Behavioural Neurology

Neuropsychological Features of Multiple Sclerosis: Impact and Rehabilitation

Lead Guest Editor: Lambros Messinis
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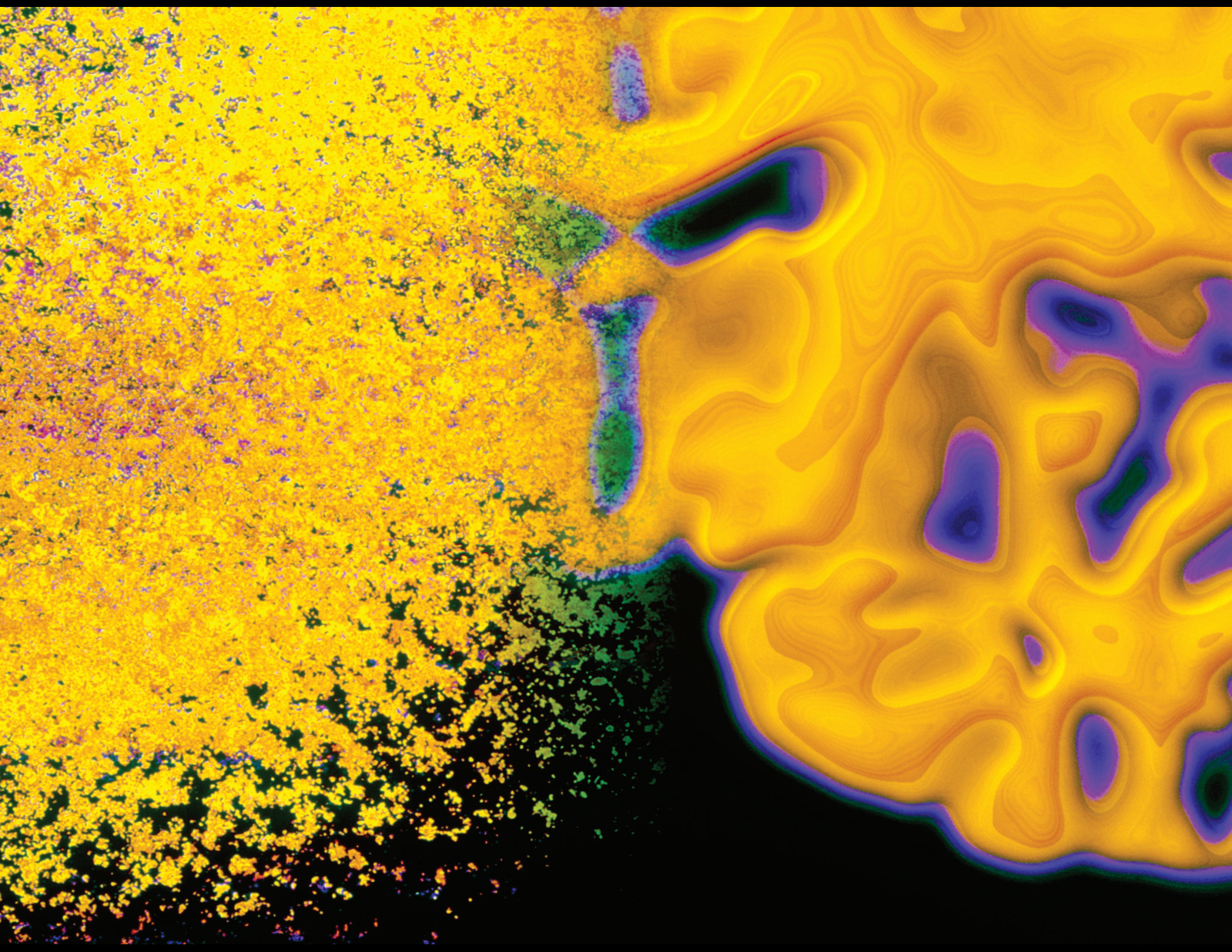

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Editorial Board

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Editorial

Neuropsychological Features of Multiple Sclerosis: Impact and Rehabilitation

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Dating back to the seminal writings on multiple sclerosis (MS), Charcot's observations of the adverse effects that MS exerts on memory, concept formation, and the intellect [1] were underestimated for many decades in the neurology literature. The medical community, due to the often subtle nature of cognitive deficits in MS and the difficulty in detecting these deficits during routine clinical practice, was initially slow to appreciate them as a core clinical symptom of the disease. Instead, they believed that cognitive impairment was a relatively rare entity in MS, which occurred only in advanced cases with a high level of physical disability and was associated with subcortical dementia [2, 3].

The way the disease was viewed from a neuropsychological perspective, however, changed significantly with the publication of large-scale studies, between 1985 and 1995, that utilized standardized neuropsychological measures and flexible comprehensive test batteries. These studies reported prevalence estimates of between 40 and 65% for cognitive dysfunction in MS, providing evidence that cognitive impairment is a core clinical symptom of MS [4–6].

Cognition is a complex process which, by utilizing cognition individuals, can process information from the environment and through past experiences form behaviors and adaptive strategies. In this sense, a dysfunction of cognition in MS may lead to profound functional limitations, affecting daily functional capacity, vocational activities, and socialization, and may also alter behavior or mood, leading to behavioral disturbances such as aggression or impulsivity and depression or apathy [7, 8]. Cognitive deficits can also affect balance and mobility since impaired attention and distractibility force MS patients to actively think about their walking to reduce potential falls. On the other hand, MS individuals with cognitive decline may limit their social interaction activities fearing apparent forgetfulness, slowness in thinking, or processing information and consequently develop depression. Moreover, they may show decreased compliance with their medication regimen by forgetting to take it or by taking it in the wrong way [9].

Although it is now commonly accepted that roughly one-half of individuals with MS will experience cognitive deficits over the course of the disease, prevalence rates are highly variable and depend to a large extent on the type of MS population studied, the clinical, demographic, and sociodemographic characteristics, and the year conducted [10–12]. In this respect and although MS is traditionally considered a disease of adult onset, with neuropsychological studies in the past focusing exclusively on adults, there are now several studies of pediatric-onset MS that

report cognitive impairments in approximately one-third of patients, mainly on motor and mental processing speed, episodic verbal and visuospatial memory, and language (see e.g., [13]).

We now know that persistent and progressive cognitive decline in MS is attributed to a neurodegenerative neuropathological disease process (i.e., diffused axonal damage and brain atrophy). Furthermore, it is well known that white matter (WM) lesions and atrophy contribute substantially to cognitive dysfunction in MS patients, although more recent studies provide evidence that pathological gray matter (GM) lesions may have a significant impact on cognitive functioning [14, 15]. On the other hand, several studies have shown that cognitive impairment is only weakly correlated with physical disability and disease duration [5, 16, 17]. Deficits on measures of information processing speed and episodic memory are the most frequent and robust findings [5, 18], although executive functions are also frequently impaired [18].

As noted previously, these deficits have a multidimensional impact on patients' activities of daily living and should be considered in their treatment and rehabilitation. Although cognitive deficits are prominent and detrimental in MS, incomplete evidence exists as to whether available pharmacological treatment (disease-modifying drugs or symptomatic treatment) might improve or stabilize cognitive deficits [19]. On the contrary, neurobehavioral and neurocognitive interventions have been reported to induce cognitive and behavioral improvements, although their efficiency remains speculative due to methodological variability and lack of ecologically valid outcome measures and investigation over long follow-up periods [20]. More recent studies have successfully applied various neuroimaging techniques (e.g., f-MRI) to study the effects of cognitive rehabilitation in MS. These studies demonstrated an improvement in cognitive functions and everyday functioning capacity by promoting adaptive changes via neuroplasticity in the brains of persons with MS, through the documentation of changes at the level of the cerebral substrate from pre- to posttreatment [21]. Another promising strategy for enhancing cognitive function in MS patients is the use of noninvasive brain stimulation. This includes techniques like repetitive transcranial magnetic stimulation (rTMS), which has recently been proven to be beneficial in MS patients [22].

This special issue entails a series of cutting-edge articles that provide innovative research findings and recent information on the impact and rehabilitation of neuropsychological impairment in MS. Specifically, the authors of this special issue addressed cognitive impairment in relapsing-remitting MS (RRMS) patients that present very mild clinical disability; clinical, neuropsychological, and neuroradiological features in pediatric onset multiple sclerosis; relationships between MS impairment, unmet family needs, and caregiver mental health; the efficacy of computer-assisted cognitive rehabilitation in RRMS patients; a proposed research protocol of an innovative efficacy study on the impact of telestimulation or distance cognitive stimulation in MS; and a review article providing the most recent information and findings on the efficacy of repetitive transcranial magnetic stimulation (rTMS) in alleviating cognitive impairment in MS.

The interesting article by our Italian colleagues S. Migliore et al. found that 51.1% of their 92 RRMS patients with very mild clinical disability (EDSS ≤ 2.5) present cognitive dysfunction confirming previous reports, for example, [9] that cognitive impairment is only weakly correlated with physical disability. Furthermore, after subgrouping their RRMS patients by EDSS level, that is, EDSS ≤ 1.5 and EDSS $2 \leq$ EDSS ≤ 2.5, they found a different pattern of impairment, with the less disabled group showing deficits in verbal memory and executive function and the more severe group having additional impairment in information processing speed and visual memory.

O. Ekmekci from Turkey provided us with a comprehensive review of the most recent clinical, neuropsychological, and neuroradiological features of pediatric-onset multiple sclerosis. In contrast to adult-onset MS, children diagnosed with MS are mostly impaired on the domains of attention, processing speed, visuomotor skills, intelligence, and language. Intriguing is the report that young age at disease onset appears to be the strongest risk factor for this impairment, implying the possibility that inflammatory demyelination and neurodegeneration may significantly impact the developing central nervous system (CNS) and neural networks. This is also evident on a pediatric MS patient's academic achievements and quality of life. The article also underlines the necessity of including cognitive screening and monitoring of cognitive impairment in the routine clinical practice of pediatric neurologists working with pediatric MS.

M.N. Mickens et al. from the USA, in an interesting study, examined the relationships between MS impairment, unmet family needs, and caregiver mental health. They provide us with a structural equation model demonstrating the mediational effect of unmet family needs (household, information, financial, social, support, and health) on the relationship between MS impairments (neurological, cognitive, behavioral, emotional, and functional) and caregiver mental health (satisfaction with life, anxiety, burden, and depression). They conclude that intervention research on MS caregivers in Latin America should consider focusing on caregiver mental health problems by addressing unmet family needs and teaching the caregiver's ways to deal with MS patient impairments. These findings may have implications not only for Latin American caregivers but also for European and potentially MS caregivers in any part of the world.

Shifting from impact to rehabilitation of cognitive impairment in MS, L. Messinis et al. from Greece provide an interesting article on a multicenter randomized controlled trial to assess the efficacy of computer-assisted cognitive rehabilitation in RRMS patients. They included fifty-eight clinically stable RRMS patients that were randomized to receive either computer-assisted (RehaCom) functional cognitive training with an emphasis on episodic memory, information processing speed/attention, and executive functions for 10 weeks (IG; $n = 32$) or standard clinical care (CG; $n = 26$). They found that only the IG group showed significant improvements in verbal and visuospatial episodic

memory, processing speed/attention, and executive functioning from pre- to postassessment. Moreover, the improvement obtained on attention was retained over 6 months providing evidence on the long-term benefits of this type of intervention. Treated patients also rated the intervention positively and were more confident about their cognitive abilities following treatment. The study provides evidence regarding the positive impact of functional cognitive training with ecologically valid computerized cognitive tasks in a Greek sample of RRMS patients with moderate cognitive impairment severity and relatively low disability status. It also confirms findings noted by previous similar cognitive rehabilitation studies (see, e.g., [20, 21]).

C. Guijarro-Castro et al. from Spain provide an important article describing the research protocol of an innovative efficacy study on the impact of telestimulation or distance cognitive stimulation, with and without the support of face-to-face cognitive stimulation in MS patients with a disability level of EDSS ≤ 6. They stipulate that this novel research could help establish the usefulness of telematic cognitive stimulation (TCS) or, in its absence, face-to-face help for the alleviation of cognitive impairments in MS.

G. Nasios et al. from Greece provide an interesting overview on the most recent information and findings regarding the efficacy of repetitive transcranial magnetic stimulation (rTMS) in alleviating cognitive impairment in MS. The article stipulates that due to the lack of effective pharmacological treatments for cognition in MS, cognitive rehabilitation and other nonpharmacological interventions such as repetitive transcranial magnetic stimulation (rTMS) have recently emerged. The article focuses on the brain's functional reorganization in MS, theoretical and practical aspects of rTMS utilization in humans, and its potential therapeutic role in treating cognitively impaired MS patients.

From the contributing articles in this special issue, it becomes obvious that tremendous progress has been made in our understanding of the neuropsychological features of MS. That being said, guidelines on dealing or treating cognitive decline in MS are not yet available. The available disease-modifying treatments have shown minimum efficacy in alleviating cognitive impairment. Cognitive rehabilitation and other noninvasive brain stimulation techniques such as rTMS have shown reasonable effectiveness in certain clinical trials. To date, cognitive rehabilitation appears to be the current intervention of choice. The need for large-scale pharmaceutical and neurobehavioral interventions to clarify this issue, however, remains a priority.

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References

[1] J. M. Charcot, *Lectures on The Diseases of the Nervous System*, New Sydenham Society, London, 1877.

[2] L. Messinis, M. H. Kosmidis, E. Lyros, and P. Papathanasopoulos, "Assessment and rehabilitation of cognitive impairment in multiple sclerosis," *International Review of Psychiatry*, vol. 22, no. 1, pp. 22–34, 2010.

[3] C. Smestad, L. Sandvik, N. I. Landro, and E. G. Celius, "Cognitive impairment after three decades of multiple sclerosis," *European Journal of Neurology*, vol. 17, no. 3, pp. 499–505, 2010.

[4] S. M. Rao, "Neuropsychology of multiple sclerosis: a critical review," *Journal of Clinical and Experimental Neuropsychology*, vol. 8, no. 5, pp. 503–542, 1986.

[5] S. M. Rao, G. J. Leo, L. Bernardin, and F. Unverzagt, "Cognitive dysfunction in multiple sclerosis: I. Frequency, patterns, and prediction," *Neurology*, vol. 41, no. 5, pp. 685–691, 1991.

[6] S. M. Rao, "Neuropsychology of multiple sclerosis," *Current Opinion in Neurology*, vol. 8, no. 3, pp. 216–220, 1995.

[7] M. D. Lezak, D. B. Howieson, E. D. Bigler, and D. Tranel, *Neuropsychological Assessment*, Oxford University Press, New York, NY, USA, 5th edition, 2012.

[8] A. Papathanasiou, L. Messinis, P. Zampakis et al., "Thalamic atrophy predicts cognitive impairment in relapsing remitting multiple sclerosis. Effect on instrumental activities of daily living and employment status," *Journal of the Neurological Sciences*, vol. 358, no. 1-2, pp. 236–242, 2015.

[9] N. Putzki, J. Fischer, K. Gottwald et al., "Quality of life in 1000 patients with early relapsing-remitting multiple sclerosis," *European Journal of Neurology*, vol. 16, no. 6, pp. 713–720, 2009.

[10] N. D. Chiaravalloti and J. DeLuca, "Cognitive impairment in multiple sclerosis," *The Lancet Neurology*, vol. 7, pp. 1139–1151, 2008.

[11] A. Papathanasiou, L. Messinis, L. V. Georgiou, and P. Papathanasopoulos, "Cognitive impairment in relapsing remitting and secondary progressive multiple sclerosis patients: efficacy of a computerized cognitive screening battery," *ISRN Neurology*, vol. 2014, Article ID 151379, 7 pages, 2014.

[12] E. Polychroniadou, C. Bakirtzis, D. Langdon et al., "Validation of the brief international cognitive assessment for multiple sclerosis (BICAMS) in Greek population with multiple sclerosis," *Multiple Sclerosis and Related Disorders*, vol. 9, pp. 68–72, 2016.

