speed in individuals with MS is independently associated with more severe depressive symptoms and reduced quality of life in their family caregivers.<sup>57</sup></li> <li>• Caregiver challenges associated with cognitive dysfunction, bowel and bladder dysfunction, and impaired mobility may predict nursing home placement for people with MS.<sup>58</sup></li> </ul>
SPMS: secondary progressive MS; MS: multiple sclerosis.

controlling for processing speed, there are no differences between healthy controls and people with MS in executive functioning.<sup>34</sup> And, cognitive speed is the primary factor impacting daily activities and participation in everyday life.<sup>35</sup>

However, like all symptoms of MS, cognitive impairment is highly variable in severity and progression. Some patients may not decline or decline slowly, while others may experience significant decline. Some changes may be relatively mild and easily compensated for, while others may impact functioning in key

areas of daily life, including work, driving, or management of business affairs. Table 2 highlights the potential impact of cognitive deficits on daily functioning and quality of life—demonstrating the need to screen for deficits, assess their severity, and remediate cognitive challenges that impair functioning.

*Establishing a standard of care for cognitive dysfunction in MS*

Appropriate management of cognitive dysfunction in MS includes education for people with MS and their

**Table 3.** Validated screening and evaluation tools used in MS.

Screening and monitoring
<p><i>Screening tools validated in MS populations</i></p> <p><i>The Symbol Digit Modalities Test (SDMT; 5 minutes)<sup>2</sup> (proprietary with associated fees)</i> is included in the Brief Repeatable Neuropsychological Battery (BRNB)<sup>10</sup> and Minimal Assessment of Cognitive Function in MS (MACFIMS)<sup>62</sup> to assess cognitive processing speed.</p> <ul style="list-style-type: none"> <li>• Recommended as the best rapid assessment tool in clinical practice with adults<sup>2,63–71</sup></li> <li>• Validated in children 8+ years;<sup>72,73</sup></li> <li>• Identified as a robust neuropsychological predictor of employment;<sup>74,75</sup></li> <li>• Sensitive to changes in mental status during clinical relapses involving evidence of cognitive change, and during isolated cognitive relapses without changes on EDSS;<sup>2,76,77</sup></li> <li>• Recommended by the Multiple Sclerosis Outcome Assessments Consortium as a cognitive outcome measure in clinical trials.<sup>2</sup></li> </ul> <p><i>Processing Speed Test (PST; 5 minutes)<sup>78</sup>(software available at no charge)</i></p> <ul style="list-style-type: none"> <li>• Self-administered iPad®-based tool, completed on a touch screen by the patient; similar to the SDMT but not identical (the key is randomly generated with each administration)</li> <li>• In one single-center study, correlated highly with the SDMT, was slightly more sensitive than the SDMT in discriminating MS patients from healthy controls, and correlated more highly with cerebral T2 lesion load.</li> </ul> <p><i>Computerized Speed Cognitive Test (CSCT; 5 minutes)<sup>79</sup> (software available at no charge)</i></p> <ul style="list-style-type: none"> <li>• Performed orally;</li> <li>• Demonstrated reliability in people with MS and healthy controls;</li> <li>• Similar to the SDMT but not identical (the key is randomly generated with each administration);</li> <li>• Correlates highly with the SDMT and has high sensitivity for predicting processing speed impairment.</li> </ul> <p><i>Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ; 5 minutes)<sup>80</sup> (proprietary with associated fees)</i></p> <ul style="list-style-type: none"> <li>• Includes a self-report component that correlates more highly with anxiety and depression than cognitive performance and an informant component that correlates more highly with cognitive performance.<sup>81,82</sup></li> </ul> <p><i>Brief Assessment Batteries</i></p> <p><i>Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS; 15 minutes)</i> for use in adults<sup>63,67</sup> and children<sup>83</sup> (proprietary with associated fees)</p> <ul style="list-style-type: none"> <li>• Includes the Symbol Digit Modalities Test, California Verbal Learning Test–2nd ed., and Brief Visuospatial Memory Test–Revised.</li> </ul> <p><i>Brief Repeatable Neuropsychological Battery (BRNB; 45 minutes)<sup>10</sup> (no longer available)</i></p> <ul style="list-style-type: none"> <li>• Includes the Paced Auditory Serial Addition Test, Single Digit Modalities Test, Selective Reminding Test, 10/36 Spatial Recall Test, and Controlled Oral Word Association Test.</li> </ul> <p><i>Minimal Assessment of Cognitive Function in MS (MACFIMS; 90 minutes)<sup>62</sup> (proprietary with associated fees)</i></p> <ul style="list-style-type: none"> <li>• Includes the Paced Auditory Serial Addition Test, Single Digit Modalities Test, California Verbal Learning Test–2nd ed., Brief Visuospatial Memory Test–Revised, Controlled Oral Word Association Test, Judgment of Line Orientation Test, and Delis–Kaplan Executive Function System Sorting Test.</li> </ul>
MS: multiple sclerosis; EDSS: Expanded Disability Status Scale.

family members, early screening and ongoing monitoring throughout the disease course, and interventions to remediate dysfunction and provide compensatory strategies to optimize function and participation.

