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COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS: FROM PATHOPHYSIOLOGY TO TREATMENT - A LITERATURE REVIEW

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ABSTRACT

Introduction and Purpose: Cognitive impairment (CI) is a frequent and often overlooked symptom of multiple sclerosis (MS). It significantly affects patients' quality of life, limiting daily functioning, independence, and social and professional engagement. While it can appear at any stage of the disease, it is particularly prevalent in progressive forms. The aim of this review is to present a comprehensive overview of cognitive dysfunction in MS, including its origins, clinical presentation, assessment, and management strategies.
Description of the State of Knowledge: CI in MS arises from complex interactions involving immune-mediated inflammation, neurodegeneration, and structural and functional brain changes. It typically affects information processing speed, attention, memory, and executive functions. Various risk factors contribute to its severity, including disease phenotype, age, comorbidities, and lifestyle factors. Despite its high prevalence, CI is underdiagnosed due to limited routine screening. Standardized cognitive assessment tools are increasingly used in clinical practice to support timely diagnosis and monitoring of cognitive decline. Both pharmacological and non-pharmacological approaches, particularly cognitive rehabilitation, have demonstrated beneficial effects.
Conclusions: Cognitive impairment should be recognized as a core symptom of MS and addressed through regular screening and individualized treatment. Early detection, interdisciplinary care, and patient education are key to reducing its impact and improving long-term outcomes.

KEYWORDS
Multiple Sclerosis, Cognitive Dysfunction, Cognition, Processing Speed, Quality of Life, Risk Factors

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1. Introduction and purpose

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease affecting the central nervous system (CNS), characterized by demyelination, axonal loss, and neurodegeneration [1, 2, 3] caused by the interaction of genetic predisposition and environmental factors [3]. It predominantly affects young adults between 20 and 40 years old [4] and represents one of the leading causes of neurological disability worldwide, with an estimated 1 to 2.5 million people affected globally [5, 6]. Women are nearly 2.5 times more likely to develop MS than men [5].

Multiple sclerosis is a clinically heterogeneous disease with several distinct subtypes, each characterized by different patterns of disease progression and symptomatology [6]. In about 85% of patients, the first manifestation of SM is clinically isolated syndrome (CIS) [7] which is a monosymptomatic attack suggestive of MS but not meeting full diagnostic criteria [8]. Studies show that between 60% and 70% of CIS patients develop clinically definite MS within 20 years [7]. Radiologically isolated syndrome refers to patients with no clinical manifestations of MS, despite abnormalities consistent with the diagnosis on MRI [1].

The most common subtype is relapsing-remitting MS (RRMS), accounting for approximately 85% of cases at onset. RRMS is marked by clearly defined relapses with full or partial recovery and periods of remission between attacks [9]. This subtype is diagnosed ini ndividuals showing multiple lesions in the central nervous system and experiencing neurologic symptoms that occur at different times [1].

Over time, many individuals with RRMS transition into secondary progressive MS (SPMS), which is defined by a gradual accumulation of disability with or without superimposed relapses. This progression typically begins about 20 years after the initial RRMS diagnosis.[10 ,9]

Another form, primary progressive MS (PPMS), occurs in about 10-15% of patients [6] and is characterized by continuous worsening of neurological function from disease onset, without distinct relapses or remissions [9]. PPMS tends to affect men and women more equally and usually has a later onset compared to RRMS ,with a peak in the fifth and sixth decades [11].

Less commonly, progressive-relapsing MS (PRMS) is described, in which patients experience steady progression of disability from the beginning of the disease, combined with occasional acute relapses [9].

Cognitive impairment is a frequent and impactful symptom in MS, being considered one of the most important determinants of the quality of life (QoL) [6]. It occurs in approximately 43% to 70% of patients across all disease stages and phenotypes [3] making MS one of the leading causes of neurological impairment in 20 to 40-yea-rold age group in developed countries [4,12]. Cognitive deficits may appear early in the disease course, or even more than a year prior to any other symptoms [4]. CI affects several domains, including attention, information processing speed, memory, executive functions, although language abilities tend to remain relatively preserved [5].

Cognitive impairment in MS is important due to its major impact on patients 'quality of life, daily activities, and social relationships [13]. It often results in decreased independence, challenges at work and social settings [13], and is commonly linked to symptoms like fatigue and depression [5,14]. Despite its prevalence and impact, cognitive impairment is often underdiagnosed and remains a major unmet therapeutic challenge in MS care.

The purpose of this article is to provide an up-to-date overview of cognitive impairment in MS, including its pathophysiology ,clinical presentation, diagnostic tools, and treatment approaches. It emphasizes the importance of early detection, highlights key risk and protective factors, and seeks to enhance understanding and improve patient care.

