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Review Article

Importance of Identifying Cognitive Impairment in Multiple Sclerosis

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ABSTRACT: This article aims to highlight the impact of cognitive impairment on outcomes and quality of life for people with multiple sclerosis (MS) and to review current evidence for the efficacy of disease-modifying therapies (DMTs) and other interventions. In addition, we provide clinical practice insights regarding screening and management of cognitive impairment in people with MS. Evidence suggests that cognitive deterioration often accompanies magnetic resonance imaging changes. Neocortical volume and deep grey matter atrophy correlate with cognitive impairment. Similarly, cognitive decline is predictive of a higher lesion burden. Cognitive impairment is an important clinical measure of disability and negatively impacts quality of life. Phase 3 studies suggest that DMTs such as natalizumab, ozanimod and fingolimod may provide long-lasting, clinically meaningful effects on cognition in people with MS. Further data are needed to support the use of adjunct cognitive behavioural and exercise interventions for people with MS who have cognitive impairment. More data are needed to define appropriate management strategies for cognitive impairment in people with MS. Baseline and periodic screening for cognitive impairment and inclusion of cognitive impairment as a clinical trial endpoint will help to inform efforts to manage this important aspect of MS.

RÉSUMÉ : De l'importance d'identifier des troubles cognitifs dans le cas de la sclérose en plaques. Cet article a pour but de souligner l'impact des troubles cognitifs sur l'évolution de l'état de santé et sur la qualité de vie des personnes atteintes de sclérose en plaques (SP) en plus d'examiner les preuves actuelles de l'efficacité des traitements modificateurs de la maladie (TMM) et d'autres interventions. Nous entendons en outre fournir des renseignements sur la pratique clinique concernant le dépistage et la prise en charge des troubles cognitifs chez les personnes atteintes de SP. Les preuves disponibles suggèrent par ailleurs qu'une forme de détérioration cognitive accompagne souvent des modifications observées au moyen de l'imagerie par résonance magnétique (IRM). Il existe ainsi une corrélation entre le volume néocortical et l'atrophie de la matière grise profonde avec la détérioration cognitive. De même, le déclin cognitif est prédictif d'une charge lésionnelle plus importante. On le sait, les troubles cognitifs sont une mesure clinique importante de l'invalidité et ont un impact négatif sur la qualité de vie des patients. Des études de phase 3 suggèrent que des TMM tels que le natalizumab, l'ozanimod et le fingolimod peuvent avoir des effets durables et cliniquement significatifs en ce qui regarde la cognition des personnes atteintes de SP. Des données supplémentaires sont par ailleurs nécessaires pour soutenir l'utilisation d'interventions cognitivo-comportementales et d'exercices complémentaires pour les personnes atteintes de SP qui présentent des troubles cognitifs. De plus, des données supplémentaires sont aussi nécessaires pour définir des stratégies de prise en charge appropriées. Enfin, le dépistage initial et périodique des troubles cognitifs et l'inclusion des troubles cognitifs comme critère d'évaluation des essais cliniques contribueront à éclairer les efforts de prise en charge de cet aspect important de la SP.

Keywords: Cognitive assessment; Cognitive impairment; Disease-modifying therapy; Relapsing multiple sclerosis

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Introduction

Cognitive impairment affects approximately 40% to 70% of people with multiple sclerosis (MS) at some point during the course of their disease.[1–4] It has also been documented before diagnosis in people with radiologically isolated syndrome and clinically isolated syndrome.[5,6] The most common cognitive domains affected in MS include information processing speed (IPS) and episodic memory. Impairment in executive function, verbal fluency and visuospatial processing have also been well documented.[4,7–9] In our MS Cognitive clinic, in London, Ontario, Canada, people with MS most commonly complain about issues with word finding, recalling names or multi-tasking, which is often due to impaired processing speed, as well as recall or difficulty learning new tasks, which can be due to impaired processing speed or episodic memory. Cognitive impairment is commonly identified in our clinic within the first year of diagnosis.[10] A number of tests have been designed to measure these aspects of cognition and provide a quantitative assessment of cognitive function.[7] However, various

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patient-specific confounders, including age, educational level, socioeconomic status, cognitive reserve and the presence of comorbid conditions, such as depression, sleep disturbances or substance abuse, can also impact cognition and must be considered as part of the assessment.[11–15] Despite current recommendations for cognitive screening, routine assessments for changes in cognitive function do not always occur.[11,16,17] Consequently, important opportunities to detect disease activity beyond physical disability are missed.

