Expert Review of Neurotherapeutics

ISSN: 1473-7175 (Print) 1744-8360 (Online) Journal homepage: www.tandfonline.com/journals/iern20

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To cite this article: Ermelinda De Meo, Emilio Portaccio, Raffaello Bonacchi, Jasmine Giovannoli, Claudia Niccolai & Maria Pia Amato (2025) An update on the treatment and management of cognitive dysfunction in patients with multiple sclerosis, Expert Review of Neurotherapeutics, 25:2, 227-243, DOI: 10.1080/14737175.2025.2450788

To link to this article: https://doi.org/10.1080/14737175.2025.2450788

Published online: 16 Jan 2025.

EXPERT REVIEW OF NEUROTHERAPEUTICS
2025, VOL. 25, NO. 2, 227–243
https://doi.org/10.1080/14737175.2025.2450788

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REVIEW

An update on the treatment and management of cognitive dysfunction in patients with multiple sclerosis

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ABSTRACT

Introduction: Cognitive impairment (CI) occurs in 34–70% of multiple sclerosis (MS) patients, significantly impacting quality of life. CI can occur independently of physical disability, even in those with 'benign MS.' Cognitive deficits are heterogeneous, but common areas affected include processing speed, memory, and executive functions.

Areas covered: A comprehensive literature search was conducted across databases such as PubMed and Google Scholar, using keywords like 'MS,' 'cognition,' and 'cognitive rehabilitation.' We focused on clinical assessment tools, emerging cognitive phenotypes, and both pharmacological and non-pharmacological treatments, including disease-modifying therapies and cognitive rehabilitation techniques.

Expert opinion: Current evidence underscores the need for a multifaceted approach to managing CI in MS, incorporating emerging pharmacological treatments, cognitive rehabilitation strategies, and exercise programs. Future research should prioritize defining optimal training intensities, integrating therapies for sustained cognitive enhancement, and exploring neuromodulation and neuroimaging biomarkers within randomized controlled trials aimed at improving cognitive functioning in MS.

ARTICLE HISTORY
Received 18 October 2024
Accepted 5 January 2025

KEYWORDS
Multiple sclerosis; cognition; cognitive rehabilitation; treatment for cognitive deficits; cognitive assessment tools; MRI; neuromodulation

1. General considerations

Multiple sclerosis (MS) is a chronic autoimmune disease in which an aberrant immune response targets the central nervous system (CNS), leading to acute inflammatory demyelinating lesions and progressive neurodegeneration [1]. This pathological process can affect any functional system within the CNS, producing a wide spectrum of symptoms. Notably, cognitive impairment (CI) has gained increasing recognition as a significant clinical feature of MS, although it is still sometimes underappreciated [1].

Cognitive deficits affect a considerable proportion of adults with MS, ranging from 34% to 70% [2,3]. and can be found in all MS subtypes, including the clinically isolated syndrome (CIS), early relapsing-remitting phases and even radiologically isolated syndrome (RIS), which suggests that they may precede the clinical onset of the disease [4]. However, secondary and primary progressive MS have the highest prevalence of cognitive deficits [2,5].

Cognitive impairment in MS presents with a highly variable temporal dynamic. It can appear either as a gradual and subtle decline or as an acute worsening of cognitive function, with or without subsequent recovery (the so-called 'cognitive relapse'). Importantly, it can occur independently of other neurological symptoms and signs, and its progression is not necessarily linked to physical disability, even though patients with CI may have an increased risk of future disability accrual [6,7]. Even subjects classified as having 'benign MS,' in which an EDSS score under 3.0 is preserved for at least 15 years, can exhibit cognitive deficits, highlighting the independent nature of cognitive impairment from other functional systems [8,9].

Cognitive impairment in MS is heterogeneous, depending on which cognitive functions are predominantly affected. As information-processing speed is typically one of the earliest cognitive domains involved in the disease, the Symbol Digit Modalities Test has become the most widely used clinical tool for screening and monitoring cognition in MS [10]. However, numerous studies have shown that a more comprehensive clinical assessment, such as the Rao Brief Repeatable Battery (BRB) or the Minimal Assessment of Cognitive Function in MS (MACFIMS), can be more sensitive and accurate [11–13]. These assessments can detect deficits in episodic memory, executive functions, visuospatial abilities, and language.

This narrative review aims to provide a comprehensive overview of current strategies for the management and treatment of cognitive dysfunction in MS. We will begin discussing the most reliable clinical and research assessment tools, followed by an examination of how age can influence cognition. Next, we will explore cutoff values for cognitive changes and consider emerging cognitive phenotypes. Additionally, we will offer a concise overview of the neuropathology and neuroimaging features linked to cognitive impairment. Finally, we will provide

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Article highlights

- Cognitive impairment affects 34–70% of MS patients, often occurring independently of physical disability.
- Commonly affected domains include information processing speed, memory, and executive functions, with variability across different MS phenotypes.
- Cognitive function is typically assessed using standardized tools like the Symbol Digit Modalities Test (SDMT), Rao's Brief Repeatable Battery (BRB), and the Minimal Assessment of Cognitive Function in MS (MACFIMS).
- Five distinct cognitive phenotypes have been identified in MS, which may guide more personalized treatment approaches: Preserved Cognition, Mild Verbal Memory/Semantic Fluency, Mild-Multidomain, Severe Executive/Attention, Severe-Multidomain.
- Optimal treatment of cognitive impairment requires a combination of appropriate DMT selection and cognitive rehabilitation, as well as 'augmentation' strategies (ie, exercise training, neuromodulation or pharmacological treatments).
- Research should focus on optimizing therapy combinations, identifying biomarkers, and exploring personalized treatment based on cognitive phenotypes to improve cognitive outcomes in MS patients.

an in-depth analysis of both pharmacological and non-pharmacological strategies for managing cognitive deficits.

2. Methods

For this narrative review, we used the terms 'MS' and 'cognition' as the main keywords to search in online databases including PubMed, Medline, Google Scholar, Clinical Trials.gov. For each section, we added related terms such as 'assessment,' 'pathology,' 'MRI,' 'randomized control trials (RCTs),' 'disease modifying treatments (DMTs)' and 'rehabilitation' to the search.

3. Cognitive impairment in MS

3.1. Cognitive assessment

The Rao's Brief Repeatable Battery of Neuropsychological Tests (BRB-N) is a widely used tool for assessing cognitive function in MS [14]. Developed in the late 1980s by the American National MS Society, the BRB-N was created to meet the growing need for a standardized, reliable, and efficient method of evaluating cognitive impairment in MS patients. Initially derived from a comprehensive battery of 23 tests, Rao and colleagues identified that the Selective Reminding Test (SRT), 7/24 Spatial Recall Test (SPART), Controlled Oral Word Association Test (COWAT), and Paced Auditory Serial Addition Test (PASAT) were the most sensitive for detecting cognitive deficits in MS. This led to modifications and refinements, resulting in the definitive BRB-N, which includes the SRT, 10/36 SPART, Symbol Digit Modalities Test (SDMT), PASAT, and Word List Generation (WLG).