2. Description of the state of knowledge

2.1. Pathophysiology

2.1.1. Neuroinflammation and metabolic dysregulation

Multiple pathogenic mechanisms contribute to CI in MS with immune cell activation (T-cells, B-cells, microglia) and as a result neuroinflammation, being considered essential in this process [6, 15, 16]. T-cells may turn autoreactive when an unidentified antigen is displayed to them by molecules of the major histocompatibility complex (MHC) class II [9]. Autoreactive T-cells migrate into lymphatic tissues, where they multiply and then move into the bloodstream. After activation, these T-cells bind to adhesion molecules and start producing matrix metalloproteinases (MMPs). MMPs contribute to the disruption of the blood-brain barrier. Once inside the central nervous system (CNS), the T-cells encounter antigen-presenting cells (APCs) and begin to proliferate .Self-reactive T-cells stimulate B-cells to produce antibodies that pass through the non-functional blood-brain barrier, leading to the production of antibodies targeting myelin. Furthermore , antibodies activate the complement system, resulting in further damage to the myelin sheath [9]. Self-reactive T-cells also engage with and activate microglial cells, intensifying inflammation and promoting oxidative stress [6]. These inflammatory responses are believed to be the primary drivers behind relapse episodes [9].

Other pathomechanisms that are also considered in the development of CI in patients with MS include dysfunction of the gut-brain axis caused by gut dysbiosis and altered GABA and glutamate (Glu) metabolism in the thalamus and hippocampus. Reduced GABA ratios in the thalamus and reduced Glu and glutathione (GSH) levels in the hippocampus are associated with poorer verbal and visuospatial memory, as well as slower processing speed. Changes in GABA levels are linked with reduced functional connectivity (FC) in cognitive brain networks (e.g., default mode network, DMN), contributing to memory deficits [6].

2.1.2. Gray matter (GM) lesions

In CIS patients, brain atrophy is less pronounced and less consistently linked to cognitive deficits; however, up to one-third exhibit reduced cognitive performance ,particularly in visuospatial functions ,which correlates with white matter volume loss.

In patients diagnosed with MS, impairments in specific cognitive functions correlate with the location of CNSatrophy.

- Cortical GM atrophy, especially in frontal, temporal, and parietal lobes, is linked to deficits in executive function, attention, and verbal memory.
- Thalamic atrophy is a consistent marker of CI, correlating with processing speed, memory, and global cognition. Subregions connected to the frontal and temporal cortex show particular relevance.
- Hippocampal atrophy is associated with impaired episodic and visuospatial memory.
- Putamen and pallidum atrophy contribute to slowed cognitive speed, particularly in later disease stages.
- Cerebellar GM reduction correlates with poorer visuospatial and information processing performance [6].

Patients with deficits across multiple cognitive domains often show widespread cortical GM atrophy [6].

2.1.3. White matter (WM) lesions

CI in MS is strongly associated with myelin loss and increased myelin heterogeneity. The best predictors of CI are:

- WM lesions in the :right longitudinal fasciculus (100%), left anterior thalamic radiation (93%), left posterior corona radiata (78%), left medial lemniscus (74%), left inferior longitudinal fasciculus (70%), left optic radiation (69%), right middle cerebellar peduncle (60%), right optic radiation (53%),
- reduced fractional anisotropy (FA), indicating microstructural abnormalities of white matter, in regions such as: in the splenium of the corpus callosum (64%), left optic radiation (53%), body of the corpus callosum (52%) and fornix (51%).

Atrophy of the corpus callosum is also reported to be significantly associated with CI in MS [6].

2.2. Risk factors of CI in MS

Although the pathogenesis of MS is primarily considered autoimmune[17 ,16] , various genetic and environmental factors also play significant roles in influencing both disease onset and progression, as well as the development of cognitive impairment [17].

Significant predictors of CI in MS are genetic susceptibility, older age at disease onset, higher EDSS scores, lower physical activity in childhood, lower premorbid IQ, lower educational level and comorbid neuropsychiatric illness [6]. Male MS patients appear to exhibit greater impairments across multiple cognitive domains—such as verbal memory, executive functions, attention, memory, visuospatial processing, and information processing speed-compared to female patients [18, 19]. Cardiovascular risk factors have been linked to increased brain lesion burden and accelerated brain atrophy in individuals with multiple sclerosis [17]. Notably, elevated cholesterol levels have been associated with poorer performance in verbal learning skills [20]. Some studies reported impaired glucose metabolism and hyperinsulinemia in MS patients compared to the general population, which may result in neurodegeneration and cognitive dysfunction [21]. Among lifestyle-related risk factors, smoking has been identified as both a susceptibility factor for the development of MS and a prognostic indicator associated with accelerated disease progression. Furthermore, smoking has been linked to greater lesion burden, increased brain atrophy, and a higher risk ofCI in individuals with MS [17] .Patients with MS who use cannabis exhibit greater cognitive impairment compared to non-users. Cannabis use may further disrupt cerebral compensatory mechanisms, which are already compromised in individuals with MS [22]. A history of thyroid disease has been associated with poorer cognitive performance [17].

