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Screening tests for the evaluation of cognitive impairment in multiple sclerosis patients

Alina Ioana Nacu-Florescu[1], Oliver Daniel Schreiner[2,3], Thomas Gabriel Schreiner[1,2]

[1]Neurology Department, Clinical Rehabilitation Hospital, Iasi, Romania
[2]"Gr.T. Popa" University of Medicine and Pharmacy, Iasi, Romania
[3]Regional Institute of Oncology, Iasi, Romania

ABSTRACT

Multiple sclerosis (MS), the most common autoimmune neurological disease of young people, is a significant burden for the patient, significantly decreasing the quality of life. Besides motor deficits, sensory problems, and vision loss, in recent years, neurologists have focused also on the cognitive impairment related to this condition. The early detection of cognitive disturbances is currently an essential part of MS patients' follow-ups, as any worsening suggests the inefficiency of the applied treatment and the need for a therapeutic switch. In this regard, this review aims to highlight the importance of cognitive screening tests in the periodical evaluation of MS patients. While in the first part, the most frequently used cognitive screening tests in Romania are presented in a detailed manner, in the second part of the article, the clinical impact of these tests is highlighted, based on the results of the most relevant randomized clinical trials published during the last 10 years. Finally, the authors suggest future research directions to improve cognitive screening testing in MS patients after exposing the limitations of currently used screening batteries.

Keywords: multiple sclerosis, cognitive impairment, Montreal Cognitive Assessment, Mini-Mental State Examination, screening

Abbreviations

BICAMS – Brief International Cognitive Assessment for Multiple Sclerosis
BRB-N – Brief Repeatable Battery of Neuropsychological Tests
CNS – central nervous system
CVLT-II – California Verbal Learning Test II
EDSS – Expanded Disability Status Scale
fMRI – functional Magnetic Resonance Imaging
MCI – mild cognitive impairment
MMSE – Mini-Mental State Examination
MoCA – Montreal Cognitive Assessment
MS – multiple sclerosis
PASAT – Paced Auditory Serial Addition Test
RRMS – relapsing-remitting multiple sclerosis
SDMT – Symbol Digit Modalities Test
SPMS – secondary progressive multiple sclerosis
SRT – Selective Reminding Test

INTRODUCTION

Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system (CNS), with increasing prevalence and incidence in the last decade [1]. This immune-mediated disorder affects young people, as it begins most frequently between the ages of twenty and forty [2], and significantly negatively impacts their quality of life [3]. Moreover, MS represents a socioeconomic burden, with the latest figures showing an increase in the need for healthcare services for MS patients in most European countries [4].

Because of the many possible locations of demyelinating plaques at the CNS level, the neurological examination can reveal multiple pathological findings in MS patients. Motor deficits, sensory problems, bowel and bladder dysfunctions, and vision

Corresponding author:
Thomas Gabriel Schreiner
E-mail: schreiner.thomasgabriel@yahoo.com

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loss are among the most common complaints, even in the early stages of the disease [5]. However, other non-specific symptoms, such as fatigue [6], depression [7], and cognitive impairment [8], are also frequently encountered. During the last decade, the interest of neurologists in cognitive impairment related to MS has significantly increased, with early detection and adequate treatment being two highly discussed topics nowadays.

The term "cognitive impairment" describes the partial or total loss of several mental functions, including, but not limited to, perception, learning, memory, and problem-solving [9]. More prominently encountered in Alzheimer's disease and other dementia patients, cognitive impairment is also relevant in other neurological disorders, including the early stages of MS. As with many other neurological (mainly neurodegenerative) conditions, the early detection of cognitive impairment should be a must in the present days of clinical practice, as no effective curative treatments exist for advanced stages. In this context, several screening tools for the early detection of cognitive impairment have already been developed and are currently used worldwide.

Thus, the first aim of this review is to present in a detailed and comparative manner the most frequently employed cognitive screening tests in Romania. Subsequently, the authors describe the clinical impact of the tests and their correlation with other relevant aspects of MS by presenting the results of the most relevant studies conducted on different European cohorts. Finally, highlighting also the tests' limitations, the authors suggest novel research directions in the field, as continuous improvements of currently available tools and the development of new, more sensitive and specific tests, should be mandatory in the near future.

Cognitive screening tests used in multiple sclerosis patients

Cognitive impairment can be encountered in various neurological disorders, with Alzheimer's disease, Parkinson's disease, MS, and other dementias being the most relevant ones. The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are two of the most frequently used questionnaires in neurological practice.

