

## Cognitive Impairment in Multiple Sclerosis

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Article information	Abstract
<p>Article history: Received: 27 May 2012 Accepted: 12 Aug 2012 Available online: 12 Mar 2013 ZJRMS 2014; 16(1): 1-7</p> <p>Keywords: Multiple sclerosis Cognitive impairment Cognitive Neuropsychological test</p> <p>*Corresponding author at: Department of Psychiatry, Sina MS Research Center, Tehran University of Medical Sciences, Tehran, Iran. E-mail: fa.etesam@gmail.com</p>	<p>Cognitive impairment can emerge in the earliest phases of multiple sclerosis. It strongly impacts different aspects of Multiple Sclerosis (MS) patients' lives, like employment, social relationships and the overall quality of life; thus, its on-time recognition and treatment is mandatory. This paper discusses issues, diagnostic methods and treatment options for cognitive dysfunctions in MS.</p> <p>This paper is a descriptive review of the related studies in the recent 10 years, performing a keyword search in the main databases.</p> <p>Cognitive impairment mostly involves aspects of information processing, memory and executive functioning in MS. Neuropsychological tests like MACFIMS and BRB-N are recommended for its assessment. Still, there is no fully efficient treatment for cognitive impairment. Researchers have shown some positive effects, using disease-modifying therapies and cognitive rehabilitation. Depression, pain, fatigue and other factors influencing cognitive functions must be paid attention to.</p> <p>Recognizing cognitive impairment as a major symptom for MS, makes studying this subject one of the priorities in dealing with the disease. Therefore, a consecutive research for identification and management of this part of quality of life in MS patients is obligatory.</p>

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### Introduction

Multiple Sclerosis (MS) is a chronic immune system disease that is characterized with demyelination and axonal destruction. The disease may emerge at any age; however, it is usually diagnosed at 20-40 years of age. Since neurons of any part of the brain or spinal cord may be involved, a wide range of symptoms in form of eye and sensory motor problems, bladder and bowel dysfunction, pain in different parts of the body, sexual problems, vertigo and imbalance can be observed in MS patients [1]. The disease is classified into four major subtypes based on its clinical course (Table 1) [2].

Since the identification of MS as a disease, physical disabilities accompanying the disease have mostly been the focus of attention for patients and physicians. However, in the past decade, impairment in different cognitive areas has been significantly considered.

Cognitive impairment with the occurrence of 40-70% is observed in all subtypes and stages of the disease, even its milder forms like clinically isolated syndrome (CIS) (incidence of the first clinical MS symptoms like inflammation of the optic nerve or sensory motor signs with/without MRI findings) and benign MS [3, 4]. Clinical presentations of the said impairment are diverse and range from milder forms like short term memory problems to rare severe impairments like dementia. According to longitudinal studies, cognitive impairment gradually progresses through time and more severe

degrees are seen in advanced phases of the disease and patients with progressive disease.

Cognitive impairment in a patient with stable physical condition predicts the future progress of the disease; likewise, cognitive deficits can predict benign MS progress and it can also demonstrate the increase in the probability of turning the disorder into MS in CIS [5]. Causes of cognitive impairment are different in patients. Various factors such as sensory problems, disruption of the connections between parts of the brain (cortico-cortical and cortico-thalamic) following brain lesions, involvement of seemingly normal white and gray matter of the brain and the direct effect of inflammation byproducts are considered effective in the emergence of the impairment in MS patients [6, 7].

Multiple sclerosis usually involves people during their first vocational years. Cognitive impairment can be fully disabling and impose heavy personal and social costs [8]. It is well recognized that cognitive impairment does not only have potential effects on decreasing the quality of life in patients, but also can influence their daily functions like the ability to make the required decisions on disease treatment, acceptance and following up treatment instructions, keeping social relations and the ability to drive. It can also play an important role in losing jobs; therefore, early diagnosis of the impairment, starting clinical interventions and preventing its progress is necessary.