[13] L. E. Charvet, E. H. O'Donnell, A. L. Belman et al., "Longitudinal evaluation of cognitive functioning in pediatric multiple sclerosis: report from the US pediatric multiple sclerosis network," *Multiple Sclerosis*, vol. 20, no. 11, pp. 1502–1510, 2014.

[14] M. A. Rocca, E. Pravata, P. Valsasina et al., "Hippocampal-DMN disconnectivity in MS is related to WM lesions and depression," *Human Brain Mapping*, vol. 36, no. 12, pp. 5051–5063, 2015.

[15] J. J. Geurts, M. Calabrese, and E. Fisher, "Measurement and clinical effect of gray matter pathology in multiple sclerosis," *The Lancet Neurology*, vol. 11, no. 12, pp. 1082–1092, 2012.

[16] R. S. Prakash, E. M. Snook, J. M. Lewis, R. W. Motl, and A. F. Kramer, "Cognitive impairments in relapsing-remitting multiple sclerosis: a meta-analysis," *Multiple Sclerosis*, vol. 14, no. 9, pp. 1250–1261, 2008.

[17] N. Staff, C. Lucchinetti, and M. Keegan, "Multiple sclerosis with predominant, severe cognitive impairment," *Archives of Neurology*, vol. 66, no. 9, pp. 1139–1143, 2009.

[18] D. W. Langdon, "Cognitive impairment in multiple sclerosis – recent advances and future prospects," *European Neurology Review*, vol. 5, no. 1, pp. 69–72, 2010.

[19] S. Roy, R. H. Benedict, A. S. Drake, and B. Weinstock-Guttman, "Impact of pharmacotherapy on cognitive dysfunction in patients with multiple sclerosis," *CNS Drugs*, vol. 30, no. 3, pp. 209–225, 2016.

[20] F. Mattioli, C. Stampatori, D. Zanotti, G. Parrinello, and R. Capra, "Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis," *Journal of the Neurological Sciences*, vol. 288, no. 1-2, pp. 101–105, 2010.

[21] S. Bonavita, R. Sacco, M. Della Corte et al., "Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study," *Journal of Neurology*, vol. 262, no. 1, pp. 91–100, 2015.

[22] H. E. Hulst, T. Goldschmidt, M. A. Nitsche et al., "rTMS affects working memory performance, brain activation and functional connectivity in patients with multiple sclerosis," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 88, no. 5, pp. 386–394, 2017.

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Review Article

Repetitive Transcranial Magnetic Stimulation, Cognition, and Multiple Sclerosis: An Overview

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Multiple sclerosis (MS) affects cognition in the majority of patients. A major aspect of the disease is brain volume loss (BVL), present in all phases and types (relapsing and progressive) of the disease and linked to both motor and cognitive disabilities. Due to the lack of effective pharmacological treatments for cognition, cognitive rehabilitation and other nonpharmacological interventions such as repetitive transcranial magnetic stimulation (rTMS) have recently emerged and their potential role in functional connectivity is studied. With recently developed advanced neuroimaging and neurophysiological techniques, changes related to alterations of the brain's functional connectivity can be detected. In this overview, we focus on the brain's functional reorganization in MS, theoretical and practical aspects of rTMS utilization in humans, and its potential therapeutic role in treating cognitively impaired MS patients.

1. What Is Multiple Sclerosis (MS)?

Multiple sclerosis (MS) is an autoimmune, chronic central nervous system disease of unknown etiology, presenting as an ongoing demyelinating, inflammatory, and degenerative process, affecting both grey and white matters of the brain and the spinal cord, and resulting in the accumulation over the years of disabling motor and cognitive handicaps. Quality of life; personal, social, and professional status; and life expectancy are all significantly challenged by the disease [1–3].

One of its most puzzling characteristics is the subclinical phase prior to diagnosis, which could last for years and subtly affect cognitive aspects of nervous system functioning. Indeed, there is evidence suggesting that deterioration of cognitive performance could be detected years (even decades) before formal diagnosis [4, 5]. Unfortunately, there are currently no validated biomarkers to preliminary track the neuroimmunological phenomena underlying this subclinically active disease phase [6].

Additionally, patients which are initially diagnosed with a radiologically isolated or clinically isolated syndrome (RIS or CIS) which years later progress to definite MS forms have only recently been targeted with disease-modifying medications during the initial phase, resulting in an overall large number of patients worldwide in whom treatment initiation comes rather late in the disease course. This disappointing fact, resulting perhaps in the accumulation of disability in the majority of MS patients over the years (especially after the 1st or 2nd decade of the disease course), may be linked to the continuing and increasing CNS lesion load and tissue damage and has fortunately forced specialists in the field to become alert of the notion that "time is brain" and that "effective intervention during a limited period early in the course of MS is critical for maintaining neurological function and preventing subsequent disability" [7].

2. Cognition in MS

The cognitive aspect of MS was not recognized widely until the last two decades, although Charcot has described it as part of its clinical picture almost 150 years ago [8]. Now we know that 40–70% of all MS patients do have cognitive impairment which affects their lives [2, 9]. Even in the so-called "benign" form of the disease, 15 years after the diagnosis with an EDDS score remaining considerably low (up to 3), cognitive disorders can be diagnosed in half of these patients [10]. The database PubMed which was accessed on 15 May 2017, with keywords "cognition in Multiple sclerosis" revealed 2256 items, 1698 of them (75.26%) were published after 2006.

Another major aspect of the disease is brain volume loss (BVL), which is present in all phases and all types (relapsing and progressive) of the disease, and it is linked to both motor and cognitive disabilities [11–13]. BVL is widespread in both white and grey matter tissues and cortical and subcortical structures. Among other sites, thalamic damage is directly related to cognitive deficits in all forms of the disease, even in clinically isolated syndromes (CIS) [14, 15]. Moreover, while white matter atrophy is 3-fold compared to that in healthy controls and remains 3-fold during the course of the disease, gray matter atrophy is initially 3-fold in CIS patients compared to healthy controls but increases to 14-fold in SPMS patients [16, 17].

The deterioration of cognitive performance, usually subtle at least during the first years of the disease course, is almost impossible to be diagnosed by routine neurological testing; therefore, special neuropsychological assessments are needed [18]. This deterioration may not be clinically evident at first and may be hidden by neuroplasticity, that is, the brain's capacity to reorganize its networks in order to keep on functioning despite tissue damage. Using state-of-the-art functional and static neuroimaging magnetic resonance imaging techniques such as fMRI and diffusion tensor imaging (DTI), we can study the brain's effort to overcome the ongoing structural damage and maintain sufficient functions and many new important insights are becoming apparent, as we will discuss them in the sections that follow.

We do not know a lot about disease-modifying medications' ability to act directly on patients' cognitive performance, or what we know is that they do not have a significant influence [19] what we suspect (and hope) is that they do so indirectly by protecting the accumulation of brain tissue damage and delaying brain volume loss. It seems that even in the small proportion of patients achieving the desired NEDA status (no evidence of disease activity) over time, cognitive deterioration was not precluded [20]. The role of cognitive rehabilitation in various central nervous system diseases and MS has recently emerged [21]. Additionally, other nonpharmacological interventions are also being discussed as having a potentially beneficial role in ameliorating physical and cognitive aspects of the disease [22]. Among these interventions, repetitive transcranial magnetic stimulation (rTMS) seems to have both the scientific and theoretical support and also evidence from experimental models of the disease and trials in patients that can play an important role in MS's management.

3. TMS and rTMS

Transcranial magnetic stimulation (TMS) is a neurostimulatory and neuromodulatory technique, based on the principle of electromagnetic induction of an electric field in the brain [23]. This method has behavioral consequences and therapeutic potentials. Barker et al. in 1985 described a method of directly stimulating the human motor cortex using a pulsed magnetic field [24]. During the last 2-3 decades, TMS has become a method of choice for noninvasive stimulation of the brain in conscious human subjects to study the excitability of different cortical areas and to map the connectivity of neuronal pathways [25, 26]. When TMS pulses are applied repetitively, they can modulate cortical excitability, either decreasing or increasing it, depending on the parameters of stimulation. TMS has immediate as well as after-effects on the human cortex. rTMS has local and remote effects on neural function which can be excitatory or inhibitory [27]. The direction, magnitude, and duration of conditioning rTMS effects depend on the stimulation site, frequency, intensity, and the duration of the rTMS training. For example, after-effects last longer when the number of rTMS stimuli applied is increased [28]. Low-frequency (1 Hz) rTMS given over the primary motor cortex reduces corticospinal excitability [29], but higher-frequency rTMS increases corticospinal excitability (Pascual-Leone et al., 1994 and [30]). It has also been shown that repeated rTMS is capable of evoking long-lasting cumulative plastic changes of cortical function not only in the stimulated cortex but also in the remote functionally interconnected areas that outlast the stimulation period [31]. The way rTMS acts on molecular and neuronal level is not yet well understood. It has become clear that rTMS can change structural, functional, and molecular properties of neurons, which may depend on the simultaneous conduction of action potentials. rTMS-mediated changes interfere with the ability of neurons to express distinct forms of plasticity beyond the stimulation period [30, 32]. Evidence is growing about the rTMS-induced modification of cerebral blood flow, glucose metabolism, and neuronal excitability in the stimulated area as well as in interconnected brain regions [33]. After-effects of rTMS may represent changes in synaptic efficacy known as long-term potentiation (LTP) and long-term depression (LTD). The balance between "LTP/LTD-like" phenomena, which underlie many processes happening in the brain, that is, learning and memory, is altered by rTMS. Esser et al. exploited a new approach based on combined rTMS/high-density electroencephalography (hd-EEG) providing a direct noninvasive evidence for LTP bilaterally over the premotor cortex in humans induced by rTMS [34].

TMS could possibly have additional effects such as endocrine after-effects, histotoxicity, and effects on neurotransmitters, immune system, and autonomic function, which are not yet fully understood [23]. Potential therapeutic effects of rTMS have already been explored, and "the use of TMS has grown dramatically in the past decade, new protocols

of TMS have been developed, changes in the devices have been implemented, TMS is being increasingly combined with other brain imaging and neurophysiologic techniques including fMRI and EEG, and a growing number of subjects and patients are being studied with expanding numbers of longer stimulation sessions" [23].

An increasing number of trials worldwide investigated the therapeutic role of rTMS in depression, schizophrenia, addictions, posttraumatic stress disorders, pain, migraine, stroke, autism, multiple sclerosis, and neurodegenerative disorders such as Alzheimer's and Parkinson's disease [35]. Accordingly, animal studies have been employed to assess the effects of rTMS on synaptic plasticity. Among them, there are studies indicating an additional therapeutic role of electromagnetic stimulation in demyelinating processes: experimental animal models of MS (experimental autoimmune encephalomyelitis) have proven that rTMS modifies astrocytosis, cell density, and lipopolysaccharide levels, suggesting that TMS could be a promising treatment for neuroinflammatory conditions such as multiple sclerosis [36].

Sherafat et al. have shown that after inducing demyelination, using local injection of lysophosphatidylcholine within the corpus callosum of adult female Sprague-Dawley rats and then applying electromagnetic fields (EMFs) postlesionally significantly reduced the extent of the demyelinated area and increased the level of myelin basic protein staining within the lesion area, suggesting that EMFs potentiate proliferation and migration of neural stem cells and enhance the repair of myelin in the context of demyelinating conditions [37].

What is very interesting—and there is accumulating evidence towards this—is that we can affect cognitive processing in healthy humans by rTMS. Guse et al. conducted a systematic overview of high-frequency rTMS (HF-rTMS) studies assessing neurocognition in order to better understand the potential of rTMS to induce long-term effects on cognition. High-frequency rTMS (10–20 Hz) is most likely to cause significant cognitive improvement when applied over the left (dorsolateral) prefrontal cortex, within a range of 10–15 successive sessions and an individual motor threshold between 80 and 110% [38].

The correct positioning of the coil is also very important for the effects of rTMS. Localization of the stimulation site by individually fMRI-guided TMS neuronavigation, instead of using the 10–20 EEG system, results in stronger and more robust TMS effects, inducing long-lasting cognitive improvement [39]. Sato et al. designed a study by using event-related potentials (ERPs) to clarify the effect of magnetic stimulation on cognitive processing. They found that a 1.00 Hz rTMS pulse train over the left dorsolateral prefrontal cortex increased P300 latencies by 8.50 ms at Fz, 12.85 ms at Cz, and 11.25 ms at Pz. In contrast, neither 0.75 nor 0.50 Hz rTMS pulse trains over the left dorsolateral prefrontal cortex nor 1.00, 0.75, and 0.50 Hz rTMS pulse trains over the right dorsolateral prefrontal cortex altered P300 latencies. These results indicate that rTMS frequency affects cognitive processing. The authors suggested that the effects of rTMS vary according to the activity of excitatory and inhibitory neurons in the cerebral cortex [40].

Esslinger et al., using a multimodal fMRI-rTMS approach, demonstrated changes in cortical plasticity in humans during executive cognition [41]. They examined 12 healthy control subjects in a crossover study with fMRI while performing an *n*-back working memory (WM) task and a flanker task engaging cognitive control, after real and sham 5 Hz rTMS to the right dorsolateral prefrontal cortex (DLPFC). Reaction times during the *n*-back task were significantly shorter after rTMS than after sham stimulation, supporting an excitatory effect of high-frequency rTMS. Interestingly, rTMS compared with sham stimulation caused no activation changes at the stimulation site (right DLPFC) itself but significantly increased connectivity within the WM network during *n*-back and reduced activation in the anterior cingulate cortex during the flanker task. These findings show the plastic changes in prefrontal connected networks downstream of the stimulation site as the substrate of the behavioral effect [31]. Li et al. investigated the effects of high-frequency (10 Hz) rTMS applied over the left DLPFC on cognitive control of young healthy participants and explored the time course changes of cognitive processing after rTMS using event-related potentials (ERPs). A Stroop task was performed, and an electroencephalogram (EEG) was recorded. The results revealed that multiple sessions of rTMS can decrease reaction time (RT) under both congruent and incongruent conditions and also increased the amplitudes of both N2 and N450 compared with sham rTMS. This observation supports the view that high-frequency rTMS over the left DLPFC not only recruits more neural resources from the prefrontal cortex by inducing an electrophysiologic excitatory effect but also enhances efficiency of resources to deploy for conflict resolution during multiple stages of cognitive control processing in healthy young people [42]. Hsu and colleagues conducted a systematic review and meta-analysis of the literature (1990–2014) to evaluate the effects of noninvasive brain stimulation (rTMS and tDCS) on cognitive function in healthy older adults and patients with Alzheimer's disease (AD). They concluded that noninvasive brain stimulation has a positive effect on cognitive function in physiological and pathological aging [43].

4. Brain's Functional Reorganization in MS

As sophisticated techniques have been introduced in the near past, we are facing a new era in which neuroplasticity can be studied not only as a unique brain ability to reorganize its functional networks in order to overcome aging and diseases but also as a new therapeutic target. In fact, neuropsychological rehabilitation (neurorehabilitation), accompanied by new noninvasive neurostimulation–neuromodulation methods, is becoming popular, partially due to the lack of effective pharmacological treatments. As Maggio and Vlachos state, "understanding the role of neural plasticity under pathological conditions, novel therapeutic approaches could be designed to promote, block, or shift the balance between distinct forms of plasticity in specific brain regions and at diverse stages of pathological brain conditions" [44].

Neuroplasticity is increasingly studied as altered brain functional connectivity both at rest (resting-state functional connectivity (rs-FC)) and during tasks. Hyperconnectivity or hypoconnectivity can be detected, depending on the severity and extension of structural brain damage, the nature of disease process, and its time course. These alterations could be adaptive or maladaptive.

