

Cognition and sleep in people with multiple sclerosis: a scoping review

Cognição e sono de pessoas com esclerose múltipla: uma revisão de escopo

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ABSTRACT

Purpose: to map, through a scoping review, evidence on the relationship between cognition and sleep in individuals with multiple sclerosis. **Research strategy:** an active search of databases and gray literature was conducted to identify primary studies with freely available texts, without time and language limits. **Selection criteria:** data were analyzed using descriptive analysis and content analysis. **Results:** thirteen publications were eligible. Mainly cross-sectional studies were found, published in English, between 2016 and 2022, mostly concentrated in the northern hemisphere. The studies reviewed show that sleep disorders, whether identified objectively or subjectively, coexisted with cognitive decline in people with multiple sclerosis. **Conclusion:** It was observed that sleep disturbances coexisted with cognitive decline, among the most described cognitive domains were memory, attention, executive functions and processing speed.

Keywords: Multiple sclerosis; Cognition; Sleep; Review; Health research evaluation

RESUMO

Objetivo: mapear, por meio de revisão de escopo, evidências sobre a relação entre cognição e sono de indivíduos com esclerose múltipla. **Estratégia de pesquisa:** foi realizada busca ativa em bases de dados e na literatura cinzenta, a fim de identificar estudos primários, com textos disponibilizados gratuitamente, sem limite temporal e de idioma. **Crterios de seleção:** os dados foram analisados por meio de análises descritivas e da análise de conteúdo. **Resultados:** treze publicações foram elegíveis. Foram encontrados, principalmente, estudos transversais, publicados em inglês, entre 2016 e 2022, concentrando-se, na sua maioria, no hemisfério norte. Os estudos revisados mostraram que as alterações do sono, identificadas de modo objetivo ou subjetivo, coexistiram com declínio cognitivo em pessoas com esclerose múltipla. **Conclusão:** Observou-se que as alterações do sono coexistiram com alterações cognitivas, dentre os domínios cognitivos mais descritos estiveram a memória, a atenção, as funções executivas e a velocidade de processamento.

Palavras-chave: Esclerose múltipla; Cognição; Sono; Revisão; Avaliação da pesquisa em saúde

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INTRODUCTION

Multiple sclerosis (MS) is a progressive, inflammatory, neurodegenerative, demyelinating, autoimmune disease, involving lesions of the myelin sheaths of the central nervous system (CNS)⁽¹⁻³⁾. The initial clinical condition usually affects young adults between 20 and 40 years old, peaking at 30^(4,5).

Due to the diversity of lesions in various areas of the CNS, MS may have a variety of symptoms and clinical evolution^(6,7). Fatigue, visual disturbances, weakness, spasticity, paresthesia, and changes in balance and coordination are the main symptoms. In addition, sleep difficulties and cognitive decline are frequent in cases of MS^(8,9). Approximately 50% of people with this disease are estimated to have some diagnosed sleep disorder and 67% report sleep-related complaints. These changes have a multifactorial etiology⁽¹⁰⁾. The prevalence of sleep disorders in people with MS is higher than in healthy controls, and the disease is strongly associated with these disorders⁽¹¹⁾. People with MS suffer from primary sleep disorders, such as obstructive sleep apnea (OSA), insomnia, and restless legs syndrome (RLS). There is also an association between poor sleep quality and worse cognitive performance⁽¹²⁻¹⁵⁾.

Sleep difficulties in MS – particularly OSA – are considered risk factors for cognitive decline⁽¹⁶⁾. Changes in sleep efficiency may be related to poorer performance in tasks involving executive function, attention, verbal memory, working memory, visual memory, and language function^(16,17).

Moreover, studies show that cognitive decline is a very common clinical characteristic of the disease, affecting 40% to 70% of people diagnosed in both the early and later stages of the disease, and the changes tend to progress over time^(16,17). It is also mentioned that, despite its high prevalence, there are no defined treatments for cognitive decline in MS⁽¹⁸⁾.

Purpose

This research aimed to contribute to the expansion of scientific knowledge on the topic in question. The objective of this work was to map, through a scoping review, evidence on the relationship between cognition and sleep in individuals with MS.