The objectives of this review are to describe the relationships between cognitive dysfunction and other MS outcomes; to characterise how cognitive dysfunction affects the lives of people with MS; to review the evidence on the effects of disease-modifying therapies (DMTs) and other interventions on cognitive function in people with MS; and to provide clinical practice insights regarding screening and management of cognitive impairment in people with MS.

Relationship Between Cognitive Dysfunction and Other MS Outcomes

Cognitive changes often accompany radiological activity, and several magnetic resonance imaging (MRI) endpoints have been associated with cognitive dysfunction in people with MS. For example, measures of cortical and deep grey matter atrophy have been associated with impaired IPS.[18–26] Schoonheim et al.[24] monitored people with relapsing multiple sclerosis (RMS) from the time of diagnosis (or closely before) through to 6 years. They found subcortical atrophy was significantly correlated with cognitive impairment on the Brief Repeatable Battery for Neurological disease (BRB-N), particularly in men; these correlations were predicted by thalamic volume.[24] Another study including people with RMS or progressive forms of MS showed that grey matter volume and T1 lesion volume, in combination with age and baseline disability, accounted for 39.4% of the variance of change in Symbol Digit Modalities Test (SDMT) performance over 10 years.[27]

In a cross-sectional study including people with RMS or secondary progressive MS, cortical lesion load detected by double inversion recovery was significantly correlated with SDMT.[28] The presence of rimmed lesions may also signify cognitive involvement, with cross-sectional data from 192 people with MS demonstrating significantly worse scores on the SDMT and the Paced Auditory Serial Addition Test (PASAT) in people with at least four rimmed lesions versus those with none.[29] Finally, damage to normal-appearing white matter has been identified as an important component of cognitive impairment, with findings from one study showing a significant relationship between heterogeneity in the normal-appearing white matter and SDMT performance in people with MS.[30]

No single MRI measure can definitively identify cognitive impairment or fully monitor changes in cognition over time. This was illustrated in a study that followed people with a baseline diagnosis of RMS or primary progressive MS (PPMS). In people with stable RMS, declines in cognitive function, using the BRB-N, correlated with increasing lesion volume over 5 years. In those who converted from RMS to progressive MS during that time, cognitive changes were predicted by deep grey matter atrophy.[31] In people with PPMS, cognitive decline was only correlated with the rate of cortical atrophy.[31]

Stratifying people with MS into different cognitive phenotypes based on severity and functional domains of impairment can pinpoint brain regions that may be substrates for that type of cognitive dysfunction. In a cross-sectional study evaluating MRI features in patient groups defined by levels of cognitive impairment, people who were categorised as having a mild, multidomain phenotype demonstrated cortical atrophy as the most common MRI characteristic, whereas those with a severe executive/attention phenotype had greater T2 lesion volume.[32] People categorised with severe multidomain cognitive dysfunction showed severe atrophy in all brain regions examined; importantly, some people with this phenotype had a short disease duration and were not severely physically impaired.[32] However, despite the fact that MRI measures are clearly associated with, and may predict the development of, cognitive impairment in persons with MS, they remain elusive in many clinical practices, including in our MS Cognitive clinic. Thus, these possible biomarkers are mainly used in research studies, although in time they may become mainstream and available clinically.

Significant relationships also have been observed between physical disability and cognition. Transient worsening of cognition, particularly on the SDMT, has been observed in the context of acute relapse.[33–38] It also may be possible to predict disability outcomes based on the evaluation of cognitive impairment using simple tests of IPS. For example, in a study following 45 people with RMS over time, lower baseline SDMT and Selective Reminding Test scores were correlated with worse outcomes on the Expanded Disability Status Scale (EDSS) at 5 and 7 years, respectively.[39]

Impact of Cognitive Dysfunction on Functional Outcomes and Quality of Life

The impact of cognitive dysfunction is widespread and affects numerous aspects of daily life. Significant limitations have been observed in the workplace, including lower income[11,40,41] and higher rates of unemployment.[41–44] In a study of 97 people with clinically definite MS, 28.9% had documented and paid disability benefits, and 45.4% reported a reduction in hours/work responsibilities. Moreover, declines in processing speed (as measured by the SDMT) and verbal memory (as measured by the California Verbal Learning Test, 2nd edition [CVLT2]) were found to be the most consistent predictors of clinically meaningful decline.[43] Declines in executive function independently predict employment deterioration (stopping employment or reduced work hours) in people with RMS.[45] Conversely, work-related improvements (such as increased work status, capacity or compensation) reported by people with MS have been associated with improved cognitive functioning.[46]