Its standardized approach allows for consistent monitoring of cognitive function over time, making it valuable in both clinical practice and research. The BRB-N takes approximately 30 minutes to be administered, can be conducted by trained non-doctoral personnel, and includes two parallel versions to reduce practice effects in repeated assessments.Another commonly used neuropsychological battery is the MACFIMS [15]. It includes: the COWAT to measure phonemic fluency or language efficiency and research speed, Brief Visuospatial Memory Test-Revised (BVMT-R) [16] as measure of visuospatial learning and memory and Judgment of Line Orientation (JLO) for visuospatial perception, California Verbal Learning Test-II (CVLT) [17] for episodic verbal learning and memory, SDMT and PASAT as above for sustained attention and information processing speed and Delis – Kaplan Executive Function System Sorting Test (D-KEFS ST) [18] as measure of executive function, in particular, assessing concept formation and the ability to explain sorting concepts abstractly. While provided with a similar sensitivity compared to BRN [13], the MACFIMS needs nearly 90 minutes to be administered, thus limiting its systematic use in a clinical setting.

In more recent years, there has been a further transition from lengthy test batteries to more focused and concise assessments [1]. Among available tests, the SDMT was chosen for its accuracy and efficiency. It primarily assesses information processing, by utilizing a key that associates the digits 1–9 with nine symbols, along with a series of these symbols randomly presented below. The subject is tasked with identifying and reporting the corresponding number associated with each symbol [19]. The test can be administered in written or preferably oral form, and various adaptations and alternative versions have been developed and used in clinical trials [20,21]. However, it goes without saying that, the test requires careful interpretations and may necessitate further testing with a more comprehensive cognitive battery for a complete assessment [22,23].

The assessment of cognitive function with the SDMT was also integrated with standardized tests evaluating other functional systems affected by MS. The Multiple Sclerosis Functional Composite (MSFC) is a well standardized, quantitative assessment instrument used in clinical trials as a measure of MS-related disability. It incorporates the SDMT, the 9-Hole Peg Test (9HPT) for upper extremity dexterity [24], and the Timed 25-Foot Walk (T25FW) for walking speed [25]. Another integrated disability assessment tool, the Multiple Sclerosis Outcomes Assessment Consortium (MSOAC), also added to the above-mentioned tests, PASAT for sustained attention and information processing speed and Low Contrast Letter Acuity (LCLA), to measure MS-related visual impairment [26].

Further efforts have been made to streamline cognitive testing with the development of the Brief International Assessment of Cognition for MS (BICAMS) [21]. BICAMS was designed to provide a validated battery that is easy to administer and requires minimal training of the assessor. It comprises the SDMT, the BVMT-R [16], which evaluates visuospatial memory, and either the Rey Auditory Verbal Learning Test (RAVLT) [13] or the CVLT-II (CVLT-II T1–5) [17] to assess verbal memory.

Along with the above-mentioned cognitive test batteries, several computerized neuropsychological batteries are available and applied in MS research [27]. However, with a few

Table 1. Summarizes computerized neuropsychological assessment devices in multiple sclerosis.

Battery	Administration	*Time to administer	Alternate forms
Automated Neuropsychological Assessment Metrics (ANAM) [29]	PC/Technician guidance	20–25 minutes	Alternate forms for each test
Central Nervous System-Vital Signs (CNSVS) [30]	iPad, PC/Technician guidance	According to test selected	Unlimited alternate forms (randomization of tests)
Cognitive Drug Research (CDR) Battery [31]	PC/Self-administered or Technician guidance	15–20 minutes	Available
NeuroTrax [32]	PC/Technician guidance	45 minutes	3 forms available
Cognitive Stability Index (CSI) [33]	PC/Technician guidance	25–35 minutes	Available
Neurobehavioral Evaluation System (NES) [34]	PC/Technician guidance	20–30 minutes	–
Amsterdam Neuropsychological Test (ANT) [35]	PC/Technician guidance	According to test selected	3 forms available
Cambridge Neuropsychological Test Automated Battery (CANTAB) [36]	iPad/Technician guidance	According to test selected	Available
CogState Brief Battery (CBB) [37]	iPad, PC/Self-administered	20 minutes	Available (randomization of tests)
Cognivue [38]	PC/Self-administered	10 minutes	Not available
Cognistat	PC/Technician guidance	20 minutes	–
NeuroCog Brief Assessment of Cognition App	iPad/Self-administered	30 minutes	Available
CogniFit [39]	iPad, PC/Self-administered	30–40 minutes	–
BrainCheck, Standardized Touchscreen Assessment of Cognition (STAC)	iPad, PC/Technician guidance	15 minutes	–
National Institutes of Health (NIH) Toolbox	iPad/Technician guidance	7 minutes	–
Brief Assessment of Cognitive Health (BACH) [40]	iPad/Self-administered	20 minutes	Available
Brief Computerized Cognitive Assessment in Multiple Sclerosis (BCCAMS) [28]	PC/Technician guidance	20 minutes	Available

*The administration time also includes the minimal pre-training required to ensure that patients fully understand the instructions for task execution.
Abbreviations: PC = Personal Computer.

exceptions, some of them require further validation [27,28]. The main computerized assessment tools are presented in Table 1.

3.2. Cognitive impairment in MS across disease subtypes, stages, and ages

Cognitive impairment in MS presents a broad spectrum of clinical manifestations that vary with the age of the individual.

In adult MS patients, the most affected cognitive domains are information processing speed, learning and memory, with executive function and visuospatial processing also frequently impacted. Basic language, semantic memory, and simple attention may remain unaffected in many cases [7,41]. When examining cognitive deficits in individual MS phenotypes, patients with clinically isolated syndrome (CIS) and relapsing-remitting (RR) MS frequently exhibit predominant impairments in information processing speed [42]. In contrast, progressive MS is more commonly associated with deficits in a wider range of cognitive functions including memory and executive functions [2,43]. The transition from RRMS to secondary progressive (SP) MS is often accompanied by a significant decline in cognitive function [44]. This deterioration can manifest in various domains, including information processing speed, memory, and executive functions. Early detection of cognitive decline is thus crucial, as it enables timely therapeutic interventions aimed at mitigating further deterioration [44].

In pediatric MS patients, the primary areas affected are information processing speed, memory, and verbal intelligence, sometimes resulting in a reduction in intelligence quotient and academic abilities compared to healthy controls [45]. Linguistic skills are also reduced in a few studies [45,46] Although the findings in the literature vary and are largely based on cross-sectional studies, there is reasonable concern that MS-related brain damage may compromise the normal maturation of nervous tissue and neural connectivity in the developing brain [47,48]. This can lead to early depletion of brain and cognitive reserve, reducing compensatory abilities later in life. These concerns highlight the importance of early diagnosis and timely management strategies in this population [48].