Research strategy

This is a scoping review – a study that maps the literature in a given field of interest, especially when reviews on the topic have not yet been published. It is considered a solid approach to synthesizing evidence in health⁽¹⁹⁻²¹⁾. This study was developed according to the methodology proposed by the Joanna Briggs Institute (JBI)⁽²¹⁾, in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – Extension for Scoping Reviews (PRISMA-ScR)^(22,23) – which proposes the steps for preparing a scoping review, as followed in this study.

The research question – “What are the clinical characteristics of cognition and sleep in people with MS, and what is the relationship between the two?” – and the search strategy were developed based on the PCC acronym (P = person; C = context; C = concept), as follows: P = human beings; C = multiple sclerosis; C = cognition and sleep.

The inclusion criteria were freely available primary national and international scientific studies characterizing and exploring the relationship between cognition and sleep in people with MS in all age groups, with no restrictions on time or language.

The exclusion criteria were duplicate studies; those that did not address the characteristics of and relationship between cognition and sleep in MS; those that cited other neurological and/or neuromuscular diseases in general; those that did not specify the characteristics in MS; and secondary studies.

The search strategies were defined by screening the LILACS, PubMed/MEDLINE, Scopus, Web of Science, and Embase databases and the gray literature, with pertinent adaptations to each database. The keywords were chosen based on the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH), as follows: “*esclerose múltipla/multiple sclerosis; cognição/cognition; linguagem/language; sono/sleep*”. The Boolean operators AND and OR were applied to cross-reference the descriptors (Appendix 1).

Selection criteria

Two researchers carried out this stage independently, analyzing the texts found according to the inclusion and exclusion criteria to define the relevant studies. When they disagreed on including or excluding a study, a third researcher resolved the issue. This process was carried out in two phases, namely:

- a) First phase: the searches were exported to the Rayyan program. Two reviewers read and analyzed the titles and abstracts blindly. The blind spot mechanism provided by the platform ensured the blinded recording of each researcher’s responses.
- b) Second phase: the studies selected in the previous stage were read in full, excluding those that did not meet the eligibility criteria. This stage was also carried out blindly by two reviewers. In cases of conflict, the third reviewer was consulted. Lastly, they defined the studies that comprised the research.

Data analysis

They began extracting data after reading and selecting the studies, using an information mapping form developed on Microsoft Word with the following variables: author(s), year and country of publication, method, objective(s), sample, instruments used to measure cognition, objective or subjective sleep assessment instrument/measure, and main results on the relationship between cognition and sleep. Then, the assessment instruments/measures were analyzed and described according to author(s) and year of publication.

Qualitative variables were analyzed using the content analysis method to identify compatibility between the selected studies. Quantitative variables were interpreted using simple descriptive statistics.

Moreover, the risk of bias was assessed by two reviewers independently, who categorized each article based on the following criteria: high, for a score of up to 49%; moderate, when the score was 50% to 69%; and low, when it exceeded 70% of “yes” scores for the questions about the risk of bias.

When necessary, disagreements were discussed, and a third reviewer was consulted.

RESULTS

This scoping review identified 735 articles in the databases. Of these, 288 were excluded for being duplicates. Of the 447 remaining studies, 416 were excluded in the first phase for not addressing the topic or not being related to the research question. Then, the articles were read in full (phase 2), and 18 studies were excluded (Appendix 2), of which 14 were conference abstracts and secondary studies, and four did not address cognition and sleep in MS or addressed other diseases.

Furthermore, 51 studies were identified in the gray literature, and 48 were excluded for not addressing the topic. In phase 2, the remaining three studies were excluded because they had already been selected. Thus, 13 articles were selected to compose the sample of this study.

The selection process is shown in Figure 1.

Chart 1 presents the main characteristics of the 13 studies that comprised the sample. All these studies performed inferential statistical analysis, with a p-value of 5% ($p < 0.05$) as the level of significance. Five of them had a low risk of bias, while eight had a moderate risk.

Regarding the year of publication, the articles were published between 2016 and 2022. Regarding the distribution by country, the studies were more concentrated in the northern hemisphere.

Various instruments were used to assess cognition, predominantly the Symbol Digit Modalities Test (SDMT)^(16-18,27-31), Paced Auditory Serial Addition Test (PASAT)^(11,17,18,25,27,29); Brief Visuospatial Memory Test (BVMt)^(17,18,28,29,31); California

Verbal Learning Test (CVLT-II)^(11,18,28,29); Stroop Test^(11,17,27,31); Controlled Oral Word Association Test (COWAT)^(11,18); and Brief International Cognitive Assessment for MS (BICAMS)^(28,29).