People with MS with cognitive impairment may have a reduced capacity to care for themselves and manage their daily lives.[41] Deficits in verbal learning, memory and verbal fluency, for example, have been linked with reasoning impairments that may limit an individual's ability to make informed decisions about their medical treatment.[11] The ability to drive and manage money, and other important measures of independence, can also be compromised.[11,47,48]

IPS deficits have been linked with symptoms of anxiety and depression in people with MS.[49,50] Moreover, these individuals appear to have reduced social support. Compared with non-impaired people with MS, those with cognitive dysfunction tend to engage in fewer social activities, as measured by the Katz Adjustment Scale.[41] Reduced IPS (as measured by the SDMT and PASAT) was strongly correlated with lower scores on the Medical Outcomes Study Social Support Survey in people with MS.[51]

The collective impact of cognitive dysfunction and its downstream effects on quality of life (QoL) in people with MS is substantial.[51,52] Even in individuals with comparable levels of physical

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Table 1: Phase 3 DMT trials with data evaluating cognition

Trial/DMT	Impact/evidence	Measure of cognition
AFFIRM/Natalizumab vs placebo ($n = 942$)[60]	Fewer people on natalizumab had progression to cognitive deficit over 2 years compared with placebo (7% vs 12%, $P = 0.013$)	PASAT
SENTINEL/Natalizumab + IFN β-1a vs IFN β-1a (n = not provided)[60]	No difference in cognitive deficit progression at 2 years between natalizumab + IFN β-1a and IFN β-1a alone	PASAT
FREEDOMS/FREEDOMS II fingolimod vs placebo (n = 1556)[61,62]	Fingolimod was associated with positive change from baseline (0.6 ± 5.93 vs -0.2 ± 6.43, $P = 0.0146$) compared with placebo at 24 months. Difference maintained out to 120 months even after patient switch from placebo to active therapy at 36 months	PASAT
SUNBEAM/ozanimod vs IFN β-1a ($n = 1345$)[63,64]	Greater mean change in SDMT Z score for ozanimod compared with IFN β-1a. More people on ozanimod had clinically meaningful (≥4 points) improvement at 6 months (30% vs 22.2%) and 12 months (35.6% vs 27.9%)	SDMT

PASAT, paced auditory serial addition test; SDMT, symbol digit modalities test; IFN, interferon; RMS, relapsing multiple sclerosis.

disability, those with cognitive impairments experience greater reductions in QoL than those who are non-impaired.[40,41] Cognitive decline can predict these effects in a clinically meaningful way and can be used for advising people regarding what to expect over time.[43]

Interventions: Impact of DMTs on Cognitive Outcomes

The goal of preserving cognitive impairment has been the mainstay of treatment in persons with MS due to the lack of evidence demonstrating that medications can restore cognitive function. Medications used to treat dementia and Alzheimer's disease, such as donepezil and memantine, have not been shown to be of any benefit.[53,54] Further, treatment with amphetamines has shown some promise, but clear evidence of long-term benefit has not yet been published.[55–57]

There have been some indications in the literature that DMTs may provide cognitive benefits for people with MS, presumably through relapse prevention and mitigation of lesion development. There is insufficient evidence that specific DMTs improve cognitive outcomes, and these changes to date have been modest. Current evidence does not support changing DMTs on the basis of cognitive assessment alone.[11,17,58,59] A summary of phase 3 clinical studies of MS DMTs that included cognitive assessment is shown in Table 1.[60–64]

Natalizumab

Findings from two phase 3 trials (AFFIRM and SENTINEL) in people with MS showed that those who received natalizumab were significantly less likely to experience cognitive deficit (defined as worsening of 0.5 SD on the PASAT-3, confirmed for 12 weeks) than those treated with placebo; however, no difference was observed between those who received natalizumab + interferon (IFN) β-1a versus IFN β-1a alone.[60]

Ozanimod

In the phase 3 SUNBEAM study in people with RMS, a numerically greater mean change in SDMT Z score was observed with ozanimod treatment compared with IFN β-1a, suggesting the potential benefits of ozanimod on IPS.[61] In exploratory post hoc analyses, ozanimod treatment was more likely to lead to clinically meaningful improvement (≥4 points) in SDMT than IFN β-1a.[62]