**Table 1.** Clinical course classification of MS

Disease course	Key characteristics
Relapsing-remitting MS (RRMS)	Acute attacks with deteriorating neurologic signs followed by variable courses of symptom remission and disease stability.
Secondary-progressive MS (SPMS)	The clinical course of initial RRMS continues with progressive deterioration of basic conditions with/without additional attacks.
Primary-progressive MS (PPMS)	The disease course is primarily a progressive and gradual worsening of basic conditions with little fluctuations and without clear attacks.
Progressive-relapsing MS (PRMS)	Progression of disability with clear acute relapses, with or without full recovery. Deterioration continues throughout attacks.

According to recent studies, the incidence of MS is increasingly spreading in Iran and our country is being located among regions with moderate-to-high incidence rate for MS in the world [9, 10]. Thus, continuous studies for determining useful strategies to prevent, manage and treat different aspects of the disease including the resulting cognitive impairments would be required. The present study evaluates different cognitive problems, diagnostic procedures and presently available treatments for patients at risk of developing the impairment.

## Materials and Methods

This is a descriptive review article resulting from studying relevant articles on major databases like Scopus, Google Scholar and PubMed. Using keywords including multiple sclerosis, cognitive impairment, cognitive and neuropsychological tests, pertinent studies published in the recent 10 years with acceptable study design, research methods and assessment tools were selected and review articles of scholars in the field of cognitive impairments in MS were also used. Moreover, it was attempted to include the most recent valid data in the related fields.

## Results

Although almost all types of cognitive deficits can be seen in MS [11], the common view includes impairment in sustained attention, information processing, memory and executive functions [12] that are described below.

**Information processing speed:** The most prevalent area of cognitive impairment in MS patients is information processing speed which refers to the speed with which a person can process any kind of information including verbal or visual [13]. Information processing speed decreases in MS patients and compared to normal people, more slowness is highlighted in performing tasks with a time limit [14]. Decrease in processing can occur, independent of other impairment areas; however, this affects the development of impairment in cognitive areas like working memory, executive functions and other aspects of memory [13].

**Attention:** Attention is a complicated cognitive function and includes different aspects like alertness, vigilance, selective, sustained and divided attention [15]. Impairment in sustained attention is more common in MS and there have been reports on divided attention

impairment (tasks that require the patient to execute more than one action at a time) [16].

**Memory:** Memory is usually classified based on time and content aspects. In case of time, memory is divided into short-term and long-term memory. Immediate memory and working memory are within the short-term memory group. Explicit memory and implicit memory are content-based memory classifications and they are divided into episode memory and semantic memory subgroups [15]. Working memory, a system with which information is saved and manipulated for a short time, is frequently impaired in MS patients and it is closely followed by verbal and visual memory impairments and is known as the most prevalent areas of impairment in MS [5]. Semantic memory impairment is also seen in MS. The said impairments claim that the prevalence of memory impairment in MS patients is 40-60% [13].

**Executive functions and other areas in cognition:** Executive functions are a series of complicated cognitive abilities including logical thinking, planning, organizing, goal-directed behaviors, evaluating and solving problems in addition to beginning, controlling and inhibiting behaviors. About 19% of the MS patients have impairment in this area. There is a significant relationship between executive function impairment and damage in pre-frontal cortex [15].

Global intellect and language function problems have been observed in children with MS more [17]; this area remains intact in adults but some latent comprehension deficits are shown related to slowed information processing [3].

Visual perception functions comprise recognizing visual stimulus and the proper perception of its features and approximately one fourth of MS patients have problems in this area. Primary visual processing problems (due to optic nerve inflammation) can have a destructive effect on visual perception, though perceptual deficits may occur, independent of these problems or other cognitive impairments [18].

### Factors affecting cognitive functioning in MS

**Disease variables:** 1) Atrophy & brain lesions: the moderate relationship between the overall volume of brain lesions and the stronger relationship between cerebral atrophy, and particularly the increase in the third ventricle size are not only correlated with cognitive impairment, but also have a predictive value [19]. Thalamus atrophy is also a powerful predictor of

cognitive function problems, though it is not as valid as cortical atrophy [20].