Regarding subjective sleep assessment instruments, 38% of the studies used the Pittsburgh Sleep Quality Index (PSQI), and 23% applied the Epworth Sleepiness Scale (ESS)^(28,30,32) as a self-reported measure of sleep. Polysomnography (PSG) was also predominant as an objective measure of sleep. The cognition and sleep assessment instruments used in the studies are summarized in Chart 2.

The main sleep difficulties were excessive daytime sleepiness (46%)^(16,18,24,28,30,32), sleep-related breathing difficulties (25%)^(18,28,29), OSA (15%)^(18,29), insomnia (7%)⁽³⁰⁾, and RLS (7%)⁽²⁶⁾.

Also, the following cognitive domains stood out: verbal, visuospatial, and working memory (84%)^(11,16-18,24,26,27,29,31,32); selective, divided, and alternating attention (76%)^(11,16-18,24,26,28-30,32); executive function (61%)^(11,18,24,26,28-30,32); processing speed (46%)^(17,18,24,26,29,30), and language (15%)^(18,28). The studies mostly reported memory decline related to sleep quality complaints^(17,26,27,31).

The results demonstrate the relationship between cognition and sleep-related complaints, describing that the interaction between factors can increase the risk of cognitive decline when such complaints are present^(11,16-18,24-32).

DISCUSSION

This review mapped and presented studies that characterize and explore cognition and sleep in people with MS. In general, the evidence selected to compose the review^(11,16-18,24-32) demonstrated

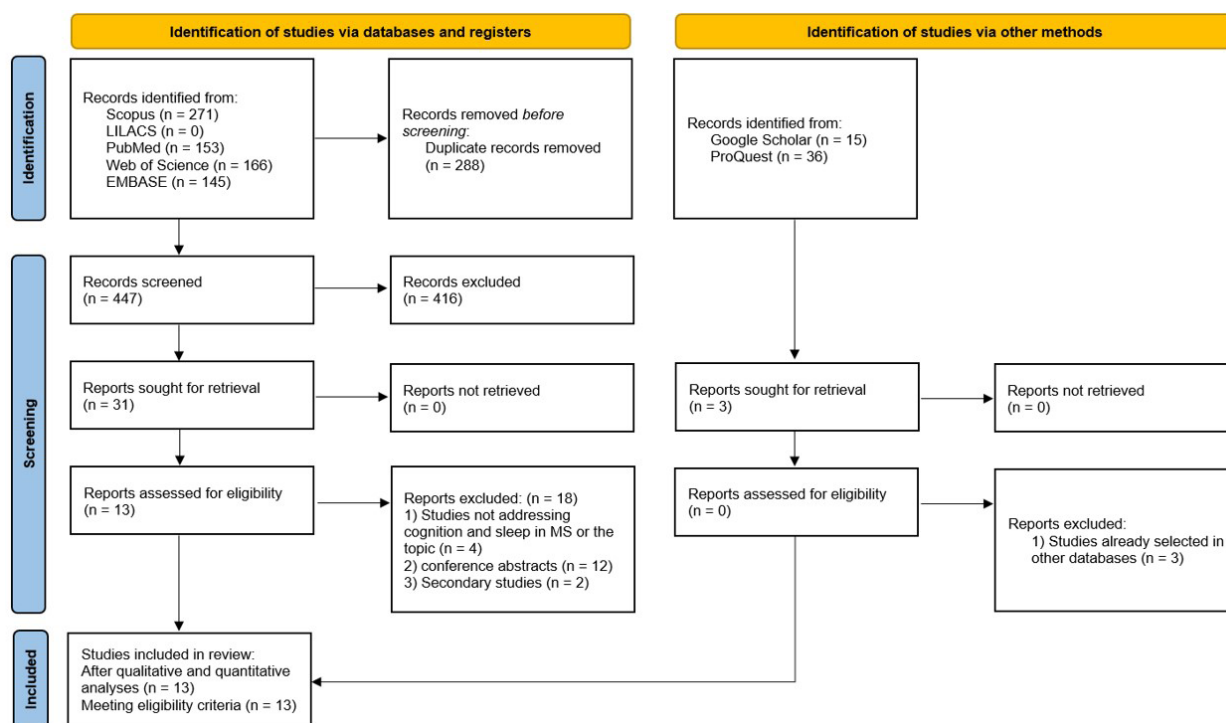


Figure 1. Process of selecting the evidence that made up the study
Caption: n = number of records/reports/studies; MS = multiple sclerosis