Particularly in multiple sclerosis, studies have shown that patients in early stages activate additional brain areas adjacent to those primarily involved during task performance, allowing patients to perform normally prior to cognitive deficits being detectable on neuropsychological assessment [45]. This additional activation serves as a compensatory mechanism allowing the individual to maintain intact cognitive functioning for a period of time, functionally compensating for injury associated with progression of the disease and thus masking defects [46, 47]. Mainero and colleagues scanned matched healthy subjects and patients with relapsing-remitting MS (RRMS) with no or only mild cognitive deficits while performing neuropsychological testing (the Paced Auditory Serial Addition Test (PASAT) and a recall task), and the relation between fMRI changes during both tasks and T2 lesion load was investigated. Patients with RRMS exhibit altered patterns of activation during tasks exploring sustained attention, information processing, and memory. During these tasks, fMRI activity was greater in patients with better cognitive function than in those with lower cognitive function. Authors concluded that functional changes in specific brain areas increase with increasing tissue damage suggesting that they may also represent adaptive mechanisms that reflect underlying neural disorganization or disinhibition, possibly associated with MS [48].

Staffen and colleagues performed a functional MRI study during PVSAT (Paced Visual Serial Addition Task), a visual analogue to PASAT (Paced Auditory Serial Addition Task), in 21 recently diagnosed RRMS patients and matched healthy controls. A group analysis of the functional imaging data during the PVSAT revealed different activation patterns for patients compared with control subjects. In healthy volunteers, the main activation was detected at the right hemispheric frontal cortex (Brodmann area 32). In patients, the main activation was detected at the right hemispheric frontal cortex (Brodmann areas 6, 8, and 9). In addition, the left hemispheric Brodmann area 39 was activated. The different patterns of activation, accompanied with intact performance in a sustained attention task of this multiple sclerosis sample compared with healthy controls, were interpreted as the consequence of compensatory mechanisms, in other words as an expression of neuronal plasticity during early stages of a chronic disease [49].

In contrast to task-based fMRI, resting-state functional connectivity (rs-FC) examines the communication between different brain regions within neural networks at "rest." Resting-state functional connectivity (rs-FC) studies have noted that increased activation could be interpreted as either adaptive or maladaptive, depending on the progression of the disease. Increased connectivity during rs-FC is thought to serve as a compensatory mechanism for cognitive deficits early in the MS disease process [21, 50, 51], but later in the disease, these extra connections are associated with worse performance [21, 52]. Cader et al. concluded that both forms of adaptive functional change, that is, the enhancement of the coherence of interactions between brain regions normally recruited (functional enhancement) and the recruitment of alternative areas or the use of complementary cognitive strategies, could limit clinical expression of the disease and particularly of cognitive impairments [51].

MS patients, trying to compensate the ongoing structural damage, do not only activate additional cerebral areas but also change strategies, and indeed, this is partially effective. An excellent proof of this is provided in the article of Bonnet et al.: while performing a go/no-go task of increasing complexity, patients could follow the performance of healthy control subjects to a point. For the most complex condition, patients presented both collapse of additional cerebral recruitment and significant lower cognitive performance compared to controls. Authors questioned the cerebral mechanisms allowing the maintenance of normal performances in patients with RRMS according to the level of cognitive demand. They found that, "contrary to healthy subjects, patients with MS did not exhibit a correlation between cerebellar activation and better performances." Patients' retained performance was correlated with higher activation in medial prefrontal regions (IG and CG), areas known to be involved in decision-making; in other words, they exhibit a transfer of function to cerebral areas skilled to manage controlled processes. This new medial frontal recruitment could support a functional strategy of compensation in patients with MS. In a multicenter study, significant correlations were found between abnormal fMRI patterns of activations and deactivations and behavioral measures, cognitive performance, and brain T2 and T1 lesion volumes. These results support the theory that a preserved fMRI activity of the frontal lobe is associated with a better cognitive profile in MS patients [53].

In an elegant recent study, Rocca and colleagues [54] investigated rs-FC abnormalities within the principal brain networks in a large cohort of MS patients, with various forms and stages of the disease. Connectivity abnormalities and correlations with clinical/neuropsychological/imaging measures were evaluated. MS patients showed reduced network average rs-FC versus controls in the default-mode network. At regional level, a complex pattern of decreased and increased rs-FC was found. Reduced rs-FC correlated with T2 lesions. Reduced thalamic rs-FC correlated with better neuropsychological performance, whereas for all the remaining networks, reduced FC correlated with more severe clinical/cognitive impairment. Similar findings have been reported for Alzheimer's disease, in which subjects in an early preclinical phase show relatively increased prefrontal cortical activation with memory deficits [55].

Sumowski and colleagues explored the cognitive reserve hypothesis by testing how could lifetime intellectual enrichment (estimated with vocabulary knowledge) lessen the negative impact of brain disease on cognition; in other words,

patients with greater enrichment are able to withstand more severe neuropathology before suffering cognitive impairment or dementia. Multiple sclerosis patients' cerebral activity (functional magnetic resonance imaging blood oxygen level-dependent signal) and behavioral performance were recorded during the visual *n*-back working memory task. Results revealed strong positive correlations between intellectual enrichment and cerebral activity within the brain's default network, indicating that patients with greater enrichment were able to maintain resting-state activity during cognitive processing better. Furthermore, intellectual enrichment was negatively associated with prefrontal recruitment, suggesting that patients with lesser enrichment required more cerebral resources to perform the same cognitive task as patients with greater enrichment [56].

However, it is important to appreciate the complexities of interpreting differences in patterns of activation across the brains of subjects with pathology relative to healthy controls. First, fMRI identifies brain regions in which activity is associated with task performance, not those that are necessary [57]. Secondly, alternative strategies for performance of a task can be associated with differences in patterns of activation without being able to be interpreted in a simple way as adaptive [58]. Schoonheim et al. reviewed the recent functional connectivity literature in MS and the potential effects on cognition that functional connectivity changes may have [59]. A "compensatory" change is seen in the brains of MS patients in the form of both increased activation and increased connectivity. Studies investigating the "default mode network" (DMN) found increased DMN connectivity in clinically isolated syndrome (CIS) patients [60] and decreased DMN connectivity in progressive MS, which was related to cognitive impairment [61]. Which reported connectivity changes can be said to be "compensatory"? Which are "maladaptive"? Authors conclude on the requirement of "a more holistic approach, encompassing both activation and connectivity data into a frame of network dynamics in a longitudinal fashion."

5. rTMS in MS

Palm et al. reviewed the application of noninvasive brain stimulation techniques for the improvement of several neurologic and psychiatric disorders in MS patients. Specifically, the efficacy of tDCS and TMS for the treatment of depressive symptoms, fatigue, tactile sensory deficit, pain, motor performance, and spasticity was assessed in several studies and showed mixed results [22].

Due to the lack of effective pharmacological treatments alone, rTMS in combination with medication has been used with significant efficacy mainly for the improvement of spasticity [62–65], fatigue and depression [22], lower urinary tract dysfunction [66], gait [67], and hand dexterity [61, 68]. Most studies however have certain methodological limitations, such as small number of participants and low-to-moderate level of efficacy, indicating the emerging need for more studies in the future. Symptoms, such as fatigue, are better targeted with tDCS [69].

6. rTMS for Cognition in MS

Considering the previously presented literature, we have several reasons why one should consider using rTMS to treat cognitively impaired MS patients: firstly, we do not have effective pharmacological treatments for the nearly two-thirds of all MS patients who become cognitively impaired through the disease course, and their lives are negatively influenced; secondly, there is an accumulating body of evidence that patients' brains undergo functional reorganization even from the initial disease phases, by altering functional connectivity in various regions, and this acts as a compensatory mechanism; thirdly, a growing number of MS patients are exposed to rTMS training protocols for other symptoms, without any major safety or adverse event considerations; and fourthly and more importantly, noninvasive neurostimulation techniques such as rTMS have shown beneficial effects on cognitive performance in healthy persons and in patients with various neurological diseases, by evoking neuroplasticity changes, in other words enhancing the brain's functional capacity.

Additionally, higher cognitive reserve [56] and cognitive rehabilitation interventions [70, 71] have proved effective in ameliorating cognitive performance in MS patients, and the underlying mechanism seems to be the induced neuroplasticity changes [21, 56, 72]. One could, therefore, consider using, and even combining, these available nonpharmacological, noninvasive interventions.

Despite the theoretical support of such clinical use, there is, to our knowledge, only one, recently published, study for the therapeutic use of rTMS on cognition in MS patients [73]. In this study, Hulst et al. investigated the effects of high-frequency rTMS of the right dorsolateral prefrontal cortex (DLPFC) on working memory performance, while measuring task-related brain activation and task-related brain connectivity in patients with MS. The authors reported that *n*-back task accuracy improved after applying real rTMS (and not after sham rTMS) only in patients. At baseline, MS patients, compared to healthy controls, showed higher task-related frontal activation, which disappeared after real rTMS. Task-related functional connectivity between the right DLPFC and the right caudate nucleus and bilateral (para) cingulate gyrus increased in patients after real rTMS when compared to sham stimulation. The authors interpret these results as an rTMS-induced change in network efficiency in MS patients, implicating a potential role for rTMS in cognitive rehabilitation in MS. With the limitation of the small sample of participants (17 MS patients and 11 HCs), the results of this study are very promising and of course call for more trials in order to provide more robust evidence of rTMS therapeutic effects on cognitively impaired MS patients.

7. Conclusions

The road that lies ahead is long, but the first steps have been made: the neurological community now recognizes that cognitive impairment is an important component of MS (with the recently introduced concept of cognitive impairment

associated with multiple sclerosis (CIAMS)) [74], stipulating that cognition must be included in diagnostic, follow-up, and therapeutic evaluations. Methods to neuropsychologically assess patients with MS and suitable imaging techniques to monitor cognitive function are now more widely accessible. Functional connectivity changes in the healthy and diseased brain can be detected and modified by interventions. We must go one step further and target cognitive functions therapeutically through well-designed clinical trials, with carefully selected large numbers of suitable patients, combining neuropsychological methods and noninvasive neurostimulation–neuromodulation and neuroimaging techniques, in order to offer widely effective treatments to our patients living with MS.

Conflicts of Interest

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.

Authors' Contributions

All authors contributed to the conception, drafting, revising, and finalizing of the manuscript and agreed to be accountable for all aspects of the work.

References

[1] V. Janardhan and R. Bakshi, "Quality of life and its relationship to brain lesions and atrophy on magnetic resonance images in 60 patients with multiple sclerosis," *Archives of Neurology*, vol. 57, no. 10, pp. 1485–1491, 2000.

[2] N. D. Chiaravalloti and J. DeLuca, "Cognitive impairment in multiple sclerosis," *Lancet Neurology*, vol. 7, no. 12, pp. 1139–1151, 2008.

[3] H. M. B. Lunde, J. Assmus, K. M. Myhr, L. Bø, and N. Grytten, "Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study," *Journal of Neurology, Neurosurgery, and Psychiatry*, vol. 88, pp. 621–625, 2017.

[4] V. Sinay, M. Perez Akly, G. Zanga, C. Ciardi, and J. M. Racosta, "School performance as a marker of cognitive decline prior to diagnosis of multiple sclerosis," *Multiple Sclerosis*, vol. 21, no. 7, pp. 945–952, 2014.

[5] M. Cortese, T. Riise, K. Bjørnevik et al., "Preclinical disease activity in multiple sclerosis: a prospective study of cognitive performance prior to first symptom," *Annals of Neurology*, vol. 80, no. 4, pp. 616–624, 2016.

[6] M. Comabella and X. Montalban, "Body fluid biomarkers in multiple sclerosis," *Lancet Neurology*, vol. 13, no. 1, pp. 113–126, 2014.

[7] T. Ziemssen, T. Derfuss, N. de Stefano et al., "Optimizing treatment success in multiple sclerosis," *Journal of Neurology*, vol. 263, no. 6, pp. 1053–1065, 2016.

[8] J. M. Charcot, *Lectures on the Diseases of the Nervous System*, New Sydenham Society, London, 1877.

[9] A. Winkelmann, C. Engel, A. Apel, and U. K. Zettl, "Cognitive impairment in multiple sclerosis," *Journal of Neurology*, vol. 254, Supplementary 2, pp. II35–II42, 2007.

[10] J. Correale, M. C. Ysrraelit, and M. P. Fiol, "Benign multiple sclerosis: does it exist?," *Current Neurology and Neuroscience Reports*, vol. 12, no. 5, pp. 601–609, 2012.

[11] T. Vollmer, L. Huynh, C. Kelley et al., "Relationship between brain volume loss and cognitive outcomes among patients with multiple sclerosis: a systematic literature review," *Neurological Sciences*, vol. 37, no. 2, pp. 165–179, 2016.

[12] N. De Stefano, A. Giorgio, M. Battaglini et al., "Assessing brain atrophy rates in a large population of untreated multiple sclerosis subtypes," *Neurology*, vol. 74, no. 23, pp. 1868–1876, 2010.

[13] E. Fisher, R. A. Rudick, J. H. Simon et al., "Eight-year follow-up study of brain atrophy in patients with MS," *Neurology*, vol. 59, no. 9, pp. 1412–1420, 2002.

[14] T. Štecková, P. Hluštík, V. Sládková, F. Odstrčil, J. Mareš, and P. Kaňovský, "Thalamic atrophy and cognitive impairment in clinically isolated syndrome and multiple sclerosis," *Journal of the Neurological Sciences*, vol. 342, no. 1-2, pp. 62–68, 2014.

[15] A. Papathanasiou, L. Messinis, P. Zampakis et al., "Thalamic atrophy predicts cognitive impairment in relapsing remitting multiple sclerosis. Effect on instrumental activities of daily living and employment status," *Journal of the Neurological Sciences*, vol. 358, no. 1-2, pp. 236–242, 2015.

[16] E. Fisher, J. C. Lee, K. Nakamura, and R. A. Rudick, "Gray matter atrophy in multiple sclerosis: a longitudinal study," *Annals of Neurology*, vol. 64, no. 3, pp. 255–265, 2008.

[17] R. A. Rudick, J. C. Lee, K. Nakamura, and E. Fisher, "Gray matter atrophy correlates with MS disability progression measured with MSFC but not EDSS," *Journal of the Neurological Sciences*, vol. 282, no. 1-2, pp. 106–111, 2009.

[18] K. Romero, P. Shammi, and A. Feinstein, "Neurologists' accuracy in predicting cognitive impairment in multiple sclerosis," *Multiple Sclerosis and Related Disorders*, vol. 4, no. 4, pp. 291–295, 2015.

[19] S. Roy, R. H. Benedict, A. S. Drake, and B. Weinstock-Guttman, "Impact of pharmacotherapy on cognitive dysfunction in patients with multiple sclerosis," *CNS Drugs*, vol. 30, no. 3, pp. 209–225, 2016.

[20] A. Damasceno, B. P. Damasceno, and F. Cendes, "No evidence of disease activity in multiple sclerosis: implications on cognition and brain atrophy," *Multiple Sclerosis*, vol. 22, no. 1, pp. 64–72, 2016.

[21] N. D. Chiaravalloti, H. M. Genova, and J. DeLuca, "Cognitive rehabilitation in multiple sclerosis: the role of plasticity," *Frontiers in Neurology*, vol. 6, p. 67, 2015.

[22] U. Palm, S. S. Ayache, F. Padberg, and J. P. Lefaucheur, "Non-invasive brain stimulation therapy in multiple sclerosis: a review of tDCS, rTMS and ECT results," *Brain Stimulation*, vol. 7, no. 6, pp. 849–854, 2014.

[23] S. Rossi, M. Hallett, P. M. Rossini, A. Pascual-Leone, and The Safety of TMS Consensus Group, "Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research," *Clinical Neurophysiology*, vol. 120, no. 12, pp. 2008–2039, 2009.

[24] A. T. Barker, R. Jalinous, and I. L. Freeston, "Non-invasive magnetic stimulation of human motor cortex," *Lancet*, vol. 1, no. 8437, pp. 1106-1107, 1985.

[25] J. C. Rothwell, "Physiological studies of electric and magnetic stimulation of the human brain," *Electroencephalography and Clinical Neurophysiology Supplement*, vol. 43, pp. 29–35, 1991.