Certain factors have also been identified as having a protective influence on the development of cognitive deficits in MS. In female patients hormonal (estroprogestinic oral contraceptives) therapy resulted in reduction in CI prevalence [23]. Physical activity is associated with increased hippocampal volume, improved white matter integrity, and more efficient white matter functioning. Consequently, exercise may enhance cognitive performance and memory, potentially through its impact on hippocampal function. In individuals with MS, physical activity may offer neuroprotective benefits against cognitive dysfunctions and could act synergistically with cognitive rehabilitation in those with established deficits [17]. Increasing evidence suggests that early initiation of appropriate disease-modifying therapy in early stages of RRMS may help stabilize cognitive function or potentially lead to cognitive improvement [4].

2.3 Cognitive reserve (CR)

Cognitive reserve (CR) ,referring to an individual's capacity for cognitive processing and typically estimated through factors such as years of education, intelligence quotient (IQ), and engagement in leisure activities ,may account for the variability in cognitive performance among patients with comparable MRI and clinical profiles [4]. MS patients who demonstrate higher cognitive reserve ,measured through indicators such as early-life cultural and educational enrichment, occupational achievement, and participation in leisure activities ,tend to report lower perceived disability, better functional health, and greater overall well-being, based entirely on self-reported assessments [24]. In patients with low cognitive reserve, participation in cognitively stimulating activities offered a level of protection comparable to that associated with higher educational attainment, highlighting the value of cognitive rehabilitation interventions [25]. However, cognitive enrichment did not significantly influence cognitive performance in individuals with a high level of education [6].

2.4. Clinical presentation of CI in MS

The severity and prevalence of cognitive impairment differ widely among all subtypes and stages of MS. Cognitive dysfunction is present in CIS and escalates as the disease progresses, more prominently in progressive forms of .MSIn fact, CI may precede detectable structural changes on MRI, suggesting its potential role as an early indicator of disease activity [26]. However, the severity and progression of cognitive impairment exhibit considerable variability among individuals with multiple sclerosis. In some cases, it significantly compromises functional independence, although in others, it remains relatively mild and slow to progress [26].

Studies show that CI is present in:

- 34.5% of patients with CIS,
- 44.5% of patients with RRMS,
- 79.4% of patients with SPMS,
- 91.3% of patients with PPMS [4].

Most commonly affected cognitive domains in MS are information processing and memory .Other cognitive symptoms include deficits in complex attention, executive functioning, verbal fluency, visuospatial perception and social cognition. Information processing deficits are found from the beginning of the disease, in CIS and RIS patients. Processing speed serves as a fundamental component of higher-order cognitive functionsthus , its decline adversely affects subsequent cognitive domains such as learning and verbal fluency [26].

In a representative sample of 291 adult patients with any type of multiple sclerosis, the frequencies of impairments (varying by test) were as follows:

- -2751% in cognitive processing speed,
- -5456% in visual memory,
- -2934% in verbal memory,
- -1528% in executive function, and
- 22% in visuospatial processing [27].

Basic language, semantic memory, and attention span are rarely impaired (in about 10% of patients with multiple sclerosis).

MS patients often experience depression (35-50%), anxiety (34-57%) and fatigue (70-75%) in association with CI [6]. These symptoms may also affect patients 'cognitive functions. They negatively impact performance of attention, working memory, executive functions and information processing speed [18]. Reduced information processing speed was associated with increased levels of depressive symptoms and fatigue, diminished verbal fluency, lower short-term memory span, decreased performance in both immediate and delayed verbal recall [28]. Patients with MSwho exhibit depressive symptoms demonstrate poorer cognitive performance not only compared to healthy controls but also relative to MS patients without depressive symptoms .Depression in MS patients is associated with a suicide rate that is twice as high as that observed in the general population. Risk factors for suicide in MS patients are female sex, young age at onset of MS, previous history of depression, social isolation, recent functional deterioration and abuse of illicit substance s[18] .It has also been found that anxiety disorders worsen performance on executive functioning, visual memory, and information processing speed. Anxiety not only exacerbates CI, but is also associated with significantly increased fatigue, pain, and sleep problems in affected patients [29] .However, due to the frequent overlap between depressive and anxiety symptoms, it remains challenging to clearly differentiate the specific effects of each disorder.

2.5 Differences in cognitive profiles between relapsing-remitting and progressive forms of MS

Patients with relapsing-remitting MS (RRMS) predominantly show learned information retrieval impairments [6]. In contrast, patients with secondary progressive (SPMS) and primary progressive MS (PPMS) display more extensive and severe cognitive deficits [30, 31], particularly in verbal episodic memory, attention, processing speed, and executive functions. These impairments are evident both when SPMS and PPMS are grouped together as progressive MS and when analyzed separately, each subtype demonstrating distinct cognitive profiles. At baseline, patients with SPMS also exhibited significantly higher levels of depression, anxiety, and fatigue compared to healthy controls [30], consistent with prior research highlighting the role of psychopathological symptoms in exacerbating CI [18]. Fatigue was elevated across all MS subtypes, with SPMS patients reporting the highest levels, underscoring its persistent and disabling impact on quality of life and brain function.

