

# Cognitive dysfunction in multiple sclerosis

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## Introduction

Multiple Sclerosis (MS) is a chronic demyelinating, inflammatory neurological disease, classically considered the most physically disabling non-traumatic neurological disease in young adults. In the last years many studies have described cognitive dysfunction in MS patients that contributes significantly to their disability status ( [Peyser et al., 1990](#) ; [Rao et al., 1991a](#) ; [Benedict et al., 2006](#) ). Prevalence studies of community and clinical samples, indicate that 45–60% of MS patients are cognitively impaired. Yet, severe dementia in accordance with the criteria of the ICD-10 is relatively uncommon, and is observed in 20–30% of cognitively impaired MS patients, mainly in the final stages of the disease ( [Rao et al., 1993](#) ). The measurement of these neuropsychological abnormalities in the clinical setting, unlike motor and sensory deficits, can be difficult; and also this difficult exists because MS-related cognitive dysfunctions were traditionally described as heterogeneous in nature. However, recent studies suggest a more specific pattern of MS-related cognitive dysfunction ( [Chiaravalloti and DeLuca, 2008](#) ).

The factors associated with cognitive dysfunction in this disease have not been fully elucidated yet, but several findings suggest that cognitive dysfunction could appear in the earliest stages of the disease as the first symptoms of MS ( [Schulz et al., 2006](#) ). Based on the recent studies appointing for the importance of MS cognitive dysfunction, the authors review the literature and describe: the cognitive domains most commonly impaired in MS, the nature of this cognitive MS-related impairments, lesion distribution in MRI or changes in brain structure and correlated cognitive dysfunctions, the influence of the course of the disease on cognitive

performance, the importance of neuropsychological assessment of MS patients, which batteries and tests in neuropsychological assessment are actually recommended and the influence of disease-modifying therapeutics in cognition.

## **Cognitive Domains Impaired in MS**

The cognitive domains impaired in MS seem to have an inter-patient variability, but a characteristic pattern may be defined: memory, information processing efficiency, executive functioning, attention, processing speed, are the most commonly compromised functions ( [Rao et al., 1991a](#) ).

Impaired *memory* is one of the most consistently impaired cognitive functions in MS and is seen in 40–65% of patients; besides, MS-related memory dysfunctions most typically affect long-term and working memory ( [Rao et al., 1993](#) ). The nature of the MS-related memory impairments is a topic of debate in the literature, some studies suggest that memory dysfunctions in MS result primarily from impaired retrieval from long-term memory, whereas encoding and storage capacity seems to remain intact ( [Thornton et al., 2002](#) ). Recent research on the nature of memory dysfunction in MS shows that MS patients have difficulty with acquisition of new knowledge as opposed to retrieval from long-term storage ( [Chiaravalloti and DeLuca, 2008](#) ). Initially, based on the work of Rao and colleagues it was thought that memory difficulty was due to impaired retrieval, but more recent explanations are based in inadequate acquisition secondary to information processing insufficiency.

Impaired *speed of information processing* has been identified as a key deficit in MS ( [Bergendal et al., 2007](#) ) and is seen in 20–30% of patients.

Information processing efficiency refers to the ability to maintain and manipulate information in the brain for short time period and to the speed with which one can process that information. Processing speed deficits are observed on even the most basic tasks in MS patients and are related with decreased neuronal conduction speed secondary to demyelinating. This slowed information processing may impact an individual's ability to complete tasks and to cope in demanding work ( [Archibald and Fisk, 2000](#) ).

*Executive functions* concern to the cognitive abilities necessary to behavior directed to objectives and to the adaptation to environment demands and changes; examples are planning, organization, reasoning, and abstract conceptualization. Deficits in executive functions in MS patients (detected in 19% of the patients) occur less frequently than memory or processing speed disability. But MS patients have specific impairment deficits in some executive functions, especially in generating strategies, divergent thinking, problem solving and estimation ( [Rao et al., 1991a](#) ). So, abstract reasoning, verbal fluency, planning, or problem solving capabilities, have been shown to be frequently reduced in MS patients.