The increase in cortical lesions was accompanied by reduction of cognitive functions through time [21]. On the other hand, studies conducted using fMRI have shown the increasing use of cortical networks through compensatory mechanisms; it theoretically preserves the cognitive function. These improved activities are demonstrated in patients with normal cognitive function and seemingly normal cerebral tissue in MRI and is interpreted as a pathology that is not clinically obvious yet. According to this method, cognitive impairment in MS does not occur just because of tissue destruction; however, the cause is the imbalance between tissue destruction, tissue restoration as well as re-organization and adaptive function. When the increase in the activity of cortical neurons cannot keep cortical activity correlation, cognitive problems emerge [22]. 2) Genetics: cognitive impairment genetics is not known in MS; yet, recent studies have mentioned a relationship between APOE $\epsilon$ 4 allele and cognitive impairment [23]. 3) Duration of disease and degree of disability: conflicting results have been reported on the relationship between cognitive impairment, duration of disease and level of disability in MS patients. According to some longitudinal studies, cognitive impairment increases following the deterioration of physical disability, duration of disease and onset of a progressive disease. On the other hand, a weak relationship is demonstrated between cognitive status and level of disability.

It is prevalently observed that there are MS patients who suffer from cognitive dysfunction despite their low EDSS score (a method of quantifying disability in multiple sclerosis). Considering the point that EDSS focuses on spinal involvement and movement in addition to cognitive impairments with a drop in cortical activities, the absence of a relationship between the two areas is not predictable. Nevertheless, better recognition of such relationships requires further studies with stronger methodologies [8, 24].

**Accompanying clinical and medical factors:** Depression, the other common syndrome accompanying MS, has a reverse effect on cognitive abilities, particularly information processing speed and executive function. The prevalence of lifetime depression in MS is estimated at approximately 50%; thus, it is more prevalent compared to the general population and other neurologic diseases [25]. There is a complicated, reciprocated relationship between depression and cognitive impairment. Depression may lead to some cognitive function impairments like lack of concentration, attention problems and slowing of information processing. On the other hand, patients' awareness of the drop of cognitive ability may lead to an increase in anxiety and depression. Depressed patients may also estimate their cognitive problems at a higher level and this intensifies depression in them [26].

Pain is another effective factor in cognitive function. Acute and chronic pain influences attention, information processing speed and encoding and can indirectly affect mood (like depression). Drugs used in treating pain or

other disease symptoms (like benzodiazepine, corticosteroids, anticonvulsant and anti-spasm drugs, etc.) can also have adverse effects on cognitive function [5, 13].

Fatigue is another factor that is frequently complained about. Patients often state that fatigue impairs cognitive function while no exact relationship has been found between the complaints and poor performance on cognitive tasks. On the other hand, it was demonstrated that fatigue can reduce the ability of patients in performing tasks that require time and attention maintenance. Indeed, the relationship between fatigue and cognition in MS is not well detected yet and further investigations are required in this field [27, 28].

**Evaluation:** 1) Neuropsychological evaluation: considering the prevalence of cognitive impairment in MS patients, its incidence in initial stages of the disease and its effect on patients' functions in different areas, the early diagnosis is useful and even essential. The clinical diagnosis of cognitive impairment is not solely possible and requires tools that can show cognitive function differences in different areas among patients and normal people. However, access to centers offering neuropsychological services and the high costs impose restrictions and in many cases, the problem remains undiagnosed [2].

Two cognitive tool batteries (MACFIMS and BRBN) are often used on research and clinical centers to comprehensively assess cognitive functions in these patients; both tools possess appropriate psychometrical features and are structurally sensitive to other impacts of MS (Table 2).