In elderly MS patients, in addition to the previously mentioned deficits, impairments in semantic fluency are also common [49,50]. As both MS patients and healthy individuals get older, prolonged exposure to vascular risk factors can lead to cerebral small vessel disease and associated vascular cognitive impairment [51]. Vascular cognitive impairment typically affects information processing speed and executive functions, domains that can be overlapping with MS-related cognitive impairment [51]. MRI can partially reveal chronic vascular damage, particularly lacunes and cortical infarcts [52,53]. However, white matter (WM) lesions caused by small vessel disease are often indistinguishable from those related to MS when present in the same patient. Furthermore, Alzheimer's disease, which predominantly impairs cortical functions, is highly prevalent in elderly people and has sometimes to be differentiated from MS-related cognitive impairment [54]. In this population, extended neuropsychological evaluation, PET and search for cerebrospinal fluid biomarkers are needed for ensuring correct diagnosis and treatment [49].

3.3. Cognitive relapses vs progression

Relapses in MS, defined as new or worsening neurological symptoms lasting longer than 24 hours, are typically associated with sensory or physical manifestations. However, acute changes in cognition during relapses have also been documented [55]. Various research groups have reported a decline in SDMT scores during relapses, corresponding with gadolinium enhancement on

MRI, with partial, variable, and often incomplete recovery following the relapse [56–59]. Emerging evidence further supports the concept of 'isolated cognitive relapse,' where cognitive changes may be the sole indicator of disease activity, occurring without any accompanying sensorimotor symptoms [57]. Consequently, brief cognitive monitoring tools can help detect disease activity that might otherwise remain unnoticed.

In contrast to the episodic nature of cognitive relapses, progressive cognitive decline in MS is characterized by a slow and steady deterioration of cognitive function over time. This gradual worsening often goes unrecognized until it significantly affects daily activities [60]. A recent meta-regression study, which analyzed 14 trials involving over 8,813 MS patients, found that treatment effects on cognition were strongly linked to reductions in the progression of brain atrophy, but not to active MRI lesions, which are commonly monitored in MS clinical practice [61], underscoring once again that disability and moreover cognitive progression are not strictly linked to WM lesion accrual.

Given the subtle progression of cognitive decline, the concept of progression independent of relapse activity (PIRA) has been extended to include cognitive function. Cognitive decline can be classified as PIRA if no clinical relapse occurs between assessments or within nine months of cognitive decline [62]. It has been suggested that in RRMS, cognitive PIRA accounts for most of the cognitive decline, compared to relapse-associated cognitive decline [62]. Moreover, cognitive PIRA often occurs independently of EDSS worsening: among the 89% of patients experiencing cognitive PIRA, such event was independent from EDSS worsening in 68% of cases [62].

3.4. Establishing cut-off values for cognitive impairment and meaningful changes

Currently, there is no standardized scale for tracking cognitive impairment and disability in MS, underscoring an urgent need for such a tool. Some studies suggest using employment status and cognitive difficulties in daily life as key milestones in the disease course, though these proposals require further validation [63].

In neuropsychology, cognitive impairment is typically defined by scores falling below 1.5 standard deviations (SD) or the 5th percentile (which corresponds to a z-score of less than – 1.645, often approximated to a z-score <−1.5 in some studies) compared to population-based norms [1,63]. Patients are often classified as either cognitively preserved or cognitively impaired based on their performance across various tests. Some studies define cognitive impairment as the failure of at least two tests, or 30% of tests, within a neuropsychological battery [64]. However, this binary classification can obscure the inherent heterogeneity within these groups. For instance, patients classified as cognitively preserved may still experience functional declines due to severe impairment in a single domain, while those labeled as cognitively impaired due to mild deficits across several tests may function well in daily life. This variability in classification thresholds can contribute to inconsistent prevalence data on MS-related cognitive impairment.

One research approach to quantify cognitive impairment involves creating a cognitive impairment index, where patient scores are graded based on the number of standard deviations below control means: 0 points for normal performance, 1 point for a z-score between – 1 and – 2, and 2 points for a z-score <−2. The sum of points across cognitive variables is then calculated, with higher scores indicating greater impairment. However, this method is impractical for clinical use, and the cutoff values differ from those mentioned earlier, contributing to further inconsistencies in the literature [65].

Assessing cognitive changes over time is even more complex. Indeed, there is limited information on the reliable measurement and quantification of cognitive change over time. This issue significantly hampers the interpretation of observed changes when monitoring cognitive function in routine clinical practice and complicates the evaluation of the efficacy and effectiveness of both rehabilitative and pharmacological interventions aimed at improving or preserving cognition in MS.

For instance, regarding the SDMT, a four-point change has been considered clinically meaningful, based on its association with deterioration in employment status among a group of MS patients followed over 2–4 years [66]. However, this threshold is applicable at a group level and is not suitable for individual assessment. More recently, the reliable change methodology has been applied to the SDMT in MS patients [67]. The reliable change index (RCI) utilizes test – retest reliability and score variance to establish a confidence interval within which a retest score is expected to fall. A score outside this interval is likely to reflect a true change [68–70]. However, this cutoff was derived from cohorts consisting entirely of MS patients, and 'physiological' longitudinal changes in healthy populations must also be considered. Indeed, changes in test performance, reliability, variance, and measurement error in retest scores may differ between healthy controls and patients, resulting in different confidence intervals for expected retest scores. This variability must be accounted for when assessing cognitive change over time. To date, only one study [71] has provided normative data from an Italian cohort of 200 healthy individuals for the assessment of statistically significant changes across all tests included in the MACFIMS battery.

3.5. Cognitive phenotypes

To improve upon the binary categorization of MS patients as either cognitively impaired or preserved, a more detailed grouping has been proposed using latent profile analysis. Latent profile analysis is a data-driven, person-centered clustering technique that identifies homogeneous subgroups of patients, without requiring *a priori* categorization. This method was used to analyze cognitive test z-scores (including the following tests: SRT, SPART, SDMT, PASAT, WLG and Stroop Color-Word Test) to uncover distinct cognitive profiles in a cohort of 1212 MS patients [72]. Five cognitive phenotypes and their MRI correlates were identified:

(1) Preserved Cognition: normal performance on all tests, common in early disease stages, associated with lower thalamic volumes and minimal physical disability.
(2) Mild Verbal Memory/Semantic Fluency: mildly decreased scores in verbal memory and semantic fluency, linked to hippocampal volume loss.
(3) Mild-Multidomain: mildly decreased performance across multiple tests, indicative of widespread cortical dysfunction and cortical atrophy, more common in late RRMS and progressive stages.
(4) Severe Executive/Attention: severely impaired attention and executive functions, with mild reductions in other tests, associated with severe fatigue and higher WM lesion load.
(5) Severe-Multidomain: markedly decreased performance across all tests, prevalent in late disease stages, characterized by severe brain atrophy and significant depressive symptoms.