*Attention* is also a complex cognitive function and comprehends different aspects like alertness, vigilance, selective or focused and divided attention. Up to 25% of MS patients have deficits in attention, especially in complex functions like selective and divided attention ( [Nebel et al., 2007](#) ).

## Neuropsychological Assessment

The assessment of cognitive functions is undoubtedly important in MS patients, however it is not wise to rely on the routine neurological consultation. Cognitive symptoms are usually hidden by more visible deficits (e. g., motor, sensory, cerebellar), may be masqueraded by emotional complains, as depression, by fatigue or pain and most times are not thoroughly recognized by the patients. Besides, the predominant subcortical nature of cognitive impairment in MS is not suited to the current tests employed more often by neurologists in the clinical setting, as, for instance the Mini-Mental State Examination (MMSE) in dementia syndromes; yet, MMSE might be useful for quick screening of cognitive impairment before the application of more specific batteries in selected cases ( [Rao, 1986](#) ).

Since the pioneering reports of Rao and co-workers in the nineties ( [Rao and Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990](#) ; [Rao et al., 1991a](#) , [b](#) ), the characteristics of cognitive dysfunction in MS and the appropriate tests for its detection have been extensively addressed in the literature ( [Benedict et al., 2002](#) ; [Montalban and Rio, 2006](#) ; [Benedict and Zivadinov, 2007](#) ; [Strober et al., 2009](#) ; [Comi, 2010](#) ; [Ferreira, 2010](#) ; [Kinsinger et al., 2010](#) ; [Lyros et al., 2010](#) ; [Messinis et al., 2010](#) ; [Arnett and Strober, 2011](#) ; [Langdon, 2011](#) ). In general, cognition in MS may be assessed by two separate, yet complementary, modes: the self-reported evaluation of MS patients and relatives and the neurocognitive batteries adapted to the disease. As elsewhere stated, the self-reported cognitive impairment is prone to depend more on the emotional status, depressive and fatigue complains rather than on real cognitive test performance; on the

contrary, the evaluation of relatives and caregivers is usual more reliable ( [Kinsinger et al., 2010](#) ). Even so, the self-perceived cognitive dysfunction is important for the patients to be aware of its impact in daily life activities and to overcome items related with the disease itself, as treatment adherence or scheduled appointments.

The neuropsychological tests and batteries indicated for measuring the cognitive domains which are compromised in MS patients require expertise and are still matter of debate in the literature. Ideally, the neuropsychological tests and batteries should be sensitive, reproducible, reliable easy to administer and last few time, taking into account the patient's comfort, the human resources of MS clinics and the implied costs. These batteries need to have good normative data, corrected for age, and education level. In parallel, tests to evaluate depression and fatigue must be performed, since those symptoms have a recognized impact in cognitive abilities ( [Kinsinger et al., 2010](#) ). In a recent systematic review, the use of 23 batteries and 74 neuropsychological tests was identified in the literature, which means a lack of homogeneity in this issue despite the recognized consensus on the characteristics of cognitive impairment in MS patients ( [Ferreira, 2010](#) ).

Two cognitive batteries are particularly relevant and validated in MS, being widely used in clinical practice and also for research purposes: the Brief Repeatable Battery of Neuropsychological tests (BRBN; [Rao and Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990](#) ) and the Minimal Assessment of Cognitive Function in MS (MACFIMS; [Benedict et al., 2002](#) ). The BRNB is composed by tests that were found to be most