Mini-Mental State Examination (MMSE)

The MMSE, also known as the Folstein test, is a 30-point questionnaire, consisting of questions that approach the following areas: orientation in time and place, repeating lists of words, attention, calculation, language comprehension and use, basic motor skills and complex commands [10]. Although not initially developed for diagnostic purposes, the MMSE can be a reliable tool in estimating the severity of cognitive impairment and in the periodic follow-up of a patient who is at risk of developing mental degradation [11]. Thus, the raw scores and thresholds such as ≤ 9 points suggestive of severe impairment, 10-18 points for a moderate deficit, and 19-23 points for mild cognitive impairment (MCI) should be interpreted with caution and must be adjusted depending on the age, socioeconomic and educational level of the patient. Even obtaining the maximum score does not completely rule out cognitive deficits, while lower scores should impose a more detailed cognitive assessment and further evaluation.

Some strong points of the MMSE are the administration in a short time (optimal for bedside examination) and the lack of specialized training or equipment requirements. The main disadvantages of this screening test remain its lack of sensitivity in detecting MCI and in differentiating between different types of dementia [12]. Additionally, criticism was raised regarding the fact that the MMSE focuses mainly on language comprehension and production, measuring inadequately or insufficiently other essential parts related to cognition such as visuospatial and/or constructional praxis [13].

Montreal Cognitive Assessment (MoCA)

With the MMSE inaccurate in detecting MCI, the MoCA was demonstrated to be a promising tool in early Alzheimer's disease screening for cognitive impairments. Similar to the MMSE, the MoCA is a 30-point test that assesses language, visuospatial abilities, attention, concentration, abstract reasoning, and short-term memory [14]. Regarding scoring, a score of 26 points and above is considered normal, scores between 18 and 25 points are encountered in persons diagnosed with MCI, 10-17 points suggest a moderate cognitive impairment, and finally, scores under 10 points are relevant for severe cognitive deficits. With a short time of administration, the absence of prior specialized training requirements, and being more sensitive and specific than the MMSE, MoCA may be the desired starting screening test for cognitive impairments in patients with various neurological disorders, including MS [15].

Among the most relevant disruptive factors, age, gender, educational status, and depression have a significant influence on MoCA scores. Moreover, the main limitation of the MoCA related to the inability of pointing to a clear pattern of an underlying cognitive domain should always be considered, with more extensive cognitive assessments being necessary for patients with a high risk of developing MCI and dementia.

Other cognitive screening tests often used in multiple sclerosis patients

Despite the possibility to use the MMSE and the MoCA for cognitive assessment in MS patients, the reduced specificity and sensitivity of these tests have led to the development of extensive batteries consisting of short or more in-depth cognitive screening more appropriate for MS patients. With different administration times (up to 90 minutes), the most frequently used in clinical and research setting is the following tests: California Verbal Learning Test II (CVLT-II), Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Selective Reminding Test (SRT). Despite the existence of variants and other additional tests used mostly for research purposes, this article aims to highlight the most relevant cognitive screening tools applicable in daily clinical practice. Thus, the authors have focused only on the four abovementioned tests that are encountered in two of the most frequently used batteries for neuropsychological assessment in Romania, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) and the Brief Repeatable Battery of Neuropsychological Tests (BRB-N).

CVLT-II, one of the most sensitive verbal learning tests, evaluates encoding, recall, and recognition in the auditory-verbal modality of item presentation [16]. Immediate, short and long delay reminds, free and cued recalls are measured, with results to be interpreted depending on age, gender, and clinical situation. Reliability data, including test-retest reliability, are adequate. More recently, a short form of the test has been developed, containing only lists of nine words from three categories, limiting its administration time to 15 minutes, more appropriate for fast, bedside use [17].

PASAT has become widely employed in MS patients' cognitive screening, being included in several testing batteries. The standard version used also in Romania involves giving the patient a number every 3 seconds (or 2 seconds for a more challenging version) and asking to perform multiple additions by adding the number head in the last call with the number heard before. This task involves attention, working memory, and calculation [18].

SDMT remains the most sensitive performance metric of cognitive function in MS patients. Despite being consistently interpreted as a marker for the patient's information processing speed, low scores in the SDMT suggest a general rather than a specific decline in cognition [19]. However, one should cautiously interpret SDMT scores, as multiple factors such as age, gender, cultural and ethnic background, educational level, and visual acuity were demonstrated to interfere with the results of this test.

SRT is another neuropsychological test that evaluates verbal learning and memory via the use of a list consisting of 12 unrelated words designed to be remembered over multiple recall trials [20]. According to the "selective reminding paradigm", learning is facilitated by presenting only the words that were missed by the candidate at the previous trial. With its variant, free and cued, SRT assesses attention, acquisition, and retrieval of memories, being a valuable tool for detecting dementia-related memory dysfunctions.

Taking into consideration each of the abovementioned cognitive screening tests addresses different aspects of cognition, table 1 summarizes their main advantages and limitations in the daily clinical use.