These cognitive phenotypes identified through an unbiased data-driven approach provided a more granular understanding of cognitive decline compared to traditional methods. This nuanced categorization captures variability within cognitive impairment, facilitating tailored rehabilitative strategies and improving clinical decision-making. Furthermore, this approach helps to account for factors like depression, psychiatric comorbidities, MS-related motor symptoms, fatigue, and medication side effects, ultimately enhancing the accuracy and effectiveness of cognitive assessments and treatments in MS patients. After this pilot study other classifications were proposed, and a collaborative effort to converge on a few well-validated phenotypes is being promoted [73]. However, none of the proposed classifications are currently suitable for clinical application, as they are heavily dependent on the specific study population, and phenotypes, as above [72], are often assigned using a probabilistic approach.

4. Neuropathology and neuroimaging of cognitive impairment

Understanding the neuropathology and neuroimaging substrates of cognitive impairment in MS is crucial for diagnosing and managing the disease. Traditionally, MS was viewed primarily as a WM disease. However, advanced research has revealed that gray matter (GM) damage also plays a significant role.

WM lesion burden and location are clearly relevant to cognitive impairment [74,75]. Numerous studies have identified a correlation between brain lesions in specific brain lobes and WM tracts, with neuropsychological performance, highlighting the role of disconnection mechanism induced by lesions in critical WM tracts [76]. Baseline T1 lesion volume in patients with clinically isolated syndrome (CIS) has been proven to predict executive function deficits within seven years, while new T2 lesions have been associated with a decline in information processing speed [77]. However, multiparametric studies indicated that WM lesions alone do not fully account for the severity of cognitive impairment.

Looking more closely at GM damage, it is important to distinguish between focal and diffuse GM damage. Focal GM pathology (GM lesions) are identified across all clinical MS phenotypes but they are more frequent in progressive MS. GM lesions have been shown to significantly contribute to cognitive dysfunction in MS [78]. Moreover, lesions in specific GM structures correspond to functional deficit associated with that structure (eg, lesions in the hippocampus are associated with memory deficits) [79]. Unfortunately, while the identification of cortical lesions has improved over the past decade, it remains challenging at clinical MRI magnetic fields (1.5 and 3.0 T), even by relying on specific sequences (phase-sensitive inversion recovery, double inversion recovery). A great accuracy is only afforded by ultra high-field (7.0 T) MRI [80]. On the other hand, atrophy measurements are among the most reproducible MRI measures across imaging centers and have been used to provide key insights into diffuse GM damage. They reflect neurodegenerative processes, as confirmed by postmortem studies linking neuronal and axonal pathology to cortical volume loss [81]. GM atrophy showed regional specificity, with early volume loss in the thalamus, basal ganglia, and limbic system, correlating with cognitive deficits [82–85].

Consistent with the specificity of GM involvement mentioned earlier, cognitive deficits in MS are associated with distinct patterns of regional GM damage that differ across clinical phenotypes. For example, individuals with SPMS and cognitive impairment often exhibit more extensive GM atrophy than those with RRMS or PPMS [86]. The thalamus has been identified as a key structure in cognitive dysfunction in MS [87], and subsequent research has consistently supported the notion that damage to deep gray matter nuclei, such as the thalamus [88,89] and putamen [90], is closely associated with both the presence and severity of cognitive impairments, even in the MS early stages. In contrast, hippocampal damage has been primarily linked to memory deficits [91].

While global cortical atrophy has been linked to cognitive decline [92], particularly in patients with long-standing MS, it has been shown to follow specific patterns [93]. Steenwijk et al. [94] identified distinct patterns of GM atrophy associated with cognitive impairment, emphasizing the role of key regions such as the bilateral posterior cingulate, lingual cortex, temporal pole, entorhinal cortex, and superior frontal gyrus in cognitive functioning. Moreover, specific patterns of cortical atrophy have been shown to correlate with performance on particular cognitive tasks [95], supporting the concept of spatially segregated neurodegenerative processes in MS. This is especially evident in the early stages of the disease, before the damage becomes more widespread [96].

Combining structural and functional imaging has revealed network abnormalities underlying cognitive impairment in MS [97]. Diffusion tensor imaging (DTI) has been pivotal in detecting changes in NAWM, particularly in the corpus callosum and WM tracts connecting prefrontal cortical regions. These changes have been associated with impaired attention, working memory, and information processing speed. Structural MRI abnormalities within WM tracts were found to be partly correlated with damage from focal lesions but also occurred independently, suggesting that axonal degeneration through lesion-independent mechanisms may contribute to cognitive impairment [76,98].

More advanced myelin imaging techniques, less affected by fiber orientation than DTI, such as myelin water imaging, have revealed that increased myelin heterogeneity index in normal-appearing WM correlates with cognitive impairment in MS [99]. This association was observed in key WM tracts linked to cognition, including the superior longitudinal fasciculus, corpus callosum, and cingulum. Specifically, increased myelin heterogeneity index in these tracts was significantly associated with slower processing speed, impaired verbal memory, and poorer performance on cognitive tests like the SDMT and SRT [99].

Notably, myelin heterogeneity index abnormalities were more pronounced in patients with progressive MS, highlighting the importance of including diverse MS phenotypes to comprehensively assess myelin damage's impact on cognition [99]. Importantly, no association was found between myelin heterogeneity index in these tracts and physical disability measures, such as walking speed or upper-limb function, supporting the specificity of myelin heterogeneity index for cognitive deficits [99].

Functional MRI (fMRI) studies have shown altered connectivity patterns in MS patients that correlate with brain structural damage, reflecting destabilization of brain network physiology. An early increase in functional connectivity is likely to represent and initial compensatory mechanisms, while a later decrease has been linked to cognitive decline and fatigue. FMRI also revealed that, during memory tasks, retrieval is more affected by lesion burden than encoding [100], underscoring the need for integrating multimodal imaging to better understand the pathophysiological mechanisms underlying MS-related cognitive decline [101].

A more recently developed imaging technique providing additional information about tissue composition – quantitative susceptibility mapping (QSM) – has offered valuable insights into the pathological substrates of cognitive impairment. Specifically, QSM has demonstrated that iron deposition in deep gray matter structures contributes to cognitive dysfunction in MS [102].

Despite these advancements, there remains an unmet need to fully characterize the pathological substrates on cognitive impairment in MS. Current quantitative MRI techniques provide valuable information, but their integration into routine clinical practice is limited. Further research is necessary to establish standardized protocols and validate these methods across diverse patient populations. Achieving this will significantly enhance clinicians' ability to monitor disease progression and tailor interventions for individuals with MS.

