Revista Iberoamericana de Neuropsicología, Vol. 9, No. 2: 83-111, julio-diciembre, 2026.

Measuring cognitive reserve in multiple sclerosis: A systematic review of neuropsychological questionnaires and instruments

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ABSTRACT

Objective: *To systematically review the instruments used to measure cognitive reserve in adults with multiple sclerosis.*
Method: *A systematic review was conducted following PRISMA guidelines. Studies published between 2013 and 2024 were identified through PubMed, SciELO, and Google Scholar. A total of 67 studies comprising 10,353 adults with MS met the inclusion criteria. The selected studies were analyzed according to their methodological design, sample characteristics, and the instruments used to assess cognitive reserve.*
Results: *Considerable heterogeneity was observed in the assessment of cognitive reserve. The most frequently used measures included questionnaires evaluating engagement in cognitively stimulating activities, particularly the Cognitive Reserve Index Questionnaire (CRIq) and related instruments, as well as word-reading tasks such as the National Adult Reading Test (NART) and the Wechsler Test of Adult Reading (WTAR). Both questionnaire-based and neuropsychological approaches were commonly used as proxy measures of cognitive reserve.*
Conclusion: *No single gold-standard instrument for assessing cognitive reserve in MS was identified. Current approaches rely on heterogeneous proxy measures that differ in their theoretical foundations and psychometric characteristics. Greater methodological standardization and validation of cognitive reserve measures in MS populations are needed to improve comparability across studies and support clinical application.*

Keywords:

cognitive reserve, multiple sclerosis, measurement instruments, neurocognitive test, questionnaires.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic, neurodegenerative, inflammatory, and demyelinating disease that affects the central nervous system. It has a variable course of progression and can lead to physical, cognitive, and emotional changes[1]. MS is twice as prevalent in women as in men and typically begins during the most productive phase of life, usually between the ages of 20 and 50. It is estimated that 40% to 60% of patients with MS experience cognitive dysfunctions, which affect specific cognitive domains and negatively impact various aspects of daily life, such as the ability to maintain employment and social life[2].

Stern[3-4] has repeatedly suggested that there is a disjunction between the level of brain damage or pathology and its clinical manifestations. He notes that it is possible to observe that individuals who did not exhibit clinical signs of dementia can meet the neuropathological criteria for Alzheimer's disease upon autopsy. This observation led Stern to develop the theoretical concept of cognitive reserve (CR). CR suggests that individual differences in cognitive processes or neural systems underlying performance on various tasks allow some people to better cope with brain damage than others; in other words, the brain actively tries to cope with damage by using pre-existing cognitive resources[3-4]. CR has been described as an individual's ability to adapt cognitive processes in response to brain atrophy and has been used to explain individual differences in cognitive outcomes following brain atrophy[5].

It is important to distinguish CR from related concepts such as brain reserve and brain maintenance. Brain reserve refers to quantitative neurobiological characteristics, including brain size, neuronal count, or synaptic density, that may provide passive protection against neuropathology. Brain maintenance, in contrast, refers to the preservation of brain integrity and the reduced accumulation of age- or disease-related neural changes over time. CR differs from both concepts in that it emphasizes the active and flexible recruitment of cognitive processes and neural networks that allow individuals to cope more effectively with brain pathology despite comparable levels of damage[5].

Initially, research on CR was primarily focused on Alzheimer's disease; however, it later expanded to other neurological diagnoses. MS constitutes a particularly valuable model for the study of cognitive reserve because of the marked heterogeneity observed in cognitive outcomes among individuals with similar disease characteristics and levels of brain pathology. Consequently, numerous studies have examined the relationship between CR and cognitive functioning in people with MS (PwMS). One of the first studies aimed at analyzing whether a higher level of cognitive reserve moderated the relationship between MS and cognitive functioning was conducted by Sumowski et al.[6]. Subsequently, various authors have dedicated themselves to expanding and continuing this line of research. They all conclude that higher levels of CR mitigate the impact of MS on various cognitive domains[7-10]. This suggests that cognitive reserve may have a protective role against cognitive decline in MS.

According to Stern[3-5], CR is commonly operationalized using various proxy indicators such as years of education, occupational complexity, leisure and physical activities, intelligence quotient, socioeconomic status, and other protective factors[3-4]. Some authors have suggested that there is a division in the methods used to measure this construct, as some studies tend to consider only premorbid indicators of CR (e.g., educational and leisure activities performed before the onset of MS), while other studies take into account continuous participation in leisure and occupational activities, including those carried out after diagnosis. Based on this, these authors mention that CR should not be limited to premorbid factors that are not susceptible to change; instead, it should be considered that CR can be built and maintained over time through participation in cognitively stimulating activities[11]. Likewise, CR should not be considered synonymous with premorbid intelligence or intellectual enrichment. Premorbid IQ represents an estimate of an individual's cognitive functioning before the onset of neurological

disease, whereas intellectual enrichment refers to lifelong exposure to cognitively stimulating experiences such as education, occupational attainment, literacy, and leisure activities. Although these variables are frequently used as proxy indicators of CR, they represent only some of the factors that may contribute to the development and expression of reserve[5,12].

The methods of measuring CR can vary depending on whether a single variable, such as education, is taken into account or tools that include several indices from which a total score is obtained are used[12]. Despite this variability, as Sierra Sanjurjo and Burin[13] suggest, estimating an individual's prior cognitive level is what will allow the determination of whether there is indeed a decline by comparing the current cognitive profile with the previous one. For this reason, it is highly relevant to have various tools, whether questionnaires or neurocognitive tasks, that allow for the estimation of patients' CR levels. Additionally, Sandroff et al.[11] suggests that CR is also a relevant factor in cognitive rehabilitation for MS patients, as rehabilitation approaches focus on modifiable goals related to building reserve, i.e., they aim to encourage participation in cognitively stimulating activities.

Given the high prevalence of cognitive impairments in PwMS, the variability in how these dysfunctions manifest, and the potential influence of CR as a protective factor against cognitive decline, this study aims to provide a comprehensive literature review of the tools used to measure cognitive reserve in adults with MS.

METHOD

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, ensuring a clear and transparent presentation of the processes and results[14].

Literature Search

A literature search was carried out for studies published between January 2013 and April 2024. Three databases were used for this work (PubMed, Scielo, and Google Scholar), and the following combination of terms was entered: "cognitive reserve and multiple sclerosis," "brain reserve and multiple sclerosis," "premorbid intelligence and multiple sclerosis," "Word Accentuation Test and premorbid intelligence," "National Adult Reading Test and multiple sclerosis," "National Adult Reading Test and premorbid intelligence."

Eligibility Criteria

Only studies that met the following eligibility criteria were included: (I) original articles, (II) published between January 2013 and April 2024, (III) written in English or Spanish, (IV) included at least one instrument measuring some aspect of CR (questionnaire or neurocognitive test), (V) evaluated patients with a diagnosis of MS in any clinical form, and (VI) patients were over 18 years of age at the time of assessment. Studies that used only sociodemographic variables as a measure of CR (e.g., years of education or employment status) were excluded. Literature reviews, meta-analyses, conference papers, theses, book chapters, and posters were not included.

Data Analysis

The articles obtained from the literature search were exported for analysis using the Mendeley Desktop reference manager. After exportation, duplicate articles were removed. The remaining studies were then screened to determine whether they met the established inclusion criteria, following these steps: 1) title and abstract screening, 2) full-text screening. The flow diagram (Figure 1) details the different phases of study selection. Two independent reviewers independently screened all titles, abstracts, and full-text articles identified through the search strategy. Any disagreements regarding study eligibility were discussed and resolved by consensus.