[26] C. Civardi, R. Cantello, P. Asselman, and J. C. Rothwell, "Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans," *NeuroImage*, vol. 14, no. 6, pp. 1444–1453, 2001.

[27] P. Fox, R. Ingham, M. S. George et al., "Imaging human intra-cerebral connectivity by PET during TMS," *Neuroreport*, vol. 8, no. 12, pp. 2787–2791, 1997.

[28] T. Touge, W. Gerschlager, P. Brown, and J. C. Rothwell, "Are the after-effects of low-frequency rTMS on motor cortex excitability due to changes in the efficacy of cortical synapses?," *Clinical Neurophysiology*, vol. 112, no. 11, pp. 2138–2145, 2001.

[29] R. Chen, J. Classen, C. Gerloff et al., "Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation," *Neurology*, vol. 48, no. 5, pp. 1398–1403, 1997.

[30] V. Kozyrev, U. T. Eysel, and D. Jancke, "Voltage-sensitive dye imaging of transcranial magnetic stimulation-induced intracortical dynamics," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 111, no. 37, pp. 13553–13558, 2014.

[31] T. Bäumer, R. Lange, J. Liepert et al., "Repeated premotor rTMS leads to cumulative plastic changes of motor cortex excitability in humans," *NeuroImage*, vol. 20, no. 1, pp. 550–560, 2003.

[32] M. Lenz, S. Platschek, V. Priesemann et al., "Repetitive magnetic stimulation induces plasticity of excitatory postsynapses on proximal dendrites of cultured mouse CA1 pyramidal neurons," *Brain Structure & Function*, vol. 220, no. 6, pp. 3323–3337, 2015.

[33] A. Conca, W. Peschina, P. König, H. Fritzsche, and A. Hausmann, "Effect of chronic repetitive transcranial magnetic stimulation on regional cerebral blood flow and regional cerebral glucose uptake in drug treatment-resistant depressives. A brief report," *Neuropsychobiology*, vol. 45, no. 1, pp. 27–31, 2002.

[34] S. K. Esser, R. Huber, M. Massimini, M. J. Peterson, F. Ferrarelli, and G. Tononi, "A direct demonstration of cortical LTP in humans: a combined TMS/EEG study," *Brain Research Bulletin*, vol. 69, no. 1, pp. 86–94, 2006.

[35] J. P. Lefaucheur, N. André-Obadia, A. Antal et al., "Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)," *Clinical Neurophysiology*, vol. 125, no. 11, pp. 2150–2206, 2014.

[36] F. J. Medina-Fernández, E. Luque, M. Aguilar-Luque et al., "Transcranial magnetic stimulation modifies astrocytosis, cell density and lipopolysaccharide levels in experimental autoimmune encephalomyelitis," *Life Sciences*, vol. 169, pp. 20–26, 2017.

[37] M. A. Sherafat, M. Heibatollahi, S. Mongabadi, F. Moradi, M. Javan, and A. Ahmadiani, "Electromagnetic field stimulation potentiates endogenous myelin repair by recruiting subventricular neural stem cells in an experimental model of white matter demyelination," *Journal of Molecular Neuroscience*, vol. 48, no. 1, pp. 144–153, 2012.

[38] B. Guse, P. Falkai, and T. Wobrock, "Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review," *Journal of Neural Transmission*, vol. 117, no. 1, pp. 105–122, 2010.

[39] A. T. Sack and D. E. Linden, "Combining transcranial magnetic stimulation and functional imaging in cognitive brain research: possibilities and limitations," *Brain Research. Brain Research Reviews*, vol. 43, no. 1, pp. 41–56, 2003.

[40] A. Sato, T. Torii, Y. Nakahara, M. Iwahashi, Y. Itoh, and K. Iramina, "The impact of rTMS over the dorsolateral prefrontal cortex on cognitive processing," *2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 2013, Osaka, Japan, July 2013, 2013.

[41] C. Esslinger, N. Schüler, C. Sauer et al., "Induction and quantification of prefrontal cortical network plasticity using 5 Hz rTMS and fMRI," *Human Brain Mapping*, vol. 35, no. 1, pp. 140–151, 2014.

[42] Y. Li, L. Wang, M. Jia, J. Guo, H. Wang, and M. Wang, "The effects of high-frequency rTMS over the left DLPFC on cognitive control in young healthy participants," *PLoS One*, vol. 12, no. 6, article e0179430, 2017.

[43] W. Y. Hsu, Y. Ku, T. P. Zanto, and A. Gazzaley, "Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis," *Neurobiology of Aging*, vol. 36, no. 8, pp. 2348–2359, 2015.

[44] N. Maggio and A. Vlachos, "Synaptic plasticity at the interface of health and disease: new insights on the role of endoplasmic reticulum intracellular calcium stores," *Neuroscience*, vol. 281C, pp. 135–146, 2014.

[45] B. Audoin, D. Ibarrola, J. P. Ranjeva et al., "Compensatory cortical activation observed by fMRI during a cognitive task at the earliest stage of MS," *Human Brain Mapping*, vol. 20, no. 2, pp. 51–58, 2003.

[46] C. Forn, A. Barros-Loscertales, J. Escudero et al., "Cortical reorganization during PASAT task in MS patients with preserved working memory functions," *NeuroImage*, vol. 31, no. 2, pp. 686–691, 2006.

[47] C. Forn, A. Barros-Loscertales, J. Escudero et al., "Compensatory activations in patients with multiple sclerosis during preserved performance on the auditory N-back task," *Human Brain Mapping*, vol. 28, no. 5, pp. 424–430, 2007.

[48] C. Mainero, F. Caramia, C. Pozzilli et al., "fMRI evidence of brain reorganization during attention and memory tasks in multiple sclerosis," *NeuroImage*, vol. 21, no. 3, pp. 858–867, 2004.

[49] W. Staffen, A. Mair, H. Zauner et al., "Cognitive function and fMRI in patients with multiple sclerosis: evidence for compensatory cortical activation during an attention task," *Brain*, vol. 125, no. 6, pp. 1275–1282, 2002.

[50] M. C. Bonnet, M. Allard, B. Dilharreguy, M. Deloire, K. G. Petry, and B. Brochet, "Cognitive compensation failure in multiple sclerosis," *Neurology*, vol. 75, no. 14, pp. 1241–1248, 2010.

[51] S. Cader, A. Cifelli, Y. Abu-Omar, J. Palace, and P. M. Matthews, "Reduced brain functional reserve and altered functional connectivity in patients with multiple sclerosis," *Brain*, vol. 129, no. 2, pp. 527–537, 2006.

[52] V. M. Leavitt, G. Wylie, H. M. Genova, N. D. Chiaravalloti, and J. DeLuca, "Altered effective connectivity during performance of an information processing speed task in multiple sclerosis," *Multiple Sclerosis*, vol. 18, no. 4, pp. 409–417, 2012.

[53] M. A. Rocca, P. Valsasina, H. E. Hulst et al., "Functional correlates of cognitive dysfunction in multiple sclerosis: a multicenter fMRI study," *Human Brain Mapping*, vol. 35, no. 12, pp. 5799–5814, 2014.

[54] M. A. Rocca, P. Valsasina, V. M. Leavitt et al., "Functional network connectivity abnormalities in multiple sclerosis: correlations with disability and cognitive impairment," *Multiple Sclerosis Journal*, vol. 1, 2017.

[55] S. Y. Bookheimer, M. H. Strojwas, M. S. Cohen et al., "Patterns of brain activation in people at risk for Alzheimer's disease," *The New England Journal of Medicine*, vol. 343, no. 7, pp. 450–456, 2000.

[56] J. F. Sumowski, G. R. Wylie, J. Deluca, and N. Chiaravalloti, "Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: functional magnetic resonance imaging evidence for cognitive reserve," *Brain*, vol. 133, no. 2, pp. 362–374, 2010.

[57] H. Johansen-Berg, M. F. Rushworth, M. D. Bogdanovic, U. Kischka, S. Wimalaratna, and P. M. Matthews, "The role of ipsilateral premotor cortex in hand movement after stroke," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 22, pp. 14518–14523, 2002.

[58] A. Cifelli and P. M. Matthews, "Cerebral plasticity in multiple sclerosis: insights from fMRI," *Multiple Sclerosis*, vol. 8, no. 3, pp. 193–199, 2002.

[59] M. M. Schoonheim, K. A. Meijer, and J. J. Geurts, "Network collapse and cognitive impairment in multiple sclerosis," *Frontiers in Neurology*, vol. 6, p. 82, 2015.

[60] C. Louapre, V. Perlbarg, D. García-Lorenzo et al., "Brain networks disconnection in early multiple sclerosis cognitive deficits: an anatomofunctional study," *Human Brain Mapping*, vol. 35, no. 9, pp. 4706–4717, 2014.

[61] E. Elzamarany, L. Afifi, N. M. El-Fayoumy, H. Salah, and M. Nada, "Motor cortex rTMS improves dexterity in relapsing-remitting and secondary progressive multiple sclerosis," *Acta Neurologica Belgica*, vol. 116, no. 2, pp. 145–150, 2016.

[62] D. Centonze, G. Koch, V. Versace et al., "Repetitive transcranial magnetic stimulation of the motor cortex ameliorates spasticity in multiple sclerosis," *Neurology*, vol. 68, no. 13, pp. 1045–1050, 2007.

[63] F. Mori, G. Koch, C. Foti, G. Bernardi, and D. Centonze, "The use of repetitive transcranial magnetic stimulation (rTMS) for the treatment of spasticity," *Progress in Brain Research*, vol. 175, pp. 429–439, 2009.

[64] F. Mori, C. Codecà, H. Kusayanagi et al., "Effects of intermittent theta burst stimulation on spasticity in patients with multiple sclerosis," *European Journal of Neurology*, vol. 17, no. 2, pp. 295–300, 2010.

[65] B. Amatya, F. Khan, L. La Mantia, M. Demetrios, and D. T. Wade, "Non-pharmacological interventions for spasticity in multiple sclerosis," *Cochrane Database of Systematic Reviews*, no. 2, article CD009974, 2013.

[66] D. Centonze, F. Petta, V. Versace et al., "Effects of motor cortex rTMS on lower urinary tract dysfunction in multiple sclerosis," *Multiple Sclerosis*, vol. 13, no. 2, pp. 269–271, 2007.

[67] A. M. Burhan, P. Subramanian, L. Pallaveshi, B. Barnes, and M. Montero-Odasso, "Modulation of the left prefrontal cortex with high frequency repetitive transcranial magnetic stimulation facilitates gait in multiple sclerosis," *Case Reports in Neurological Medicine*, vol. 2015, Article ID 251829, 6 pages, 2015.

[68] G. Koch, S. Rossi, C. Prosperetti et al., "Improvement of hand dexterity following motor cortex rTMS in multiple sclerosis patients with cerebellar impairment," *Multiple Sclerosis Journal*, vol. 14, no. 7, pp. 995–998, 2008.

[69] J. P. Lefaucher, M. A. Chalah, A. Mhalla, U. Palm, S. S. Ayache, and V. Mylius, "The treatment of fatigue by non-invasive brain stimulation," *Neurophysiologie Clinique*, vol. 47, no. 2, pp. 173–184, 2017.

[70] S. Bonavita, R. Sacco, M. Della Corte et al., "Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study," *Journal of Neurology*, vol. 262, no. 1, pp. 91–100, 2015.

[71] M. Mitolo, A. Venneri, I. D. Wilkinson, and B. Sharrack, "Cognitive rehabilitation in multiple sclerosis: a systematic review," *Journal of the Neurological Sciences*, vol. 354, no. 1-2, pp. 1–9, 2015.

[72] L. De Giglio, F. Tona, F. De Luca et al., "Multiple sclerosis: changes in thalamic resting-state functional connectivity induced by a home-based cognitive rehabilitation program," *Radiology*, vol. 280, no. 1, pp. 202–211, 2016.

[73] H. E. Hulst, T. Goldschmidt, M. A. Nitsche et al., "rTMS affects working memory performance, brain activation and functional connectivity in patients with multiple sclerosis," *Journal of Neurology, Neurosurgery, and Psychiatry*, vol. 88, no. 5, pp. 386–394, 2017.

[74] B. Brochet, "Functional training is a senseless strategy in MS cognitive rehabilitation: strategy training is the only useful approach – commentary," *Multiple Sclerosis Journal*, vol. 23, no. 7, pp. 932-933, 2017.

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Research Article

Mediational Model of Multiple Sclerosis Impairments, Family Needs, and Caregiver Mental Health in Guadalajara, Mexico

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Individuals with multiple sclerosis (MS), especially those living in Latin America, often require assistance from family caregivers throughout the duration of the disease. Previous research suggests that family caregivers may experience positive and negative outcomes from providing care to individuals with MS, but few studies have examined the unmet needs of individuals providing care to family members with MS and how these unmet needs may mediate the relationship between MS symptoms and caregiver mental health. The current study examined the relationships among MS impairments (functional, neurological, cognitive, behavioral, and emotional), unmet family needs (household, informational, financial, social support, and health), and caregiver mental health (satisfaction with life, anxiety, burden, and depression) in a sample of 81 MS caregivers from Guadalajara, Mexico. A structural equation model demonstrated the mediational effect of unmet family needs on the relationship between MS impairments and caregiver mental health. These findings suggest that intervention research on MS caregivers in Latin America may consider focusing on caregiver mental health problems by addressing unmet family needs and teaching caregivers ways to manage the impairments of the individual with MS.

1. Introduction

Multiple sclerosis (MS) is a chronic neurological illness that eventually results in physical disability and cognitive impairments which limit an individual's ability to function independently [1]. Approximately 2.5 million people have been diagnosed with MS worldwide [2], and research demonstrates that worldwide prevalence rates are increasing [3]. As with other countries, researchers have observed that MS prevalence rates may be higher than previously reported in Latin American countries such as Mexico, where current prevalence rates vary by region and range from 7 to 30 cases per 100,000 people [4, 5].

In Latin America, where rates of MS are increasing but disparities still exist in its diagnosis and treatment [6, 7], sociocultural values such as allocentrism, familism, and filial obligation [8, 9] increase the likelihood that family members will serve as informal caregivers to individuals with MS. When compared to other racial/ethnic groups, Latino caregivers often report limited use of formal support services [10, 11], larger informal social networks [8], increased role strain [12], lower rates of institutionalization [10], and higher rates of depression [13]. However, very few studies have examined MS caregiving in Latin America [14, 15], and associations in this region among MS impairments, needs of family members providing care,

and caregiver mental health remain largely unknown. Because of this major gap in the research literature, there is a great need for research addressing the process of MS caregiving in Latin America, as well as the impact of MS impairments on family needs and caregiver mental health in this region.

International research has established that compared to noncaregivers, MS caregivers report higher levels of depression [16], anxiety [17], and decreased social support [18]. Patient factors such as level of disability [19–21], cognitive impairments [22–25], behavioral changes [22, 23], incontinence, and fatigue [26] contribute to increased caregiver depression, strain, and burden. Although many of the findings on MS caregiver functioning emphasize the negative aspects of caregiving, the literature also demonstrates that MS caregivers report salubrious outcomes such as personal growth, role fulfillment, positive emotions, and satisfaction as a result of caregiving [11, 27].

MS caregiving can be understood using Pearlin et al.'s [28] conceptual model of caregiver stress. This model identifies three domains of caregiving stress: (a) background and context of the caregiving situation (i.e., caregiver age, gender, ethnicity, socioeconomic status, relationship with the patient, and family and social network composition), (b) primary stressors (i.e., cognitive functioning of patient, behavioral changes, problematic behaviors of the patient, activities of daily living (ADLs), and instrumental ADLs), and (c) secondary stressors (i.e., unmet needs for information, reduced access to employment or need for financial assistance, limited social support, family conflict, conflict with occupational and social role fulfillment, economic strain, changes in self-concept, loss of self, role captivity, mastery, competence, and gain). The model identifies physical and emotional outcomes associated with stressors and alleviated by mediators of stress (i.e., coping strategies and social support). Moreover, Pearlin et al. indicate that stressors, mediators, and outcomes often interact and individually or collectively influence caregiver mental health in a direct, indirect, or cyclical pattern [28]. Because unmet family needs can comprise both background (i.e., affecting family prior to involvement in caregiving roles) variables and stressors associated with the caregiving experience (i.e., lack of knowledge about disease process or need for specific care information), clinicians and providers have increased interest in studying the role of unmet needs on caregiver psychological functioning.