5. Pharmacological treatment

Current evidence on the pharmacological treatment of MS-related cognitive impairment, is scarce and there are no approved medications. In principle, since brain atrophy and MR imaging lesions are reduced with disease-modifying therapies (DMTs), it is reasonable to assume that these treatments have the potential to limit cognitive dysfunction by helping to preserve anatomic structures of the brain. A meta-analysis of 44 studies (only 17 randomized trials) on patients with RRMS showed that the benefits of DMTs can extend to cognition, as the use of DMTs was associated with improved cognitive outcomes, but the effect size on cognition was modest (Hedge's $g = 0.27$). Moreover, the analysis mainly regarded information processing speed as the only cognitive outcome measure and did not include newer drugs [103].

Focusing on the most recent studies, several have involved drugs targeting the sphingosine-1-phosphate (S1P) receptor pathway. Earlier studies demonstrated improvements in visuospatial abilities and executive functioning, while more recent trials have shown improvements in processing speed in both relapsing and progressive MS. A post-hoc analysis of FREEDOMS and FREEDOMS II trials [104] showed greater improvement of PASAT scores in relapsing patients taking fingolimod from baseline compared to those switching from placebo-arm to active treatment. Similarly, a reduction by 23% of confirmed cognitive worsening was observed in a post-hoc analysis of EXPAND trial [105] in secondary progressive patients taking Siponimod from baseline compared to those switching to Siponimod from placebo. More recently, trials of ozanimod in relapsing patients (SUNBEAM, RADIANCE, DAYBREAK and ENLIGHTEN) showed that preserved brain and thalamic volume observed in early treated patients correlated with better cognitive outcomes [106–108].

In addition, a post-hoc analysis of OPERA I and II demonstrated a positive effect of ocrelizumab on cognitive functions, especially in those patients showing a moderate impairment at baseline [109–111]. Moreover, the 1-year interim analysis of the CONSONANCE [109], which evaluated 629 patients (325 SPMS; 304 PPMS) treated with ocrelizumab, suggested a possible beneficial effect of this treatment in improving or at least stabilizing cognitive function also in primary progressive MS [112]. Along with clinical trials post-hoc analyses, also a number of observational studies have suggested the positive effect of both moderate and high efficacy DMTs on cognitive functioning, although the inherent limitations of observational, non-randomized studies can limit the validity of conclusions [113].

Randomized controlled trials investigating symptomatic pharmacological treatment with drugs such as modafinil, donepezil, l-amphetamine sulfate and memantine have been conducted, providing conflicting or mainly negative results [114]. Evidence on the effectiveness of dalfampridine, a potassium channel blocker that can improve ambulation [80] is mixed, with one randomized trial reporting significant, albeit transient, improvements in processing speed [115] and a second trial reporting no effect on processing speed [116].

6. Cognitive rehabilitation

In the last decade, several studies focused on cognitive rehabilitation strategies, designed to improve specific cognitive domains, but also including psychotherapy targeting emotional symptoms, behavioral interventions, and interventions targeting psychomotor issues such as motor – cognitive interference. Table 2 reports the main randomized controlled trials on cognitive rehabilitation in MS.

Table 2. Summarizes the randomized controlled cognitive rehabilitation trials in multiple sclerosis.

Cognitive Function	RCT primary endpoint	RCT population	Treatment duration	Timing and test used for efficacy evaluation	Results
Memory	MEMREHAB [117:] Efficacy of modified Story Memory Technique (mSMT) to improve learning and memory abilities	86 participants with clinically definite MS: 41 in the treatment group and 45 in the placebo control group	2 times per week for 5 weeks, with sessions lasting 45 to 60 minutes. Re-evaluation after 6 months	Latest evaluation after 6 months. Objective memory (CVLT-II learning slope), and everyday memory (Rivermead Behavioural Memory Test [RBMT])	Improved objective memory and everyday memory over 5 weeks, with treatment effects lasting over a 6-month period.
	Efficacy of imagery and context (SMT) for improving new learning deficits in MS [118]	29 MS patients with learning deficit 15 assigned to experimental and 14 to control ($n = 14$) group	8 therapeutic sessions (2 per week for 4 weeks)	Latest evaluation 5 weeks later. Hopkins Verbal Learning Test-Revised (HVLT-R)	Self-reported improvements in memory in treated MS participants
	Efficacy of mSMT in a progressive MS [119]	30 individuals with progressive MS, naïve to the mSMT, randomized to the treatment or control group.	10 therapeutic sessions (2 per week for 5 weeks)	Latest evaluation after 3 months. Objective memory (CVLT-II learning slope), and everyday memory (Rivermead Behavioural Memory Test [RBMT])	Improvements in learning in the experimental group maintained over 3 months later
	Self-GEN trial: Evaluate the impact of a self-generation learning strategy on memory and learning [120]	35 participants with clinically definite MS, 19 in the treatment group and 16 in the placebo control group	6 sessions (2 per week over 3 weeks)	No evaluation for sustained treatment effect. Contextual Memory Test (CMT) and Self-Regulation Skills Interview (SRSI)	Improved learning and memory, self-regulation, and metacognition relative in treatment group
	Efficacy of Strategy-based Training to Enhance Memory (STEM) for daily functioning [121]	20 individuals 9 randomized to the treatment and 11 to placebo control group.	8 sessions of STEM (2 sessions per week for 4 weeks)	No evaluation for sustained treatment effect. Learning ability (CVLT-II), subjective report of overall functioning and behavioral symptoms associated with MS: Health Status Questionnaire, Mental Health Inventory, Functional Assessment of Multiple Sclerosis	Effects on self-report measures of daily functioning (primary outcome) and on verbal learning and memory in the experimental group
Attention, processing speed and working memory	Efficacy of Attention Processing Training (APT) on attention and processing speed [122]	88 patients with RRMS 55 randomized to treatment and 33 to placebo	12 weeks, two sessions per week, 1 h per session	No evaluation for sustained treatment effect. Paced Auditory Serial Addition Test (PASAT)	Improvements exclusively on tasks of sustained attention in the experimental group
	Efficacy of RehaCom on attention [123]		12 weeks, two sessions per week, 1 h per session	No evaluation for sustained treatment effect. Rao's BRB and Stroop task	Improvements in Stroop task in the experimental group
Executive functions	Efficacy of an executive function intervention (from RehaCom) programme in MS [124]	40 MS patients (Cognitive intervention group $n = 11$, placebo group $n = 14$, untreated group $n = 15$).	6 weeks, 5 days per week for 40 minutes a day	1 year after enrollment. Executive function computer tasks and CVLT-II	Executive functioning and verbal learning improvement in treated group
Multiomodal cognitive rehabilitation	Dr Kawashima Brain Training (Nintendo) efficacy on global cognition [125]	34 MS patients, 18 in the experimental group and 16 in placebo group	8 weeks, 5 days per week	No evaluation for sustained treatment effect. Stroop Test, PASAT and Symbol Digit Modalities Test (SDMT)	Significant effect on Stroop test in treated group
	Efficacy of MS-Line! On global cognition [126]	43 MS patients, 22 in the experimental group and 21 in the control group	6 months, 2 sessions per week.	No evaluation for sustained treatment effect. Selective reminding test (SRT) 10/36 spatial recall test (10/36 SPART) (and letter-number sequencing (LNS)	Significant improvement related to learning and visual memory, executive functions, attention and information processing speed, and naming ability in in treated group

(*Continued*)

Table 2. (Continued).