Longitudinal observations revealed cognitive improvement in RRMS patients, particularly in tasks involving verbal memory and attention. While the exact cause remains unclear, potential contributing factors include cognitive recovery during disease stability, effects of cognitive reserve, or treatment-related improvements. In contrast, no significant cognitive gains were observed in SPMS and PPMS groups, suggesting that progressive neurodegeneration may diminish cognitive plasticity and limit response to repetition or stabilization. Moreover, psychological symptoms and fatigue remained relatively stable over time across all subgroups, indicating their entrenched nature within the disease process. These findings emphasize the importance of early cognitive assessment and individualized intervention strategies, particularly in progressive MS, where the burden of CI is greater and less amenable to spontaneous recovery [30].

2.6. Effects of relapse

CI in MS is generally characterized by a gradual decline, however growing evidence suggests that acute cognitive deterioration may also manifest during disease relapses [33 ,6 ,32]. This phenomenon, referred to as inflammatory cognitive relapse (ICR), is defined as an acute worsening of cognitive function in the context of active disease, occurring independently of physical neurological symptoms [34]. ICRs are not linked to changes in mood, fatigue, or self-perceived cognitive performance. They may present as marked, yet transient, declines in cognitive functioning, typically followed by partial recovery at follow-up. Neuropsychological assessment is essential to confirm cognitive relapse and to exclude alternative explanations such as depression, fatigue, or psychosocial stressors. Cognitive relapses are characterized by abrupt but reversible impairments in neurocognitive function, occurring without concurrent neurological deficits [6].

2.7 Diagnostics

2.7.1. MRI assessment

Compared to cognitively stable individuals, patients who experienced cognitive decline exhibited more pronounced structural brain abnormalities at baseline, including greater lesion volume, reduced white matter integrity, and lower volumes of both cortical and deep grey matter. Cross-sectional analyses identified deep grey matter volume as the strongest MRI correlate of cognitive performance at baseline, whereas cortical grey matter volume emerged as the most robust baseline MRI predictor of future cognitive decline. More severe structural damage at baseline predicted a higher probability and rate of cognitive decline during follow-up. In early-stage MS, CI was primarily associated with reductions in white matter integrity (for global cognitive decline) and deep grey matter volume (for declines in information processing speed). In contrast, cortical atrophy was the dominant predictor of cognitive decline in more advanced relapsing-remitting and progressive forms of the disease. Furthermore, regression models incorporating regional MRI measures of brain structure accounted for substantially more variance in cognitive outcomes than models relying solely on global brain metrics, underscoring the added value of assessing region-specific damage in understanding and predicting cognitive trajectories in multiple sclerosis [12].

The ability to accurately predict cognitive decline in individual patients using MRI alone remains limited. Among the various MRI-derived parameters, grey matter atrophy has demonstrated the strongest and most consistent association with future cognitive impairment. Evidence suggests that individuals presenting with more extensive grey matter damage at the initial assessment are more likely to experience progressive cognitive deficits over time [1].

In addition to structural damage, recent studies using resting-state functional MRI have examined altered connectivity in grey matter regions such as the thalamus, hippocampus, and cortex in patients with cognitive impairment in multiple sclerosis. While some studies report increased functional connectivity- possibly reflecting compensatory mechanisms in early disease ;others show decreased connectivity, likely indicating network failure in later stages. Despite inconsistent findings, these studies suggest that cognitive decline in MS is linked to progressive disruption of brain network function [1].

2.7.2 Screening and monitoring tools in MS associated CI

There are several neuropsychological tests that can be used to assess cognitive decline in people with MS. Current guidelines recommend that, at a minimum, patients should undergo a baseline cognitive screening using the Symbol Digit Modalities Test (SDMT) or another validated tool, as part of regular monitoring and care. Annual re-evaluation using the same cognitive screening tool is recommended, or more frequently if needed, to: detect signs of active disease; monitor treatment effects, such as starting or changing disease-modifying therapies or recovering from a relapse; track the progression of cognitive impairment; and identify any new cognitive symptoms.

For adults aged 18 and older, a more detailed cognitive assessment is advised for anyone who shows impairment on initial screening or experiences noticeable decline, especially if there are concerns about comorbidities or the individual is applying for disability due to cognitive impairment [26].

2.7.3. Symbol Digit Modalities Test (SDMT)

The Symbol Digit Modalities Test (SDMT) is the most widely utilized screening instrument for the detection of cognitive impairment in individuals with MS. It primarily assesses information processing speed—the cognitive domain most frequently affected in MS. The SDMT is brief (approximately 5 minutes), easy to administer, and demonstrates high sensitivity to cognitive deficits [35]. It is recommended as a core cognitive outcome measure in both clinical trials and routine practice. Moreover, it has been identified as a strong neuropsychological predictor of employment status and is sensitive to fluctuations in cognitive function during clinical relapses, including both relapses with physical symptoms and isolated cognitive relapses not reflected by changes on the Expanded Disability Status Scale (EDSS) [26].