Findings from studies of MS caregivers demonstrate that primary stressors (i.e., patient functioning) have been associated with depression and burden. Although these studies have examined aspects such as the patient's cognitive functioning, psychological functioning, physical disability, and ADL impairments, few have examined unmet family needs in the context of these patient-related stressors. Within the framework of Pearlin et al.'s model [28], family needs (i.e., household needs, informational needs, financial needs, health needs, and social support) are an extension of the background/context and secondary stressor domains. Findings from a previous study demonstrate that unmet family needs are also are a central determinant of caregiver adjustment, as they have been associated with increased burden and depression among MS caregivers [14].

Given the often significant impairments documented in individuals with MS, the unknown levels of unmet family needs, and the generally poor mental health that MS caregivers report, many questions remain regarding the specific connections among these sets of variables, especially in Latin America. As such, the objective of the present study is to examine unmet family needs as a mediator of the established relationship between the care recipients' MS impairments (primary stressor) and caregivers' mental health (outcome). Based on prior research which suggests strong associations between patients' MS symptoms and their caregivers' psychosocial distress [16, 17, 19, 22, 24], it is hypothesized that the relationship between MS impairments and caregiver mental health will be significantly mediated by unmet family needs. At present, no studies in the MS caregiver literature have examined this possible effect, but based on Pearlin et al.'s [28] model, primary stressors (e.g., patient functioning) should be associated with reduced caregiver mental health outcomes. Secondary stressors such as family needs should be associated with both primary stressors (MS impairments) and negative caregiver mental health outcomes and could possibly account for the connection between these two sets of constructs.

2. Method

2.1. Participants. Participants ($n = 81$) were a convenience sample of self-identified MS caregivers recruited from The Mexican Foundation for Multiple Sclerosis and the Department of Neurosciences of the University Center for Health Sciences, University of Guadalajara, Mexico. In order to participate in the study, caregivers had to (a) be the primary caregiver of an individual with a diagnosis of MS who was at least six months past the date of diagnosis, (b) have provided care to the person with MS for a minimum of six months, and (c) have had no history of a cognitive, serious psychiatric, or neurological disorder themselves. Initially, 86 participants were approached, but after screening, five declined or did not meet study criteria. Data were collected from a final sample of 81 caregivers. Demographic information for the caregiver sample is provided in Table 1 and for the patient sample in Table 2.

2.2. Measures. Eligible caregivers completed a battery of questionnaires in Spanish that assessed the following domains: demographic information, MS-related impairments as observed by the caregiver, family needs, and mental health. Measures of depression, anxiety, caregiver burden, satisfaction with life, and caregiver needs had been previously translated to Spanish and validated in Spanish-speaking samples prior to their use in this study. Spanish-speaking norms were used for scoring and interpreting these measures where available. The measure of MS impairments was translated (forward and backward) into Spanish and then English using methods published by Chapman and Carter [29] and Guillemin et al. [30] to ensure cross-cultural equivalence. Both translations were compared by a

Table 1: Characteristics of MS caregivers ($n = 81$).

Demographic variable	Value
Age, years, mean (SD)	43.37 (15.32)
Sex, %	
Female ($n = 54$)	66.7%
Male ($n = 26$)	33.3%
Years of education, mean (SD)	11.74 (4.42)
Marital status, %	
Married or partnered ($n = 55$)	67.9%
Single ($n = 19$)	23.5%
Widowed ($n = 4$)	4.9%
Divorced or separated ($n = 3$)	3.7%
Relationship to individual with MS, %	
Parent ($n = 37$)	45.7%
Spouse/romantic partner ($n = 26$)	32.1%
Sibling ($n = 10$)	12.3%
Child ($n = 5$)	6.2%
Friend ($n = 1$)	1.2%
Professional caregiver ($n = 1$)	1.2%
Other ($n = 1$)	1.2%
Duration of caregiving	
Number of months, mean (SD)	52.31 (59.29)
Hours per week of care, mean (SD)	70.96 (60.66)
Current occupation, %	
Homemaker ($n = 25$)	30.9%
Full-time employment ($n = 21$)	25.9%
Part-time employment ($n = 19$)	23.5%
Student ($n = 7$)	8.6%
Unemployed ($n = 4$)	4.9%
Retired ($n = 3$)	3.7%
Other ($n = 2$)	2.5%
Monthly household income, %	
Less than minimum wage ($n = 1$)	1.2%
Minimum wage ($n = 6$)	7.4%
1-2 times minimum wage ($n = 11$)	13.6%
2-3 times minimum wage ($n = 10$)	12.3%
3-4 times minimum wage ($n = 7$)	8.6%
4-5 times minimum wage ($n = 11$)	13.6%
More than 5 times minimum wage ($n = 35$)	43.2%

monolingual psychologist from Mexico and a bilingual psychologist living in Spain. No discrepancies were identified. The final version was reviewed by the monolingual psychologist from Mexico. Participants completed a demographic form created by the investigators. On this form, household income in Mexico was calculated by monthly salary, where the monthly minimum wage at the time of data collection was 2018.70 pesos or approximately 155.40 USD per month [31].

2.2.1. MS Impairments. Caregivers completed the MS Impairment Questionnaire (MS-IQ) [26], a 30-item checklist

Table 2: Characteristics of individuals with MS as reported by caregivers ($n = 81$).

Demographic variable	Value
Age, years, mean (SD)	33.25 (10.78)
Sex, %	
Female ($n = 56$)	69.1%
Male ($n = 25$)	30.9%
Years of education, mean (SD)	13.34 (3.97)
Marital status, %	
Single ($n = 40$)	49.4%
Married or partnered ($n = 36$)	44.4%
Divorced or separated ($n = 5$)	6.2%
MS clinical course, %	
Relapse remitting ($n = 64$)	79.0%
Secondary progressive ($n = 16$)	19.8%
Primary progressive ($n = 1$)	1.2%
Age of symptom onset, mean (SD)	26.29 (9.76)
Age at diagnosis, mean (SD)	28.17 (10.17)
Current occupation, %	
Full-time employment ($n = 22$)	27.2%
Homemaker ($n = 19$)	23.5%
Part-time employment ($n = 15$)	18.5%
Student ($n = 11$)	13.6%
Unemployed ($n = 6$)	7.4%
Receiving disability ($n = 7$)	8.6%
Other ($n = 1$)	1.2%

of common MS impairments. Assessed impairments are grouped into five subscales: cognitive, emotional, behavioral, neurological, and functional. Caregivers completed this measure by reporting "yes" for the specific impairments that their care recipient experienced and "no" for the impairments that the care recipient did not experience. Item scores are summed (yes = 1, no = 0) so that subscale scores with higher values indicate domains with a larger number of impairments. Although it is possible to calculate a total score, only the subscale scores were used in the current study in order to generate a latent construct.

2.2.2. Anxiety. Caregivers completed the Spielberger State-Trait Anxiety Inventory (STAI) [32] as a measure of anxiety. The STAI is a 40-item self-report measure with a two-factor structure. The S-anxiety subscale measures anxiety as a temporary emotional state, while the T-anxiety subscale assesses anxiety as a fixed personality trait [32, 33]. Both subscales can be combined to create a total scale which was used in the current study. Total scale scores range from 40 to 160, with higher scores indicating increased anxiety. The Spanish version of the STAI [34] was used in this study and has demonstrated very good construct validity and internal consistency in samples of male (state $\alpha = 0.93$, trait $\alpha = 0.96$) and female (state $\alpha = 0.88$, trait $\alpha = 0.82$) Spanish speakers [35, 36].

2.2.3. Burden. Caregivers completed the Zarit Burden Inventory (ZBI) [37]. Item scores are summed, and total scores

range from 0 to 88 with higher scores indicating greater burden [38]. The ZBI has been validated and used in numerous neurological caregiver populations including TBI caregivers [39], dementia caregivers [37], and Parkinson's caregivers [40]. The Spanish version of the ZBI has demonstrated excellent construct validity and internal reliability ($\alpha = 0.92$) in samples of Spanish-speaking individuals [41].

2.2.4. Depression. Caregivers completed the Patient Health Questionnaire-9 (PHQ-9) [42] as a measure of depressive symptoms experienced within a two-week period. Total scores range from 0 to 27 with higher scores reflecting more severe symptoms of depression. The Spanish version has demonstrated strong construct and criterion validity, as well as excellent internal consistency and convergent validity in Spanish-speaking validation samples [43–45].

2.2.5. Satisfaction with Life. Participants completed the Satisfaction with Life Scale (SWLS) [46]. Higher total scores represent higher life satisfaction [47]. Participants completed the Spanish version of the SWLS, which has high internal consistency ($\alpha = 0.88$) and good construct validity in Spanish-speaking samples [48, 49].

2.2.6. Family Needs. The Family Needs Assessment Tool (FNAT) [50] assesses the degree to which needs are met in family caregivers of individuals with neurological conditions in Latin America. The FNAT is comprised of 14 items and has five unmet needs subscales: household (two items), informational (three items), financial (three items), health (four items), and social support (two items). Higher scores indicate greater areas of unmet needs. As with the MS-IQ, although it is possible to calculate a total score on the FNAT, only the subscale scores were used in the current study in order to generate a latent construct.

2.3. Procedure. Prior to recruitment, the Institutional Review Board of the Mexican Foundation of Multiple Sclerosis reviewed and approved the study protocol. Staff at the Mexican Foundation for Multiple Sclerosis and the Department of Neurosciences of the University Center for Health Sciences, University of Guadalajara recruited prospective study participants from a neurology clinic using verbal and written advertisements. Interested participants contacted the research staff and were screened for eligibility. Eligible caregivers completed informed consent forms prior to data collection. During a 40-minute appointment at the Mexican Foundation for Multiple Sclerosis, a staff psychologist collected sociodemographic information and administered a battery of questionnaires to caregivers using a structured interview format to ensure that the participants understood the item content and did not skip any items.

2.4. Data Analysis

2.4.1. Preliminary Analyses. Frequencies and descriptive statistics were run to summarize MS impairments reported by caregivers, frequently reported unmet family needs, and clinically significant caregiver mental health problems.

2.4.2. Hypothesis Testing. A structural equation model (SEM) was created with three latent variables: MS impairments, family needs, and caregiver mental health. MS impairments was comprised of shared variance from the five impairment variables: functional, cognitive, behavioral, emotional, and physical. Family needs were comprised of shared variance from the five types of family needs: household, informational, financial, health, and social needs. Caregiver mental health was comprised of shared variance from the four mental health variables: depression, burden, anxiety, and satisfaction with life. This SEM was conducted using AMOS 20 [51]. Because most traditional SEMs in rehabilitation research are run with at least 200 participants [52], and the sample size in the current study is 81 participants, estimates of model fit are likely to be inaccurate; we report indices of model fit solely for reference. Instead, the focus of this analysis was on the size and significance level of the standardized β weight for the indirect effect of MS impairments on caregiver mental health through family needs.

3. Results

Participants reported patient impairments in all five domains, as seen in Table 3. Of the neurological impairments reported, more than 75% of participants reported tiring easily, while over half reported paralysis, poor eyesight, loss of sensation, and clumsiness. More than half of the sample reported the following emotional symptoms: depression, easily upset, irritability, and mood changes. Commonly reported functional and cognitive impairments were difficulty walking, doing things slowly, forgetfulness, and difficulty concentrating. Less than half of participants reported behavioral symptoms but endorsed acting impulsively as the most commonly observed behavioral symptom. Caregivers' item responses to the FNAT were ranked (identifying the top five) by the percentage of unmet need endorsements. As illustrated in Table 4, a majority of the unmet needs identified were from the informational domain, while the remaining needs were from the social support domain.

Total scores on the PHQ-9 ranged from 0 to 21 out of a possible maximum score of 27. The sample mean of 5.92 (SD = 5.27) indicated frequent endorsement of mild symptoms of depression. As seen in Table 5, nearly half of the sample reported clinically significant levels of depression, with 26% reporting mild symptoms, 16% reporting moderate symptoms, and 1.2% reporting severe symptoms of depression. Both total and subscale scores (e.g., state and trait) of the STAI were examined. Participants' total scores ranged from 11 to 93 out of a maximum score of 160. Nearly one-third of participants reported clinically significant symptoms of state or trait anxiety with 32% reporting moderate symptoms on the state subscale and 2.5% reporting severe symptoms on the state subscale of the measure. Responses on the trait subscale demonstrated that 31% of participants reported moderate symptoms on the trait subscale, while 3.7% reported severe symptoms. Total scores on the ZBI ranged from 0 to 62 out of a maximum score of 88. The sample mean of 22.02 (SD = 14.72) indicated that on average participants reported mild to moderate symptoms of burden.

Table 3: Summary of MS impairments reported by caregivers ($n = 81$).

Impairment domain	Impairments endorsed	% endorsing impairment	Number of patients with observed impairments
Neurological	Tiring easily	79%	64
	Paralysis	69%	56
	Poor eyesight	62%	50
	Loss of sensation	54%	44
	Clumsiness	52%	42
	Pain	36%	29
	Incontinence	27%	22
	Seizures	14%	11
Emotional	Depression	68%	55
	Easily upset	68%	55
	Irritability	58%	47
	Mood changes	58%	47
	Anxiety	49%	40
	Loss of interest	33%	27
Functional	Difficulty walking	69%	56
	Doing things slowly	56%	45
	Trouble reading	33%	27
	Difficulty writing	32%	26
	Difficulty talking	27%	22
	Difficulty eating	22%	18
	Difficulty hearing	20%	16
Cognitive	Forgetfulness	62%	50
	Difficulty concentrating	53%	43
	Difficulty thinking	38%	31
	Poor decision making	30%	24
	Difficulty learning	27%	22
	Denying problems	27%	22
Behavioral	Acting impulsively	35%	28
	Upsetting other people	28%	23
	Not being reliable	12%	10

Further review of clinically significant scores revealed that 29.6% reported mild to moderate symptoms, 12.3% reported moderate to severe symptoms, and 1.2% reported severe symptoms of burden. Total scores on the SWLS ranged from 10 to 35 out of a maximum score of 35. The sample mean of 23.43 (SD = 6.35) indicated an overall feeling of general satisfaction.

Two structural equation models (SEMs) were created to examine whether unmet family needs mediated the relationship between MS impairments and caregiver mental health. Both models included three latent variables: MS impairments, family needs, and caregiver mental health. MS impairments was comprised of the following five manifest variables (i.e., subscale scores from the MS-IQ): neurological, cognitive, functional, behavioral, and emotional symptoms. Family needs was created using the five manifest variables (i.e., subscale scores from the FNAT) of financial, informational, household, health, and social support needs. Caregiver mental health was created using four manifest variables of depression (PHQ-9 total score), anxiety (total STAI score), burden (total ZBI score), and satisfaction with life (total SWLS score). In total, the models were comprised of 33 variables, of which 14 were observed, 16 were unique, and 3 were factors. The manifest variables are directly measured by a total score or subscale score, represented in Figure 1 (the second, structural model) by rectangles. The latent variables are measured indirectly and inferred mathematically from the shared variance of the manifest variables. In Figure 1, the latent variables are represented by ovals.

Normality tests revealed that the distributions of the measured variables were all normal in a univariate sense in terms of skewness (all coefficients $\leq$ an absolute value of 0.93) and kurtosis (all coefficients $\leq$ an absolute value of 1.17). Similarly, a Mardia's coefficient of 2.23 suggested that the variables were not multivariate kurtotic. It was further found by the calculation of Mahalanobis distance that no single observation was meaningfully far from the multivariate centroid (all ps ≥ 0.01), and therefore there were no multivariate outliers.