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sensitive to the cognitive impairment in MS, after a previous application of a comprehensive neuropsychological battery ( [Rao and Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990](#) ), as follows: the selective reminding test (SRT), the 7/24 (later substituted by the 10/36) spatial recall test, the controlled oral word association test (COWAT), and the paced auditory serial addition test (PASAT). These measures achieved 71% sensitivity and 94% specificity when compared with the more comprehensive neuropsychological battery. Later the authors revised the battery to include the symbol digit modality test (SDMT) that evaluates the speed of information processing. In 2002 a group of experts on neuropsychological functioning in MS from different countries created by consensus the MACFIMS battery ( [Benedict et al., 2002](#) ), choosing tests according to their sensitivity to the disease, reliability, validity, ease of administration and the presence of alternate types to make the repeat testing feasible. This battery is composed of seven neuropsychological tests, covering five cognitive domains commonly impaired in MS (processing speed/working memory, learning and memory, executive function, visual-spatial processing, and word retrieval) and takes around 90 min to administer. Specifically, the battery includes the PASAT and the SDMT for Processing speed/Working memory, the California Verbal Learning Test-II and the Brief Visuospatial Memory Test – Revised (BVMTR) for Learning and Memory, the D-KEFS Sorting Test for Executive Functions, the Judgment of Line Orientation Test for Visual perception/Spatial processing and the COWAT for Language. Besides, additional tests are recommended in the MACFIMS, such as measures of premorbid ability with word recognition tests which are not affected in MS, visual screening to evaluate the impact of visual symptoms

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on neuropsychological tests based in visual tasks, screening of motor problems with the 9-Hole Peg Test, screening of oral motor speed deficits since some tests require rapid answers, and also fatigue evaluation with the Fatigue Impact Scale ( [Benedict et al., 2002](#) ).

Briefly, the BRNB and the MACFIMS batteries are quite similar, only differing in the tests that assess the specific auditory-verbal and visual-spatial memory: whereas the former employs the SRT and the 10/36 Spatial Recall Test (10/36), the latter uses the California Verbal Learning Test, Second Edition (CVLT2) and BVMTR. Nevertheless, both batteries were found to have identical sensitivity in a comparative study ( [Strober et al., 2009](#) ), being the SDMT the most sensitive measure.

Despite the consortium recommendation for the use of MACFIMS ( [Benedict et al., 2002](#) ) in MS, the BRNB ( [Rao and Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990](#) ) remains, up to now, the most widely used neuropsychological battery for assessing cognitive functions in the disease. The longer experience in applying the BRNB, and the fact that it has been traduced and validated in some populations might explain its traditional use. The BRBN is also routinely since several years in our MS Clinic, where the neuropsychologists have acquired expertise in the performance of the tests and interpretation of the results ( [Rio et al., 2004](#) ; [Barbosa et al., 2011a](#) ). Nonetheless, it must be highlighted that the MACFIMS presents some advantages regarding the BRBN, as it is easy to administer and the included measures demonstrate good psychometrics. Besides the MACFIMS battery is suited to repeated assessments which,



ideally, should be periodically conducted in the follow-up of the disease progression ( [Benedict et al., 2002](#) ).

## **Nature of Cognitive MS-Related Impairments**

The mechanism underlying cognitive impairment in MS has not been fully elucidated. Cognitive decline in MS patients has been correlated with both macro- and microscopic changes in brain anatomy; and this has been demonstrated by using structural and functional brain imaging. Recent studies have shown that both gray and white-matter lesions contribute to mental dysfunction in MS ( [Morgen et al., 2006](#) ; [Dineen et al., 2009](#) ). Initially, some studies correlate white-matter lesions localizations with specific cognitive impairments ( [Rao et al., 1989](#) ). For example a white matter lesion in frontal lobe lesions has been shown to affect performance in tests of frontal lobe function ( [Rovaris et al., 1998](#) ). Also it was demonstrated that there is a significant association between executive deficits and damage in the prefrontal cortex ( [Foong et al., 1997](#) ) and frontal and parietal lesion burden has been shown to correlate with performance on tests of complex attention and verbal working memory ( [Sperling et al., 2001](#) ). This relationship between specific white lesion location and cognitive performance was also demonstrated in early stage of MS. For example [Ranjeva \(2006\)](#) studied patients with clinically isolated syndromes and cognition impairment and conclude that poorer performance in processing speed and working memory was associated with abnormalities in the splenium of the corpus callosum and in the right superior longitudinal fasciculus.