Correlations of cognitive screening tests with other pathological aspects of multiple sclerosis

Relevant clinical aspects

While the MMSE and the MoCA are short, examiner-friendly bedside tests that can be applied to a variety of neurological disorders associated with cognitive impairment, they are useful in MS patients only for a quick, general assessment. The main drawback when using these two questionnaires is the impossibility of precisely determining the affected cognitive domain. Or, according to research conducted during the last 20 years, the most affected cognitive domains in MS patients are working and long-term memory, information processing speed, attention, verbal fluency, and executive function [21]. The use of more complex batteries containing specific tests that focus on a specific cognitive domain is the natural second step of the neuropsychological assessment in MS. For example, CVLT-II evaluates mainly language, and in a more reduced manner, attention and short-term memory. The SDMT remains the most relevant test for detecting altering of information processing speed, however, other cognitive domains such as attention and language also play a role in modulating SDMT's scores.

Studies conducted so far using BICAMS and BRB-N testing batteries have detected heterogeneous results regarding the prevalence of cognitive dysfunctions in MS patients. 40 to 65% of the tested candidates showed impaired learning memory, with variable rates depending on MS onset and duration, or on personal characteristics such as age, gender, and educational level [22]. Furthermore, another explanation for variable rates between different studies is directly related to the test's acuity and sensitivity, one of the major problems with many neuropsychological questionnaires that must be intensely addressed and improved in the next years. Similarly, a variable prevalence for language deficits including naming, word finding, and fluency was obtained in different MS cohorts. A recent study reported that between 20% and 58% of relapsing-remitting MS (RRMS) or secondary-progressive MS

TABLE 1. Advantages and limitations of cognitive screening tests

Screening test for cognitive impairment	Advantages	Limitations
Mini-Mental State Examination (MMSE)	• Short-time administration • No special equipment or training requirements • Diagnostic and longitudinal assessment of – Alzheimer's disease	• Lack of sensitivity to mild cognitive impairment • Inadequate for measuring visuospatial and/or constructional praxis • Scores affected by age and education
Montreal Cognitive Assessment (MoCA)	• Short-time administration • No special equipment or training requirements • Generally superior to the MMSE • Adequate for the detection of mild cognitive impairment	• Scores affected by age, education, male sex, and depression • Impossible to determine precisely the affected cognitive domain
California Verbal Learning Test II (CVLT-II)	• Adequate reliability • More sensitive than other verbal learning tests	• Scores affected by age, gender, and clinical context • Screening only for auditory-verbal memory
Paced Auditory Serial Addition Test (PASAT)	• Widely employed in multiple sclerosis • No special training requirement • Reliable for working memory testing	• Limited value in patients with aphasia and hearing impairment • Susceptibility to practice effects and calculation ability • Scores affected by age and intelligence quotient (IQ)
Symbol Digit Modalities Test (SDMT)	• Short-time and easy administration • Adequate predictor for mild cognitive impairment • High reliability and validity	• Scores affected by age, educational level, and inconstantly gender and cultural background • Not a pure test for processing speed • Influenced by visual acuity and oculomotor functions
Selective Reminding Test (SRT)	• Good inter-rater and test-retest reliability • Adequate sensitivity to many neurological disorders (including mild cognitive impairment)	• Scores affected by age, gender, and educational level • (Potential) Long-time administration

(SPMS) patients had language impairments [23], however, available literature on this topic is highly heterogeneous, with other studies revealing intact functionality.

An important aspect that advocates the importance of cognitive screening of MS patients is the correlation between cognitive impairment and other clinical features of the disorder. More frequent and severe cognitive deficits were reported in SPMS compared to RRMS, together with advanced age and longer disease duration [24]. A higher Expanded Disability Status Scale (EDSS) score and an increased rate of relapses were associated with greater impairment in cognitive functions. Another interesting element to consider is the type of the first attack and the later development of cognitive problems, with cerebellar symptoms followed by motor or sensory attacks more prone to worse performance in attention and language tasks [25]. This can be partially explained by the incompletely known roles of the cerebellum in cognition. Cognitive impairments were also correlated with the type of treatment, with a recent study demonstrating the negative impact of immunosuppressive treatment compared to immunomodulatory drugs [25]. By inhibiting inflammation at the CNS level, reducing brain atrophy, and having possible neuroprotective effects, the choice of a specific disease-modifying drug could also be related in the future to the cognitive deficits encountered in MS candidates.