Cognitive Function	RCT primary endpoint	RCT population	Treatment duration	Timing and test used for efficacy evaluation	Results
	Determine the feasibility of an 8-week, hybrid-variable priority training (HVT) [127]	28 MS patients, 14 in the experimental group and 14 in the control group	10 weeks, 20 sessions of training	No evaluation for sustained treatment effect. Rao's BRB	No effect on cognition
	Compare specific vs aspecific treatment on cognitive functioning [128]	28 MS patients, 14 in the experimental group and 14 in the control group	15 weeks, 2 sessions per week	2 years after enrollment. SRT, 10/36 SPART and Controlled Oral Words Association (COWA) with the Phoneme (P) and Category (C) modalities	Patients belonging to the specific group showed significantly less impaired tests compared with the aspecific group ones and significant amelioration in most of the tests
	Determine the effectiveness of a computer-assisted cognitive rehabilitation intervention MAPSS-MS (Memory, Attention, Problem Solving Skills in MS) [129]	183 MS patients, 93 in the experimental group and 90 in the control group	8 weeks, 2 hours per week	No evaluation for sustained treatment effect. Controlled Oral Word Association Test (COWAT), CVLT-II, Brief Visuospatial Memory Test – Revised (BVMT-R), PASAT, SDMT, Everyday Problems Test-Revised (EPT-R), 10-item Center for Epidemiologic Studies Depression Scale (CES-D), Strategy Subscale of the Multi-Factorial Memory Questionnaire, ROMIS v1.0-Applied Cognition-Abilities-Short Form 8a, 17-item General Self-Efficacy Scale	The intervention group outperformed the comparison group on all measures
	Determine effectiveness of cognitive rehabilitation for attention and memory problems in people with multiple sclerosis [130]	449 MS patients, 245 in the experimental group and 204 in the control group	10 weeks, 1 session per week	12 months after enrollment. Multiple Sclerosis Impact Scale Psychological	No long-term benefits on the impact of multiple sclerosis on quality of life, some evidence of an effect on everyday memory problems and mood
	Determine the efficacy of the integrative group-based cognitive rehabilitation programme, REHACOP, on improving cognitive functions [131]	42 MS patients, 21 in the experimental group and 21 in the control group	4 weeks of training in attention; 3 weeks focused on learning and memory; 3 weeks focused on language; 3 weeks exercising executive functioning; and 1 week of training in social cognition	No evaluation for sustained treatment effect. Brief Test of Attention (BTA), SDMT, Trail Making Test A (TMT-A), Salthouse Perceptual Comparison Test (PCT), Backward Digits subtest (BD), Hopkins Verbal Learning Test-Revised (HVLT-R), Calibrated Ideational Fluency Assessment (CIFA), Stroop Color-Word Test,	Improvements in several cognitive domains in patients receiving REHACOP

Abbreviations: MS=Multiple Sclerosis; RR=Relapsing Remitting; RCT=Randomized Control Trial.

6.1. Memory

The memory domain has been a frequent focus of cognitive rehabilitation in MS [132]. The Kessler Foundation modified Story Memory Technique (KF-mSMT) [117–119] has been identified as an innovative cognitive rehabilitation intervention designed to improve memory by using story-based learning and visual imagery to enhance information encoding and recall. Its use was tested in double-blind, placebo-controlled RCTs showing significantly improved learning abilities and self-reported memory functioning in patients with all MS subtypes [117,118] and progressive MS [119]. Other strategies applying experimental manipulations of stimulus presentations to maximize learning and memory abilities were subsequently tested. Furthermore, the implementation of established learning strategies such as self-generation [120,133,134], spaced learning [135], and self-testing [136,137] has led to significant enhancements in learning and memory in both laboratory and real-world environments. These strategies have inspired a new treatment approach aimed at teaching patients to use these techniques in their daily lives, known as Strategy-based Techniques to Enhance Memory (STEM) [121]. Preliminary studies in individuals with MS have shown marked improvement in daily functioning following this approach.

More recent studies explored feasibility and preliminary efficacy of remotely delivered rehabilitation strategies. A first pilot study showed a positive effect of self-generated learning strategy delivered by Zoom on memory performance, perceived memory ability in daily life, and functional performance [138]. In this framework, the Telehealth prospective memory intervention [139] is the first cognitive rehabilitation treatment designed specifically to improve prospective memory in MS. In details, it involved twice a week, one-on-one sessions that teach visual imagery, followed by implementation intentions and showed its potential benefit for improving time-based prospective memory.

6.2. Attention, processing speed and working memory

Several studies have focused on improving attention in people with MS, reporting positive outcomes. One successful approach is the Attention Process Training (APT), which has significantly enhanced performance on the PASAT and improved executive functions and quality of life [122,140]. Although research on APT in MS is limited, it is well-supported in other neurological conditions. The latest version, APT-3, includes various attention exercises and has transitioned to a computer-based format, facilitating administration and data collection [140].

Other methods for enhancing attention in MS patients include computerized cognitive rehabilitation programs. For instance, RehaCom has been shown to improve attention with increased activity in specific brain regions [123]. The home-based Freshminder-2 program significantly enhanced attention, processing speed, and verbal memory [141].

Impaired processing speed, often linked to attention deficits, is a common cognitive issue in MS. Many interventional studies target both processing speed and working memory. BrainHQ, a telerehabilitation program, has shown efficacy in improving cognitive scores with high patient adherence [142,143]. COGNI-TRAcK, another home-based program, demonstrated improvements in various cognitive functions, with some benefits persisting for six months [144]. Digital therapeutics and the BrainStim computer program have also been explored, with mixed results for working memory and processing speed [145,146]. A more recent study showed that the intensive and adaptive n-back training produced improvements in the specific working memory task in MS patients independently from their cognitive statuses. Interestingly these gains were not only observed on the trained task, but they seemed to be also transferred to other tests that measured information processing speed [147].

Overall, these approaches highlight the potential for computerized and home-based cognitive training to improve cognitive functions in people with MS.

6.3. Executive functions

Several studies have also explored treatments for executive dysfunction in individuals with MS. Research indicates that interventions using textbook exercises for executive functioning and goal attainment scaling (GAS) to address cognitive challenges can enhance executive function in these patients [124,148]. GAS involves setting specific goals and determining the extent of desired change [149]. Improvements in executive functions, psychological well-being, and quality of life have been observed following these interventions in MS patients [150]. More recently the use of rehabilitation according to Bobath Concept has proven to specifically improve executive functions in MS [151].