*Early screening followed by ongoing monitoring.* The standard components of the neurologic exam, including the Mini-Mental State Exam or asking patients to remember three words or objects are not sufficient to detect cognitive impairment in MS.<sup>1,59–61</sup> Several valid and reliable brief screening and evaluation tools have been used in MS (See Table 3).

Assessment of cognitive function early in the disease course has been shown not only to identify individuals with cognitive impairment but also to predict future impairments, limitations, and MS disease progression. Therefore, early detection of cognitive change may lead to earlier, more targeted treatment interventions:

- Given that significant cognitive impairment has been found in individuals with CIS and RIS,<sup>16,18</sup> and that cognitive relapses can occur independent of sensorimotor changes or subjective cognitive deficits,<sup>76,84</sup> early, regular cognitive

assessments can help clinicians recognize MS disease activity and tailor treatment recommendations.

- Clinically silent T2 lesions in the frontal, parietal, and temporal lobes impact cognition, with deficits in cognitive processing speed, executive function, and memory occurring in the absence of Expanded Disability Status Scale (EDSS) progression.<sup>85</sup>
- Cognitive impairment at the time of diagnosis, particularly processing speed and memory, predicts disability progression and conversion to SPMS.<sup>86–88</sup> In a 10-year longitudinal study, patients with cognitive impairment at baseline had a three times greater rate of reaching an EDSS of 4.0 and two times greater rate of conversion to SPMS compared to patients without cognitive impairment.<sup>88</sup>
- Early and ongoing cognitive screening could identify:
  - Patients at risk of income or job loss<sup>43,44,74</sup> so that potential accommodations could be implemented in the workplace. In addition, successful applications for Social Security Disability Insurance (SSDI) and Supplemental Security Income (SSI) require clear documentation in the medical record of symptom worsening over time;
  - Deficits that interfere with driving and inform necessary accommodations to improve safety;
  - Individuals who may have difficulties with self-care, treatment adherence and medical decision-making—thereby enabling providers to tailor patient interactions.<sup>52,89</sup>
- Since cognitive deficits in children can be present as early as the first relapse or diagnosis of CIS,<sup>12</sup> early recognition and monitoring are essential for ensuring optimal academic, social, and emotional support and for minimizing future vocational problems.<sup>11,90</sup> Such monitoring can also assist with planning as pediatric-onset MS patients may be at greater risk for physical and cognitive disability than adult-onset patients.<sup>91</sup>
- Current definitions of “benign MS” take physical disability into account but do not consider cognitive impairment.<sup>92,93</sup>
  - In a study comparing non-benign and benign patients, Gajofatto and colleagues found that both groups were cognitively impaired at baseline. Although significantly more subjects in the non-benign group progressed on the Expanded Disability Status Scale (EDSS) after 5 years, the proportion of

subjects with cognitive impairment increased by the same amount in both groups during the same time period.<sup>94</sup>

- No evidence of disease activity (NEDA) diminishes from 31% to 17% when cognitive function is accounted for in MS.<sup>95</sup>
- Cognitive assessment and MRI metrics in people with benign MS can predict short-term disease evolution to SPMS and EDSS  $\geq 4$ .<sup>96</sup>
- A longitudinal cohort study of benign MS patients led investigators to conclude that routine monitoring of non-motor symptoms (including cognitive dysfunction) and imaging studies can improve diagnostic accuracy and treatment recommendations.<sup>97</sup>
- A positive cognitive screen at any point in time may indicate the need for a more comprehensive evaluation to assess a person’s cognitive and emotional status and suggest accommodations to enhance functioning at home and work.