RESULTS

The literature search yielded a total of 1,268 articles, of which 67 were ultimately included in this work for meeting all inclusion criteria. Among all

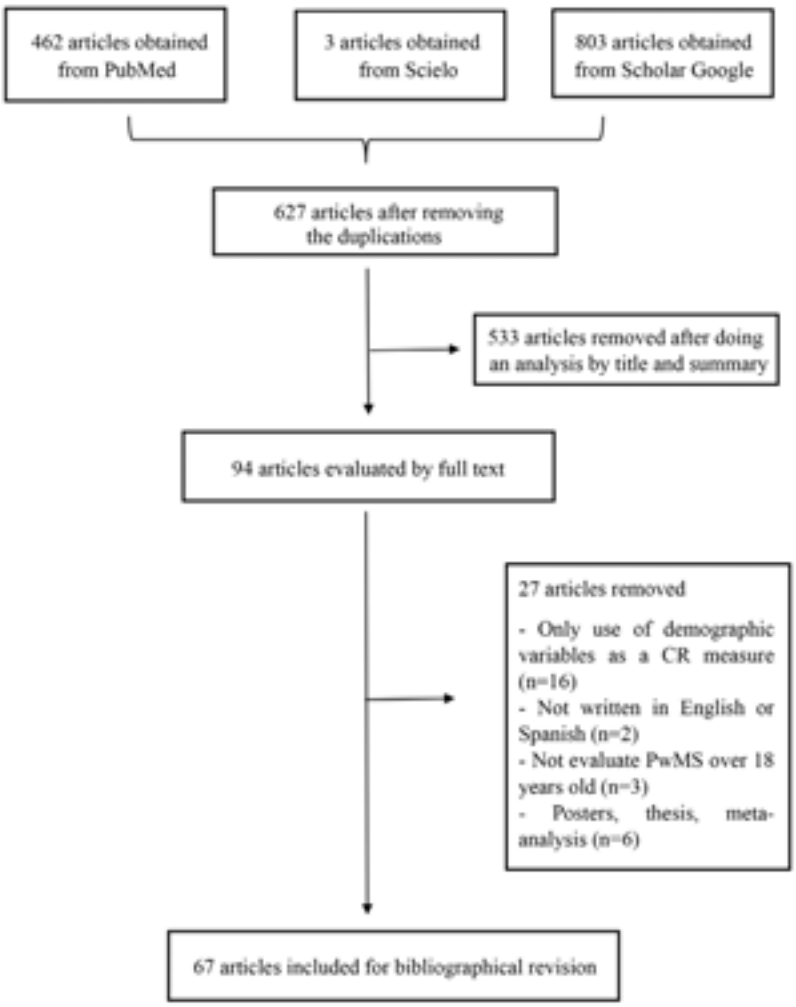

Figure 1. Stages of Article Selection

the included studies, data were collected from a total of 10.353 adult PwMS, who could have received the diagnosis either in childhood or adulthood, but who were over 18 years old at the time of cognitive reserve assessment. Table 1, Table 2 and Table 3 present the characteristics of the studies included in this literature review.

Use of questionnaires for measuring cognitive reserve

Regarding the use of questionnaires, eleven different tools were identified. These include: the DeltaQuest Cognitive Reserve (DQCR)[15], which assesses participation in past and current activities involved in the creation of cognitive reserve; the Recreation and Pastimes scale from the Sickness Impact Profile[16-17], which measures the reduction in participation in various domains since the time of diagnosis; the Solé-Padullés Childhood Enrichment[18], which evaluates factors such as the respondent's educational level, parental educational level, and childhood participation in cognitively stimulating activities; the Stern Leisure Activities[19], which consists of a scale that assesses participation in current hobbies, cultural activities, and leisure; the Cognitive Leisure Activity Questionnaire or Leisure Activity Scale[20], which measures the level of participation in cognitive leisure activities within the twenty years prior to diagnosis.

Table 1. Description of Included Articles

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
A new perspective on proxy report: Investigating implicit processes of understanding through patient–proxy congruence. (Schwartz C. et al., 2015)	To investigate the relationship among implicit comprehensive processes, reserve, and the healthy lifestyle in patients with Multiple Sclerosis.	118	DeltaQuest Cognitive Reserve (DQCR). North American Reading Test (NART).
A simple measure of cognitive reserve is relevant for cognitive performance in MS patients. (Della Corte M. et al., 2018)	To determine the relation between two cognitive reserve measures and cognition in Multiple Sclerosis.	147	Vocabulary (VOC) subtest of the Italian version of the Wechsler Abbreviated Scale of Intelligence-Revised (WAIS-R).
Active cognitive reserve influences the regional atrophy to cognition link in multiple sclerosis. (Booth, A. et al., 2013)	To evaluate the moderate effect of changes in the participation of recreational activities over the relation between brain atrophy and information processing speed.	57	North American Adult Reading Test (NAART). Recreation and Pastimes scale from the Sickness Impact Profile.
Adjustments in torque steadiness during fatiguing contractions are inversely correlated with IQ in persons with multiple sclerosis. (Gould, J. et al., 2018)	To analyze the influence of the intelligence level over the fatigability in persons with Multiple Sclerosis.	12	Verbal IQ of the Wechsler Abbreviated Scale of Intelligence (WASI).
Adverse Childhood Experiences Are Linked to Age of Onset and Reading Recognition in Multiple Sclerosis. (Shaw, M. et al., 2017)	To evaluate the relation in facing adverse experiences during childhood and clinical characteristics in Multiple Sclerosis.	67	Reading subtest of the Wide Range Achievement Test third edition (WRAT-3).
Alemtuzumab improves cognitive processing speed in active multiple sclerosis—A longitudinal observational study. (Riepl, E. et al., 2018)	To investigate the influence of alemtuzumab in the cognitive performance during the first year of treatment.	21	Standard Progressive Matrices (SPM).
Altruism and health outcomes in multiple sclerosis: The effect of cognitive reserve. (Schwartz, C. et al., 2013)	To analyze the influence of altruism and cognitive reserve in health and well-being in people with Multiple Sclerosis.	1523	Sole-Padulles Childhood Enrichment. Stern Leisure Activities.
Anterior Insular Resting-State Functional Connectivity is Related to Cognitive Reserve in Multiple Sclerosis. (Bizzo, B. et al., 2021)	To evaluate Intrinsic Functional Connectivity (IFC) of the Dorsal Anterior Insula (DAI) and its relation with cognitive reserve.	28	Test of Premorbid Function (TOPF). Cognitive Leisure Activity Questionnaire.
Applying the British picture vocabulary scale to estimate premorbid cognitive ability in adults. (Ezard, G. et al., 2020)	To analyze the effectivity of British Picture Vocabulary Scale II (BPVS) as an alternative tool to The National Adult Reading Test (NART) to evaluate the premorbid intelligence when there is an alteration in the oral language.	4	British Picture Vocabulary Scale II (BPVS). National Adult Reading Test - Revised (NART-R). Wechsler Abbreviated Scale of Intelligence (WASI). Weschler Adult Scale of Intelligence-Third Edition (WAIS III).