2.7.4 Brief International Cognitive Assessment for MS (BICAMS)

BICAMS is a standardized and validated battery developed for quick cognitive screening in MS, consisting of three tests:

- Symbol Digit Modalities Test (SDMT) - assesses information processing speed;
- California Verbal Learning Test- Second Edition (CVLT-II) (or its international versions) - assesses verbal learning and memory;
- Brief Visuospatial Memory Test- Revised (BVMT-R) - assesses visuospatial memory.

BICAMS can be administered in about 15 minutes and is suitable for clinical settings ,requires no specialist equipment and no specialist expertise in cognitive assessment [36].

It has been translated and culturally adapted for use in 26 countries to date. BICAMS demonstrated validity as a measure of cognitive functioning in individuals with multiple sclerosis on a global scale. Across diverse languages, cultures, and geographic regions, BICAMS effectively distinguishes cognitive impairment in people with MS compared to healthy control groups [37].

2.7.5 Minimal Assessment of Cognitive Function in MS (MACFIMS)

A more comprehensive battery (90 minutes) assessing a wider range of cognitive domains:

- SDMT- processing speed
- CVLT-II - verbal memory
- BVMT-R - visuospatial memory
- Controlled Oral Word Association Test (COWAT) - verbal fluency
- Paced Auditory Serial Addition Test (PASAT) - working memory and attention
- Delis-Kaplan Executive Function System Sorting Test - executive functions
- Judgment of Line Orientation - visuospatial processing

MACFIMS is useful in research and specialized cognitive assessment, but less practical for routine clinical use due to its length [13].

Early assessment of cognitive function in multiple sclerosis has been shown to not only identify individuals with existing cognitive impairment but also to predict future cognitive decline, functional limitations, and overall disease progression. As such, detecting cognitive changes at an early stage may enable more timely and targeted therapeutic interventions [26].

2.8. Treatment

2.8.1 Pharmacological therapy

Early initiation of appropriate disease-modifying therapies (DMTs) in the initial stages of RRMS may contribute to the stabilization or even improvement of cognitive function [38]. Certain DMTs have also demonstrated potential cognitive-enhancing effects ,particularly high-efficacy DMTs [5, 39]. The mechanisms underlying the potential cognitive benefits of disease-modifying therapies (DMTs) are not yet fully understood. It is hypothesized that DMTs may enhance cognitive function primarily through their anti-inflammatory effects-particularly by improving the efficiency of neural networks or by slowing brain atrophy, which currently represents the most reliable correlate of cognitive impairment [40, 41]. For symptomatic treatment, dalfampridine is currently the only medication supported by strong evidence for its beneficial effects on cognitive function [50]. Medications traditionally used for dementia) acetylcholinesterase inhibitors, memantine, donepezil, gink(go biloba, as well as stimulants, have been largely dismissed following two meta-analyses that found no significant evidence of their effectiveness in treating cognitive impairment in MS [42, 43].

2.8.2. Non-pharmacological therapy

Cognitive rehabilitation and physical exercise have emerged as promising non-pharmacological interventions for addressing CI in individuals with MS [44]. Cognitive rehabilitation can lead to improvements in verbal and visual memory, information processing speed, and QoL [45]. Similarly, home-based programs such as the Integral Cognitive Rehabilitation Program (ICRP), which target both restorative and compensatory mechanisms, have shown potential in enhancing cognitive function and slowing the progression of cognitive decline in MS [46]. A 2024 meta-analysis reviewed 19 clinical trials and found moderate-to-strong evidence for improvements in specific cognitive outcomes such as PASAT performance, though effects on measures like the SDMT and overall disability were less conclusive [47]. Patient-reported outcomes highlight perceived improvements in everyday functioning, self-efficacy, and quality of life following cognitive training—even when objective performance gains are limited—suggesting that subjective measures should be included in future studies [48].

3. Conclusions

The severity and prevalence of cognitive impairment differs widely among all subtypes and stages of MS. Cognitive dysfunction is present in CIS and escalates as the disease progresses, more prominently in progressive forms of .MSIn fact, CI may precede detectable structural changes on MRI, suggesting its potential role as an early indicator of disease activity [26]. However, the severity and progression of cognitive impairment exhibit considerable variability among individuals with multiple sclerosis. In some cases, it significantly compromises functional independence, although in others, it remains relatively mild and slow to progress. [26]