The first measurement model SEM examined correlations (e.g., bidirectional paths) between each of the latent variables as opposed to directional paths. In this model, only one statistically significant correlation emerged between MS impairments and caregiver mental health at $r = -0.64$ ($p < 0.01$). The bivariate relationships between MS impairments and family needs ($r = 0.34$, $p = 0.39$) and family needs and caregiver mental health ($r = -0.55$, $p = 0.37$) were not statistically significant. Although two of these correlations were not statistically significant, all three were in the expected direction and were at least medium sized.

In the second SEM (Figure 1), MS impairments were specified to lead directly to caregiver mental health, as well as to have an indirect effect on caregiver mental health through family needs. In this model, MS impairments was significantly associated with caregiver mental health ($\beta = -0.51$, $p = 0.003$). MS impairments were not significantly associated with family needs ($\beta = 0.34$, $p = 0.39$), nor was family needs associated with caregiver mental health ($\beta = -0.38$, $p = 0.39$). However, again all three directional paths were in the hypothesized direction. The indirect effect of MS impairments on caregiver mental health through family needs was statistically significant ($\beta = 0.13$, $p = 0.008$), suggesting the presence of an indirect effect. The following fit indices are presented only for reference: the ratio of the χ^2 statistic to the degrees of freedom in the model was 1.59; the goodness of fit index (GFI) was 0.85; the adjusted goodness of fit index (AGFI) and the normed fit index (NFI) were 0.78 and 0.72, respectively; the incremental fit index (IFI), Tucker-Lewis index (TLI), and comparative fit index (CFI) were 0.87, 0.84, and 0.87, respectively; and the root mean square error of approximation (RMSEA) was 0.09.

Table 4: Summary of unmet family needs ($n = 81$).

Family need	% endorsed as unmet	Number of caregivers reporting need	Domain
I need complete information.	71.6%	58	Information
I need specialized information about the patient.	70.3%	57	Information
I get help from the community (reverse coded).	65.5%	53	Social support
I get support from my church (reverse coded).	61.7%	50	Social support
I need to discuss my feelings with someone who has been through the same experience.	45.7%	37	Information

Table 5: Summary of caregiver mental health variables.

Variable	Value
PHQ-9 total score, mean (SD)	5.92 (5.27)
Mild depression (%)	26%
Moderate depression (%)	16%
Moderate–severe depression (%)	3.7%
Severe depression (%)	1.2%
STAI total score, mean (SD)	47.01 (21.40)
STAI state, mean (SD)	22.67 (11.82)
STAI trait, mean (SD)	24.34 (10.97)
State moderate anxiety (%)	32%
State severe anxiety (%)	2.5%
Trait moderate anxiety (%)	31%
Trait severe anxiety (%)	3.7%
ZBI total score, mean (SD)	22.02 (14.72)
Mild to moderate burden (%)	29.6%
Moderate to severe burden (%)	12.3%
Severe burden (%)	1.2%
SWLS total score, mean (SD)	23.43 (6.35)
Life dissatisfaction (%)	26%
Neutral (%)	7%
Life satisfaction (%)	67%

4. Discussion

The present study examined the caregiving experiences of MS caregivers living in Guadalajara, Mexico, with a specific emphasis on identifying unmet family needs as a possible mediator of the relationship between MS impairments and caregiver mental health. As hypothesized, this study's findings supported that unmet family needs mediated the relationship between MS impairments and caregiver mental health.

Prior to this study, several researchers had identified a very strong relationship between patients' clinical symptoms and their caregivers' psychosocial functioning. However, few, if any, researchers have been able to identify specific mechanisms or correlates that account for this relationship. The statistically significant indirect effect of MS impairments on caregiver mental health through unmet family needs is the first time this finding has emerged in the research literature. One possible interpretation of this finding is that as patients experience impairments in multiple domains, family caregivers may need additional support or may have new needs that they did not have when the patient's health was more stable [53]. When these needs are unmet, the family has fewer coping resources to draw upon and family members may experience greater distress. Previous research on caregivers of individuals with moderate to severe MS impairments has consistently identified increased needs for social, informational, and financial support, as well as higher rates of burden, strain, and depression [22, 54–57].

Findings from this study suggest that parents are providing the majority of the care for their children. This expands the definition of MS caregiver often seen in previous studies from a singular perspective that includes a spouse or romantic partner to a broader definition that can include parents, siblings, or other individuals providing care to the patient within their family system. As such, health care providers may need to focus on the impact of the patient and their illness on family overall. Consideration for the needs of the family system is particularly warranted in this sample as the overall health of the family unit is an important part of Mexican and Latino American cultures. Because unmet family needs were identified as a mediator of the relationship between MS impairments and caregiver mental health, health care providers may also want to assess the psychosocial functioning of family members in the household and target interventions toward the family system. There is the potential for a multifamily group intervention that informs caregivers about the effects of caregiving on families. Such an intervention may help bring together families within the community and could help normalize feelings of burden, disappointment, guilt, and fear that caregivers may be too guarded to share with others.

With regard to primary unmet needs identified in this study, a large number of participants reported unmet informational needs, which included specific requests for "specialized information about the patient," "complete information," and "to share [their] feelings with someone who has been in the same situation." Caregivers in this sample may benefit from general education about MS (e.g., disease course, symptom types, and treatments), as well as specific information about behavioral and emotional impairments (e.g., psychoeducation, resource identification, and symptom management strategies). Data from caregivers of individuals with Alzheimer's disease [58] and Parkinson's disease [59] have demonstrated decreased burden and caregiver stress among individuals who complete psychoeducational programs for management of symptoms associated with these

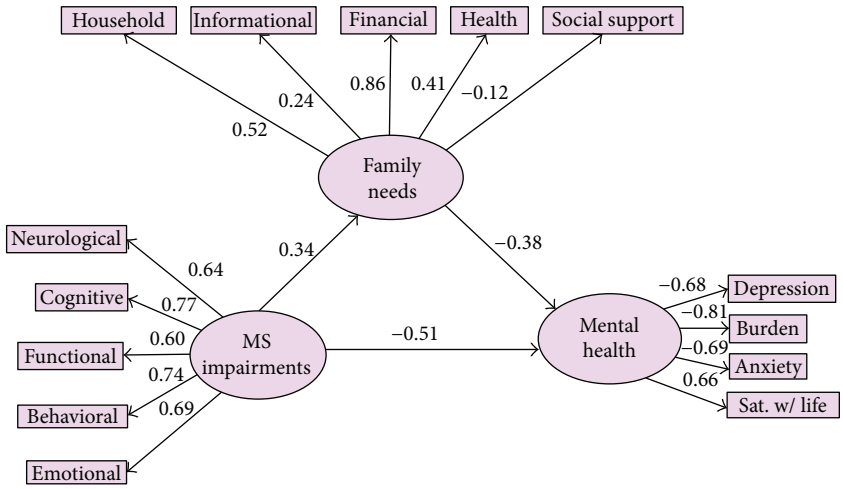

Figure 1: SEM of the mediation of family needs on the relationship between MS impairments and caregiver mental health.

illnesses [60]. Likewise, because of the specific interest identified by these caregivers, MS caregivers could possibly benefit from education that assists with daily care needs or helps caregivers understand and anticipate possible sequelae of the disease.

Additionally, the caregivers may have had informational needs that were not assessed. As such, a focus group or follow-up survey to assess the type of information that caregivers need is a feasible way to help meet the needs of caregivers in this sample or other samples as different caregiver cohorts will likely have different needs dependent on the patient's course, family composition, and family's access to medical resources. Moreover, although caregivers were requesting information in this study, they indicated a need to speak with other caregivers and to receive social support in addition to pragmatic suggestions, recommendations, and information. Interventions designed to facilitation dissemination of information through peer support, mentoring, and support groups offered in person or via telephone or internet have demonstrated efficacy in other caregiver populations [61] and could provide MS caregivers with increased access to these resources as well.

Interventions designed to help caregivers determine how to meet financial and household needs could help alleviate the negative mental health outcomes that caregivers in this sample experienced. Addressing these needs may include education about resources in the community (e.g., grants, supplemental income, and respite care services) that are available to families in the region or education about how to delegate household tasks. Addressing these needs may also require education about when to seek support outside of the family (e.g., respite care) and ways to overcome cultural barriers to accepting and accessing care outside of a kinship network.

In addition to this key finding, mental health outcomes reported by this sample differed somewhat from other studies of MS caregivers and individuals in Mexico. Epidemiological data from Mexico suggest a lifetime prevalence of 7.2% for major depressive disorder [62], which demonstrates that reported rates of depression in the current study are higher than those generally reported in the Mexican population. Although few studies have examined anxiety among MS caregivers, Argyriou et al. [63] reported mean scores that reflected mild anxiety in their sample, while the scores in the current study demonstrated subclinical mean values for state and trait anxiety, even though one-third of the sample endorsed moderate symptoms of anxiety. When comparing this sample's scores to epidemiological lifetime prevalence data for anxiety in Mexico, participants in this sample reported higher than expected anxiety (i.e., 14.3% prevalence rate as reported by Medina-Mora et al. [62]). A comparison with other studies of MS caregivers demonstrates that the current sample's percentages of MS caregivers experiencing mild, moderate, and severe burden are much lower than rates reported in other samples. For example, in another sample of MS caregivers, Akkus [18] reported a mean ZBI score of 36.42 (SD = 18.41), while Buchanan and Huang [64] found that 40% of their sample described caregiving as burdensome some of the time and 11.4% reported that caregiving was burdensome all of the time. These findings suggest the need for health care providers to continuously assess the mental health of caregivers and to provide them with access to services that can include emotional support (e.g., support groups, volunteer organizations, nursing care, spiritual/religious leaders, and communities) throughout the disease's duration.

4.1. Limitations and Future Research. The findings of this study should be viewed in light of several limitations, which can be considered potential areas for future research. Unlike many samples of MS caregivers, caregivers in the current study were predominately women who were mothers of the care recipients. This is indeed a rarity in the MS literature, as generally caregivers are male spouses providing care for their wives with MS. Future studies should examine the influence of gender roles prominent in Latino cultures on caregiving behaviors in both women and men MS caregivers and how these

roles might play out in same-gender and opposite-gender caregiving relationships.

Because of the strong cultural values of familism and the stigma associated with neurological illness, caregivers within this sample may have underreported symptoms of burden, depression, and anxiety. Given the desire to fulfill cultural roles, Latina women, especially mothers, may not perceive caregiving as burdensome or they may be reluctant to disclose feelings of strain, anxiety, and sadness. By contrast, in other countries where male spouses or romantic partners typically fulfill MS caregiving roles, perceptions of burden may be stronger, as caregiving is a new skill set for them.

Additionally, the reported household incomes of the families in this sample may be higher than other caregivers who do not receive subsidized care and who are not employed while providing care. This study's participants were recruited from an urban university medical center and a local chapter of the MS foundation. As such, this sample's utilization of care and access to resources may be greater than most caregivers, especially those living in rural areas or individuals living in underdeveloped societies where health care is not as accessible. The findings in this sample may overlook or underestimate the true needs and psychosocial functioning of caregivers who do not have adequate resources and thus cannot acquire medical care for their loved ones and are not as well connected with community-based organizations.

Unmet family needs was one of the most important constructs assessed in the current study. At present, there are few empirically validated neurological-specific family needs assessments for use in Latin America other than that used in the current study. As such, the FNAT was used because the measure had been validated in a sample of caregivers of individuals with neurological conditions in Latin America [50]. Despite this strength, this measure's limitations include a narrow assessment of additional possible family needs which may or may not be MS-specific. As administered in the current study, only one individual in the family completed the questionnaire. However, in order to truly assess family needs, administration of the measure should include reports from all family members of the individual receiving care. As the measure is currently written and administered, the results only offer the perspective of one reporter but attribute this variance to the perspectives of others within the family unit. By including multiple reporters, researchers can then differentiate between variance observed within reporters (unique reporter variance) and across reporters (e.g., shared variance).

Another way to improve the measure is to increase the comprehensiveness and specificity of the constructs being assessed. Although the items in the current measure come from an aggregate of items from needs assessments of caregivers of individuals with MS and other neurological disorders, the current measure does not include items that assess potentially important aspects such as the need for respite care, the specific types of information that caregivers need, assistance with obtaining medical equipment, and the need for holistic or nontraditional medical practices that may be common and useful in Latin America. Including these items may come from additional focus groups and surveys with MS caregivers in other communities, especially communities of individuals who are hard to reach or who do not regularly access medical care. As such, the literature could greatly benefit from an MS-specific measure of family needs that has been developed using a Spanish-speaking sample and has been empirically validated in similar samples.

Similarly, the current study used the MS Impairments Questionnaire, a 30-item checklist of MS symptoms developed by Knight et al. [26] to assess the types of symptoms that patients experience. Although this questionnaire assesses the general clusters of symptoms shown to be common in individuals with MS, the measure itself has not gone through extensive psychometric evaluation. Additionally, several of the items comprising this questionnaire are vague and may not translate well into Spanish (e.g., "being unreliable"). Because of the importance of accurate assessment of MS symptoms, this measure should undergo further revision and evaluation in an attempt to assess additional symptoms of MS, as some of the common symptoms such as sexual dysfunction, attention problems, and heat sensitivity were omitted. A revised version should also include a factor analysis of items, as well as measure of disease severity or disability since the presence of a symptom does not necessarily indicate its functional impact or severity. As with the FNAT, a measure of MS symptoms should include multiple raters and/or a review of medical records to support self-reported and caregiver-reported data. Relying on the caregiver's perspective may overlook symptoms that the caregiver is unaware of (e.g., sexual dysfunction) and result in an incomplete assessment of patient functioning.

Finally, although the assumptions of normality were met for the SEM in the current study, the sample size was too small to generate accurate fit indices. Though they were presented for reference, they likely lack the stability that would occur with sample sizes greater than 200. As a result, these fit indices should be interpreted with extreme caution, and similar models should be run with larger samples in order to more accurately assess whether the current model or other models better fit the patterns in the data.

5. Conclusions

This study provided empirical support for the mediational role of unmet family needs in the relationship between MS impairments and caregiver mental health in Guadalajara, Mexico. These findings suggest that MS impairments may affect both the individual caregiver and the family unit. As a result, MS rehabilitation interventions, especially in Mexico and other Latin American countries, should comprehensively assess and target the patient's functioning, the family's unmet needs, and the caregiver's mental health functioning. Doing so—if supported by future research—could improve services for a population that has faced marginalization and a dearth of care within traditional rehabilitation settings.

Disclosure

The present work was developed as part of the Ph.D. dissertation of Dr. Melody N. Mickens, presented and approved at Virginia Commonwealth University in 2014 [65].

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

[1] R. Dutta and B. Trapp, "Pathogenesis of axonal and neuronal damage in multiple sclerosis," *Neurology*, vol. 68, no. 22, Supplement 3, pp. S22–S31, 2007.

[2] National Multiple Sclerosis Society, "Multiple sclerosis: just the facts, general information. (No. ER6007)," March 2016, http://www.nationalmssociety.org/downlad.aspx?id=22.

[3] N. Koch-Henriksen and P. SØrenson, "The changing demographic pattern of multiple sclerosis epidemiology," *Lancet Neurology*, vol. 9, no. 5, pp. 520–532, 2010.

[4] M. De la Maza Flores and G. Arrambide García, "Prevalencia de esclerosis multiple en el municipio de San Pedro Garza García," *Nuevo León Avances*, vol. 3, pp. 7–10, 2006.

[5] M. Veláquez-Quintana, M. A. Macías-Islas, V. Rivera-Olmos, and J. Lozano-Zárate, "Multiple sclerosis in Mexico: a multicentre study," *Revista de Neurologia*, vol. 36, pp. 1019–1022, 2003.

[6] A. Carrá, M. Á. Macías-Islas, A. A. Gabbai et al., "Optimizing outcomes in multiple sclerosis: consensus guidelines for the diagnosis and treatment of multiple sclerosis in Latin America," *Therapeutic Advances in Neurological Disorders*, vol. 4, no. 6, pp. 349–360, 2011.