Table 1. Description of Included Articles (continuation)

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
Assessment of intelligence quotient in patients with neuromyelitis optica spectrum disease and multiple sclerosis. (Ashtari, F. et al., 2023)	To compare the score of intelligence quotient among patients with Optic Neuromyelitis (NMOSD), Multiple Sclerosis (MS) and controls.	41	Wechsler Adult Intelligence Scale-Revised (WAIS-R).
Avoidant Coping Is Associated with Quality of Life in Persons with Multiple Sclerosis with High Cognitive Reserve. (Vervoordt S. M. et al., 2022)	To determine the relationship between cognitive reserve and coping strategies in their quality of life.	97	Vocabulary subtest of the Shipley-2.
Brain reserve and cognitive reserve in Multiple sclerosis: What you've got and how you use it. (Sumowski, J. F. et al., 2013)	To investigate if the early participation in leisure activities (source of cognitive reserve) protects from cognitive impairment independently of the brain reserve in patients with Multiple Sclerosis.	62	Cognitive Leisure Activity Questionnaire.
Brain reserve and cognitive reserve protect against cognitive decline over 4.5 years in MS. (Sumowski, J. F. et al., 2014)	To analyze if brain and cognitive reserve protect from impairment.	40	Vocabulary (VOC) subtest of Wechsler Scale
Clinical profiles in multiple sclerosis: cognitive reserve and motor impairment along disease duration. (Maffezzini S. et al., 2023)	To study if higher levels of cognitive reserve interacts with the duration of the disease and the motor alterations in the prediction of cognitive results.	100	Cognitive Reserve Index questionnaire (CRIq).
Cognition in multiple sclerosis: Between cognitive reserve and brain volume. (Fenu, G. et al., 2018)	To analyze the relationship between cognitive alterations and brain volume, considering cognitive reserve as a mitigating factor.	195	Cognitive Reserve Index questionnaire (CRIq).
Cognitive and brain reserve in multiple sclerosis––A cross-sectional study. (Ifantopoulou, P. et al., 2019)	To analyze the effect of brain and cognitive reserve in cognitive functions and brain alterations.	128	Cognitive Reserve Index questionnaire (CRIq).
Cognitive enrichment and education quality moderate cognitive dysfunction in black and white adults with multiple sclerosis. (Grant J. et al., 2023)	To examine how three factors related to cognitive reserve (years of education, educational quality and cognitive enrichment) differs in the prediction of cognitive performance among different white and black patients with Multiple Sclerosis.	82	Wechsler Test of Adult Reading (WTAR). Cognitive Reserve Scale (CRS).
Cognitive impairment in multiple sclerosis: An exploratory analysis of environmental and lifestyle risk factors. (Amato, M. P. et al., 2019)	To evaluate the risk factors for cognitive alterations in Multiple Sclerosis, focusing on environmental exposures, quality of life and comorbidities.	150	National Adult Reading Test (NART, Italian version). Cognitive Leisure Activity Questionnaire.

Table 1. Description of Included Articles (continuation)

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
Cognitive performance in multiple sclerosis: the contribution of intellectual enrichment and brain MRI measures. (Santangelo, G. et al., 2018)	To investigate the association between cognitive reserve, brain reserve and cognitive functions, and evaluate how cognitive reserve could lessen the negative impact of brain atrophy in cognitive functions.	98	Vocabulary (VOC) subtest of Wechsler Adult Intelligence Scale Revised
Cognitive processess and cognitive reserve in multiple sclerosis. (Chillemi, G. et al., 2015)	To evaluate the role of cognitive reserve over cognitive dysfunctions in patients with MS.	29	Cognitive reserve index questionnaire (CRIq).
Cognitive rehabilitation program in patients with multiple sclerosis: A pilot study. (Jiménez Morales R. M. et al., 2021)	To analyze the effect of a cognitive rehabilitation program whose objective is to improve cognitive performance, and cognitive reserve index.	50	Cognitive Reserve Scale (CRS).
Cognitive reserve and appraisal in multiple sclerosis. (Schwartz C. et al., 2013)	To analyze the influence of a passive and an active cognitive reserve on the quality of life.	860	Sole-Padulles Childhood Enrichment. Stern Leisure Activities.
Cognitive reserve and cortical atrophy in multiple sclerosis: A longitudinal study. (Amato, M. P. et al., 2013)	To test the hypothesis of cognitive reserve in the Multiple Sclerosis model, analyzing the interaction between CR, brain atrophy and cognitive efficiency.	52	National Adult Reading Test (NART, Italian version). Cognitive Leisure Activity Questionnaire.
Cognitive Reserve and symptom experience in multiple sclerosis: A buffer to disability progression over time? (Schwartz, C. et al., 2013)	To investigate the possible dampening effect of cognitive reserve on symptoms experienced in the course of the disease of Multiple Sclerosis.	859	Sole-Padulles Childhood Enrichment. Stern Leisure Activities.
Cognitive reserve as a moderating factor between EDSS and cognition in multiple sclerosis. (Tremblay, A. et al., 2023)	To examine the protective rol of cognitive reserve on cognition, using standarized tools of cognitive reserve, and the rate of disability of the disease (EDSS).	84	Cognitive reserve index questionnaire (CRIq).
Cognitive Reserve attenuates the effect of disability on depression in multiple sclerosis. (Cadden, M. H. et al., 2019)	To explore the moderate effect of cognitive reserve on the relationship between disability and depression in patients with MS.	54	Vocabulary subtest from the Shipley Institute of Living Scale (SILS). Cognitive Health Questionnaire (CHQ).
Cognitive reserve is a determinant of social and occupational attainment in patients with pediatric and adult onset multiple sclerosis. (Portaccio E. et al., 2020)	To analyze socioprofessional results in patients with MS of childhood beginning, as well as in adulthood, evaluating the media that influence in these results and determine the impact of CR.	226	National Adult Reading Test (NART, Italian version). Barratt Simplified Measure of Social Status.
Cognitive reserve, cognition, and regional brain damage in MS: A 2-year longitudinal study. (Rocca M. A. et al., 2018)	To analyze the interaction between cognitive reserve and grey and withe matter brain measures, and its effect on neurocognitive performance.	54	National Adult Reading Test (NART, Italian version). Cognitive Leisure Activity Questionnaire.

Table 1. Description of Included Articles (continuation)

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
Computerized cognitive rehabilitation for treatment of cognitive impairment in multiple sclerosis: an explorative study. (Vilou I. et al., 2020)	To evaluate the result of a cognitive rehabilitation program.	47	Cognitive reserve index (CRI, Greek version).
Demographic features, behavioral measures, and clinical factors as predictors of cognitive function in patients with multiple sclerosis. (Alirezaei M. et al., 2021)	To evaluate predictive factors of cognitive functioning in MS.	92	National American Adult Reading Test (NAART).
Depression and cognitive function in early multiple sclerosis: Multitasking is more sensitive than traditional assessments. (Glukhovsky L. et al., 2020)	To analyze the relation between depression symptoms and their capacity to perform one or diverse activities simultaneously.	185	Wechsler test of adult reading (WTAR).
Dynamic assessment of social cognition in individuals with multiple sclerosis: A pilot study. (Genova H. 2016)	To examine social cognition in patients with MS.	15	Vocabulary Subtest from Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II).
Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of- life measures in secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomised, placebo-controlled trial. (Chan D. et al., 2017)	To analyze cognitive alterations, psychiatric symptoms and quality of life related to health, as well as the treatment effect with simvastatin in patients with secondary progressive multiple sclerosis (SPMS).	140	National Adult Reading Test (NART). Wechsler Abbreviated Scale of Intelligence (WASI).
Estimates of premorbid ability in a neurodegenerative disease clinic population: comparing the Test of Premorbid Functioning and the Wide Range Achievement Test, 4th Edition. (Berg J. L. et al., 2016)	To compare the results obtained from two instruments that observed cognitive reserve in patients with different neurodegenerative diseases.	1	Reading Subtest Wide Range Achievement Test, 4th Edition (WRAT-4). Test of Premorbid Functioning (TOPF).
Event related potential and response time give evidence for a physiological reserve in cognitive functioning in relapsing–remitting multiple sclerosis. (Sundgren M. et al., 2015)	To distinguish different mechanisms of cognitive reserve in RRMS.	71	Test de Vocabulario (SRB).
Exploring cognitive reserve in multiple sclerosis: New findings from a cross-sectional study. (Nunnari D. et al., 2016)	To evaluate the impact of clinical and demographical variables on the cognitive performance, assuming that CR performs a protective role in cognitive impairment.	66	Cognitive Reserve Index questionnaire (CRIq).