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REFERENCES

1. Benedict, R. H. B., Amato, M. P., DeLuca, J., & Geurts, J. J. G. (2020). Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. The Lancet Neurology, 19(10), 860–871. https://doi.org/10.1016/s1474-4422(20)30277-5
2. Lisak M, Špiljak B, PašićH, Trkanjec Z. (2021). Cognitive Aspects in Multiple Sclerosis. ,.Psychiatr Danub .33(Suppl 13):177-182
3. Mitolo, M., Venneri, A., Wilkinson, I. D., & Sharrack, B. (2015). Cognitive rehabilitation in multiple sclerosis: A systematic review. Journal of the Neurological Sciences, 354(1–2), 1–9. https://doi.org/10.1016/j.jns.2015.05.004
4. Oset, M., Stasiolek, M., & Matysiak, M. (2020). Cognitive Dysfunction in the Early Stages of Multiple Sclerosis—How Much and How Important? Current Neurology and Neuroscience Reports, 20(7), 22. https://doi.org/10.1007/s11910-020-01045-3
5. Miller, E., Morel, A., Redlicka, J., Miller, I., & Saluk, J. (2018). Pharmacological and Non-pharmacological Therapies of Cognitive Impairment in Multiple Sclerosis. Current Neuropharmacology, 16(4), 475–483. https://doi.org/10.2174/1570159x15666171109132650
6. Jellinger, K. A. (2024). Cognitive impairment in multiple sclerosis: from phenomenology to neurobiological mechanisms. Journal of Neural Transmission, 131(8), 871–899. https://doi.org/10.1007/s00702-024-02786-y
7. López-Gómez, J., Enciso, B. S., Miró, M. C., & Pascual, Q. (2023). Clinically isolated syndrome: Diagnosis and risk of developing clinically definite multiple sclerosis. Neurología (English Edition), 38(9), 663 .670– https://doi.org/10.1016/j.nrleng.2021.01.010
8. Olek MJ, Howard J, González-Scarano F, Dashe JF. .(2024)Evaluation and diagnosis of multiple sclerosis in adults. *UpToDate*.
9. Haki, M., Al-Biati, H. A., Al-Tameemi, Z. S., Ali, I. S., & Al-Hussaniy, H. A. (2024). Review of multiple sclerosis: Epidemiology, etiology, pathophysiology, and treatment. Medicine, 103(8), e37297. https://doi.org/10.1097/md.0000000000037297
10. Cree, B. A., Arnold, D. L., Chataway, J., Chitnis, T., Fox, R. J., Ramajo, A. P., Murphy, N., & Lassmann, H. (2021). Secondary progressive multiple sclerosis. Neurology, 97(8), 378–388. https://doi.org/10.1212/wnl.0000000000012323
11. Antel, J., Antel, S., Caramanos, Z., Arnold, D. L., & Kuhlmann, T. (2012). Primary progressive multiple sclerosis: part of the MS disease spectrum or separate disease entity? Acta Neuropathologica, 123(5), 627–638. https://doi.org/10.1007/s00401-012-0953-0
12. Eijlers, A. J. C., Van Geest, Q., Dekker, I., Steenwijk, M. D., Meijer, K. A., Hulst, H. E., Barkhof, F., Uitdehaag, B. M. J., Schoonheim, M. M., & Geurts, J. J. G. (2018). Predicting cognitive decline in multiple sclerosis: a 5-year follow-up study. Brain, 141(9), 2605–2618. https://doi.org/10.1093/brain/awy202
13. Meca-Lallana, V., Gascón-Giménez, F., Ginestal-López, R. C., Higueras, Y., Téllez-Lara, N., Carreres-Polo, J., Eichau-Madueño, S., Romero-Imbroda, J., Vidal-Jordana, Á., & Pérez-Miralles, F. (2021). Cognitive impairment in multiple sclerosis: diagnosis and monitoring. Neurological Sciences, 42(12), 5183–5193. https://doi.org/10.1007/s10072-021-05165-7
14. Roheger, M., Grothe, L., Hasselberg, L., Grothe, M., & Meinzer, M. (2024). A systematic review and meta-analysis of socio-cognitive impairments in multiple sclerosis. Scientific Reports, 14(1), 7096. https://doi.org/10.1038/s41598-024-53750-5
15. Barros, C., & Fernandes, A. (2020). Linking Cognitive Impairment to Neuroinflammation in Multiple Sclerosis using neuroimaging tools. Multiple Sclerosis and Related Disorders, 47, 102622. https://doi.org/10.1016/j.msard.2020.102622
16. Dendrou, C. A., Fugger, L., & Friese, M. A. (2015). Immunopathology of multiple sclerosis. Nature Reviews. Immunology, 15(9), 545–558. https://doi.org/10.1038/nri3871
17. Kappus, N., Weinstock-Guttman, B., Hagemeier, J., Kennedy, C., Melia, R., Carl, E., Ramasamy, D. P., Cherneva, M., Durfee, J., Bergsland, N., Dwyer, M. G., Kolb, C., Hojnacki, D., Ramanathan, M., & Zivadinov, R. (2015). Cardiovascular risk factors are associated with increased lesion burden and brain atrophy in multiple sclerosis. Journal of Neurology Neurosurgery & Psychiatry, 87(2), jnnp-2014. https://doi.org/10.1136/jnnp-2014-31051
18. Margoni, M., Preziosa, P., Rocca, M. A., & Filippi, M. (2023). Depressive symptoms, anxiety and cognitive impairment: emerging evidence in multiple sclerosis. Translational Psychiatry, 13(1), 264. https://doi.org/10.1038/s41398-023-02555-7
19. Schoonheim, M. M., Vigeveno, R. M., Lopes, F. C. R., Pouwels, P. J., Polman, C. H., Barkhof, F., & Geurts, J. J. (2013). Sex-specific extent and severity of white matter damage in multiple sclerosis: Implications for cognitive decline. Human Brain Mapping, 35(5), 2348–2358. https://doi.org/10.1002/hbm.22332

