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## Modern neuropsychological assessment methods for cognitive impairments in multiple sclerosis: a literature review

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease that according to the Atlas of MS of the Multiple Sclerosis International Federation affects nearly 3 million people worldwide, predominantly young adults (70–80 %) and 3–5 % of children. Motor impairments are among the leading MS symptoms as well as cognitive impairments (CI) which occur in 40–60 % of MS patients. However, due to their minimal impact on the overall EDSS score, disorders of cognitive functions are often overlooked, negatively affecting patients' quality of life and work capacity. Diagnosing CI is a crucial aspect of providing proper care, improving social adaptation, and expanding cognitive rehabilitation opportunities. This review aimed to systematize current knowledge about neuropsychological diagnostic methods for CI in patients with MS. We conducted a computerized search in PubMed, Scopus, and Web of Science using the keywords «multiple sclerosis», «cognitive impairment», and «assessment». In neuropsychology, CI is usually defined as performance falling more than 1.5 standard deviations below normative expectations, adjusted for demographic variables such as age and educational level. When diagnosing CI in MS, it is essential to consider comorbid psychiatric conditions, adverse effects of pharmacological treatment, and MS-related symptoms that may negatively influence cognitive function. Despite the wide range of existing methods for assessing CI in patients with MS, there is no consensus or clear recommendation regarding the use of specific tests, as no single tool provides comprehensive coverage of the patients' cognitive profile. The existing batteries of tests are well-constructed, yet have their limitations and challenges as long duration, necessity of experienced well-trained personnel or restricted coverage of cognitive domains. Further research is needed to identify the optimal assessment approach.

**Keywords:** multiple sclerosis, cognitive impairment, assessment methods.

**M**ultiple sclerosis (MS) is a chronic inflammatory autoimmune disease that affects the myelin sheath of neural pathways in the central nervous system (CNS). According to the Atlas of MS of the Multiple Sclerosis International Federation, MS affects nearly 3 million people worldwide, predominantly young adults (70–80 %) and 3–5 % of children [3, 23].

Motor impairments are among the leading symptoms in patients with MS and often serve as the primary reason for seeking neurological care. Motor function plays the most significant role in calculating the Expanded Disability Status Scale (EDSS) score. However, cognitive impairments (CI) occur in 40–60 % of patients [11, 16] and may arise independently

of the degree of neurological deficit [2, 19]. Despite this, due to their minimal impact on the overall EDSS score, cognitive functions are often overlooked, negatively affecting patients' quality of life and work capacity. Diagnosing CI is a crucial aspect of providing proper care, improving social adaptation, and expanding cognitive rehabilitation opportunities [11].

Although CI can be present in patients with all MS phenotypes, they are more pronounced in individuals with progressive forms (primary and secondary progressive MS) [17]. This review aimed to systematize current knowledge about neuropsychological diagnostic methods for CI in patients with MS and analyze the limitations of these tools.

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## Materials and methods

This review aimed to systematize current knowledge about neuropsychological diagnostic methods for CI in patients with MS and analyze the limitations of these tools. We conducted a computerized search in PubMed, Scopus, and Web of Science using the keywords «multiple sclerosis», «cognitive impairment», and «assessment».

## Results and discussion

### *Diagnostic criteria for cognitive impairment*

According to the fifth edition of the «Diagnostic and Statistical Manual of Mental Disorders» (DSM-5), CI are evaluated across six major cognitive domains: (1) complex attention; (2) learning and memory; (3) language abilities; (4) executive function; (5) perceptual—motor function; (6) social cognition. DSM-5 considers CI of various origins and classifies them by severity as either «major» or «mild». In the context of MS, cognitive impairment is typically classified under «mild neurocognitive disorders» [16].

In neuropsychology, CI is usually defined as performance falling more than 1.5 standard deviations below normative expectations, adjusted for demographic variables such as age and educational level. When diagnosing CI in MS, it is essential to consider comorbid psychiatric conditions, adverse effects of pharmacological treatment, and MS-related symptoms that may negatively influence cognitive function [2, 17].

At the same time, neither the current international literature nor DSM-5 provides recommended, standardized, and globally accepted neuropsychological tests or cutoff scores for domain-specific cognitive impairment, which represents a critical barrier to accurate and consistent identification of cognitive dysfunction in MS [16].

M. Fisher et al. proposed identifying such impairments based on the following neuropsychological assessment criteria [9, 18]:

- Performance falling 1.5 or 2 standard deviations (SD) below the normative mean in at least 20—30 % of the test parameters.
- Performance falling 1.5 or 2 SD in at least two cognitive domains.

### *Cognitive domains being affected*

The cognitive domains most frequently affected in patients with MS were first described by S.M. Rao and colleagues in 1991 [26] and have since been confirmed by subsequent studies [2, 12, 19]. These domains include [11, 15, 19, 27]:

- Information processing speed.
- Complex attention.
- Learning and memory.
- Executive functions (problem solving).
- Visuospatial abilities.