Table 1. Description of Included Articles (continuation)

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
Exploring the relation between reserve and fatigue in multiple sclerosis. (Tranfa M. et al., 2023)	To analyze the association between cognitive and brain reserve and fatigue symptoms.	48	Cognitive Reserve Index questionnaire (CRIq). Cognitive Leisure Activity Questionnaire. National Adult Reading Test (NART, Italian version).
General Mathematical Ability Predicts PASAT Performance in MS Patients: Implications for Clinical Interpretation and Cognitive Reserve. (Sandry J. et al., 2016)	To study if the relation between education, intelligence, and performance in PASAT is mediated by specific domains of knowledge.	45	Wechsler Test of Adult Reading (WTAR).
Hippocampal volume is more related to patient-reported memory than objective memory performance in early multiple sclerosis. (Glukhovsky L. et al., 2020)	To investigate if the impairment of subjecive memory and the performance of the objective memory are related to the volume of hippocampus and ... of hippocampus in an early MS.	185	Wechsler Test of Adult Reading (WTAR).
Impact of cognitive reserve and structural connectivity on cognitive performance in multiple sclerosis. (Lopez-Soley E. et al., 2020)	To analyze the relationship between cognitive reserve and the structural brain connectivity and its role on cognition.	181	Cognitive Reserve Questionnaire (CRQ).
Impairment of daily occupations in multiple sclerosis: analysis of neuroimaging, general and social cognition, and reserve. (Rodrigues Gómes L. et al., 2024)	To explore clinical and cognitive factors associated with alterations in different tasks of their daily life in patients with MS.	62	Cognitive Reserve Index questionnaire (CRIq).
Individual reserve in aging and neurological disease. (Holtzer Roee J. C. et al., 2023)	To examine the concept known as individual reserve, which is made up of cognitive reserve and brain reserve, in patients with MS.	66	Repeatable battery for the assessment of neuropsycholo gical status (RBANS).
Longitudinal stability of cognition in Early phase relapsing-remitting multiple sclerosis. (Barbu R. M. et al., 2018)	To asses cognitive performance over a 3-year period and investigate how cognitive reserve may explain whether performance is maintained through time.	32	North American Adult Reading Test (NAART). Cognitive Reserve Index (CRI)
Perspective taking deficits and their relationship with theory of mind abilities in patients with relapsing-remitting multiple sclerosis (RRMS). (Bruno D. et al., 2022)	To investigate perspective-taking in patients with MS and determine its relationship with deficiencies in theory of mind skills.	36	The revised Word Accentuation Test (WATBA-r).
Premorbid cognitive functioning influences differences between self-reported cognitive difficulties and cognitive assessment in multiple sclerosis. (Stein, C. et al., 2023)	To assess the influence of premorbid cognitive functioning over cognitive performance.	87	Test of Premorbid Functioning (TOPF).

Table 1. Description of Included Articles (continuation)

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
Premorbid functional reserve modulates the effect of rehabilitation in multiple sclerosis. (Castelli L. et al., 2020)	To analyze whether premorbid physical activities, cognitive reserve and personality are related to the results of rehabilitation.	60	Cognitive reserve index questionnaire (CRIq).
Presence and significant determinants of cognitive impairment in a large sample of patients with multiple sclerosis. (Borghi, M. et al., 2013)	To examine clinical and demographical factors of cognitive alterations.	303	Brief Intelligence Test (TIB). Vocabulary of the Wechsler Adult Intelligence Scale (WAIS).
Preserved network functional connectivity underlies cognitive reserve in multiple sclerosis. (Fuchs, T. A. et al., 2019)	To investigate if the preservation of functional connectivity explains the cognitive reserve.	74	North American Adult Reading Test (NAART).
Reading, writing, and reserve: Literacy Activities are linked to hippocampal volume and memory in multiple sclerosis. (Sumowski, J. F. et al., 2016)	To analyze the relationship between three types of cognitive activities with the size of the hippocampus and memory.	187	Cognitive Leisure Activity Questionnaire.
Reserve-building activities in multiple sclerosis patients and healthy controls: A descriptive study. (Schwartz, C. et al., 2015)	To describe the differences in the reserve creation activities in the course of the multiple sclerosis disease and healthy controls.	467	Cuestionario ad-hoc sobre actividades pasadas y presentes involucradas en la construcción de RC.
Reserve-related activities and MRI metrics in multiple sclerosis patients and healthy controls: an observational study. (Schwartz, C. et al., 2016)	To examine whether past and present activities related to the reserve result in the brain being less susceptible to MS.	461	Cuestionario ad-hoc sobre actividades pasadas y presentes involucradas en la construcción de RC.
Revisiting cognitive reserve and cognition in multiple sclerosis: A closer look at depression. (Patel, V. et al., 2018)	To analyze the relationship between cognitive reserve and depression.	155	Wechsler Test of Adult Reading (WTAR). Leisure Activity Scale (LAS).
Searching for the neural basis of reserve against memory decline: intellectual enrichment linked to larger hippocampal volume in multiple sclerosis. (Sumowski, J. F. et al., 2015)	To evaluate whether participation in mentally stimulating activities (i) are related to a higher volume of the hippocampus in patients with MS (ii) lessen the negative impact of the disease over the volume of the hippocampus (iii) whether a higher volume in the hippocampus measures a positive relationship between cognitive activities and memory.	187	Cognitive Leisure Activity Questionnaire
Sub-threshold cognitive impairment in multiple sclerosis: the association with cognitive reserve. (Feinstein A, et al., 2013)	To explore neurological aspects and behavioural characteristics of people with MS.	144	American National Adult Reading Test (ANART).

Table 1. Description of Included Articles (continuation)

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
Synergistic effects of reserve and adaptive personality in multiple sclerosis. (Roy, S. et al., 2016)	To analyze the relationship between cognitive reserve and five factors of personality.	67	DeltaQuest Cognitive Reserve (DQCR).
The effects of aging and disease duration on cognition in multiple sclerosis. (Tremblay A, et al., 2020)	To analyze the impact of MS, ageing, and years of evolution of the disease on cognition in patients with MS.	84	Vocabulary subtest of Wechsler Adult Intelligence Scales (WAIS IV).
The effects of long-term interferon-beta-1b treatment on cognitive functioning in multiple sclerosis: a 16-year longitudinal study. (Lacy M, et al., 2013)	To assess the effect of interferona beta on the cognitive performance in patients with MS.	16	National Adult Reading Test (NART).
The Montreal Cognitive Assessment (MoCA) as a screening test for cognitive dysfunction in multiple sclerosis. (Freitas, S. et al., 2016)	To study the profit of implement the portuguese version of MoCa as a screening test to detect cognitive alterations in MS.	59	The Portuguese irregular word reading test (TeLPI)
The protective effects of high-education levels on cognition in different stages of multiple sclerosis. (Rimkus, C. et al., 2018)	To investigate the frequency and characteristics of cognitive alterations in patients with MS with different educational levels.	136	Wechsler Adult Intelligence Scale (WAIS III).
The relationship between executive functions and fluid intelligence in multiple sclerosis. (Goitia, B et al., 2020)	To test whether frontal deficits measured by frontal tests in patients with MS can be explained by a deficit in fluent intelligence (g).	36	Word Accentuation Test-Buenos Aires edition (WAT).
The role of cognitive reserve in multiple sclerosis: A cross-sectional study in 526 patients. (Artemiadis, A. et al., 2020)	To evaluate the impact of cognitive reserve on the cognitive performance in MS.	526	Cognitive Reserve Index questionnaire (CRIq).
Trait Conscientiousness predicts rate of longitudinal SDMT decline in multiple sclerosis. (Fuchs, T. et al., 2019)	To characterize the cognitive impairment rate and investigate initial clinical predictors.	531	North American Adult Reading Test (NAART).
Validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) in Greek population with multiple sclerosis. (Polychroniadou, E. et al., 2016)	To validate the BICAMS battery for the population of patients with MS in Greece.	46	Cognitive Reserve Index questionnaire (CRIq).
Vocabulary knowledge as a reliable proxy of cognitive reserve in multiple sclerosis: a validation study. (Maggi, G. et al., 2024)	To explore if the Vocabulary test WAIS is valid to evaluate cognitive reserve, compared with other cognitive reserve measures used in multiple sclerosis.	68	Vocabulary (VOC) subtest of the Wechsler Adult Intelligence Scale (WAIS). Cognitive Reserve Index Questionnaire (CRIq)