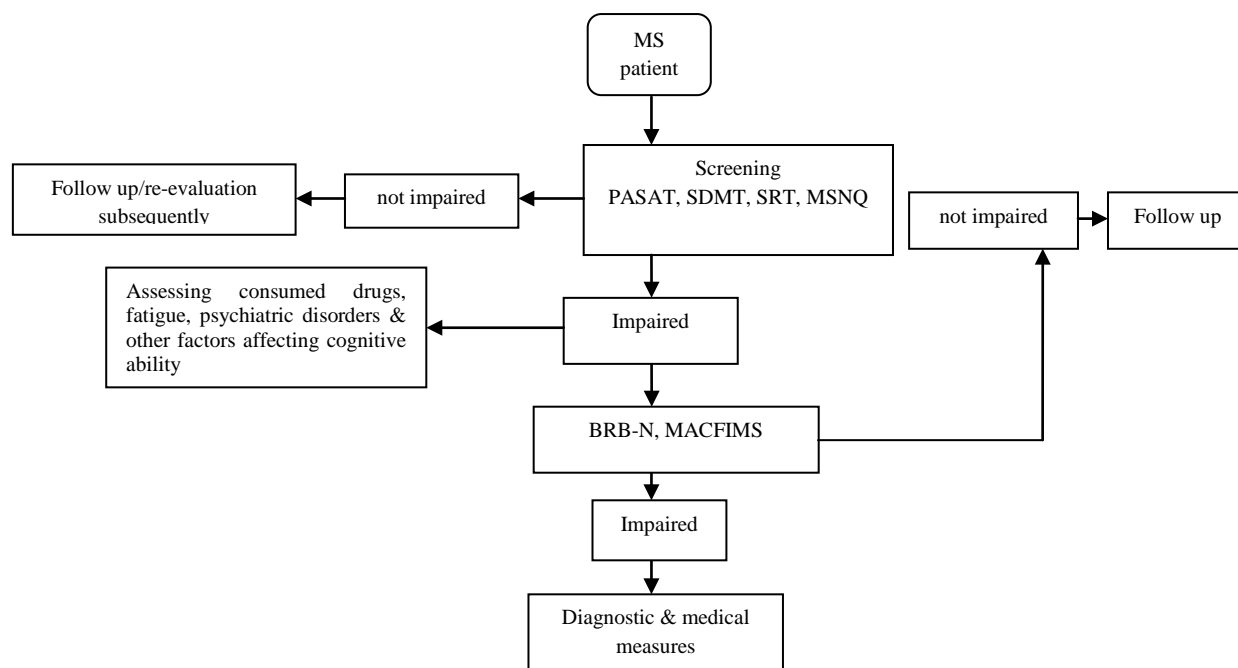
MACFIMS (Minimal Assessment of Cognitive Function in MS) battery was approved as a test for assessing cognitive impairment in MS patients in a panel consisting of experienced MS researchers in 2001. It comprises 7 tests measuring 5 cognitive areas; assessing each person takes about 90 minutes [29]. The Persian version of the test battery with appropriate validity and reliability has been recently published for Persian speakers [30].

BRB-N (The Brief Repeatable Battery of Neuropsychological Tests) also includes some tools measuring the most prevalent cognitive impairments like episodic, verbal and visual memory as well as information processing speed and working memory. This test battery is adjusted for use in a few countries and is commonly used in MS-related neuropsychological studies [31].

The major difference between MACFIMS and BRB is the method of assessing memory. As it is shown in table 1, these two test batteries use different tools for assessing auditory-verbal and visuospatial memory. A study comparing the tools on MS patients and normal control cases revealed that both are similarly sensitive to disease conditions. It was mentioned in this study that SDMT has the highest level of sensitivity. The Selective Reminding test was more sensitive for assessing auditory-verbal memory than CVLT-II and in visuospatial assessment; BVM-T-R was more sensitive than 10/36 Spatial Recall test [32].