6.4. Multimodal cognitive rehabilitation

RehaCom, a computer-based cognitive rehabilitation program with multiple modules targeting various cognitive domains, has been widely utilized in people with RRMS [152]. It can address specific cognitive domains, but numerous studies have assessed its impact on multiple cognitive processes simultaneously [125–127]. Small trials have demonstrated improvements in processing speed, attention, executive functions, and depression symptoms, with effects observed immediately and long-lasting up to two years post-treatment [128].

Neuroimaging studies have shown that RehaCom treatment induces neurofunctional changes in the brain [153,154]. Improved attention performance was linked to increased activity in the posterior cerebellar regions and superior parietal lobules [153,155]. Enhanced performance in attention, executive functions, and quality of life (QOL) correlated with changes in resting-state functional connectivity (RSFC) of cognitive-related networks and the anterior cingulum [155]. Changes in the default mode network (DMN) predicted better cognitive performance and reduced depression, while executive network changes predicted improved QOL. These findings suggest that cognitive rehabilitation through RehaCom can induce adaptive cortical reorganization, improving cognitive performance, and that neuroimaging can be

a valuable tool for monitoring rehabilitative strategies in MS patients.

Other computer-based cognitive rehabilitation programs show promise too, including MS-Line! [126], Memory, Attention, and Problem Solving Skills in MS [129], the preliminary work of Cognitive Rehabilitation for Attention and Memory in MS [130], the Cognitive Occupation-based Programme for MS [156], and Dr Kawashima's Brain Training [157].

Importantly, these computer-based programs were also tested in a group setting: an RCT of REHACOP, a multidomain cognitive rehabilitation protocol delivered in a group setting, showed improvements in processing speed, working memory, verbal memory, and executive functions in patients with MS [131].

7. Exercise training and cognition

Based on correlative evidence from animal studies and neuroimaging research, exercise can promote the cellular and molecular processes of angiogenesis, neurogenesis and synaptogenesis which can in turn result in improved cognitive function [158]. To date, several meta-analyses, systematic reviews, and narrative reviews have described the overall effects of exercise therapy (ET) on mobility and cognition in individuals with MS [158–161]. Collectively, these reviews generally support ET as a promising approach for improving neuropsychological outcomes in this population.

A recent meta-analysis found that exercise, particularly multicomponent training, significantly enhanced cognitive function, especially cognitive memory, in MS patients. Subgroup analyses revealed that exercise performed for 8 to 10 weeks, at least three times per week, with sessions lasting up to [78] minutes and totaling 180 minutes or more per week, led to significant improvements in cognitive function. Furthermore, worse initial MS status or older age was associated with a greater effect on cognitive function [162].

The CogEx trial [163] investigated the effects of a combination of cognitive rehabilitation of information processing speed using the Rehacom and aerobic exercise on cognitive impairment in a large cohort of patients with progressive MS. Conducted across six countries (Belgium, Canada, Denmark, Italy, UK, and U.S.A.) with 311 participants, this double-blind randomized study enrolled patients into four groups: cognitive rehabilitation plus exercise, cognitive rehabilitation plus sham exercise, exercise plus sham cognitive rehabilitation, and sham-sham interventions. Results demonstrated no significant differences between the four groups in SDMT scores, which was the primary trial end-point, after 12 weeks and 6 months. Therefore, the study found no evidence supporting a synergistic effect of combined cognitive rehabilitation and exercise on processing speed. However, improvements in SDMT observed across all groups seem to indicate that cognitive improvement is possible even in the more advanced progressive stages of the disease. A subgroup of patients ($n = 104$) participated in the CogEx MRI substudy [164], where a significant effect of cognitive rehabilitation on cortical GM volume increase was observed, also associated with improved performance at CVLT-II. The same group of patients also experienced increased activity in the bilateral insula during the Go-NoGo task. These findings suggest that cognitive rehabilitation can promote GM plasticity, and thus cognitive improvements in MS patients.

Several other trials combining multiple approaches are ongoing. A randomized clinical trial [165] is testing the effect on cognition of a remotely delivered, exercise training program in older adult with MS, thus improving the accessibility to training in older patients. Another [166] investigates the combined effects of 12-weeks of aerobic exercise training integrated with virtual reality and cognitive rehabilitation on new learning and memory in 78 persons with multiple sclerosis (MS) who have motor disability and objective impairments in learning and memory. The TRAIN-MS trial [167] aims to determine the feasibility, acceptability, and impact of 8-weeks of backward walking training as compared to forward walking training, including the effect on cognition as secondary outcome. Another trial assessing the effect of high-intensity interval training compared to moderate-intensity continuous training on physical disability and cognition in primary progressive MS patients is ongoing [168].

8. Neuromodulation

Another emerging approach is based on neuromodulation. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive outpatient procedure that applies magnetic pulses on the surface of the scalp to reach underlying brain tissue, stimulating neural activity and modulating cortical excitability in targeted regions [169]. rTMS can induce long-lasting effects on synaptic plasticity, influencing brain networks involved in mood regulation, motor function, and cognitive processing. It is already approved by the National Institute for Health and Care Research for the treatment of depression and migraine, and it is being tested in MS [169]. A recent meta-analysis investigating the use of rTMS in addressing cognitive dysfunction across various brain disorders found that it may enhance cognitive abilities, particularly working memory, with more pronounced improvements observed in older adults [170]. Hulst et al. explored the effects of rTMS on working memory in MS patients using the n-back task, reporting improved task accuracy following rTMS [171]. Compared with healthy controls, MS patients exhibited greater task-related frontal activation, suggesting that rTMS may improve the efficiency of the bilateral frontoparietal neural network in MS patients, facilitating a shift in brain function toward a healthier state [171]. However, the number of studies examining rTMS in MS remains limited, and the evidence is therefore not yet conclusive.

Considering the increased risk for seizure, headache and neck pain in patients undergoing high-frequency rTMS intermittent theta-burst stimulation (iTBS) has been identified as a promising approach. ITBS, a variation of rTMS, delivering brief bursts of three high-frequency pulses with short inter-burst intervals, should better mimic the firing rates of specific neurons and significantly reduces the administration time. iTBS has been shown to enhance the plasticity of brain circuits in healthy individuals, with effects that persist longer than those produced by standard rTMS protocols [172]. While iTBS

has proven its efficacy in alleviating several MS symptoms including: spasticity, fatigue, pain, gait, and balance [173], no evidence of iTBS efficacy in treating cognitive dysfunction in MS is available. However, a single-center mixed-methods feasibility randomized controlled trial (NCT04931953) is ongoing [169].