Chart 1. Description of information on the cognitive and sleep patterns of people with multiple sclerosis (n = 13)

Author(s), Year, and country	Method	Objective(s)	Sample	Cognition assessment instrument	Sleep assessment instrument/measure	Main results on the relationship between sleep and cognition
Hughes et al., 2017 ⁽¹¹⁾ Estados Unidos	Cross-sectional	To examine the relationship between self-reported sleep and objective and perceived cognitive impairment in MS.	121 people with MS.	CVLT-II; SCWT; PASAT; COWAT; and PDQ	PSQI	Self-reported sleep in MS has been linked to cognitive impairment, particularly impairments in planning, organization, and prospective memory.
Siengsakon et al., 2018 ⁽¹⁷⁾ Estados Unidos	Cross-sectional	To examine the relationship between sleep quality and cognitive and physical function in individuals with mild MS.	40 people with MS.	BVMT; HVL; PASAT; SDMT; and SCWT	PSQI	Individuals who reported good sleep quality performed significantly better on visuospatial memory tests and had greater functional abilities than those with poor sleep quality.
Van Geest et al., 2018 ⁽¹⁶⁾ Holanda	Case-control	To investigate the relationship between sleep, cognitive functioning, and resting-state cognitive fatigue of the hippocampus and thalamus in MS.	71 people with MS and 40 healthy controls.	VLGT; LDST; LLT; DGS; WLG; and CFS	AIS	People with sleep difficulties reported more subjective cognitive problems and had decreased functional connectivity than people without sleep difficulties.
Braley et al., 2016 ⁽¹⁸⁾ Estados Unidos	Cross-sectional	To examine associations between objective measures of obstructive sleep apnea and cognitive function in patients with MS.	38 adults with MS.	MACFIMS	PSG	Obstructive sleep apnea and other sleep difficulties have been associated with decreased visual memory, verbal memory, executive function, attention, processing speed, and working memory.
Borrágan et al., 2018 ⁽²⁴⁾ Bélgica	Case-control	To investigate the association between the triggering of cognitive fatigue, brain activity, and sleep characteristics.	10 people with MS and 11 healthy controls.	TloadBack	PSG	In people with MS, activation of the dorsolateral prefrontal cortex (DLPFC) had a statistically significant effect on triggering cognitive and physical fatigue (42% variance). Furthermore, total sleep time had a statistically significant effect on triggering cognitive and physical fatigue (29% variance).
Berard et al., 2018 ⁽²⁵⁾ Canadá	Cohort	To examine the interrelationship between fatigue, depression, sleep difficulties, and cognitive fatigue in MS.	58 people with MS.	PASAT	PSQI	Sleep quality was considered the greatest predictor of cognitive fatigue in MS, according to subjective measures.
Cederberg et al., 2020 ⁽²⁶⁾ Estados Unidos	Cross-sectional	To examine the relationships between prevalence and severity of restless legs syndrome, perceived sleep quality, and perceived cognitive impairment in a sample of adults with MS.	275 people with MS.	MSNQ	PSQI; CH-RLSq, and IRLS.	Greater severity of restless legs syndrome-related symptoms was significantly associated with more severe cognitive impairment and poorer overall sleep quality.
Chinnadurai et al., 2018 ⁽²⁷⁾ India	Cross-sectional	To determine the existence of a relationship between objective measures of sleep and measures of physical and cognitive fatigue in patients with MS.	113 participants with EM.	MFIS-C; Stroop, modified version; SDMT; PASAT	PSG	Polysomnographic sleep measures had a strong, positive, and statistically significant correlation with objective cognitive fatigue measures, which was not observed with physical fatigue measures.
Hashim et al., 2020 ⁽²⁸⁾ Egito	Cross-sectional	To explore the relationship between respiratory function and cognitive profile in a cohort of people with MS.	146 people with MS.	BICAMS and PDQ	ESS; Spirometry and functional assessment of respiratory muscles	Impaired respiratory functions in MS were associated with self-reported sleep difficulties and cognitive impairment.
McNicholas et al., 2021 ⁽²⁹⁾ Irlanda	Cohort	To investigate the effects of OSA treatment on cognitive function and fatigue in people with MS.	23 participants with MS.	BICAMS and PASAT	PSG	People treated for OSA, compared with those who were not treated for a sleep disorder, had better verbal learning at the follow-up assessment.
Patel et al., 2017 ⁽³⁰⁾ Canadá	Cross-sectional	To explore the association between a sleep index, distraction, and cognitive impairment in people with MS.	102 participants with MS.	SDMT	ESS	Participants with excessive daytime sleepiness performed significantly slower on the distractor c-SDMT than those with normal sleepiness.
Sumowski et al., 2021 ⁽³¹⁾ Estados Unidos	Case-control	To investigate whether subjective sleep disorder is linked to worse memory in early MS.	185 patients with MS and 50 healthy controls.	CANTAB; BVMT; SRT; VPA; SDMT; SCWT; and NIH Toolbox	ISI	Participants with sleep difficulties had worse memory than people who denied these difficulties.