**Table 2.** Common tools in MS neuropsychological assessment

Minimal Assessment of Cognitive Function in MS		Brief Repeatable Battery of Neuropsychological tests
Processing speed/Working memory	Paced Auditory Serial Addition Test Symbol Digit Modalities Test	Paced Auditory Serial Addition Test Symbol Digit Modalities Test
Learning and Memory	California Verbal Learning Test-II Brief Visuospatial Memory Test-Revised	Selective Reminding Test 10/36 Spatial Recall Test
Visual perception/Spatial processing	Judgment of Line Orientation Test	
Executive functions	Delis-Kaplan Card Sorting Test	
Language	Controlled Oral Word Association Test	Controlled Oral Word Association Test

**Figure 1.** Diagnostic assessment of cognitive impairment in MS patients

Although the said tools provide us with comprehensive information on cognitive functions, their time-consuming nature restricts their daily application. Various tests like PASAT and SDMT (Table 2) and MMSE (Mini-Mental State Examination) have been known as useful measures for primary screening of cognitive impairment; yet, their application was accompanied with some problems like low sensitivity or specificity for MS. Some self-reporting measures like Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) are designed for quick assessment of cognitive impairments and can be filled out by patients and their families within a short time. However, a recent study showed that personal reports of patients on their cognitive impairment had a strong relationship with their depression, anxiety or personal characteristics and were less associated with their performance in cognitive tests [33]. Despite these restrictions, the application of the mentioned tools provides an overall assessment of patients' perceptions of their cognitive abilities and comparing the results with performance neuropsychological tests, offer considerable information on the insight of patients towards their problems [5]. Figure 1 illustrates a suggestive process for studying and diagnosing cognitive impairment in MS patients.

In a cohort study conducted on MS patients, a summarized version of BRB test battery consisting of

PASAT, SDMT and Selective Reminding test were assessed for quick cognitive screening. According to the findings, these tools could detect cognitive impairment in patients with 94% sensitivity, 84% specificity and 89% accuracy. Accordingly, cognitive impairment can be screened in 5-15 minutes using these tests [34]. Also, BICAMS (Brief International Cognitive Assessment for MS) is another summarized package, including SDMT, CVLT-II and BVMC-R, suggested by Benedict et al. for conditions requiring short-time assessment which can be used in small clinics and by one staff, even without formal neuropsychological knowledge [35].

2) Imaging techniques: Recent studies have emphasized the validity of MRI as a predictor of cognitive impairment in future and consider this tool as one of the components of cognitive studies. Beside the high sensitivity of this technique in clarifying the relationship between cerebral atrophy and cognitive status, it can be used to achieve more precise information about the relation between functional problems and structural defects. For instance, left frontal atrophy is associated with dysfunction in verbal memory while right frontal atrophy is accompanied with some deficits in visual and working memory [36].

Compared to MRI, the application of fMRI in evaluating brain functions of MS patients is still a new research area. Achievements associated with this technique have

provided valuable information on brain function in MS patients and neuroplasticity in the last 10 years. fMRI with non-invasive mapping of different parts of the brain show how brain, despite the developed lesions, can continue its normal function by making changes in the organization of functions in different parts. Moreover, this technique offers useful information on the relationship between different parts of the brain, cognitive activities and changes made in activating these parts in MS [37]. Diffusion-tensor MRI, also, provides more information on changes in the apparently normal brain tissue and the integrity of white matter, compared to common imaging methods. In some other studies, some relations between fractional anisotropy and disconnection between different cortical and subcortical parts due to MS lesions and cognitive function are demonstrated [12, 38].

**Treatment:** The two major approaches in treating cognitive impairment include pharmacological and non-pharmacological treatments that are discussed below.