Table 1. Description of Included Articles (continuation)

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
White matter tract abnormalities are associated with cognitive dysfunction in secondary progressive multiple sclerosis. (Meijer, K. A. et al., 2016)	To assess how damages in White matter differ in patients with MS with and without cognitive alterations.	30	Wechsler Test of Adult Reading (WTAR).
Working memory mediates the relationship between intellectual enrichment and long-term memory in multiple sclerosis: An exploratory analysis of cognitive reserve. (Sandry, J. et al., 2014)	To test the hypothesis that suggests that working memory measures the relation between intelligence and long-term memory decline in MS.	70	Wechsler Test of Adult Reading (WTAR). Peabody Picture Vocabulary Test (PPVT).
Working memory phenotypes in early multiple sclerosis: appraisal of phenotype frequency, progression and test sensitivity. (Clough M. et al., 2022)	To determine the phenotypes in working memory disorders in patients with MS.	49	National Adult Reading Test (NART).

Table 1. Articles that used neurocognitive tests and scales.

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
A new perspective on proxy report: Investigating implicit processes of understanding through patient–proxy congruence. (Schwartz C. et al., 2015)	To investigate the relationship among comprehensive implicit processes, reserve, and the healthy lifestyle in PwMS.	118	DeltaQuest Cognitive Reserve (DQCR). North American Reading Test (NART).
Active cognitive reserve influences the regional atrophy to cognition link in multiple sclerosis. (Booth, A. et al., 2013)	To evaluate the moderate effect of changes in the participation of recreational activities about the relation between brain atrophy and information processing speed.	57	North American Adult Reading Test (NAART). Recreation and Pastimes scale from the Sickness Impact Profile.
Anterior Insular Resting-State Functional Connectivity is Related to Cognitive Reserve in Multiple Sclerosis. (Bizzo, B. et al., 2021)	To evaluate Intrinsic Functional Connectivity of the Dorsal Anterior Insula and its relation with CR.	28	Test of Premorbid Function (TOPF). Cognitive Leisure Activity Questionnaire.
Cognitive enrichment and education quality moderate cognitive dysfunction in black and white adults with multiple sclerosis. (Grant J. et al., 2023)	To examine how three factors related to cognitive reserve (years of education, educational quality and cognitive enrichment) differ in the prediction of cognitive performance among different white and black PwMS.	82	Wechsler Test of Adult Reading (WTAR). Cognitive Reserve Scale (CRS).

Cognitive impairment in multiple sclerosis: An exploratory analysis of environmental and lifestyle risk factors. (Amato, M. P. et al., 2019)	To assess the risk factors for cognitive alterations in MS, focusing on environmental exposures, quality of life and comorbidities.	150	National Adult Reading Test (NART, Italian version). Cognitive Leisure Activity Questionnaire.
Cognitive reserve and cortical atrophy in multiple sclerosis: A longitudinal study. (Amato, M. P. et al., 2013)	To test the hypothesis of cognitive reserve in the MS model, analyzing the interaction among CR, brain atrophy and cognitive efficiency.	52	National Adult Reading Test (NART, Italian version). Cognitive Leisure Activity Questionnaire.
Cognitive reserve attenuates the effect of disability on depression in multiple sclerosis. (Cadden, M. H. et al., 2019)	To explore the moderate effect of CR on the relationship between disability and depression in PwMS.	54	Vocabulary subtest from the Shipley Institute of Living Scale (SILS). Cognitive Health Questionnaire (CHQ).
Cognitive reserve is a determinant of social and occupational attainment in patients with pediatric and adult onset multiple sclerosis. (Portaccio E. et al., 2020)	To analyze socioprofessional results in patients with MS of childhood beginning, as well as in adulthood, evaluating the media that influence in these results and determine the impact of CR.	226	National Adult Reading Test (NART, Italian version). Barratt Simplified Measure of Social Status.
Cognitive reserve, cognition, and regional brain damage in MS: A 2-year longitudinal study. (Rocca M. A. et al., 2018)	To analyze the interaction between cognitive reserve and grey and withe matter brain measures, and its effect on neurocognitive performance.	54	National Adult Reading Test (NART, Italian version). Cognitive Leisure Activity Questionnaire.
Exploring the relation between reserve and fatigue in multiple sclerosis. (Tranfa M. et al., 2023)	To analyze the association between cognitive and brain reserve with fatigue symptoms	48	National Adult Reading Test (NART, Italian version). Cognitive Reserve Index questionnaire (CRIq). Cognitive Leisure Activity Questionnaire.
Longitudinal stability of cognition in Early phase relapsing-remitting multiple sclerosis. (Barbu R. M. et al., 2018)	To asses cognitive performance over a 3-year period and investigate how CR may explain whether performance is maintained through time.	32	North American Adult Reading Test (NAART). Cognitive Reserve Index (CRI).
Revisiting cognitive reserve and cognition in multiple sclerosis: A closer look at depression. (Patel, V. et al., 2018)	To analyze the relationship between CR and depression.	155	Wechsler Test of Adult Reading (WTAR). Leisure Activity Scale (LAS).
Vocabulary knowledge as a reliable proxy of cognitive reserve in multiple sclerosis: a validation study. (Maggi, G. et al., 2024)	To explore if the Vocabulary test is valid to evaluate CR, compared with other cognitive reserve measures used in MS.	68	Vocabulary (VOC) subtest of the Wechsler Adult Intelligence Scale (WAIS). Cognitive Reserve Index Questionnaire (CRIq)

Abbreviations: MS = multiple sclerosis; PwMS = people with multiple sclerosis; CR = cognitive reserve.

Table 2. Articles that used neurocognitive tests.

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
A simple measure of cognitive reserve is relevant for cognitive performance in MS patients. (Della Corte M. et al., 2018)	To determine the relation between two CR measures and cognition in MS.	147	Vocabulary (VOC) subtest of the Italian version of the Wechsler Abbreviated Scale of Intelligence-Revised (WAIS-R).
Adjustments in torque steadiness during fatiguing contractions are inversely correlated with IQ in personswith multiple sclerosis. (Gould, J. et al., 2018)	To analyze the influence of the intelligence level over the fatigability in PwMS.	12	Verbal IQ of the Wechsler Abbreviated Scale of Intelligence (WASI).
Adverse childhood experiences are linked to age of onset and reading recognition in multiple sclerosis. (Shaw, M. et al., 2017)	To evaluate the relation between facing adverse experiences during childhood and clinical characteristics in MS.	67	Reading subtest of the Wide Range Achievement Test third edition (WRAT-3).
Alemtuzumab improves cognitive processing speed in active multiple sclerosis—A longitudinal observational study. (Riepl, E. et al., 2018)	To investigate the influence of alemtuzumab in the cognitive performance during the first year of treatment.	21	Standard Progressive Matrices (SPM).
Applying the British picture Vocabulary scale to estimate premorbid cognitive ability in adults. (Ezard, G. et al., 2020)	To analyze the effectiveness of British Picture Vocabulary Scale II (BPVS) as an alternative tool to The National Adult Reading Test (NART) to evaluate the premorbid intelligence when there is an alteration in the oral language.	4	British Picture Vocabulary Scale II (BPVS). National Adult Reading Test - Revised (NART-R). Wechsler Abbreviated Scale of Intelligence (WASI). Weschler Adult Scale of Intelligence-Third Edition (WAIS III).
Assessment of intelligence quotient in patients with neuromyelitis optica spectrum disease and multiple sclerosis. (Ashtari, F. et al., 2023)	To compare the score of IQ among patients with Optic Neuromyelitis (NMOSD), Multiple Sclerosis (MS) and controls.	41	Wechsler Adult Intelligence Scale-Revised (WAIS-R).
Avoidant coping is associated with quality of life in persons with multiple sclerosis with High cognitive reserve. (Vervoordt S. M. et al., 2022)	To determine the relationship between CR and coping strategies in their quality of life.	97	Vocabulary subtest of the Shipley-2.
Brain reserve and cognitive reserve protect against cognitive decline over 4.5 years in multiple sclerosis. (Sumowski, J. F. et al., 2014)	To analyze if brain and CR protect from impairment.	40	Vocabulary (VOC) subtest of Wechsler Scale.