Caption: MS = multiple sclerosis; OSS = obstructive sleep apnea; REM = rapid eyes movement

Abbreviations for language/cognition measurement instruments: BICAMS = Brief International Cognitive Assessment for Multiple Sclerosis; BRB-N = The Brief Repeatable Battery of Neuropsychological Tests; BVMT = Brief Visuospatial Memory Test; CANTAB = The Cambridge Neuropsychological Test Automated Battery; CFS = Cognitive Function Scale; COWAT = Controlled Oral Word Association Test; CVLT-II = California Verbal Learning Test-II; DGS = Digit Span; HVL = Hopkins Verbal Learning Test; LDST = Letter Digit Substitution Test; LLT = Location Learning Test; MACFIMS = Minimal Assessment of Cognitive Function in MS; MFIS-C = version of Modified Fatigue Impact Scale; MSNQ = Multiple Sclerosis Neuropsychological Screening Questionnaire; NIH Toolbox = Pattern Comparison Processing Speed Test; PASAT = Paced Auditory Serial Addition Test; PDQ = Perceived Deficits Questionnaire; SCWT = Stroop Color and Word Test; SDMT = Symbol Digit Modalities Test; SRT = Selective Reminding Test; TloadBack = The Time Load Dual-Back; VPA = Verbal Paired Associate; VLGT = Verbale Leer Geheugen Test; WLG = Word List Generation

Abbreviations for sleep assessment measures/instruments: AIS = Athens Insomnia Scale; CH-RLSq = Cambridge-Hopkins Questionnaire; ESS = Epworth Sleepiness Scale; IRLS = Restless Legs Syndrome Rating Scale; ISI = Insomnia Severity Index; PSG = Polysomnography; PSQI = Pittsburgh Sleep Quality Index

Chart 1. Continued...

Author(s), Year, and country	Method	Objective(s)	Sample	Cognition assessment instrument	Sleep assessment instrument/measure	Main results on the relationship between sleep and cognition
Riccitelli et al., 2022 ⁽³²⁾ Suiça	Cross-sectional	To investigate the relationship between cognitive impairment and sleep disorders and the role of anxiety and depression in this relationship in people with MS.	80 people with MS.	BRB-N	PSQI and ESS	In the study group, the global cognitive scores and the cognitive functions of memory and attention were statistically significantly related to greater sleep efficiency and a lower occurrence of awakening after the onset of sleep. The percentage of REM sleep was statistically significantly related to the cognitive domain of attention.