*Comprehensive evaluation as needed to identify areas of cognitive deficit and strength.* Following a positive screen with the Symbol Digit Modalities Test (SDMT) or other validated measure, a more thorough assessment by a neuropsychologist or other trained specialist (psychologist, speech/language pathologist, or occupational therapist) is recommended to assess areas of cognitive deficit and strength, as well as to evaluate all factors that could be impacting cognitive functioning, such as cognitive reserve,<sup>98–101</sup> depression and/or anxiety<sup>102–107</sup> fatigue, co-morbid health conditions, and medications. Studies have demonstrated the importance of identifying a person’s areas of deficit in order to determine which remedial interventions are likely to be of greatest benefit and in which order they should be provided.<sup>102,103</sup> For example, processing speed, which impacts a variety of cognitive functions,<sup>2,108</sup> also impacts a person’s ability to benefit from memory retraining interventions. However, these assessments are long, expensive, not always covered by insurance, and may be unavailable in some areas of the country (see potential barriers below). Some speech/language pathologists and occupational therapists also provide evaluations, although their assessment tools may be less sensitive and comprehensive.

For a person who is planning to apply for private disability or SSDI/SSI with cognitive impairment as a reason for leaving the workforce, a thorough assessment is essential, even if the person must travel some distance for that evaluation.<sup>109</sup>

The Minimal Assessment of Cognitive Function in MS (MACFIMS) covers the essential components of a neuropsychological assessment to quantify MS-associated neurocognitive disorder.<sup>62</sup> In the absence of a complete neuropsychological assessment, the Brief Repeatable Neuropsychological Battery (BRNB),<sup>10</sup> and the shorter Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)<sup>63</sup> assess the cognitive functions that are most likely to be impaired in MS. The MACFIMS is unique in assessing executive function (Delis–Kaplan Executive Function Scale; D-KEFS). The BICAMS has been shown to predict actual performance of everyday tasks more accurately than self-report.<sup>45</sup>

*Treatment to address functional deficits.* Various treatment modalities have been studied to address cognitive dysfunction in MS, including cognitive remediation, exercise, and pharmacologic management. Although studies have been limited by symptom variation, as well as design issues, recent findings highlight the positive impact of cognitive remediation<sup>110</sup> and suggest a potential benefit of some exercise strategies. The evidence for pharmacologic interventions remains very limited (See Table 4).

An updated review of the literature on cognitive rehabilitation for people with MS identifies specific tools that can be considered as practice standard for use by rehabilitation specialists.<sup>137</sup> Patients who require rehabilitation to address cognitive changes impacting their functioning at home or at work should be referred to a specialist. The optimal referral is to a specialist in MS neuropsychological rehabilitation (neuropsychologist, speech/language pathologist or occupational therapist); the second option is referral to a neuropsychological rehabilitation specialist without MS-specific expertise; the third option is referral to a behavioral health specialist who is willing to learn about MS and cognition.

*Managing other factors that impact cognition.* The assessment and management of cognitive impairment must take into account a variety of factors that are known to impact cognition since adequate management of those factors may improve cognitive performance.

The interaction of mood, fatigue, sleep problems, and cognition.

The research in this area suggests a complex interrelationship between mood, fatigue, and sleep in people with MS, which in turn have a variable impact on both objective and self-reported cognitive functioning.

Effective management of each of these factors is likely to improve the accuracy of both objective and subjective assessments of cognitive dysfunction:

- Depression and anxiety appear to worsen memory, processing speed and executive functioning in people with MS.<sup>105–107,138,139</sup>
- Self-reported sleep problems in MS patients with depression, fatigue, or pain, contribute to perceived cognitive problems above and beyond the impact of depressive symptoms.<sup>140</sup>
- Sleep disturbance and obstructive sleep apnea are associated with decreased visual and verbal memory, executive function, attention, processing speed and working memory, such that optimal management of sleep problems may improve cognitive functioning in people with MS.<sup>141,142</sup>

Medications and Cannabis.

- Anticholinergic medications used on a chronic basis to treat overactive bladder significantly reduce information processing speed and some memory functions.<sup>143</sup>
- Because polypharmacy may result in cognitive impairment and/or fatigue that can compound the cognitive issues, a thorough medication review is recommended.<sup>144</sup>
- Smoked cannabis users are more cognitively impaired than non-users, particularly in information processing speed and memory,<sup>145–147</sup> with more marked cognitive deficits associated with decreased gray and white matter volume.<sup>148</sup> Male users are potentially more vulnerable to cognitive deficits.<sup>149</sup>

### **Acknowledging and addressing the barriers to optimal care**

Information about the barriers to optimal care comes primarily from anecdotal reporting by people with MS and healthcare providers in various clinical settings. The authors of this paper represent the perspectives of patients and providers as well as the experiences in MS specialty centers, academic centers, and community settings. Based on these sources, the following barriers have been identified:

- Insufficient knowledge on the part of people with MS, family members, and healthcare professionals regarding:
  - Prevalence, scope, and impact of cognitive dysfunction.