Table 2. Articles that used neurocognitive tests (continuation)

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
Cognitive performance in multiple sclerosis: the contribution of intellectual enrichment and brain MRI measures. (Santangelo, G. et al., 2018)	To investigate the association between CR, brain reserve and cognitive functions, and evaluate how CR can mitigate the negative impact of brain atrophy on cognitive functions.	98	Vocabulary (VOC) subtest of Wechsler Adult Intelligence Scale Revised
Demographic features, behavioral measures, and clinical factors as predictors of cognitive function in patients with multiple sclerosis. (Alirezaei M. et al., 2021)	To evaluate predictive factors of cognitive functioning in MS.	92	National American Adult Reading Test (NAART).
Depression and cognitive function in early multiple sclerosis: Multitasking is more sensitive than traditional assessments. (Glukhovsky L. et al., 2020)	To analyze the relation between depression symptoms and their capacity to perform one or diverse activities simultaneously.	185	Wechsler test of adult reading (WTAR).
Dynamic assessment of social cognition in individuals with multiple sclerosis: A pilot study. (Genova H. 2016)	To examine social cognition in PwMS.	15	Vocabulary Subtest from Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II).
Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of- life measures in secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomised, placebo-controlled trial. (Chan D. et al., 2017)	To analyze cognitive alterations, neuropsychiatric symptoms and health-related quality of live, as well as the effect of treatment with simvastatin in patients with SPMS.	140	National Adult Reading Test (NART). Wechsler Abbreviated Scale of Intelligence (WASI).
Estimates of premorbid ability in a neurodegenerative disease clinic population: comparing the Test of Premorbid Functioning and the Wide Range Achievement Test, 4th Edition. (Berg J. L. et al., 2016)	To compare the results obtained from two instruments that observed CR in patients with different neurodegenerative diseases.	1	Reading Subtest Wide Range Achievement Test, 4th Edition (WRAT-4). Test of Premorbid Functioning (TOPF).
Event related potential and response time give evidence for a physiological reserve in cognitive functioning in relapsing–remitting multiple sclerosis. (Sundgren M. et al., 2015)	To distinguish different mechanisms of cognitive reserve in RRMS.	71	Test de Vocabulario (SRB).

Table 2. Articles that used neurocognitive tests. (continuation)

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
General mathematical ability predicts PASAT performance in MS patients: Implications for clinical interpretation and cognitive reserve. (Sandry J. et al., 2016)	To study if the relation between education, intelligence, and performance in PASAT is mediated by specific domains of knowledge.	45	Wechsler Test of Adult Reading (WTAR).
Hippocampal volume is more related to patient-reported memory than objective memory performance in early multiple sclerosis. (Glukhovsky L. et al., 2020)	To investigate whether the decline in subjective memory or the performance in objective memory is related to the volumes of hippocampus and hippocampal subfield in early MS.	185	Wechsler Test of Adult Reading (WTAR).
Individual reserve in aging and neurological disease. (Holtzer Roee J. C. et al., 2023)	To examine the concept known as individual reserve, which is made up of CR and brain reserve, in PwMS.	66	Repeatable battery for the assessment of neuropsycholo gical status (RBANS).
Perspective taking deficits and their relationship with theory of mind abilities in patients with relapsing-remitting multiple sclerosis (RRMS). (Bruno D. et al., 2022)	To investigate perspective-taking in PwMS and determine its relationship with deficiencies in theory of mind skills.	36	The revised Word Accentuation Test (WATBA-r).
Premorbid cognitive functioning influences differences between self-reported cognitive difficulties and cognitive assessment in multiple sclerosis. (Stein, C. et al., 2023)	To assess the influence of premorbid cognitive functioning over cognitive performance.	87	Test of Premorbid Functioning (TOPF).
Presence and significant determinants of cognitive impairment in a large sample of patients with multiple sclerosis. (Borghi, M. et al., 2013)	To examine clinical and demographical factors of cognitive alterations.	303	Brief Intelligence Test (TIB). Vocabulary of the Wechsler Adult Intelligence Scale (WAIS).
Preserved network functional connectivity underlies cognitive reserve in multiple sclerosis. (Fuchs, T. A. et al., 2019)	To investigate if the preservation of functional connectivity explains the CR.	74	North American Adult Reading Test (NAART).
Sub-threshold cognitive impairment in Multiple sclerosis: the association with cognitive reserve. (Feinstein A, et al., 2013)	To explore neurological aspects and behavioural characteristics of PwMS.	144	American National Adult Reading Test (ANART).

Table 2. Articles that used neurocognitive tests. (continuation)

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
The effects of aging and disease duration on cognition in multiple sclerosis. (Tremblay A, et al., 2020)	To analyze the impact of MS, ageing, and years of evolution of the disease on cognition in PwMS.	84	Vocabulary subtest of Wechsler Adult Intelligence Scales (WAIS IV).
The effects of long-term interferon-beta-1b treatment on cognitive functioning in multiple sclerosis: a 16-year longitudinal study. (Lacy M, et al., 2013)	To assess the effect of interferona beta on the cognitive performance in PwMS.	16	National Adult Reading Test (NART).
The Montreal Cognitive Assessment (MoCA) as a screening test for cognitive dysfunction in multiple sclerosis. (Freitas, S. et al., 2016)	To study the profit of implement the portuguese version of MoCa as a screening test to detect cognitive alterations in MS.	59	The Portuguese irregular word reading test (TeLPI)
The protective effects of high-education levels on cognition in different stages of multiple sclerosis. (Rimkus, C. et al., 2018)	To investigate the frequency and characteristics of cognitive alterations in PwMS with different educational levels.	136	Wechsler Adult Intelligence Scale (WAIS III).
The relationship between executive functions and fluid intelligence in multiple sclerosis. (Goitia, B et al., 2020)	To test whether frontal deficits measured by frontal tests in PwMS can be explained by a deficit in fluent intelligence (g).	36	Word Accentuation Test-Buenos Aires edition (WAT).
Trait conscientiousness predicts rate of longitudinal SDMT decline in multiple sclerosis. (Fuchs, T. et al., 2019)	To characterize the cognitive impairment rate and investigate initial clinical predictors.	531	North American Adult Reading Test (NAART).
White matter tract abnormalities are associated with cognitive dysfunction in secondary progressive multiple sclerosis. (Meijer, K. A. et al., 2016)	To assess how damages in White matter differ in PwMS with and without cognitive alterations.	30	Wechsler Test of Adult Reading (WTAR).
Working memory mediates the relationship between intellectual enrichment and long-term memory in multiple sclerosis: An exploratory analysis of cognitive reserve. (Sandry, J. et al., 2014)	To test the hypothesis that suggests that working memory measures the relation between intelligence and long-term memory decline in MS.	70	Wechsler Test of Adult Reading (WTAR). Peabody Picture Vocabulary Test (PPVT).

Table 2. Articles that used neurocognitive tests. (continuation)

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
Working memory phenotypes in early multiple sclerosis: appraisal of phenotype frequency, progression and test sensitivity. (Clough M. et al., 2022)	To determine the phenotypes in working memory disorders in PwMS.	49	National Adult Reading Test (NART).