CI observed at the earliest stages of MS, such as during a clinically isolated syndrome, typically involve

reduced information processing speed and executive function. In contrast, patients with a relapsing—remitting course (RRMS) additionally show deficits in verbal and visual memory [19].

Patients with primary and secondary progressive MS exhibit a broader spectrum of cognitive dysfunctions, including impairments in attention, working memory, executive functions, as well as the aforementioned deficits in processing speed and verbal and episodic memory [27]. These patients often experience a reduced ability to sustain attention over time and to perform multiple tasks simultaneously. They may also show signs of visuospatial dysfunction and spatial disorientation, ultimately leading to reduced capacity for processing new information and learning [15].

A study by V. Planche et al. demonstrated that processing speed is the most commonly affected domain in MS, regardless of disease course. Other frequently impaired domains included:

1. Verbal episodic memory.
2. Executive functions.
3. Visuospatial construction.
4. Verbal fluency/speed.
5. Working memory.
6. Language abilities.

Notably, patients with secondary progressive MS showed more severe cognitive impairment than those with late-stage relapsing—remitting MS (disease duration over 10 years), across all cognitive domains except language abilities [25].

Based on the severity of cognitive deficits, patients may be categorized into five cognitive phenotypes: preserved cognition (56 %), mild impairment in a single domain (15 %), mild impairment in multiple domains (9 %), severe impairment in a single domain (12 %), and severe impairment in multiple domains (8 %) [6, 10, 20].

### *Assessment methods of cognitive function*

A wide variety of neuropsychological tests have been developed to assess specific cognitive domains. Some of these tools have been grouped into diagnostic batteries for more practical application in patients with MS.

The most commonly used tools for assessing cognitive impairment in MS include:

- Paced Auditory Serial Addition Test (PASAT) — assesses working memory;
- Symbol Digit Modalities Test (SDMT) — evaluates processing speed and complex attention;
- Word List Generation (WLG) — measures language functions and verbal fluency;
- Trail Making Test (TMT) — assesses visual attention, task-switching ability, and cognitive flexibility;
- 10/36 Spatial Recall Test (SPART) — evaluates visuospatial and perceptual—motor memory, as well as aspects of executive function;
- Wisconsin Card Sorting Test (WCST) — assesses executive function and the ability to adapt to changing task rules;

- Brief Visuospatial Memory Test—Revised (BVMT-R) — measures visuospatial memory;
- California Verbal Learning Test—Second Edition (CVLT-II) — assesses verbal memory;
- Selective Reminding Test (SRT) — evaluates learning and verbal memory [1, 14, 25].

Among these, the SDMT is considered the most sensitive tool for detecting cognitive impairment in MS. It is a quick test based on pairing nine single-digit numbers with nine unique symbols. These symbols are presented in random sequences over eight rows, and the participant is required to name the corresponding digit for each symbol within 90 seconds. SDMT is sensitive to subtle cognitive shifts, even in cases where EDSS score remains stable, and it is frequently used to detect isolated cognitive relapses [2, 21, 27].

The PASAT is part of the Multiple Sclerosis Functional Composite (MSFC) and has historically been regarded as the gold standard for assessing cognitive functions [4, 22]. In this test, the participant hears a series of 60 single-digit numbers, presented one every three seconds over a span of three minutes. The task is to continuously add each new number to the one immediately preceding it. PASAT evaluates processing speed, working memory, and complex auditory attention. However, it has several limitations:

- it requires a well-trained examiner to administer;
- audio equipment is necessary;
- it is often poorly tolerated by MS patients;
- performance may be affected by mathematical ability, dysarthria, and anxiety [4].

In addition to individual tests, several neuropsychological batteries have been developed specifically for MS populations: The Brief Repeatable Battery of Neuropsychological Tests (BRB-N), which takes approximately 45 minutes; The Minimal Assessment of Cognitive Function in MS (MACFIMS), which takes around 90 minutes; The Brief International Cognitive Assessment for MS (BICAMS), a screening battery that can be completed in 15 minutes [15].

BICAMS combines the SDMT, CVLT-II, and BVMT-R, enabling rapid assessment of processing speed, verbal memory, and visuospatial memory. Due to its brevity, BICAMS is classified as a screening tool; however, it is highly practical, particularly in the early stages of the disease. Research has demonstrated a strong association between CI as detected by BICAMS and MRI-based measurements of total brain volume in newly diagnosed young MS patients [29].

BRB-N has a sensitivity of 71 % and specificity of 94 %. It includes the following tests [11]: (1) PASAT-3, (2) SDMT, (3) WLG, (4) 10/36 SPART, (5) SRT). BRB-N is considered one of the gold standards in the neuropsychological assessment of cognitive impairment in MS due to its comprehensiveness and effectiveness [16].

According to current understanding, MACFIMS represents the most comprehensive cognitive battery available. It includes the SDMT, PASAT, CVLT-II, BVMT-R, the

Delis—Kaplan Executive Function System (D-KEFS), the Controlled Oral Word Association Test (COWAT), and the Judgment of Line Orientation test (JLO). This battery allows for in-depth evaluation of processing speed, episodic memory, executive functions, and other domains frequently affected in MS. However, due to its length and complexity, it is often poorly tolerated by patients [22].