**Table 4.** Treatment modalities for cognitive impairment in MS.

Remediation
<p><i>Contextualized treatment impacting everyday life activities</i></p> <ul style="list-style-type: none"> <li>• Building on prior research demonstrating that items self-generated by an individual are remembered more accurately than items presented by someone else,<sup>111,112</sup> a randomized controlled trial involving six training sessions provided Class I evidence that the self-generated intervention improves memory, some aspects of self-awareness related to the learning process, functional status, mood, and quality of life in people with MS. This technique is beneficial for remembering laboratory-based activities as well as for activities of daily living.<sup>110,113</sup></li> <li>• Combining self-generated learning with a spaced learning strategy, in which learning trials are spread out over time rather than massed, may provide added benefit.<sup>114</sup></li> <li>• Chiaravalloti et al.<sup>33</sup> have provided Class I evidence that the modified Story Memory Technique (mSMT), in which patients are taught to use context and imagery to improve learning, improves immediate and longer-term objective and everyday memory. On fMRI, the mSMT is accompanied by increased activation in frontal and temporal regions.<sup>115</sup></li> </ul> <p><i>Non-contextualized treatment</i></p> <ul style="list-style-type: none"> <li>• Sumowski et al.<sup>116</sup> demonstrated that memory retrieval practice through spaced testing (the testing effect) is more effective than restudy for improving memory in people with MS.</li> <li>• An 8-week computer-based, controlled cognitive rehabilitation trial demonstrated improved processing speed and visual and verbal sustained memory, as well as increased functional connectivity in areas of the default mode network in persons with MS.<sup>117</sup></li> <li>• In the largest randomized clinical trial (RCT) of cognitive rehabilitation to date, a home-based, remotely supervised and delivered, 60-hour (over 12 weeks) cognitive remediation program, compared to ordinary computer games, provided Class I evidence of high compliance as well as improved performance on cognitive measures and motor tasks.<sup>118</sup></li> <li>• In another RCT, individuals who underwent an intensive at-home, computer-based attention intervention accompanied by in-person psychological counseling, demonstrated significantly improved simple and divided attention as well as cued alertness.<sup>119</sup></li> <li>• Parisi et al.<sup>120</sup> demonstrated that changes in brain resting state functional connectivity helped to explain the lasting effects of cognitive rehabilitation in patients with RRMS several months after the intervention, as well as improvements in depression and quality of life.</li> <li>• Remediation for pediatric patients has not been extensively studied; however, accommodations in the academic setting, careful attention to the mood and behavioral disorders that appear to accompany cognitive impairment, and education and support for the family are essential.<sup>11</sup></li> </ul>
Exercise
<ul style="list-style-type: none"> <li>• In an RCT of a multimodal exercise training program in persons with marked mobility impairment, Sandroff et al.<sup>121</sup> demonstrated significant improvements in walking performance and cognitive processing speed, perhaps related to increased cardiorespiratory capacity.</li> <li>• Several small studies pointing to a relationship between cardiovascular fitness and different measures of brain volume and functional connectivity<sup>122–124</sup> have stimulated significant interest in evaluating the impact of combining cognitive rehabilitation with exercise training to impact both cognitive functioning and walking ability in people with MS.<sup>125</sup></li> </ul>
Pharmacologic management
<ul style="list-style-type: none"> <li>• The variable rate at which cognitive changes progress in MS makes it difficult to study pharmacological interventions in controlled clinical trials. To date, clinical trials of symptomatic treatments for cognitive impairment in MS have produced mixed results, although some individuals appear to have derived limited benefit (amantadine,<sup>126</sup> fampridine-SR,<sup>127</sup> l-amphetamine,<sup>128,129</sup> lisdexamfetamine dimesylate,<sup>130</sup> memantine,<sup>131</sup> rivastigmine,<sup>132,133</sup> donepezil,<sup>134,135</sup> and ginkgo biloba<sup>136</sup>).</li> <li>• Very few of the pivotal trials of the disease-modifying therapies have included cognitive outcome measures and those that have produced mixed results, most likely due to the short duration of the trials and/or methodological problems. The recommended inclusion of the SDMT as an outcome measure in future trials may shed additional light.<sup>2</sup></li> </ul>
MS: multiple sclerosis.