Abbreviations: MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; PwMS = people with multiple sclerosis; CR = cognitive reserve; IQ = intelligence quotient; SDMT = Symbol Digit Modalities Test.

Table 3. Articles that used scales.

Article (author and year)	Objective of study	People with MS (n)	Measurement Instruments of CR
Altruism and health outcomes in multiple sclerosis: The effect of cognitive reserve. (Schwartz, C. et al., 2013)	To analyze the influence of altruism and CR on health and well-being in PwMSs.	1523	Sole-Padulles Childhood Enrichment. Stern Leisure Activities.
Brain reserve and cognitive reserve in Multiple sclerosis: What you've got and how you use it. (Sumowski, J. F. et al., 2013)	To investigate if the early participation in leisure activities (source of CR) protects from cognitive impairment independently of the brain reserve in PwMS.	62	Cognitive Leisure Activity Questionnaire.
Clinical profiles in multiple sclerosis: cognitive reserve and motor impairment along disease duration. (Maffezzini S. et al., 2023)	To study if higher levels of CR interacts with the duration of the disease and the motor alterations in the prediction of cognitive results.	100	Cognitive Reserve Index questionnaire (CRIq).
Cognition in multiple sclerosis: Between cognitive reserve and brain volume. (Fenu, G. et al., 2018)	To analyze the relationship between cognitive alterations and brain volume, considering CR as a mitigating factor.	195	Cognitive Reserve Index questionnaire (CRIq).
Cognitive and brain reserve in multiple sclerosis––A cross-sectional study. (Ifantopoulou, P. et al., 2019)	To analyze the effect of brain and CR in cognitive functions and brain alterations.	128	Cognitive Reserve Index questionnaire (CRIq).
Cognitive processess and cognitive reserve in multiple sclerosis. (Chillemi, G. et al., 2015)	To evaluate the role of CR on the cognitive dysfunctions of PwMS.	29	Cognitive Reserve Index questionnaire (CRIq).
Cognitive rehabilitation program in patients with multiple sclerosis: A pilot study. (Jiménez Morales R. M. et al., 2021)	To analyze the effect of a cognitive rehabilitation program that aims to improve cognitive performance, emotional state, and CR index.	50	Cognitive Reserve Scale (CRS).

Cognitive reserve and appraisal in multiple sclerosis. (Schwartz C. et al., 2013)	To analyze the influence of a passive and an active CR on the quality of life.	860	Sole-Padulles Childhood Enrichment. Stern Leisure Activities.
Cognitive reserve and symptom experience in multiple sclerosis: A buffer to disability progression over time? (Schwartz, C. et al., 2013)	To investigate the possible dampening effect of CR on symptoms experienced in the course of the disease of MS.	859	Sole-Padulles Childhood Enrichment. Stern Leisure Activities.
Cognitive reserve as a moderating factor between EDSS and cognition in multiple sclerosis. (Tremblay, A. et al., 2023)	To examine the protective rol of CR on cognition, using standarized tools of CR, and the rate of disability of the disease (EDSS).	84	Cognitive Reserve Index questionnaire (CRIq).
Computerized cognitive rehabilitation for treatment of cognitive impairment in multiple sclerosis: an explorative study. (Vilou I. et al., 2020)	To evaluate the result of a cognitive rehabilitation program.	47	Cognitive reserve index (CRI, Greek version).
Exploring cognitive reserve in multiple sclerosis: New findings from a cross-sectional study. (Nunnari D. et al., 2016)	To evaluate the impact of clinical and demographical variables on the cognitive performance, assuming that CR performs a protective role in cognitive impairment.	66	Cognitive Reserve Index questionnaire (CRIq).
Impact of cognitive reserve and structural connectivity on cognitive performance in multiple sclerosis. (Lopez-Soley E. et al., 2020)	To analyze the relationship between CR and the structural brain connectivity and its role on cognition.	181	Cognitive Reserve Questionnaire (CRQ).
Impairment of daily occupations in multiple sclerosis: analysis of neuroimaging, general and social cognition, and reserve. (Rodrigues Gómes L. et al., 2024)	To explore clinical and cognitive factors associated with alterations in different tasks of their daily life in PwMS.	62	Cognitive Reserve Index questionnaire (CRIq).
Premorbid functional reserve modulates the effect of rehabilitation in multiple sclerosis. (Castelli L. et al., 2020)	To analyze whether premorbid physical activities, CR and personality are related to the results of rehabilitation.	60	Cognitive Reserve Index questionnaire (CRIq).
Reading, writing, and reserve: literacy activities are linked to hippocampal volume and memory in multiple sclerosis. (Sumowski, J. F. et al., 2016)	To analyze the relationship between three types of cognitive activities with the size of the hippocampus and memory.	187	Cognitive Leisure Activity Questionnaire.
Reserve-building activities in multiple sclerosis patients and healthy controls: A descriptive study. (Schwartz, C. et al., 2015)	To describe the differences in the reserve creation activities in the course of the MS disease and healthy controls.	467	Ad-hoc questionnaire about past and present activities involved in reserve construction.

Reserve-related activities and MRI metrics in multiple sclerosis patients and healthy controls: an observational study. (Schwartz, C. et al., 2016)	To examine whether past and present activities related to the reserve result in the brain being less susceptible to MS.	461	Ad-hoc questionnaire about past and present activities involved in reserve construction.
Searching for the neural basis of reserve against memory decline: intellectual enrichment linked to larger hippocampal volume in multiple sclerosis. (Sumowski, J. F. et al., 2015)	To evaluate whether participation in mentally stimulating activities (i) are related to a higher volume of the hippocampus in PwMS (ii) lessen the negative impact of the disease over the volume of the hippocampus (iii) whether a higher volume in the hippocampus measures a positive relationship between cognitive activities and memory.	187	Cognitive Leisure Activity Questionnaire.
Synergistic effects of reserve and adaptive personality in multiple sclerosis. (Roy, S. et al., 2016)	To analyze the relationship between CR and five factors of personality.	67	DeltaQuest Cognitive Reserve (DQCR).
The role of cognitive reserve in multiple sclerosis: A cross-sectional study in 526 patients. (Artemiadis, A. et al., 2020)	To evaluate the impact of CR on the cognitive performance in MS.	526	Cognitive Reserve Index questionnaire (CRIq).

Abbreviations: MS = multiple sclerosis; PwMS = people with multiple sclerosis; CR = cognitive reserve; EDSS = Expanded Disability Status Scale; MRI = Magnetic Resonance Imaging.

Other questionnaires focused on broader aspects of CR. These included the Cognitive Reserve Index questionnaire (CRIq)[21], which evaluates the duration and frequency of participation in three areas (work, education, leisure activities) and provides a total cognitive reserve score; the Cognitive Reserve Scale (CRS)[22-23], which measures participation in four types of activities (basic daily activities, training activities, hobbies, and social activities) across three life periods; and the Cognitive Health Questionnaire (CHQ)[24], composed of three subscales (exercise, socialization, and cognitive effort) related to cognitively healthy lifestyles.

Additional scales assessed socioeconomic and intellectual enrichment factors. These included the Barratt Simplified Measure of Social Status, a semi-structured interview that evaluates the socioeconomic status of both the subject and their parents; the Cognitive Reserve Questionnaire (CRQ)[25], which measures various factors of intellectual enrichment of both the patient and their parents; and the Ad-Hoc Questionnaire[26], which estimates participation in strenuous and non-strenuous activities while also considering demographic characteristics such as educational level.

Among all the instruments mentioned, the most commonly used was the CRIq, which was administered in thirteen studies, with twelve using the original version of the questionnaire[27-38] and one study[39] using the adaptation of the CRIq for the Greek population[40]. The second most commonly used questionnaire was the Cognitive Leisure Activity Questionnaire or Leisure Activity Scale, which was employed in a total of nine studies[7,37,41-47]. It was also observed that the Sole-Padulles Childhood Enrichment and the Stern Leisure Activities were applied in three studies and were always administered together[48-50]. The DeltaQuest Cognitive Reserve was used in two articles[51-52], as was the Ad-Hoc Questionnaire measuring participation in strenuous and non-strenuous activities[26,53], and the Cognitive Reserve Scale[54-55].