20. Reia, A., Petruzzo, M., Falco, F., Costabile, T., Conenna, M., Carotenuto, A., Petracca, M., Servillo, G., Lanzillo, R., Morra, V. B., & Moccia, M. (2021). A retrospective exploratory analysis on cardiovascular risk and cognitive dysfunction in multiple sclerosis. Brain Sciences, 11(4), 502. https://doi.org/10.3390/brainsci11040502
21. Ayromlou, H., Hosseini, S., Khalili, M., Ayromlou, S., Khamudchiyan, S., Farajdokht, F., Hassannezhad, S., & Moghadam, S. A. (2023). Insulin resistance is associated with cognitive dysfunction in multiple sclerosis patients: A cross-sectional study. Journal of Neuroendocrinology, 35(6), e13288. https://doi.org/10.1111/jne.13288
22. 'Pavisian, B., MacIntosh, B. J., Szilagyi, G., Staines, R. W., OConnor, P., & Feinstein, A. (2014). Effects of cannabis on cognition in patients with MS. Neurology, 82(21), 1879–1887. https://doi.org/10.1212/wnl.0000000000000446
23. De Giglio, L., Marinelli, F., Barletta, V. T., Pagano, V. A., De Angelis, F., Fanelli, F., Petsas, N., Pantano, P., Tomassini, V., & Pozzilli, C. (2016). Effect on Cognition of Estroprogestins Combined with Interferon Beta in Multiple Sclerosis: Analysis of Secondary Outcomes from a Randomised Controlled Trial. CNS Drugs, 31(2), 161–168. https://doi.org/10.1007/s40263-016-0401-0
24. Della Corte, M., Santangelo, G., Bisecco, A., Sacco, R., Siciliano, M., D'Ambrosio, A., Docimo, R., Cuomo, T., Lavorgna, L., Bonavita, S., Tedeschi, G., & Gallo, A. (2018). A simple measure of cognitive reserve is relevant for cognitive performance in MS patients. Neurological Sciences, 39(7), 1267–1273. https://doi.org/10.1007/s10072-018-3422-2
25. Grant, J. G., Rapport, L. J., Darling, R., Waldron-Perrine, B., Lumley, M. A., Whitfield, K. E., & Bernitsas, E. (2023). Cognitive enrichment and education quality moderate cognitive dysfunction in black and white adults with multiple sclerosis. Multiple Sclerosis and Related Disorders, 78, 104916. https://doi.org/10.1016/j.msard.2023.104916
26. Kalb, R., Beier, M., Benedict, R. H., Charvet, L., Costello, K., Feinstein, A., Gingold, J., Goverover, Y., Halper, J., Harris, C., Kostich, L., Krupp, L., Lathi, E., LaRocca, N., Thrower, B., & DeLuca, J. (2018). Recommendations for cognitive screening and management in multiple sclerosis care. Multiple Sclerosis Journal, 24(13), 1665–1680. https://doi.org/10.1177/1352458518803785
27. Benedict, R. H., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., & Weinstock-Guttman, B. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). Journal of the International Neuropsychological Society, 12(4), 549–558. https://doi.org/10.1017/s1355617706060723
28. Diamond, B., Johnson, S., Kaufman, M., & Graves, L. (2007). Relationships between information processing, depression, fatigue and cognition in multiple sclerosis. Archives of Clinical Neuropsychology, 23(2), 189–199. https://doi.org/10.1016/j.acn.2007.10.002
29. Goretti, B., Viterbo, R. G., Portaccio, E., Niccolai, C., Hakiki, B., Piscolla, E., Iaffaldano, P., Trojano, M., & Amato, M. P. (2013). Anxiety state affects information processing speed in patients with multiple sclerosis. Neurological Sciences, 35(4), 559–563. https://doi.org/10.1007/s10072-013-1544-0
30. Taranu, D., Balz, L. T., Holbrook, J., Tumani, V., Schreiber, H., Tumani, H., & Uttner, I. (2025). Cognitive impairment, mood, and fatigue in various multiple sclerosis subtypes: a one-year follow-up study. Journal of Neurology, 272(6), 398. https://doi.org/10.1007/s00415-025-13115-y
31. Planche, V., Gibelin, M., Cregut, D., Pereira, B., & Clavelou, P. (2015). Cognitive impairment in a population-based study of patients with multiple sclerosis: differences between late relapsing−remitting, secondary progressive and primary progressive multiple sclerosis. European Journal of Neurology, 23(2), 282–289. https://doi.org/10.1111/ene.12715
32. Morrow, S. A. (2024). Cognitive impairment in multiple sclerosis. Neuroimaging Clinics of North America, 34(3), 469–479. https://doi.org/10.1016/j.nic.2024.03.010
33. Morrow, S. A., Jurgensen, S., Forrestal, F., Munchauer, F. E., & Benedict, R. H. B. (2011). Effects of acute relapses on neuropsychological status in multiple sclerosis patients. Journal of Neurology, 258(9), 1603–1608. https://doi.org/10.1007/s00415-011-5975-3
34. Morrow, S. A., Weinstock, Z. L., Mirmosayyeb, O., Conway, D., Fuchs, T., Jaworski, M. G., Eckert, S., Hojnacki, D. H., Dwyer, M. G., Zivadinov, R., Weinstock-Guttman, B., & Benedict, R. H. B. (2023). Detecting isolated cognitive relapses in persons with MS. Multiple Sclerosis Journal, 29(14), 1786–1794. https://doi.org/10.1177/13524585231201219
35. Benedict, R. H., DeLuca, J., Phillips, G., LaRocca, N., Hudson, L. D., & Rudick, R. (2017). Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. Multiple Sclerosis Journal, 23(5), 721–733. https://doi.org/10.1177/1352458517690821
36. Langdon, D., Amato, M., Boringa, J., Brochet, B., Foley, F., Fredrikson, S., Hämäläinen, P., Hartung, H., Krupp, L., Penner, I., Reder, A., & Benedict, R. (2011). Recommendations for a brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Multiple Sclerosis Journal, 18(6), 891–898. https://doi.org/10.1177/1352458511431076
37. Potticary, H., & Langdon, D. (2023). A Systematic Review and Meta-Analysis of the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) International Validations. Journal of Clinical Medicine, 12(2), 703. https://doi.org/10.3390/jcm12020703