1) Pharmacological treatments: Using effective treatments for advancing cognitive function has been studied for several years. Drugs like: interferon, glatiramer acetate and natalizumab can be helpful by inhibiting inflammatory products quickly; preventing the development of new lesions and some neuroprotective effects. According to clinically controlled studies, there is no evidence proving the effect of natalizumab, glatiramer acetate or fingolimod on improving cognitive function in multiple sclerosis [39]. Studies conducted on impacts of interferon  $\beta$  has shown its positive effects on cognitive function with 1-3 years stability; it was even revealed that the early start of interferon treatment in CIS patients can be effective in preventing cognitive dysfunction [40, 41]. However, it should be considered that such studies are not often specifically designed for examining the effect of the drugs on patients' cognition; therefore, there is no available data on their baseline cognitive level in advance. Lack of a control group, small sample sizes, high percentage of excluded patients, absence of frequent and regular assessments and choosing retrospective study approach are among the limitations of these studies. There have been no strong and sufficient clinically controlled studies on determining the degree and manner of effective treatments for cognitive impairment status. Cogni MS is a longitudinal study on the effect of Interferon  $\beta$ - $b_1$  on cognition of 1520 MS patients in 33 countries. The primary data of the study showed that specifications of cognitive impairment in MS patients were similar in 61% of them; however, no information has been published on the effect of Interferon  $\beta$ - $b_1$  on cognitive function [3, 42]. In addition to findings of MS-specific treatments, some studies have examined the effect of drugs proven to modify cognitive status in other neurologic diseases. Donepezil is an approved central cholinesterase inhibitor for treating dementia and was the first drug studied in MS cases. Primary clinically controlled studies stated some positive responses to this drug in neuropsychological tests and clinical observations of patients; nevertheless, the two recent studies have not confirmed its impact on improving cognitive status [43, 44]. Memantine is an NMDA-

receptor antagonist confirmed for administering in alzheimer cases. It is assumed that the drug can facilitate nerve signal transfer and reduce glutamate - induced neurotoxicity. Studying the impact of this drug in improving cognitive impairment in MS patients has not been promising [45].

2) Non-pharmacological interventions: A series of non-pharmacological approaches like cognitive-behavioral treatments (CBT), psychotherapies, occupational therapy and cognitive rehabilitation are used aiming at preventing the progress of cognitive loss and preserving function in this area. Making simple changes in patients' lifestyle like preventing smoking, sufficient sleep, regular exercise, balanced diet and reducing the consumption of processed foods, alcohol and stimulants like coffee and chocolate are said to be helpful. Considering various results published in this regard, no non-pharmacological treatment of choice has been approved for cognitive impairment in MS.

Cognitive rehabilitation has been the focus of attention in recent years and consists of specific plans for patients in order to adjust with cognitive impairments more effectively or improve some cognitive abilities. Cognitive rehabilitation is based on two approaches that can be used in combination, as well:

a) Compensative strategies aiming at reducing the effect of cognitive impairment on everyday function of the patient include training time management skills and determining priorities, memory improvement methods like using a notebook to record important information, enclosing reminder notes in front views, carrying a calendar and computerized pocket memories, etc.

b) Restorative strategies: According to the neuroplasticity theory, the very approach states that in order to increase individual ability of the person in processing and interpreting data, the brain can undergo cortical re-organization following damage. So, training and practice for developing different cognitive skills like attention and memory can increase the degree of plasticity and consequently reinforce the abilities in the patient [2].

Primary studies conducted with the aim of cognitive rehabilitation have different weak points like lack of controlled tests, basic differences in groups under study and focusing on case studies. In a few controlled studies conducted on the subject, interventions were not made on all impaired cognitive aspects of the disease, but, memory and learning were emphasized more. The said studies mostly used computer programs for cognitive reinforcement and some positive results are also obtained [46].

Cognitive rehabilitation can lead to the best results if specific plans are developed for individuals considering their needs and personal specifications (age, educational level, occupational status, mood and degree of fatigue). However, it should be considered that designing separate rehabilitation programs for reducing impairment in different areas like attention, memory and executive skills is complicated due to complex connections between neuroanatomical substrates [2].

## Discussion

The progressive trend of MS in Iran requires large range studies for learning more about the disease, its prevention and treatment. Cognitive impairment is of particular significance due to its early incidence during the course of MS, impact on the prognosis of the disease and destructive effects on patients' quality of life.

Despite promising findings in cognitive rehabilitation researches, future studies would need larger sample sizes, longer follow up periods, application of standard educational tools and examining the effect of clinical interventions on everyday functioning of the patients. Offering information in the field of cognitive impairment in MS is difficult due to lack of sufficient studies carried out on the subject in Iran; therefore, there is a great need

for considering the issue from clinical and research aspects.

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## Authors' Contributions

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## Conflict of Interest

The authors declare no conflict of interest.

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