Transcranial direct current stimulation (tDCS) is another neuromodulation approach, which consists in transmitting weak direct current to the surface of the cerebral cortex through at least two electrodes to achieve the purpose of neural regulation. Significant effects on central pain, depression and fatigue have been proven [174,175], together with improvement in attention and inhibitory control, although not always persisting at follow-up [176]. The evidence in this area remains limited. A recent meta-analysis demonstrated a short-term positive effect of active tDCS on executive function and attention when compared with sham stimulation [177]. Similarly, cognitive training combined with anodal tDCS applied to the dorsolateral prefrontal cortex showed greater improvements in attention test performance compared with the sham condition [178]. Remotely-supervised tDCS paired with cognitive training significantly enhanced complex attention and reduced response variability [179]. Furthermore, a randomized controlled trial assessed the effects of tDCS [176], cognitive training alone, and their combination on various cognitive functions, including attention, response control, working memory, visuospatial skills, and episodic memory in patients with MS. In this study, consistent with earlier findings, a positive effect of tDCS was observed; however, it was not superior to cognitive training alone [176].

9. Other approaches

The benefits of music- and rhythm-based interventions in people with neurological conditions have been demonstrated by numerous studies [180,181]. However, a recent randomized clinical showed no significant effect of Music-Cued Gait Training [182] on cognition in MS patients. Mindfulness based intervention have shown positive effect on quality-of-life, depression and fatigue up to 6 months after the intervention [183]. A recent clinical trial [184] based on both mindfulness cognitive therapy and cognitive rehabilitation treatment showed not only improvement on a wide array of psychological symptoms and mental quality of life, but also objective cognitive improvements independent from psychological effects.

In the past decade, conventional rehabilitative strategies have been supplemented with technological advancements like virtual reality and exergaming, providing engaging, multisensory rehabilitation options [185]. Exergaming showed promise for enhancing cognitive and motor functions [186], motivation, adherence, and quality of life in MS patients. It can be tailored to individual preferences and easily conducted at home, potentially serving as a viable alternative to traditional rehabilitative programs [185].

Among more experimental approaches a recent study indicated the possible beneficial effects on cognition of long-term Tai-chi training on patients with MS [187]. The Authors reported significantly improvements at PASAT and a trend toward improved performance at SDMT and in quality of life [187].

10. Limitations and future directions

This review provides a comprehensive summary of cognitive impairment in MS, yet several limitations warrant attention. The reliance on studies with small sample sizes, cross-sectional designs, and varied cognitive assessment tools poses challenges in generalizing findings and comparing results across studies. The lack of standardized thresholds for defining and tracking cognitive impairment further complicates the evaluation of treatment efficacy and contributes to inconsistent prevalence estimates. Evidence for many interventions, particularly non-pharmacological and multimodal approaches, remains preliminary, with limited support from large-scale randomized controlled trials. Furthermore, the scarcity of longitudinal studies impedes a thorough understanding of the progression of cognitive deficits over time and the long-term effects of interventions. Certain subgroups, such as pediatric patients, individuals with PPMS, and those from resource-limited settings, are often underrepresented, limiting the applicability of findings to the broader MS population.

Future research should prioritize addressing these gaps by developing standardized cognitive assessment tools, conducting long-term, multi-center randomized controlled trials, and exploring the potential of personalized approaches based on cognitive phenotypes. Integrating advanced neuroimaging and biomarkers into both research and clinical practice could enhance the ability to monitor cognitive changes and assess the efficacy of emerging interventions. These steps are essential for advancing the understanding and management of cognitive impairment in MS and ensuring that future strategies meet the diverse needs of patients.

11. Expert opinion

Given the detrimental impact of cognitive impairment on daily life, social interactions, and work activities, current guidelines recommend the systematic cognitive assessment of both adult and pediatric patients in routine practice, enabling timely intervention with appropriate management strategies [10]. DMTs remain the gold standard for preventing relapses and slowing disability progression in multiple sclerosis (MS), but their effects on cognitive impairment, a key symptom of the disease, remain largely unknown. Future clinical trials should therefore include brief multidomain cognitive batteries as outcome measures, assessing their relationship with established imaging and fluid biomarkers of inflammation and neurodegeneration. This approach could enhance our understanding of the cognitive benefits or limitations of DMTs, addressing a critical gap in current MS management.

A growing body of evidence supports the effectiveness of various cognitive rehabilitation strategies, yet significant challenges persist in translating these approaches into long-term, sustainable benefits. Future research should focus on defining the optimal style, intensity, and duration of cognitive training to fully exploit neuroplasticity. Long-term follow-up studies are essential to evaluate the persistence of functional improvements after the discontinuation of training and to investigate potential transfer effects between motor performance and cognition (and vice versa). Additionally, understanding the predictors of individual responses to rehabilitation, such as premorbid cognitive

reserve and cognitive phenotype, would enable clinicians to tailor interventions more effectively. Another promising avenue is the combination of cognitive rehabilitation with pharmacological treatments, exercise training, and neuromodulation – approaches that could be considered 'augmentation' strategies. Early studies suggest that a multifaceted approach may yield better outcomes, but these combined strategies require further investigation and validation in larger clinical trials.

One significant barrier to the adoption of more comprehensive, tailored and timely rehabilitation strategies is the assessment of cognitive dysfunction itself, as comprehensive cognitive evaluations demand time and resources. While brief tools such as the Symbol Digit Modalities Test (SDMT) are widely used, they may not capture the full extent of cognitive deficits. The use of multi-domain batteries (e.g. BICAMS [21], BRB [14], MACFIMS [15] would allow for a detailed cognitive evaluation but would require longer duration of assessments (from a minimum of 15 minutes to a maximum of around 90 minutes) and a trained neuropsychologist to administer, to score and interpret the results. The challenge lies in balancing practicality with the need for more in-depth assessments. Another critical obstacle is the under-recognition of cognitive impairment as a major concern in MS management, with clinical attention still predominantly focused on physical disability. Increased awareness and training among clinicians are essential to incorporate cognitive health into routine MS care.

Looking ahead, from the assessment of cognitive dysfunction to the understanding of its pathological substrates, advanced neuroimaging techniques and biomarkers hold great promise for guiding cognitive interventions. By correlating specific brain regions and pathways with cognitive phenotypes, researchers may soon be able to predict cognitive decline more accurately and monitor treatment efficacy through imaging. Additionally, functional and structural neuroimaging could enhance our understanding of the compensatory mechanisms involved in early-stage cognitive decline, paving the way for therapies that target and enhance these mechanisms.

As cognitive assessment tools become more widely available and rehabilitation strategies are increasingly tailored to individual cognitive profiles and the underlying neuroanatomical pathways, MS management is likely to become more holistic, with cognitive health given equal importance to physical disability. This shift could lead to better long-term outcomes for patients, not only in terms of cognitive function but also in overall quality of life and social engagement. For this vision to become a reality, continued collaboration between researchers and clinicians is essential to refine diagnostic tools, optimize therapeutic strategies, and ensure that research findings are effectively translated into clinical practice, ultimately delivering tangible benefits to patients.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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