38. Freedman, M. S. (2006). Disease-modifying drugs for multiple sclerosis: current and future aspects. Expert Opinion on Pharmacotherapy, 7(sup1), S1–S9. https://doi.org/10.1517/14656566.7.1.s1
39. Bellinvia, A., Portaccio, E., & Amato, M. P. (2022). Current advances in the pharmacological prevention and management of cognitive dysfunction in multiple sclerosis. Expert Opinion on Pharmacotherapy, 24(4), 435–451. https://doi.org/10.1080/14656566.2022.2161882
40. Branger, P., Parienti, J., Sormani, M. P., & Defer, G. (2016). The Effect of Disease-Modifying Drugs on Brain Atrophy in Relapsing-Remitting Multiple Sclerosis: A Meta-Analysis. PLoS ONE, 11(3), e0149685. https://doi.org/10.1371/journal.pone.0149685
41. Sormani, M. P., Arnold, D. L., & De Stefano, N. (2013). Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. Annals of Neurology, 75(1), 43–49. https://doi.org/10.1002/ana.24018
42. Chen, M. H., Goverover, Y., Genova, H. M., & DeLuca, J. (2020). Cognitive Efficacy of pharmacologic Treatments in Multiple sclerosis: a Systematic review. CNS Drugs, 34(6), 599–628. https://doi.org/10.1007/s40263-020-00734-4
43. Cotter, J., Muhlert, N., Talwar, A., & Granger, K. (2018). Examining the effectiveness of acetylcholinesterase inhibitors and stimulant-based medications for cognitive dysfunction in multiple sclerosis: A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews, 86, 99–107. https://doi.org/10.1016/j.neubiorev.2018.01.006
44. DeLuca, J., Chiaravalloti, N. D., & Sandroff, B. M. (2020). Treatment and management of cognitive dysfunction in patients with multiple sclerosis. Nature Reviews Neurology, 16(6), 319–332. https://doi.org/10.1038/s41582-020-0355-1
45. Taylor, L. A., Mhizha-Murira, J. R., Smith, L., Potter, K., Wong, D., Evangelou, N., Lincoln, N. B., & Nair, R. D. (2021). Memory rehabilitation for people with multiple sclerosis. Cochrane Database of Systematic Reviews, 2021(10). https://doi.org/10.1002/14651858.cd008754.pub4
46. Sharbafshaaer, M., Trojsi, F., Bonavita, S., & Azimi, A. (2022). Integrated Cognitive Rehabilitation Home-Based Protocol to improve Cognitive functions in multiple sclerosis patients: a randomized controlled study. Journal of Clinical Medicine, 11(12), 3560. https://doi.org/10.3390/jcm11123560
47. Rayegani, S. M., Heidari, S., Seyed-Nezhad, M., Kiyani, N., & Moradi-Joo, M. (2024). Effectiveness of cognitive rehabilitation in comparison with routine rehabilitation methods in patients with multiple sclerosis: A systematic review and meta-analysis. Multiple Sclerosis Journal - Experimental Translational and Clinical, 10(3), 20552173241272561. https://doi.org/10.1177/20552173241272561
48. Klein, O. A., Drummond, A., Mhizha-Murira, J. R., Mansford, L., & dasNair, R. (2017). Effectiveness of cognitive rehabilitation for people with multiple sclerosis: a meta-synthesis of patient perspectives. Neuropsychological Rehabilitation, 29(4), 491–512. https://doi.org/10.1080/09602011.2017.1309323