Caption: MS = multiple sclerosis; OSS = obstructive sleep apnea; REM = rapid eyes movement

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Chart 2. Characterization of the most used instruments for assessing cognition and sleep in multiple sclerosis

Instruments for assessing cognition and sleep in people with MS	Description	Authors that used them/year
COGNITION		
Symbol Digit Modalities Test (SDMT) ⁽³³⁾	Objective assessment of psychomotor speed, attention, and working memory.	Braley et al., 2016 ⁽¹⁸⁾ Chinnadurai et al., 2018 ⁽²⁷⁾ Hashim et al., 2020 ⁽²⁸⁾ McNicholas et al., 2021 ⁽²⁹⁾ Patel et al., 2017 ⁽³⁰⁾ Siengsukon et al., 2018 ⁽¹⁷⁾ Sumowski et al., 2021 ⁽³¹⁾ Van Geest et al., 2016 ⁽¹⁶⁾
Paced Auditory Serial Addition Test (PASAT) ⁽³⁴⁾	Objective assessment of processing speed, working memory, and divided attention.	Braley et al., 2016 ⁽¹⁸⁾ Berard et al., 2018 ⁽²⁵⁾ Chinnadurai et al., 2018 ⁽²⁷⁾ Hughes et al., 2017 ⁽¹¹⁾ McNicholas et al., 2021 ⁽²⁹⁾ Siengsukon et al., 2018 ⁽¹⁷⁾
Brief Visuospatial Memory Test (BVMT) ⁽³⁵⁾	Objective assessment of visuospatial memory.	Braley et al., 2016 ⁽¹⁸⁾ Hashim et al., 2020 ⁽²⁸⁾ McNicholas et al., 2021 ⁽²⁹⁾ Siengsukon et al., 2018 ⁽¹⁷⁾ Sumowski et al., 2021 ⁽³¹⁾
California Verbal Learning Test (CVLT-II) ⁽³⁶⁾	Objective assessment of memory, verbal learning, and executive functioning.	Braley et al., 2016 ⁽¹⁸⁾ Hashim et al., 2020 ⁽²⁸⁾ Hughes et al., 2017 ⁽¹¹⁾ McNicholas et al., 2021 ⁽²⁹⁾
Stroop Test ⁽³⁷⁾	Objective assessment of selective attention, inhibition, cognitive flexibility, processing speed, and verbal fluency.	Chinnadurai et al., 2018 ⁽²⁷⁾ Hughes et al., 2017 ⁽¹¹⁾ Siengsukon et al., 2018 ⁽¹⁷⁾ Sumowski et al., 2021 ⁽³¹⁾
Controlled Oral Word Association Test (COWAT) ⁽³⁸⁾	Objective assessment of verbal fluency.	Braley et al., 2016 ⁽¹⁸⁾ Hughes et al., 2017 ⁽¹¹⁾
Brief International Cognitive Assessment for MS (BICAMS) ⁽³⁹⁾	Objective assessment of processing speed and learning.	Hashim et al., 2020 ⁽²⁸⁾ McNicholas et al., 2021 ⁽²⁹⁾
Perceived Deficits Questionnaire (PDQ) ⁽⁴⁰⁾	Questionnaire on the frequency of cognitive problems from the person's perspective.	Hashim et al., 2020 ⁽²⁸⁾ Hughes et al., 2017 ⁽¹¹⁾
Neuropsychological screening questionnaire (MSNQ) ⁽⁴¹⁾	Questionnaire related to deficits in processing speed, attention, memory, executive function, and behavior.	Cederberg et al., 2020 ⁽²⁶⁾

Caption: MS = multiple sclerosis

Source: Developed by the authors

Chart 2. Continued...

Instruments for assessing cognition and sleep in people with MS	Description	Authors that used them/year
SLEEP		
Pittsburgh Sleep Quality Index (PSQI) ⁽⁴²⁾	Subjective sleep quality assessment questionnaire.	Berard et al., 2018 ⁽²⁵⁾ Cederberg et al., 2020 ⁽²⁶⁾ Hughes et al., 2017 ⁽¹¹⁾ Siegnasukon et al., 2018 ⁽¹⁷⁾ Riccitelli et al., 2022 ⁽³²⁾
Epworth Sleepiness Scale (ESS) ⁽⁴³⁾	Subjective scale of the probability of dozing or falling asleep in routine situations.	Hashim et al., 2020 ⁽²⁸⁾ Patel et al., 2017 ⁽³⁰⁾ Riccitelli et al., 2022 ⁽³²⁾
Polysomnography (PSG) ⁽¹⁶⁾	Objective assessment that records physiological variables during sleep. It assesses sleep onset latency, total sleep time, distribution and time of each sleep stage, awakening rate, and sleep efficiency.	Braley et al., 2016 ⁽¹⁸⁾ Borrogán et al., 2018 ⁽²⁴⁾ Chinnadurai et al., 2018 ⁽²⁷⁾ McNicholas et al., 2021 ⁽²⁹⁾

Caption: MS = multiple sclerosis

Source: Developed by the authors

that complaints of sleep difficulties coexisted with changes in cognitive function and were related to other clinical variables in this disease.