Finally, the instruments used in only one study were the Recreation and Pastimes Scale from the Sickness Impact Profile[56], the Cognitive Health Questionnaire[57], the Barratt Simplified Measure of Social Status[58], and the Cognitive Reserve Questionnaire[59].

Use of neurocognitive tests for measuring cognitive reserve

Regarding the use of neuropsychological tests or batteries to measure CR, a total of 21 different neurocognitive tests were identified. Most of the instruments used focus on premorbid intelligence measured through tasks involving the reading of infrequent or irregular words. These include the North American Reading Test or National American Adult Reading Test (NART or NAART)[60], the North American Adult Reading Test (NAART)[61], the vocabulary subtest of the Wide Range Achievement Test Third Edition and Fourth Edition (WRAT-3 and WRAT-4)[62-63], the Test of Premorbid Function (TOPF)[64], the National Adult Reading Test (NART)[65], the National Adult Reading Test Revised (NART-R)[66], the Wechsler Test of Adult Reading (WTAR) [67-68], and the American National Adult Reading Test (ANART)[69].

Adaptations of these instruments were also identified in different languages, including the National Adult Reading Test Italian version or Brief Intelligence Test (Italian NART or TIB)[70], the Revised Word Accentuation Test or Word Accentuation Test–Buenos Aires edition (WATBA-r)[71-72], and the Portuguese irregular word reading test (TeLPI)[73].

Less frequently, studies used neurocognitive batteries that provide multiple subindices and an overall intelligence score, such as the Wechsler Adult Intelligence Scale-Revised (WAIS-R)[74], the Wechsler Abbreviated Scale of Intelligence (WASI) and its Second Edition (WASI II)[75-76], and the Wechsler Adult Intelligence Scale-Third and Four Editions (WAIS III and WAIS IV)[77-78].

Additionally, measures included the Standard Progressive Matrices (SPM)[79], which assesses abstract visual reasoning ability; the Shipley Institute of Living Scale[80] and Shipley-2[81], which provide measures of crystallized and fluid intelligence; and the British Picture Vocabulary Scale (BPVS)[82] and Peabody Picture Vocabulary Test (PPVT)[83], which assess receptive vocabulary through picture selection task. Finally, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[84] was also utilized; this battery evaluates visuoconstruction, language, attention, immediate memory, and delayed memory.

Of all the reviewed articles, thirty-one used some test involving the reading or pronunciation of words to measure cognitive reserve, specifically premorbid intelligence or IQ[7,37,41-44,50,54,56,58,85-105]. On the other hand, regarding the use of neurocognitive batteries, some studies opted to administer complete batteries such as Wechsler Adult Intelligence Scale[90,92,106-107], while others only used the vocabulary subtest to estimate the level of CR[33,57,88,108-114], and one article used the verbal index from the aforementioned battery[115]. Finally, some studies employed individual vocabulary tests as a measure of cognitive reserve—these tests were not part of a larger battery[92,102]—as well as tasks assessing abstract reasoning[116] and batteries designed to evaluate general cognitive performance1[117]

DISCUSSION

The objective of this study was to revise the bibliography to gather information about the different instruments used to evaluate CR in patients with MS. In regard to this objective, it is possible to suggest that, firstly, a great heterogeneity was observed in terms of the tools used to assess the level of CR in patients, since a total of thirty-two different instruments were found in the study's revision, eleven of them being scales or questionnaires, and twenty-one being cognitive tests. Secondly, it is important to highlight the variability observed in these thirty-two instruments concerning which aspect of CR is measured. Scales that measure a specific aspect of CR, such as participation in leisure activities, considered as cognitively stimulating, were found, as well as more comprehensive questionnaires that measure various factors

of CR, like the patient and his or her parents' educational level, occupational status, performance in intellectual and leisure activities, etc., thus obtaining a total index of reserve from multiple aspects. The same was found in relation to neurocognitive tests used, which ranged from tasks that evaluated a specific function, such as vocabulary or premorbid intelligence, to complete batteries that allowed getting a total index of intelligence from diverse subtests. Lastly, even though there is great heterogeneity, it could be seen that certain instruments were more prevalent than others, considering their use. Regarding the use of questionnaires that assess CR, it was found that the instrument most used was the Cognitive Reserve Index questionnaire (CRIq)[21]. Regarding neurocognitive tests, it was seen that the majority of the studies revised consisted of tests that implied reading words aloud to measure the patients' level of premorbid intelligence, such as the National Adult Reading Test (NART)[65], the Test of Premorbid Function (TOPF)[64] or the Word Accentuation Test-Buenos Aires edition (WATBA-r)[70-71] in Spanish, among others. Regarding the use of questionnaires and neuropsychological tests, it shall be possible considering that, even though cognitive assessments allow obtaining a more specific estimation of the patient's premorbid level, it is also necessary to clarify the limitations they present, since they exclude the evaluation of aspects linked to quality of life and demographical variables, which actively participate in the development of CR and are generally evaluated through questionnaires. For this reason, it would be more convenient to consider that CR evaluation should include both tools: neurocognitive tests and questionnaires.

An important issue that emerged from the present review concerns the conceptual validity of the instruments used to operationalize CR. Although many of the identified measures are commonly employed as indicators of CR, several of them do not assess the construct directly. Reading-based tests such as the NART, TOPF, WTAR, or WATBA-r primarily estimate premorbid intellectual functioning, whereas questionnaires such as the CRIq or the Cognitive Reserve Scale aim to capture lifetime exposure to cognitively stimulating experiences. Consequently, differences across studies may reflect variability in the operationalization of CR rather than true differences in reserve itself. This highlights the need for greater conceptual clarity and standardization when selecting measures of CR in MS research.

Another relevant consideration involves the cultural and linguistic adaptation of CR measures. Several of the neuropsychological instruments identified in this review were originally developed in English-speaking populations and later adapted to different languages and cultural contexts. Variations in educational systems, literacy levels, socioeconomic opportunities, and cultural experiences may influence performance on these measures and limit comparability across studies. These factors may be particularly important when assessing individuals with lower educational attainment or reduced literacy skills, emphasizing the importance of culturally sensitive assessment procedures.

From a clinical perspective, the selection of CR measures should be guided by the purpose of the assessment. Questionnaire-based measures may provide a broader estimate of lifetime cognitive enrichment and reserve-building activities, whereas neuropsychological measures may offer a more objective estimate of premorbid cognitive functioning. Questionnaire-based measures may be particularly useful in large-scale studies or routine clinical settings because they are brief and easy to administer, whereas neuropsychological measures may be preferable when a more objective estimate of premorbid cognitive functioning is required. Therefore, combining both approaches may provide the most comprehensive characterization of CR in PwMS. Furthermore, because reserve is considered a potentially modifiable construct, its assessment may be particularly relevant when designing cognitive rehabilitation programs aimed at promoting engagement in cognitively stimulating activities and supporting long-term cognitive functioning.

Finally, it is important to mention that, as a systematic review, this work has certain limitations.

First, the inclusion and exclusion criteria may have led to the omission of potentially relevant studies. Second, no formal methodological quality assessment or risk-of-bias evaluation was conducted for the included studies; therefore, the findings should be interpreted as a descriptive synthesis of the available instruments rather than an appraisal of the strength of the evidence. In addition, the considerable methodological heterogeneity across studies complicated direct comparisons between findings. Future research should focus on developing standardized and psychometrically robust measures of CR specifically for PwMS, as well as on conducting cross-cultural validation studies and longitudinal investigations that further clarify the role of reserve across different stages of the disease.

Conflicts of interest

This systematic review received no funding from any organization or entity. The authors report no conflicts of interest.

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