[7] V. M. Rivera, "Multiple sclerosis in Latin America: reality and challenge," *Neuroepidemiology*, vol. 32, no. 4, pp. 294-295, 2009.

[8] M. S. Hinojosa, B. Zsembik, and M. R. Rittman, "Patterns of informal care among Puerto Rican, African American and white stroke survivors," *Ethnicity & Health*, vol. 14, pp. 591–606, 2009.

[9] M. C. Zea, T. Quezada, and F. Belgrave, "Cultural values and adjustment to disability among Latinos," *Journal of Social Behavior and Personality*, vol. 199, no. 9, pp. 185–200, 1994.

[10] P. Dilworth-Anderson, I. C. Williams, and B. E. Gibson, "Issues of race, ethnicity, and culture in caregiving research: A 20-Year Review (1980–2000)," *The Gerontologist*, vol. 42, pp. 237–272, 2002.

[11] M. Pinquart and S. Sörenson, "Ethnic differences in stressors, resources, and psychological outcomes of family caregiving: a meta-analysis," *The Gerontologist*, vol. 45, no. 1, pp. 90–106, 2005.

[12] C. Cox and A. Monk, "Strain among caregivers: comparing the experiences of African American and Hispanic caregivers of Alzheimer's relatives," *The International Journal of Aging and Human Development*, vol. 43, no. 2, pp. 93–105, 1996.

[13] K. E. Covinsky, R. Newcomer, P. Fox et al., "Patient and caregiver characteristics associated with depression in caregivers of patients with dementia," *Journal of General Internal Medicine*, vol. 18, no. 12, pp. 1006–1014, 2003.

[14] J. C. Arango-Lasprilla, P. Premuda, A. Aguayo, K. Francis, M. A. Macias, and T. Villaseñor, "Needs and psychosocial outcomes of caregivers of individuals with multiple sclerosis in Guadalajara, Mexico," *International Journal of MS Care*, vol. 12, no. 2, pp. 71–80, 2010.

[15] T. Lehan, J. C. Arango-Lasprilla, M. Á. Macias, A. Aguayo, and T. Villaseñor, "Distress associated with patients' symptoms and depression in a sample of Mexican caregivers of individuals with MS," *Rehabilitation Psychology*, vol. 57, no. 4, pp. 301–307, 2012.

[16] M. Buhse, "Assessment of caregiver burden in families of persons with multiple sclerosis," *Journal of Neuroscience Nursing*, vol. 40, no. 1, pp. 25–31, 2008.

[17] K. I. Pakenham, "Couple coping and adjustment to multiple sclerosis in care receiver-carer dyads," *Family Relations*, vol. 47, no. 3, pp. 269–277, 1998.

[18] Y. Akkus, "Multiple sclerosis patient caregivers: the relationship between their psychological and social needs and burden levels," *Disability and Rehabilitation*, vol. 33, no. 4, pp. 326–333, 2011.

[19] K. J. Aronson, G. Cleghorn, and E. Goldenberg, "Assistance arrangements and use of services among persons with multiple sclerosis and their caregivers," *Disability and Rehabilitation*, vol. 18, no. 7, pp. 354–361, 1996.

[20] M. Finlayson and C. Cho, "A descriptive profile of caregivers of older adults with MS and the assistance they provide," *Disability and Rehabilitation*, vol. 30, no. 24, pp. 1848–1857, 2008.

[21] K. M. Myhr, T. Riise, C. Vedeler et al., "Disability and prognosis in multiple sclerosis: demographic and clinical variables important for the ability to walk and awarding of disability pension," *Multiple Sclerosis Journal*, vol. 7, no. 1, pp. 59–65, 2001.

[22] S. Y. Chipchase and N. B. Lincoln, "Factors associated with carer strain in carers of people with multiple sclerosis," *Disability and Rehabilitation*, vol. 23, pp. 768–776, 2001.

[23] J. Dunn, "Impact of mobility impairment on the burden of caregiving in individuals with multiple sclerosis," *Expert Review of Pharmaeconomics & Outcomes Research*, vol. 10, pp. 433–440, 2010.

[24] M. Figved, K. Myhr, J. Larsen, and D. Aarsland, "Caregiver burden in multiple sclerosis: the impact of neuropsychiatric symptoms," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 78, pp. 1097–1102, 2007.

[25] F. Khan, J. Pallant, and C. Brand, "Caregiver strain and factors associated with caregiver self-efficacy and quality of life in a community cohort with multiple sclerosis," *Disability and Rehabilitation*, vol. 29, no. 16, pp. 1241–1250, 2007.

[26] R. G. Knight, R. C. Devereux, and H. P. Godfrey, "Psychosocial consequences of caring for a spouse with multiple sclerosis," *Journal of Clinical and Experimental Neuropsychology*, vol. 19, pp. 7–19, 1997.

[27] K. I. Pakenham, "Relations between coping and positive and negative outcomes in carers of persons with multiple sclerosis (MS)," *Journal of Clinical Psychology in Medical Settings*, vol. 12, no. 1, pp. 25–38, 2005.

[28] L. I. Pearlin, J. T. Mullan, S. J. Semple, and M. Skaff, "Caregiving and the stress process: an overview of concepts and their measures," *The Gerontologist*, vol. 30, no. 5, pp. 583–594, 1990.

[29] D. W. Chapman and J. F. Carter, "Translation procedures for the cross cultural use of measurement instruments,"

Educational Evaluation and Policy Analysis, vol. 1, no. 3, pp. 71–76, 1979.

[30] F. Guillemin, C. Bombardier, and D. Beaton, "Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines," *Journal of Clinical Epidemiology*, vol. 46, no. 12, pp. 1417–1432, 1993.

[31] M. Schiaffino and R. Espiritu Santo, "Mexico approves an increase to the minimum wage for 2014 for geographic zones "A" and "B"," August 2015, http://www.littler.com/files/press/pdf/2014_1_Mexico_Approves_Increase_Minimum_Wage_2014_Geographic_Zones_A_B_.pdf.

[32] C. D. Spielberger, R. L. Gorsuch, R. E. Lushene, R. E. Vagg, and G. A. Jacobs, *Manual for the State-Trait Anxiety Inventory (STAI)*, Consulting Psychologists Press, Palo Alto, CA, USA, 1983.

[33] C. D. Spielberger, "State-trait anxiety inventory," in *Corsini Encyclopedia of Psychology*, I. B. Weiner and W. E. Craighead, Eds., p. 1, Wiley, New York, NY, USA, 4th edition, 2010.

[34] C. D. Spielberger and R. Diaz-Guerrero, *IDARE, Inventario de ansiedad*, Rasgo-Estado [State-Trait Anxiety Inventory], Mexico: El Manual Moderno, S.A, 1975.

[35] D. M. Novy, D. V. Nelson, K. G. Smith, P. A. Rogers, and R. D. Rowzee, "Psychometric comparability of the English-and Spanish-language versions of the state-trait anxiety inventory," *Hispanic Journal of Behavioral Sciences*, vol. 17, no. 2, pp. 209–224, 1995.

[36] B. Virella, C. Arbona, and D. M. Novy, "Psychometric properties and factor structure of the Spanish version of the state-trait anxiety inventory," *Journal of Personality Assessment*, vol. 63, no. 3, pp. 401–412, 1994.

[37] S. H. Zarit, K. E. Reever, and J. Bach-Peterson, "Relatives of the impaired elderly: correlates of feelings of burden," *The Gerontologist*, vol. 20, no. 6, pp. 649–655, 1980.

[38] G. Karlikaya, G. Yukse, F. Varlibas, and H. Tireli, "Caregiver burden in dementia: a study in the Turkish population," *The Internet Journal of Neurology*, vol. 4, pp. 12–26, 2005.

[39] R. Siegert, D. M. Jackson, A. Tennant, and L. Turner-Stokes, "Factor analysis and Rasch analysis of the Zarit burden interview for acquired brain injury carer research," *Journal of Rehabilitation Medicine*, vol. 42, no. 4, pp. 302–309, 2010.

[40] P. Martínez-Martín, M. J. Forjaz, B. Frades-Payo et al., "Caregiver burden in Parkinson's disease," *Movement Disorders*, vol. 22, no. 7, pp. 924–931, 2007.

[41] M. Martín-Carrasco, I. Salvadó, S. Nadal et al., "Adaptación para nuestro medio de la Escala de Sobrecarga del Cuidador (Caregiver Burden Interview) de Zarit," *Review of Gerontology*, vol. 6, pp. 338–346, 1996.

[42] K. Kroenke, R. L. Spitzer, and J. B. W. Williams, "The PHQ-9: validity of a brief depression severity measure," *Journal of General Internal Medicine*, vol. 16, no. 9, pp. 606–613, 2001.

[43] C. Diez-Quevedo, T. Rangil, L. Sanchez-Planell, K. Kroenke, and R. L. Spitzer, "Validation and utility of the patient health questionnaire in diagnosing mental disorders in 1003 general hospital Spanish inpatients," *Psychosomatic Medicine*, vol. 63, no. 4, pp. 679–686, 2001.

[44] W. Donlan and J. Lee, "Screening for depression among indigenous Mexican migrant farmworkers using the patient health questionnaire-9," *Psychological Reports*, vol. 106, no. 2, pp. 419–432, 2010.

[45] L. W. Wulsin, E. Somoza, and J. Heck, "The feasibility of using the Spanish PHQ-9 to screen for depression in primary care in Honduras," *Primary Care Companion Journal of Clinical Psychiatry*, vol. 4, no. 05, pp. 191–195, 2002.

[46] E. Diener, R. A. Emmons, R. J. Larsen, and S. Griffin, "The satisfaction with life scale," *Journal of Personality Assessment*, vol. 49, no. 1, pp. 71–75, 1985.

[47] W. Pavot and E. Diener, "Review of the satisfaction with life scale," *Psychological Assessment*, vol. 5, no. 2, pp. 164–172, 1993.

[48] F. L. Atienza, D. Pons, I. Balaguer, and M. L. Garcia-Merita, "Satisfaction with life scale: analysis of factorial invariance for adolescents and elderly persons," *Perceptual and Motor Skills*, vol. 91, pp. 62–68, 2000.

[49] C. Vázquez, A. Duque, and G. Hervás, "Satisfaction with life scale in a representative sample of Spanish adults: validation and normative data," *The Spanish Journal of Psychology*, vol. 16, article E82, 2013.

[50] D. Rivera, P. B. Perrin, H. Senra et al., "Development of the family needs assessment tool for caregivers of individuals with neurological conditions in Latin America," *Psicología desde el Caribe*, vol. 3, pp. 1–20, 2013.

[51] J. L. Arbuckle, *Amos 20 User's Guide*, SPSS, Chicago, IL, USA, 2011.

[52] R. Weston, P. Gore, F. Chan, and D. Catalano, "An introduction to using structural equation models in rehabilitation psychology," *Rehabilitation Psychology*, vol. 53, pp. 340–356, 2009.

[53] K. I. Pakenham and S. Cox, "Development of the benefit finding in multiple sclerosis (MS) caregiving scale: a longitudinal study of relations between benefit finding and adjustment," *British Journal of Health Psychology*, vol. 13, no. 4, pp. 583–602, 2008.

[54] H. Carton, R. Loos, J. Pacolet, K. Versieck, and R. Vlietnck, "A quantitative study of unpaid caregiving in multiple sclerosis," *Multiple Sclerosis*, vol. 6, no. 4, pp. 274–279, 2000.

[55] M. Corry and A. While, "The needs of carers of people with multiple sclerosis: a literature review," *Scandinavian Journal of Caring Sciences*, vol. 23, no. 3, pp. 569–588, 2009.

[56] L. J. Kristjanson, S. M. Aoun, and L. Oldham, "Palliative care and support for people with neurodegenerative conditions and their carers," *International Journal of Palliative Nursing*, vol. 12, pp. 368–377, 2005.

[57] K. I. Pakenham, "The nature of caregiving in multiple sclerosis: development of the caregiving tasks in multiple sclerosis scale," *Multiple Sclerosis Journal*, vol. 13, no. 7, pp. 929–938, 2007.

[58] N. Beinart, J. Weinman, D. Wade, and R. Brady, "Caregiver burden and psychoeducational interventions in Alzheimer's disease: a review," *Dementia and Geriatric Cognitive Disorders Extra*, vol. 2, no. 1, pp. 638–648, 2012.

[59] M. Martín-Carrasco, M. F. Martín, C. P. Valero et al., "Effectiveness of a psychoeducational intervention program in the reduction of caregiver burden in Alzheimer's disease patients' caregivers," *International Journal of Geriatric Psychiatry*, vol. 24, no. 5, pp. 489–499, 2009.

[60] M. Y. Savundranayagam, R. J. Montgomery, K. Kosloski, and T. D. Little, "Impact of a psychoeducational program on the three types of caregiver burden among spouses," *International Journal of Geriatric Psychiatry*, vol. 26, pp. 338–396, 2011.

[61] L. N. Gitlin, S. H. Belle, L. D. Burgio et al., "Effect of multicomponent interventions on caregiver burden and depression: the

REACH multisite initiative at 6-month follow-up," *Psychology and Aging*, vol. 18, pp. 361–374, 2003.

[62] M. E. Medina-Mora, G. Borges, C. Benjet, C. Lara, and P. Berglund, "Psychiatric disorders in Mexico: lifetime prevalence in a nationally representative sample," *The British Journal of Psychiatry*, vol. 190, pp. 521–528, 2007.

[63] A. A. Argyriou, P. Karanasios, A. A. Ifanti et al., "Quality of life and emotional burden of primary caregivers: a case-control study of multiple sclerosis patients in Greece," *Quality of Life Research*, vol. 20, no. 10, pp. 1663–1668, 2011.

[64] R. Buchanan and C. Huang, "Informal caregivers assisting people with multiple sclerosis: factors associated with the strength of the caregiver/care recipient relationship," *International Journal of MS Care*, vol. 13, no. 4, pp. 177–187, 2011.

[65] M. N. Mickens, *Todo en la familia: Examining the Relationships Among MS Impairments, Family Needs, and Caregiver Mental Health in Guadalajara, Mexico, [Ph.D. thesis]*, Virginia Commonwealth University, Richmond, VA, USA, 2014.

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Research Article

Efficacy of a Computer-Assisted Cognitive Rehabilitation Intervention in Relapsing-Remitting Multiple Sclerosis Patients: A Multicenter Randomized Controlled Trial

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Cognitive impairment is frequently encountered in multiple sclerosis (MS) affecting between 40–65% of individuals, irrespective of disease duration and severity of physical disability. In the present multicenter randomized controlled trial, fifty-eight clinically stable RRMS patients with mild to moderate cognitive impairment and relatively low disability status were randomized to receive either computer-assisted (RehaCom) functional cognitive training with an emphasis on episodic memory, information processing speed/attention, and executive functions for 10 weeks (IG; $n = 32$) or standard clinical care (CG; $n = 26$). Outcome measures included a flexible comprehensive neuropsychological battery of tests sensitive to MS patient deficits and feedback regarding personal benefit gained from the intervention on four verbal questions. Only the IG group showed significant improvements in verbal and visuospatial episodic memory, processing speed/attention, and executive functioning from pre - to postassessment. Moreover, the improvement obtained on attention was retained over 6 months providing evidence on the long-term benefits of this intervention. Group by time interactions revealed significant improvements in composite cognitive domain scores in the IG relative to the demographically and clinically matched CG for verbal episodic memory, processing speed, verbal fluency, and attention. Treated patients rated the intervention positively and were more confident about their cognitive abilities following treatment.

1. Introduction

Cognitive impairment is frequently encountered in multiple sclerosis (MS) affecting between 40–65% of individuals, irrespective of disease duration, severity of physical disability, and at both the earlier and later disease stages [1, 2]. Moreover, cognitive dysfunction in this population may have a significant negative impact on quality of life [3], activities of daily living and independence [4], and employment status [5]. Furthermore, past and current pharmacological

treatments have shown inconsistent findings in alleviating cognitive impairment in individuals with MS requiring further clarification [6]. This inconsistency regarding the effects of pharmacological interventions on cognition, coupled with the reduced ability to effectively handle everyday tasks, loss of employment and social interaction capacity, and overall poorer quality of life prioritizes the need for utilizing potentially more effective nonpharmacological, neurobehavioural interventions to address cognitive dysfunction and everyday functioning abilities.