Among self-assessment tools, the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) serves as a brief screening instrument. It contains 15 items that assess self-perceived cognitive symptoms, some of which correlate with levels of anxiety, depression, and cognitive function. However, MSNQ scores show weak correlation with performance on objective neuropsychological tests. A high MSNQ score is more indicative of depression than CI [31].

Some neuropsychological screening tools not specific to MS are also commonly used, including the Montreal Cognitive Assessment (MoCA) and the Adenbrooke's Cognitive Examination—Revised (ACE-R). Both tools evaluate five cognitive domains: attention/orientation, memory, verbal fluency, language, and visuospatial abilities. According to K. Charest et al., MoCA demonstrates a sensitivity of 87 % and specificity of 68 % for identifying cognitive impairment in MS patients [5]. However, these tools assess domains that are often unaffected in MS — such as spatial and temporal orientation — and fail to include key domains like processing speed. Therefore, they are limited in their utility for comprehensive cognitive assessment in MS [8].

In parallel with traditional paper-based tests, a number of digital tools have been developed for use on smartphones and tablets. These enable longitudinal monitoring of cognitive function in MS patients in outpatient settings over extended periods. Among them:

1. NIHTB iPad App, which includes tasks from the NIH Toolbox aimed at assessing receptive vocabulary, attention control, working memory, processing speed, verbal learning, and delayed recall [13].
2. The Multiple Screener tool combines two components: 1) online questionnaires assessing levels of anxiety, depression, and subjective cognitive complaints; 2) three neuropsychological tests for objective cognitive evaluation — SDMT, CVLT-II, and SPART [30].
3. DigiCog, a tablet-based digital version of the BICAMS battery [28].
4. sSDMT, a smartphone-adapted version of the Symbol Digit Modalities Test. It has demonstrated a high correlation with the traditional paper-based version, supporting its potential for broader clinical application [32].
5. The icognition screening battery, designed for smartphone use, includes three tests: SDMT, a dot-position test for assessing visuospatial

short-term memory, and a visual backward digit span test for evaluating working memory [7].

## Conclusions

Despite the wide range of existing methods for assessing cognitive impairment in patients with multiple sclerosis, there is no consensus or clear recommendation regarding the use of specific tests, as no single tool provides comprehensive coverage of the patients'

cognitive profile. The number and variety of assessment tools continue to grow and are increasingly being combined into test batteries, while digital instruments are being developed to allow for more precise and long-term monitoring. Nevertheless, each of them have their limitations whether the long duration, necessity of well-trained experienced personnel and restricted coverage of cognitive domains. Further research is needed to identify the optimal assessment approach.

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## Сучасні методи нейропсихологічної оцінки когнітивних порушень у пацієнтів з розсіяним склерозом: огляд літератури

Розсіяний склероз (РС) — це хронічне запальне автоімунне захворювання, яке, за даними Атласу розсіяного склерозу Міжнародної федерації розсіяного склерозу, вражає майже 3 млн людей у всьому світі, переважно молодих дорослих (70—80 %) та 3—5 % дітей. Серед провідних симптомів РС є моторні порушення, а також когнітивні порушення (КП), які виникають у 40—60 % пацієнтів із РС. Проте через їхній мінімальний вплив на загальний показник EDSS розлади когнітивних функцій часто залишаються поза увагою, що негативно позначається на якості життя та працездатності хворих. Діагностика КП є важливим аспектом надання належної допомоги, покращення соціальної адаптації та розширення можливостей когнітивної реабілітації. Цей огляд мав на меті систематизувати сучасні знання про нейропсихологічні методи діагностики КН у пацієнтів з РС. Ми провели комп'ютерний пошук у PubMed, Scopus та Web of Science, використовуючи ключові слова «розсіяний склероз», «когнітивні порушення» та «оцінка». У нейропсихології КН зазвичай визначається як зниження показників більше ніж на 1,5 стандартного відхилення від нормативних очікувань, скоригованих на демографічні змінні, такі як вік та рівень освіти. При діагностиці КП у пацієнтів із РС важливо враховувати супутні психіатричні стани, побічні ефекти фармакологічного лікування та симптоми, пов'язані з РС, які можуть негативно впливати на когнітивні функції. Незважаючи на широкий спектр наявних методів оцінки КП у пацієнтів із РС, на сьогодні відсутній консенсус або чіткі рекомендації щодо використання конкретних тестів, оскільки жоден із них не забезпечує повного охоплення когнітивного профілю пацієнта. Чинні тестові комплекси добре розроблені, однак мають свої обмеження та виклики, зокрема тривалість проведення, необхідність залучення досвідченого персоналу або обмежений спектр оцінюваних когнітивних доменів. Необхідні подальші дослідження для визначення оптимального підходу до оцінки.

**Ключові слова:** розсіяний склероз, когнітивні порушення, методи оцінки.

### ДЛЯ ЦИТУВАННЯ

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