Fingolimod

Pooled data from the phase 3 FREEDOMS and FREEDOMS II trials showed that people with MS who received fingolimod had significantly greater improvements on their PASAT score over time compared with those receiving placebo.[63] These results were consistently observed from 6 months of treatment through to 36 months when people receiving placebo were switched to fingolimod. Ten-year extension data showed continued benefits of fingolimod treatment.[64]

Interventions: Impact of Cognitive Rehabilitation/Behavioural Techniques

Solid evidence from well-designed studies of cognitive rehabilitation/behavioural techniques and physical exercises that may improve cognition in people with MS is limited, but has been increasing.[11,65] In a randomised controlled trial (RCT) comparing a 12-week, remotely supervised, computer-based adaptive cognitive remediation program to an active computer game control, people with MS who participated in the cognitive remediation program improved on a neuropsychological composite measure compared with those assigned to the control group.[66] The MEMREHAB trial was another RCT that demonstrated the use of the modified Story Memory Technique, a 10-session behavioural intervention, is effective for improving memory and learning in people with MS.[67] Promising results were observed in an RCT evaluating the effects of a progressive aerobic exercise program on IPS,[68] although more evidence is needed in this area before exercise programs can be considered part of recommended treatment.[11,68] Despite data demonstrating the benefits of cognitive rehabilitation/behavioural techniques, rehabilitation programs may be difficult to access due to a lack of trained clinicians, travel and/or time restrictions, or financial barriers.[11,66]

In our MS Cognitive clinic, our main approach is the use of behavioural techniques that can be used at work, school, or home to compensate for any impact noted by cognitive impairment in the lives of our patients with MS. Although there are limited options to improve cognitive function in persons with MS, using appropriate aids and techniques – the equivalent of using a cane to help with ambulation – can have a significant impact on quality of life.

Rationale for Routine Screening for Cognitive Dysfunction

The substantial negative impact of cognitive impairment on the lives of people with MS underscores the importance of regular

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Table 2: Validated screening tools for cognitive assessment in MS

Screening tool	Time to administer	Cognitive domain measured	Recommendations/comments
PASAT – Paced Auditory Serial Addition Test[71]	~10–15 min	Information processing speed, attention	• Reliable and sensitive screening tool • Relies on maths ability • Can cause anxiety
SDMT – Symbol Digit Modalities Test[11,72]	5 min	Information processing speed	• Recommended test for baseline and periodic screening in MS • Used in clinical trials as an outcome measure • Sensitive to change during relapse or without evidence of disability on EDSS • 3- to 4-point change is considered clinically meaningful • Included in all cognitive batteries
MSNQ – Multiple Sclerosis Neuropsychological Screening Questionnaire[11,73,74]	5 min	Attention, processing speed, memory	• Quick and easy self-report and informant-reported questionnaire • Self-report results can be affected by depressive symptoms • Informant report version correlates with multiple measures of cognitive function
BICAMS – Brief International Cognitive Assessment for MS[11]	15 min	Multiple domains	• Includes SDMT, California Verbal Learning Test, Brief Visuospatial Memory Test • Can be used for follow-up after positive SDMT
MACFIMS – Minimal Assessment of Cognitive Function in MS[11]	90 min	Multiple domains	• Includes SDMT, PASAT, California Verbal Learning Test 2nd edition, Brief Visuospatial Memory Test—Revised, Controlled Oral Word Association Test, Judgement of Line Orientation Test, Delis-Kaplan Executive Function System Sorting Test • Can be used for follow-up after positive SDMT

EDSS, expanded disability status scale; MS, multiple sclerosis.

screening and management of cognitive symptoms.[4,11] Although there is insufficient evidence at this time to recommend specific DMTs to address cognitive impairment, awareness of these symptoms could indirectly impact treatment decisions, for example, by avoiding treatments with complex administration or reporting schedules.[17] Moreover, recognition of changes in cognition may alert clinicians to ongoing disease activity that is not captured using more traditional assessments, such as the EDSS, which emphasise ambulation and other aspects of physical disability. In fact, recent evidence suggests that the EDSS alone underestimates the degree of disability before and during relapses and that incorporating the SDMT and the fatigue severity scale into the EDSS score improves the accuracy of disability assessment by accounting for cognitive changes during relapse.[69] The concept of isolated cognitive relapse, described as a transient worsening of performance on cognitive tests that are accompanied by the observance of gadolinium-enhancing brain lesions, but in the absence of any physical relapse symptoms, has been suggested by multiple studies.[16] A standard protocol for neuropsychological evaluation that can reliably detect such isolated cognitive relapses is necessary and would first require the presence of baseline cognitive assessment.[16]