**Table 5.** Strategies to address barriers to optimal care.

## Strategies to increase early screening and ongoing monitoring

- Enhancing education, via the development and dissemination of “toolkits” for everyone affected by MS (patients, family members, and healthcare providers) about the impact of MS on cognition and available screening and treatment options.
- Utilizing social media to expand online conversations about cognition and empower people with MS to self-advocate for adequate screening.
- Gaining acknowledgment by the neurologic community that assessment and management of cognitive function is as critical as the assessment and management of physical symptoms of MS.
- Allotting time at every neurology visit for the SDMT or a self-administered, computerized version of the SDMT or other brief screening tool.
- Including the SDMT or other cognitive outcome measure in every MS clinical trial.
- Identifying existing or creating new screening tools that can be used remotely and evaluation and cost/benefit analysis of these strategies.
- Advocating for adequate reimbursement for screening and monitoring during neurology visits.

## Strategies to increase access to more complete cognitive evaluation

- Providing referral resources for patients and providers, including the National MS Society (800-344-4867); American Psychological Association (APA—[www.apa.org/helpcenter/index.aspx](http://www.apa.org/helpcenter/index.aspx)); individual state Psychology, Speech/Hearing, and Occupational Therapy associations.
- Increasing the number of clinicians who are trained to assess MS-related cognitive dysfunction via increased online training opportunities and collaboration with professional organizations and graduate programs.
- Completing an environmental scan of reimbursement for cognitive care in MS and initiating advocacy activities to increase access to this care.

## Strategies to enhance comprehensive management of cognitive dysfunction

- Increasing the number of clinicians who are trained to treat cognitive dysfunction by integrating educational content into existing training programs for psychologists, occupational therapists, speech/language pathologists, brain injury specialists, and others.
- Promoting awareness of the ways in which mood, fatigue, sleep disturbances, and cognition interact with one another.
- Supporting research to evaluate treatment options, including in-person and remote remedial strategies, pharmaceutical interventions, and exercise.
- Encouraging more posters, presentations, workshops, seminars, webinars, and stories in traditional and online media to raise awareness of the impact of cognitive changes in MS and the strategies to manage them.
- Encouraging governments, non-profit organizations, and industry to support research and training in MS cognition.

MS: multiple sclerosis; SDMT: Symbol Digit Modalities Test.

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>○ Impact of mood changes, fatigue, sleep disruption, and medications on cognition.</li> <li>○ Availability of, or access to, validated screening and assessment tools and remediation strategies.</li> </ul>  | <ul style="list-style-type: none"> <li>○ Insufficient numbers of trained clinicians to do screening, testing, and remediation.</li> <li>○ Poor communication and coordination of care either within a single care team or from one provider to another.</li> <li>○ Cost of screening tools.</li> <li>○ Inadequate reimbursement for screening and treatment.</li> <li>○ Inadequate financial resources for MS treatment centers to hire the appropriate staff.</li> </ul> |
| <ul style="list-style-type: none"> <li>• Reluctance to discuss cognitive symptoms on the part of:           <ul style="list-style-type: none"> <li>○ Clinicians who feel they do not have referral options or the time or expertise to address assessment and treatment options.</li> <li>○ Patients who feel embarrassed or are afraid to report changes because it might threaten their employment, custody of children, license to drive, and/or independence.</li> </ul> </li> <li>• Reluctance to address cognitive symptoms due to:           <ul style="list-style-type: none"> <li>○ Number of disease- and symptom management issues needing attention during an office visit.</li> </ul> </li> </ul> | <p>Although these barriers must be acknowledged and overcome, doing nothing in the meantime to address cognitive challenges among people living with MS is not acceptable. The critical steps going forward are to ensure that people with MS get the care they need while efforts are made to reduce the barriers. Strategies to address barriers to optimal care are listed in Table 5.</p>   |

### Summary

Comprehensive MS care requires (1) improved education about cognition for healthcare providers and individuals and families affected by MS; (2) baseline screening, *as a minimum*, with the SDMT or other validated screening tool when the patient is stable; annual re-assessment *with the same tool* for all adults and children 8 years of age or older to (a) detect acute disease activity, (b) assess for treatment effects (e.g. starting or switching disease-modifying therapy) or recovery from relapses, (c) evaluate progression of cognitive impairment, and/or (d) screen for new-onset cognitive problems; (3) a more comprehensive cognitive assessment for any adult or child who tests positive on initial cognitive screening or demonstrates a significant cognitive decline, as well as any individual who is applying for private disability, SSDI/SSI due to cognitive impairment; and (4) remedial interventions to improve functioning at home, work, or school.

Together, the MS community—including people with MS, family members, healthcare providers, MS advocacy organization—can improve the quality of care and access to care for MS-related cognitive dysfunction.

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