More recent investigation, discussed the contribution of ultrastructural tissue injury in normal-appearing white-matter and the correlation between cognitive dysfunction and gray-white-matter lesions ( [Kidd et al., 1999](#) ; [Geurts et al., 2005](#) ; [Sanfilippo et al., 2006](#) ). The correlation between multifocal white-matter and gray-matter lesions in cognitive dysfunction pathology has geared the disconnection theory. This model is based in the predilective topology of MS-associated lesions, predominantly involving subcortical periventricular fiber systems, which hinders distal flow of cortical cholinergic pathways. Disconnection occurs between cortical and subcortical regions interactions ( [Amato et al., 2004](#) ; [Morgen et al., 2006](#) ). Cortical involvement related to MS is heterogeneous since it may arise from local demyelinating lesions, meningeal inflammation, neuronal injury, and Wallerian or transsynaptic degeneration ( [Nelson et al., 2011](#) ). As well, selective decrease of the cortical volume was found in patients with relapsing–remitting (RR) MS and mild cognitive deficits; this was associated with poorer performance on tests of verbal and spatial memory, attention and concentration, and verbal fluency ( [Piras et al., 2003](#) ). MS patients with cognitive deficits showed more cortical lesions and more severe cortical atrophy than patients who were cognitively preserved ( [Calabrese et al., 2009](#) ). But this cortical involvement is better understand by subcortico-cortical involvement with the multiple disconnection syndrome, in which a more than one cognitive domain can be interrupted in its afferent or efferent loop, producing a variety of neuropsychological defects ( [Calabrese and Penner, 2007](#) ). Also in recent study, [Dineen et al. \(2009\)](#) confirm that MS-related cognitive dysfunction results from a series of domain-specific disconnection phenomena. As such, disruption of critical white-matter tracts

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will lead to reduced functional connectivity between cortico-cortical and cortico-subcortical cognitive processing regions, resulting in impairment to specific cognitive domains.

## **Magnetic Resonance Imaging and Cognitive Impairment**

Conventional and non-conventional magnetic resonance imaging (MRI) measures have been correlated with cognitive impairment in MS. Initially [Rao et al., 1991a](#)) examined by a conventional way a number of MRI variables including total lesion area, ventricular-brain ratio and size of the corpus callosum. In the past few years, a large effort has been devoted to the development of MRI techniques with the ability to characterize *in vivo* the different substrates of gray-matter and white-matter damage to improve the understanding of its clinical consequences in MS patients ( [Rinaldi et al., 2010](#) ).

Measures of brain atrophy are particularly sensitive in elucidating the relation between brain integrity and cognitive status ( [Calabrese et al., 2009](#) ). Longitudinal imaging studies have shown a strong correlation between changes in cognitive functioning, suggesting that a progression of brain atrophy early in the disease can predict cognitive impairment 5 years later ( [Summers et al., 2008](#) ). Recent MRI studies, which assessed the extent of brain tissue loss on a regional basis, have suggested that cortical volume loss is more closely associated with cognition than whole-brain atrophy. More recently, the application of double inversion recovery (DIR) sequences has convincingly demonstrated that cortical lesions are a frequent finding in patients with MS, even at the earliest clinical stages ( [Calabrese et al., 2009](#) ).

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Quantitative imaging techniques, such as diffusion tensor imaging (DTI) are a powerful non-invasive technique for exploring cerebral ultrastructure.

Fractional anisotropy (FA), a parameter derived from DTI data provides a quantification of ultrastructural fiber organization ( [Basser and Pierpaoli, 1996](#) ). DTI examination of MS patients has revealed reduced FA in plaques, adjacent to plaques and to varying degrees in normal-appearing white-matter ( [Kealey et al., 2005](#) ). Measures derived from magnetization transfer ratio have also consistently been shown to be associated with cognition, as documented with many types of brain tissue, including cortical and subcortical regions and normal-appearing white-matter tissue on conventional imaging. Magnetic resonance spectroscopy, which provides a measure of metabolic changes in the cerebral cortex and white-matter, is also a sensitive indicator of cognitive functioning in MS, particularly in normal-appearing white-matter ( [Staffen et al., 2002](#) ).