From a research perspective, accrual of longitudinal cognitive data in people with MS will provide a valuable resource that may be used to help advise people with MS and their caregivers on appropriate expectations for disease progression, as well as important context for the development of clinical trials aimed at identifying pharmacologic and other strategies to treat cognitive decline.[4] The first step, however, is recognition, and thus it is recommended that neurologists promote awareness of this common symptom, how best to test for it, how to overcome barriers to testing that may exist in the clinic, and include cognition as an outcome measure in clinical trials.[4,11,58,70]

Recommended Screening Tools

Clinical practice recommendations that include guidance on the assessment of cognitive impairment in people with MS have been published by the National MS Society and the Canadian MS working group.[11,17] In general, early baseline screening with the SDMT or a similarly validated test (Table 2)[11,71–74] is recommended if the person is clinically stable.[11,17] Reassessment with the same instrument is recommended on a regular basis (2–3 years) for screening for new-onset problems or for progression of cognitive impairment over time, detecting acute disease activity, and assessing treatment effects or relapse recovery.[11,17] Awareness and treatment of comorbid factors that could confound test results, such as depression, anxiety, sleep disorders, and polypharmacy/cannabis use, are also important.[11,13] Indeed, testing for depression is recommended annually.[11] In addition, individual patient factors such as education level, socio-economic status, and cognitive reserve can impact the rate of cognitive decline and test performance and should be taken into consideration.[7,12,14,15] Positive tests or evidence of significant cognitive decline should be followed up with more comprehensive testing.[11,17]

A summary of validated tools for measuring cognitive dysfunction in MS is included in Table 2. The PASAT, a digit-summing activity that measures IPS as well as aspects of attention, has been widely used to assess cognitive impairment in people with MS.[71] Despite being a reliable and sensitive test, the PASAT is largely unpopular with people with MS and medical staff. It has been criticised for being affected by age and IQ and for creating psychological stress and agitation during administration.[71,75–78] Furthermore, there is a significant practice effect with the PASAT as well as a ceiling effect with this test (a maximal score of 60), which limits longitudinal follow-up. Additionally, a low score does not confirm cognitive impairment.[71]

The SDMT is a short symbol/digit-substitution task that measures IPS.[79] It demonstrates the best sensitivity to changes in cognition that correlate well with MRI measures of disease[38,70,72] and with measures of work or activities of daily living.[72] Compared with the PASAT, the SDMT is easier to administer and has a better longitudinal sensitivity to cognitive impairment.[70,76,80,81] Raw score changes ranging from 3 to 4 points and changes ≥10% have been reported as clinically meaningful.[17]

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The Multiple Sclerosis Neuropsychological Questionnaire is a 15-item questionnaire that involves questions about activities of daily living and is administered as both a patient report and an informant report.[82] The informant report is more strongly correlated with cognition and the self-report can be impacted by depressive disorder, so the use of the informant report as a screening tool, in addition to the self-report when possible, is recommended.[73,74] The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), a 15-minute test used in adults and children, assesses cognitive functions that are most likely to be impaired in MS using the SDMT, CVLT2, and Brief Visuospatial Memory Test-Revised.[11,83,84] Although BICAMS is not intended to replace a full neuropsychological assessment, it is a rapid tool that can be used in everyday practice that screens in more than one cognitive domain.[83,85]

After a positive screening test indicating cognitive impairment in a person with MS, a more comprehensive battery of neurophysiological tests can be conducted, such as the Minimal Assessment of Cognitive Function in MS (MACFIMS), which includes tests for information processing, memory, visuospatial function, verbal function, and executive function, or the shorter BICAMS, which includes SDMT and measures of verbal learning and visuospatial functioning, as noted previously, included in the MACFIMS.[11]

Conclusion

Cognitive impairment is a prevalent symptom of MS with a substantial influence on patient outcomes and should be measured at baseline and monitored routinely (e.g. every 2–3 years) throughout the MS disease course.[11,17] Establishment of validated MRI and clinical markers capable of predicting cognitive change would provide a critical context for patient management and the development of clinical trials. More data are needed regarding the assessment of cognitive relapses that occur in the absence of motor-sensory symptoms in terms of progression, prognosis, and management.[16,86] Further research is warranted concerning the efficacy of interventions to improve or preserve cognition in people with MS, and cognitive endpoints, particularly SDMT, should be included as endpoints in prospective clinical trials.[11,87]

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