Conventional and advanced imagistic correlations

The imagistic aspect in cognitively impaired MS patients remains a topic of great significance, as an increasing number of studies have drawn interesting conclusions between structural magnetic resonance imaging (MRI) biomarkers and cognitive dysfunctions. A multicenter study showed that cognitively impaired MS patients had a higher degree of gray matter atrophy in the left thalamus, right hippocampus, and several parietal regions, white matter atrophy in the posterior brain regions,

and white matter diffusivity abnormalities in cognitive-relevant tracts [26]. The number of plaques is another potential imagistic-based biomarker for the correlation between MS and cognitive impairment. According to a recent study, impaired abstraction was associated with a higher number of MS plaques in the temporal lobe, but not in other parts of the brain such as the frontal lobe, the parietal lobe, the occipital lobe, or corpus callosum [27]. In line with this conclusion, we mention the study conducted by Curti et al., 2018 where the multivariate analysis revealed a significant correlation between the total number of cortical lesions and mild cognitive impairment [28]. Similarly, by using phase-sensitive inversion recovery as an additional tool to conventional MRI, leukocortical lesion volumes were correlated with lower information-processing speed and poorer verbal fluency [29].

In the era of functional MRI (fMRI), recent studies tried to investigate whether there are specific patterns of alteration in the principal cognitive networks of the MS brain. No clear conclusions are available at the present; however, some studies have shown increased recruitment of several brain areas with an augmented load of demyelinating lesions. Normal appearing white matter injuries measured via MR spectroscopy and other white matter lesions analyzed via several MR advanced techniques are supposed to be the major triggers for cognitive impairment, even in the early stages of the disease [30]. Results are inconclusive also regarding the adaptive/compensation hypothesis, as some studies did not demonstrate a correlation between increased resting-state functional connectivity and an expected improved cognitive performance [31]. Furthermore, the implication of the thalamus is increasingly evident, with the thalamocortical network abnormalities highlighted by fMRI in several ways: increased functional connectivity of the thalamic network was associated with reduced cognitive performance, while its enhancement during cognitively challenging tasks demonstrates the incapacity of compensating for the general cognitive impairment in MS patients [32]. Finally, the hippocampus is another essential target for fMRI studies in the near future because of both its role in active episodic and special memory, and its multiple connections with other essential cortical and subcortical areas.

Current limitations of the neuropsychological assessment

The first limitation in the currently used neuropsychological evaluation is related to the incomplete understanding and inappropriate testing of cognitive impairment. Social cognition, a cognitive domain intensely studied in the last few years, was determined to be altered in MS patients. However, alterations of social cognition are frequently overlooked and underestimated in the daily clinical setting because of the lack of a precise definition, the incompletely understood relationship with the general cognitive impairment, and the absence of specific screening tests [33]. Another particular cognitive domain severely under-addressed in clinical studies involves high-level cognitive skills. Scarce data on this topic is currently available, mainly because of the difficulty in assessing high-level cognitive skills via specific tests, combined with incomplete scientific knowledge [34].

A second relevant hindrance is the use of the current screening batteries, comprising tests with suboptimal sensitivity and specificity. The data has limited reliability mainly because it was obtained from small samples, but also because of multiple inferences that may produce significant biases. Language and cultural influences demand increased attention, especially in MS patients with cognitive decline. Lastly, some tests might be to deviate from real-world demands, questioning whether lower scores in experimental conditions truly have an impact on practical activities of daily life [35].

Finally, a better understanding of the anatomical and pathophysiological basics of cognitive impairment in MS patients remains the key to a faster diagnostic and effective therapy. fMRI and other advanced imagistic techniques will facilitate the discovery of novel neural circuits among key structures of the CNS, such as the thalamus, the hippocampus, and other language-related areas that are directly and indirectly involved in cognitive processes. One could also expect that these new discoveries may infirm earlier theories about the natural evolution of cognitive impairment in MS.

CONCLUSION AND FUTURE RESEARCH DIRECTIONS

Screening for cognitive impairment has become an important part of the expanded clinical examination of the MS patient. Several screening tests forming more complex neuropsychological testing batteries are currently employed worldwide. We reviewed within this article the most commonly used cognitive screening tests available in Romania at the present.

With short administration time, minimal preparation, and fast conclusions, currently available cognitive screening tests such as the MMSE, the MoCA, PASAT, SDMT, and SRT are valuable tools in the neurocognitive assessment of MS patients. However, after reviewing their strengths and limitations, one must recognize the urgent need for improvement and the development of additional, more sensitive screening tools. In this context, the correlation with data obtained from imagistic studies could bring

new evidence related to the basic neuroscience on which cognitive impairment might be based.

Three main research directions should be followed in the near future in order to improve the neuropsychological assessment of MS patients. A better understanding of the underlining processes related both to MS pathogenicity and cognitive impairment is mandatory, while the development of new screening tools that are more sensitive but remain examiner-friendly is another must. Finally, correlating the findings obtained via cognitive testing with the other clinical and paraclinical aspects of the disease will lead to the validation of imagistic and biological biomarkers with a great impact on screening and treatment.

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