Functional MRI (fMRI) has brought new insight into a better understanding of cognitive impairment at the very early stage of MS ( [Audoin et al., 2006](#) ).

Brain connectivity assessed by fMRI have provided new data about the real influence of diffuse white-matter damage on connectivity efficiency. fMRI has evidenced how the brain accommodates to diffuse white-matter injury during controlled information processing task. Brain activation observed by fMRI permits the understanding of cortical reorganization processes and the disturbance in brain connectivity ( [Ranjeva et al., 2005](#) ).

## **Course of the Disease and Cognitive Performance**

Some studies suggest an influence of the course of the disease on cognitive performance. Although some studies indicate that cognitive dysfunction is

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more frequent and severe in the progressive forms of MS ( [Beatty et al., 1989](#) ), cognitive impairment can be present since the early clinical stages of the disease. Moreover, another study pointed out that different courses of the disease are associated with different cognitive profiles ( [Huijbregts et al., 2004](#) ). It was shown that chronic progressive MS patients were more likely than RRMS patients to suffer from attention deficits, in particular reduced speed of information processing, executive dysfunctions, verbal intelligence and abstraction deficits. Also a recent study ( [Schulz et al., 2006](#) ) investigated patterns of cognitive decline in MS patients in the early stage of the disease and neuropsychological assessment revealed cognitive impairments of MS patients in the early stage of their disease. Between 10 and 38% of the MS patients displayed significantly lengthened reaction times and deficient attention. Reduced speed of information processing may be a fundamental neuropsychological deficit in the earliest stages of the disease.

Throughout the course of the disease, some other clinical problems can intensify or simulate cognitive deficits. Specifically, depression or fatigue must be discriminated from cognitive dysfunctions. Up to 90% of MS patients suffer from fatigue, a subjective lack of energy, which can reduce cognitive performance; on the other hand, cognitive deficits can produce exhaustion ( [Engel et al., 2007](#) ). Fatigue might affect performance over time in tasks that require sustained mental effort, specially in cognitive tasks of working memory and visual vigilance ( [Krupp and Elkins, 2000](#) ). Psychiatric symptoms of MS, like anxiety and depression, which can appear in up to 50% of the patients, have a significant effect on subjective perceived performance ( [Landro et al., 2004](#) ). Depression affects many aspects of

cognitive functioning in MS, including working memory, processing speed, learning and memory functions, abstract reasoning, and executive functioning ( [Chiaravalloti and DeLuca, 2008](#) ). In addition, an anamnesis of medication is necessary, because many therapeutic agents like antidepressants, anticonvulsants, antispastics, glucocorticosteroids, or neuroleptics can produce cognitive impairment, especially in attention ( [Engel et al., 2007](#) ).

## **Treatment of Cognitive Dysfunction**

The treatment of cognitive symptoms in MS patients begins with the patient education about the possibility of their occurrence and with an open relation with the MS team, to favor the earliest recognition as possible. As soon as the patients become aware of cognitive impairment the better, because they may be quickly submitted to neuropsychological assessment and request someone's help, if needed, for daily life activities.

At first, some general advices may be provided, as simple tools to improve cognitive abilities: strategies to organize the information (use of scheduled agendas and elaboration of lists of tasks), offer more time to perform usual tasks and process information, taking into account that the impairment of information processing speed is characteristic of cognitive dysfunction in MS. As elsewhere described, paring down information to the essentials and avoiding unnecessary or unrelated details are advantageous ( [Langdon, 2010](#) ).