The discussion will address the following analysis subtopics based on collected data and study analysis: 1) Clinical characteristics of cognition in MS patients; 2) Clinical characteristics of sleep in MS patients; 3) Relationship between cognition and sleep in MS.

Clinical characteristics of cognition in MS patients

The cognitive functions associated with sleep in MS were memory^(17,18,28,29,32), attention^(18,28,30), processing speed⁽¹⁸⁾, and executive function⁽¹⁸⁾, repeatedly demonstrating that MS has cognitive decline as a very common clinical characteristic. PSG measures showed reduced/absent results in N3 (deep sleep stage) and REM (rapid eye movement stage), which may compromise memory and learning⁽²⁷⁾. One possible explanation is that sleep is involved in aspects of brain plasticity and can restore cellular homeostasis, allowing the brain to cope with daily cognitive demands^(34,35).

Thus, cognitive decline in MS was related to OSA^(18,29). Hypoxia⁽¹⁸⁾ and nighttime oxygen desaturation in OSA⁽²⁹⁾ may influence cognitive decline. Impaired respiratory muscles were associated with sleep disorders, mainly excessive daytime sleepiness and cognitive decline⁽²⁸⁾. It is important to note that respiratory disorders are common throughout the disease, such as respiratory muscle weakness, central sleep apnea, OSA, sleep-disordered breathing, and so forth⁽³³⁾.

On the other hand, a study⁽¹⁶⁾ did not find differences in objective cognitive functioning between people with and without sleep difficulties who had the same level of education and similar structural magnetic resonance imaging measures. However, those with sleep difficulties reported an increase in subjective cognitive problems. Moreover, subjective cognitive decline was associated with sleep quality and RLS⁽²⁶⁾. The study used the PSQI and the MS Neuropsychological Screening Questionnaire (MSNQ) as self-report measures and suggested that RLS symptoms may be a predictor of poor sleep quality and further aggravate the cognitive impairments perceived in people with MS⁽²⁶⁾.

Authors⁽²⁸⁾ have suggested that early assessment and treatment of respiratory functions may reduce respiratory complications and sleep and cognition impairments in MS. The studies assessed sleep quality using subjective scales and questionnaires, with a predominance of the PSQI and ESS^(11,17,25,26,28,30,32). These self-reported measures are quick-to-apply screenings, an important starting point for sleep intervention⁽³⁶⁾. Objective assessments were also used, such as PSG^(18,24,27,29), considered the gold standard method for diagnosing sleep disorders. The literature reinforces the importance of PSG as an objective measure to quantify sleep, as it is a more accurate method than self-reported measures^(36,37). The need for objective measures to assess sleep behavior associated with memory was highlighted in a study that found that people with sleep difficulties in MS reported worse memory than controls. They also stated that the potential mechanisms linking sleep difficulties with memory are still poorly understood³¹. However, studies have already demonstrated an association between fatigue in MS and brain atrophy, changes in brain connectivity, dopamine alterations, and variations in neuroendocrine levels⁽²⁴⁾.

Clinical characteristics of sleep in MS patients

The evidence found in this review presented factors associated with cognitive decline and sleep in MS, such as fatigue, depression, anxiety, and physical functions.

Fatigue is one of the most reported symptoms in people with MS⁽²⁴⁾, developing faster than in the general population^(38,39). Variations in fatigue in MS can affect different cognitive demands, making it more likely to trigger cognitive fatigue (CF)⁽²⁴⁾. Impaired sleep efficiency can reduce brain compensatory mechanisms, increase CF onset, and reduce cognitive performance⁽²⁴⁾. Furthermore, one study⁽²⁵⁾ showed that sleep quality was the strongest predictor of CF, in which sleep quality and depression are suggested to play a predictive role.