Most important, the treatment of MS with disease-modifying drugs (DMD) is naturally expected to bring some benefits in cognitive functioning, in parallel

with the improvement in clinical outcomes (reduction of the annualized relapse rate, disability progression) and MRI parameters (new T2 lesions, gadolinium-enhancing lesions), in as much as DMD act by controlling inflammation, reduce the accumulation of lesions and somewhat might have a neuroprotective role ( [Mendes and Sá, 2011](#) ; [Sá et al., 2011](#) ). However, as repeatedly emphasized in the literature (for review see [Comi, 2010](#) ), the results of DMD in cognition must be cautiously interpreted because they generally have considerable drawback. In effect, the largest clinical trials (pivotal phase III studies, extension phases) of DMD do not include cognitive parameters in the primary outcomes and when those assessments were done the psychometric measures vary with different studies, use different samples sizes, MS populations, and statistic analyses, which altogether prevents their comparability ( [Montalban and Rio, 2006](#) ; [Comi, 2010](#) ; [Lyros et al., 2010](#) ). Focusing only on randomized double-blind, placebo-controlled studies, some positive results in cognition were seen with interferon beta-1a in RR forms ( [Fischer et al., 2000](#) ), with interferon beta-1b in RR ( [Pliskin et al., 1996](#) ), secondary progressive forms ( [European Study Group, 1998](#) ), and clinically isolated syndromes ( [Kappos et al., 2009](#) ); on the contrary, glatiramer acetate showed no cognitive benefit in RR patients ( [Weinstein et al., 1999](#) ). In addition, clinical trials specifically designed to evaluate cognition are scarce. In the IMPACT trial, designed to assess whether weekly intramuscular IFN b-1a reduces disability progression in SPMS, the MS functional composite (MSFC) that includes PASAT was used as primary endpoint, a modest effect 2 years after the baseline evaluation was detected ( [Cohen et al., 2002](#) ). In the CogniMS study, performed to evaluate cognition, fatigue, depression, and quality of life in patients with early MS

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treated with interferon beta-1b, cognitive scores improved over time, which seemed to be due to practice effects ( [Langdon et al., 2010](#) ); however data have not yet been published so far. With respect to natalizumab, an improvement was noticed in the PASAT tests performed during the MSFC evaluations, and in the mental component of SF-36 in both pivotal trials ( [Polman et al., 2006](#) ; [Rudick et al., 2006](#) ).

Another pharmacological attempt to ameliorate cognitive dysfunction in MS has been the use of licensed drugs for dementia diseases, despite the existence of substantive differences between the nature of cognitive deficits in both situations and their respective underlying pathogenetic processes in the CNS. Even so, some authors have tried acetylcholinesterase inhibitors, as donepezil, rivastigmine, and galantamine, as well as memantine, an antagonist of NMDA receptors ( [Doraiswamy and Rao, 2004](#) ). Donepezil (10 mg/day) showed an improvement in learning and memory in a randomized placebo-controlled trial enrolling 69 MS patients ( [Krupp et al., 2004](#) ), further showing clinical benefit to patients and physicians ( [Christodoulou et al., 2006](#) ); however negative results were recently reported by other groups which found that donepezil 10 mg daily for 24 weeks is not superior to placebo in improving MS-related cognitive dysfunction, in randomized control trials ( [Krupp et al., 2011](#) ; [O'Carroll et al., 2012](#) ). Rivastigmine has also been tested in MS patients with neurocognitive dysfunction, where no benefit in a general score memory in comparison to placebo ( [Shaygannejad et al., 2008](#) ) or a trend to an improvement in cognitive processing speed by enhancing compensatory brain activation ( [Huolman et al., 2011](#) ) have been found so far; positive effects were detected in imaging studies, since MS



patients treated with rivastigmine displayed increased brain activity during cognitive tasks in fMRI studies ( [Parry et al., 2003](#) ). The effect of memantine given 10 mg twice a day in MS patients with cognitive impairment has been evaluated in a randomized placebo-controlled trial, which failed to show any positive result ( [Lovera et al., 2010](#) ). Based on the assumption that these drugs might have positive effects in cognitive impairment of MS, they are sometimes used off label in the clinical setting, especially in cases with overt dementia symptoms, mimicking primary degenerative dementias. However, up to now there is insufficient evidence of the efficiency of these drugs in MS and their role in the cognitive decline of MS patients is still controversial ( [Christodoulou et al., 2008](#) ), awaiting specifically designed trials allowing longitudinal assessments. As stated in a recent Cochrane review of this subject, until the results of ongoing studies are available, there is no convincing evidence to support pharmacologic intervention as an effective treatment for memory disorder in MS patients ( [He et al., 2011](#) ).

Finally, the importance of cognitive rehabilitation must be stressed, which is a field that needs to be better explored, bearing in mind that it still lacks a consistent evidence base. The concept of submitting cognitively impaired MS patients to techniques of cognitive rehabilitation was based in the knowledge obtained in other CNS pathologies, as stroke. As cognitive dysfunction was more and more studied in MS, the need for the development of cognitive rehabilitation increased, originating an extensive literature that is rather difficult to appreciate because methods and technologies vary with the study. The rationale for cognitive rehabilitation relies upon the stimulation of the natural restorative phenomena taking place in CNS in response to some

kind of injury, as inflammation and demyelination, which is commonly called neuroplasticity. Recent fMRI studies showed that brain activity in the cerebellum of cognitively impaired MS patients increased with a cognitive rehabilitation program ( [Sastre-Garriga et al., 2011](#) ).

Briefly, two types of strategies have been pointed out: compensatory and restorative. Compensatory approaches are easier for patients and caregivers to carry out and include all measures that favor learning and memory, as above-mentioned organizers of information and memory aids in general. Restorative strategies are based in the plastic properties of the nervous system (e. g., cortical reorganization), and are more ambitious because they identify specific impaired cognitive functions in each patient and then introduce techniques that aim to increase the performance in those tasks, ideally to provide a successful recover or remediation ( [Messinis et al., 2010](#) ). As part of restorative strategies, several computerized programs have been developed and applied to MS patients with cognitive impairment targeting different cognitive domains. In general, most studies suggest that memory is the cognitive domain with major improvement, namely spatial memory ( [Barbosa et al., 2011b](#) ) and episodic memory ( [Brissart et al., 2011](#) ). The studies of memory training suggest that specific patient-individualized computerized schemas are more effective ( [Langdon, 2011](#) ); conversely, programs focusing working memory, attention and executive functions are less developed so far. With respect to executive skills, the direct training by a therapist seems to be more successful ( [Langdon, 2010](#) ). The effects of neuropsychological rehabilitation in MS has been recently addressed in an extensive systematic review that only included randomized controlled trials

and quasi-randomized trials in comparison with other interventions or any kind of intervention; the authors stress methodological limitations and heterogeneity in the interventions included in the review, the low level evidence for the positive effects of neuropsychological rehabilitation in MS, and give recommendations to improve the quality of futures studies about this issue ( [Rosti-Otajärvi and Hämäläinen, 2011](#) ).

## **Conclusion**

Neuropsychological assessment is not required to diagnose MS ( [Polman et al., 2005](#) ) and cognitive deficits may not be evident during a follow-up consultation in clinical practice. But with the advent of DMD for MS and emphasis on early intervention and treatment, detection of cognitive impairment at its earliest stage becomes particularly important, in as much as the patients may also benefit of symptomatic and rehabilitation interventions.

Thus, with this revision the authors are able to conclude that: it is important to include cognitive evaluation of MS patients in clinical routine, since these cognitive deficits may be present in early phases of disease; the standardization of cognitive profile evaluation seems to be mandatory in MS patients; MRI is crucial in the understanding and follow-up of MS cognitive impairment; the therapeutic strategies to improve cognitive abilities need to be better evaluated with appropriately designed randomized controlled trials.

## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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