Relationship between cognition and sleep in MS

Various studies^(25,30,32,40,41) have reported the relationship between sleep difficulties, cognitive impairment, and psychiatric

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Appendix 1. Database search strategy

Database	Search (July 10, 2022)
LILACS 0	("Language" OR "linguagem" OR "lenguaje" OR "Transtornos da Linguagem" OR "Trastornos del lenguaje" OR "Language Disorders" OR "Language Disorder" OR "Cognition" OR "Cognitions" OR "Cognición" OR "Cognição" OR "Cognitive Function" OR "Cognitive Functions" OR "Cognition Disorders") AND ("sueño" OR "sono" OR "Sleep") AND ("Multiple Sclerosis" OR "Esclerosis Múltiple" OR "esclerose múltipla") AND (db:("LILACS"))
PubMed/MEDLINE 153	("Language"[MeSH Terms] OR "Language"[All Fields] OR "Language Disorders"[MeSH Terms] OR "Language Disorders"[All Fields] OR "Language Disorder"[All Fields] OR "Cognition"[MeSH Terms] OR "Cognition"[All Fields] OR "Cognitions"[All Fields] OR "Cognitive Function"[All Fields] OR "Cognitive Functions"[All Fields] OR "Cognition Disorders"[MeSH Terms] OR "Cognition Disorders"[All Fields]) AND ("Sleep"[MeSH Terms] OR "Sleep"[All Fields]) AND ("Multiple Sclerosis"[MeSH Terms] OR "Multiple Sclerosis"[All Fields])
EMBASE 145	#4 #1 AND #2 AND #3 #3 ('language':ab,ti OR 'language disorders':ab,ti OR 'language disorder':ab,ti OR 'cognition':ab,ti OR 'cognitions':ab,ti OR 'cognitive function':ab,ti OR 'cognitive functions':ab,ti OR 'cognition disorders':ab,ti) #2 'sleep':ab,ti #1 'multiple sclerosis':ab,ti
Scopus 271	(TITLE-ABS-KEY ("Language" OR "Language Disorders" OR "Language Disorder" OR "Cognition" OR "Cognitions" OR "Cognitive Function" OR "Cognitive Functions" OR "Cognition Disorders") AND TITLE-ABS-KEY ("sleep") AND TITLE-ABS-KEY ("Multiple Sclerosis"))
Web of Science 166	("Language" OR "Language Disorders" OR "Language Disorder" OR "Cognition" OR "Cognitions" OR "Cognitive Function" OR "Cognitive Functions" OR "Cognition Disorders") (Todos os campos) AND ("Sleep") (Todos os campos) AND ("Multiple Sclerosis") (Todos os campos)
Google Scholar (analyzing the first 100)	("Language") AND ("Sleep") AND ("Multiple Sclerosis") filetype:PDF
ProQuest 37	NOFT("Language" OR "Language Disorders" OR "Language Disorder" OR "Cognition" OR "Cognitions" OR "Cognitive Function" OR "Cognitive Functions" OR "Cognition Disorders") (Todos os campos) AND NOFT("Sleep") (Todos os campos) AND NOFT("Multiple Sclerosis") (Todos os campos)

Appendix 2. Articles excluded and reasons

Author, year	Reason for exclusion
Rajizadeh et al., 2019 ⁽¹⁾	1
Kotterba et al., 2003 ⁽²⁾	1
Motaharinezhad et al., 2016 ⁽³⁾	1
Türkoğlu et al., 2020 ⁽⁴⁾	1
Kopchak et al., 2020 ⁽⁵⁾	2
Motyl et al., 2018 ⁽⁶⁾	2
McNicholas et al., 2018 ⁽⁷⁾	2
Van Geest et al., 2015 ⁽⁸⁾	2
Turner et al., 2019 ⁽⁹⁾	2
Hughes et al., 2017 ⁽¹⁰⁾	2
Conti et al., 2017 ⁽¹¹⁾	2
Braley et al., 2017 ⁽¹²⁾	2
Braky e Katz, 2015 ⁽¹³⁾	2
Chernenko et al., 2020 ⁽¹⁴⁾	2
Braley et al., 2014 ⁽¹⁵⁾	2
Hughes et al., 2015 ⁽¹⁶⁾	2
Arnett e Strober, 2011 ⁽¹⁷⁾	3
Malhotra, 2016 ⁽¹⁸⁾	3

Caption: 1 = Studies that do not address cognition and sleep in multiple sclerosis or do not address the topic (n = 4); 2 = Conference abstracts (n = 12); 3 = Secondary studies (n = 2)

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