Neurobehavioral interventions utilizing cognitive rehabilitation have shown favorable effects on MS patients' cognitive performance and other related skills and, in some cases, have managed to generalize these positive effects to an MS individual's everyday life functioning ability [7–10]. While as described previously, there is evidence to support cognitive rehabilitation interventions in the MS population, the results of past and present clinical trials have been marred by numerous methodological limitations. These include lack of appropriate control groups and objective neuropsychological status assessment at baseline, utilization of inappropriate randomization methods, single-site studies, and inconsistency regarding the specific target of the rehabilitation intervention and outcome measures (especially as regards the use of ecologically valid interventions and measures) [11]. Therefore, it becomes obvious that there is a need for rigorous new cognitive rehabilitation studies that may overcome some of these limitations and provide robust evidence regarding the efficiency of such interventions.

The purpose of this study was to investigate the effectiveness of a 10 week (2 days a week for approximately 60 minutes) computer-assisted cognitive rehabilitation intervention, utilizing the RehaCom® software (RehaCom Cognitive Therapy Software. https://www.rehacom.co.uk) on cognitive functioning in Greek relapsing-remitting MS (RRMS) patients, who on baseline assessment had mild to moderate cognitive impairments. We hypothesized that patients (IG) receiving the individualized 10-week intervention will show improved pre- to postintervention performance on neuropsychological measures in the related trained cognitive domains relative to control group (CG) participants who will receive only usual-standard clinical care. Moreover, we hypothesized that the positive training effects on specific cognitive domains (episodic memory, information processing speed/attention and executive functions) would be retained over time (6 months in this case) providing evidence on the long-term benefits of such interventions. We also hypothesized that control participants will show either further cognitive decline or remain cognitively stable as the period of the intervention may be inadequate to produce significant cognitive changes in these patients.

2. Methods

2.1. Participants. Between March of 2014 and December of 2015, 98 patients who had been previously diagnosed with relapsing-remitting MS (RRMS) based on the McDonald criteria [12], attending either the outpatient neurology department at the University Hospital of Patras in Greece or the "Society of friends of patients with multiple sclerosis" situated in Ioannina, and who reported cognitive difficulties or were judged by clinical neurological evaluation to have cognitive deficits were referred for neuropsychological assessment at the outpatient memory and neuropsychological unit of the same hospital or the laboratory of audiology, neurotology, and neurosciences of the Higher Educational Institute of Epirus, Ioannina, Department of Speech and Language Therapy. Clinicians assessing patients at both sites were supervised by the clinical neuropsychologist (LM) and lead consulting neurologists (PP) in Patras and (GN) in Ioannina.

Of the 98 patients initially screened, fifty-eight were included in the study after meeting specific inclusion criteria. These patients were randomly assigned to either receive treatment with the RehaCom software (IG; $n = 32$) or placed in the control group condition (CG; $n = 26$) and received usual-standard clinical care. Demographic and clinical characteristics of both groups at baseline are provided in Table 1.

All patients met the criteria for the diagnosis of MS according to [12]. Additional study inclusion criteria were (i) patients aged between 21 and 60, (ii) educational level of at least 6 years (primary school graduates in Greece), (iii) relapsing-remitting MS (RRMS), (iv) EDSS score of between 0–5, (v) cognitive deficit on at least one domain of the Central Nervous System Vital Sign neuropsychological screening battery [13], (vi) native Greek speakers, (vii) provision of written informed consent to take part in the study, and (viii) IQ score of ≥80 on the Greek-validated Wechsler Abbreviated Scale of Intelligence (WASI) [14]. Exclusion criteria were as follows: (i) ongoing major psychiatric disorders (e.g., psychotic symptoms or disorders, illegal drugs, or alcohol abuse); (ii) presence of another neurological disorder (e.g., dementia, stroke, epilepsy, and traumatic brain injury resulting in a loss of consciousness for more than 30 minutes); (iii) Mini-Mental State Examination score MMSE ≥ 24; (iv) one or more exacerbations in the 3 months prior to enrollment and immunological or immunosuppressant treatment initiated within 4 months prior to enrollment or treated with cognitive rehabilitation in the 12 months prior to enrollment; (v) initiation of psychotropic medications or medications for spasticity, tremor, bladder disturbances, and fatigue, if already taking such medications, doses and schedules had to be held constant during the study period; and (vi) normal or corrected hearing and vision.

2.2. Procedure. After been initially evaluated on a brief screening neuropsychological battery (Central Nervous System Vital Signs—CNSVS [13, 15]), patients with a diagnosis of RRMS that were found to have cognitive deficits on at least one domain of the CNSVS (performance between the 2nd and 8th percentile based on CNSVS demographically corrected normative data) were informed of the opportunity to participate in a 10-week cognitive rehabilitation intervention by the lead consulting neurologists (PP) and (GN) or clinical neuropsychologist (LM) supervising the

Table 1: Demographic and clinical characteristics of the sample at baseline.

	MS RehaCom group ($n = 32$) Mean (95% CI) n (%)	SD	MS control group ($n = 26$) Mean (95% CI) n (%)	SD	t/U x^2	df	p
Age (years)	46.03 (43.16–48.90)	7.97	45.15 (41.26–49.05)	9.65	0.379	56	0.706
Education (years)	12.12 (10.87–13.38)	3.47	12.73 (11.46–14.01)	3.15	−0.945		0.345
Gender							
Males	10 (31.25)		8 (30.76)				
Females	22 (68.75)		18 (69.24)		0.002	1	0.969
EDSS-median (range)	3.0 (1.5–5.5)		3.5 (1.0–5.0)		−0.126		0.899
Disease duration (years)	13.31 (11.46–15.17)		11.27 (9.39–13.14)		−1.515		0.130
MMSE	27.97 (27.54–28.39)	1.17	28.42 (28.06–28.79)	0.90	−1.578		0.115
WASI (IQ)	102.31 (99.49–105.14)	7.83	103.96 (100.37–107.55)	8.89	−.959		0.338
Premorbid intelligence							
WASI (Voc)			46.2		−0.785		0.680
T-score	45.5						
Fatigue (FSS)	4.38 (4.04–4.48)	1.80	4.35 (3.98–4.55)	1.75	−0.297		0.486
BDI-FS	4.31 (3.31–5.32)	2.78	4.46 (3.01–5.91)	3.09	0.178	56	0.859
Medication at enrolment							
Interferon	25 (78.12)		17 (65.38)				
Fingolimod	2 (6.25)		3 (11.53)				
Natalizumab	5 (15.63)		6 (23.07)				

Notes: All values are raw scores. EDSS: Expanded Disability Status Scale; MMSE: Mini Mental State Examination; WASI: Wechsler Abbreviated Scale of Intelligence; WASI (VOC): vocabulary subscale of the Wechsler Abbreviated Scale of Intelligence; FSS: Fatigue Severity Scale; BDI-FS: Beck Depression Inventory-Fast Screen; SD; standard deviation; CI: confidence interval; df: degrees of freedom; t: independent sample t-test; U: Mann–Whitney U test; x^2; chi-squared.

study and were invited to take part after providing written informed consent.

In order to overcome the limitations of recruiting patients from only one site, Southwestern Greece in this particular case, and to provide a more representative sample of MS patients, RRMS patients included in the intervention protocol, as mentioned previously, were also recruited from a second site, the national Society of MS attendees in Northwestern Greece known as the "Society of friends of patients with multiple sclerosis" situated in Ioannina, by following the exact same protocol as the patients recruited from Southwestern Greece. Eligible patients were randomized by a computer -generated, site-stratified, independent randomization schedule to either undergo cognitive rehabilitation (IG; intervention group) with the RehaCom software or were placed in the placebo arm (CG; control group) and spent the same portion of time (10 weeks) receiving usual clinical care. Before initiating the intervention (pretreatment), patients in both groups were administered a flexible battery of neuropsychological tests and measures of mood. Both groups were then evaluated within one week after completing the intervention (posttreatment), and the RehaCom-treated group was also evaluated at a six month follow-up (see Figure 1). All patients were noncompensated volunteers.

In both settings, qualified clinicians which had previously attended training sessions in order to ensure uniform test administration and application of the rehabilitation intervention, following a strict protocol, and under the supervision of an experienced clinical neuropsychologist (LM) administered the screening CNSVS battery and the flexible comprehensive neuropsychological battery of tests with well-validated psychometric properties in MS individuals and all other measures (excluding the EDSS scale which measures disability and was administered by specialist neurologists) at all the evaluation stages. Moreover, they conducted the rehabilitation interventions for the entire 10-week duration. The participants and clinicians taking part in the assessments and intervention were not blind to the allocated treatments. However, scoring of neuropsychological measures at baseline, posttreatment, and at 6-month follow-up was performed by two blinded observers, in order to avoid interrater variability.

Thirty-two participants diagnosed with RRMS completed the intervention, whereas twenty-six were included in the control group and received usual-standard clinical care for the entire 10 weeks as mentioned previously. Six months following the intervention and continuing with usual clinical care for this time period, only patients that had undergone cognitive rehabilitation were evaluated neuropsychologically in a follow-up session in order to establish the effects of the intervention over time. Furthermore, although no formal posttreatment or follow-up questionnaire was used as an outcome measure to determine the personal benefit of each patient gained from the intervention, we informally asked treated patients to provide feedback regarding the intervention on four verbal questions at posttreatment assessment.

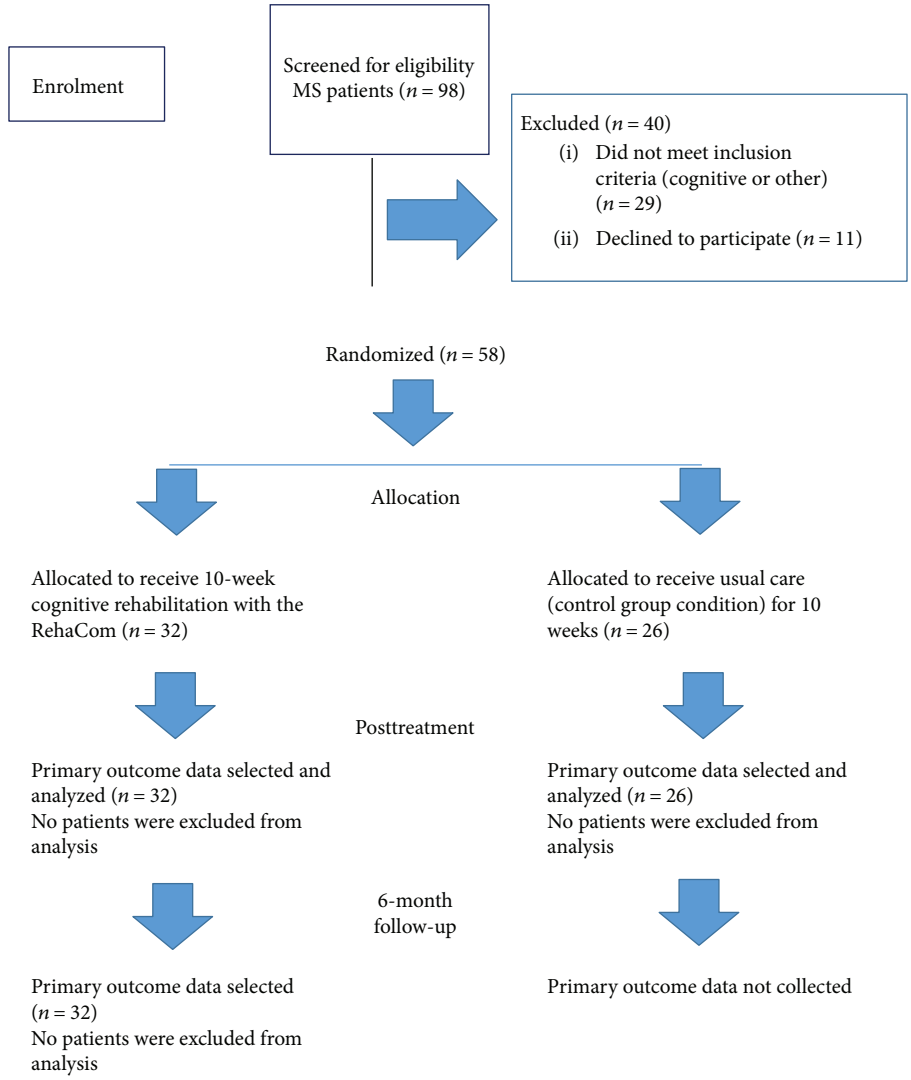

Figure 1: Consort flow diagram.

The questions were (i) how much have you personally benefited from this type of treatment? (ii) have your cognitive difficulties improved after the program? (iii) has this program helped you to improve your everyday life activities (e.g., can you now remember more items of a shopping list without writing down the list or do you now need less time to complete mental tasks or plan a trip)? and (iv) would you recommend this intervention to other MS patients? Patients had to rate their response on a Likert-type Scale ranging from 1–5, where 1 was indicative of no benefit, 2 (minor benefit), 3 (medium benefit), 4 (moderate benefit), and 5 (large benefit). Patients assigned to the control condition were for ethical reasons provided the opportunity to participate in a cognitive rehabilitation intervention similar to the one utilized in this study once they completed the research protocol. The research protocol was approved by the ethics committee of the University of Patras Medical School and was conducted in accordance with the principles of the Declaration of Helsinki (WMA, 2013). Patients recruited from both sites provided written informed consent to take part in the study.

2.3. Instruments: Outcome Assessment

2.3.1. Clinical Assessment. Clinical characteristics of MS patients were assessed by specialist neurologists with significant experience in the MS population. These neurologists provided the diagnosis of MS based on the [12] criteria, type of disease course, disability rating on the EDSS scale [15], fatigue rating on the Greek-validated Fatigue Severity Scale (FSS) [16], types of medications patients were taking, duration of illness, and differential diagnostic issues and also screened patients to ensure eligibility of inclusion and exclusion criteria (with the exception of cognitive criteria and mood). If deemed necessary, patients were also assessed psychiatrically to ensure correct differential diagnosis of behavioral and mood disorders and to exclude patients with ongoing major psychiatric disorders.

2.3.2. Initial Screening Assessment of Cognitive Functions and Intelligence Level. As noted previously, all MS patients that were referred for neuropsychological assessment were initially screened on a brief neuropsychological battery (Central

Nervous System Vital Signs—CNSVS [12]) in order to evaluate their cognitive status and to determine whether they had impaired cognitive performance (one of the study inclusion criteria) on any of the CNSVS-tested domains defined as performance between the 2nd and 8th percentile based on demographically corrected normative data. The CNSVS battery provides core neuropsychological assessment utilizing seven neuropsychological tests [12]. These include the Verbal and Visual Memory Test, Finger Tapping Test, Symbol Digit Coding Test, Stroop Test, Shifting Attention Test, and Continuous Performance Test.

Intelligence level of MS patients at this stage was also estimated by administering the vocabulary and matrix reasoning subscales of the Greek-adapted version of the Wechsler Abbreviated Scale of intelligence WASI [14, 17]. The vocabulary subscale is a good measure of crystallized intelligence, correlates well with general intellectual ability, and is relatively insensitive to cortical insults (i.e., considered a good measure of premorbid intellectual ability). For this reason, the demographically corrected *T*-score of the vocabulary scale was used as an estimate of premorbid intelligence level in this study. The Matrix Reasoning subscale is a measure of nonverbal fluid reasoning and correlates well with general intellectual ability. These two subscales yield an estimated full-scale IQ.

At this screening stage, patients were further administered the Greek-validated version of the Mini-Mental State Examination (MMSE) [18]. The MMSE assesses a restricted set of cognitive functions simply and quickly and is utilized as a dementia-screening measure in everyday clinical practice. Recently, Solias et al. [19] provided MMSE "cutoff scores" for discriminating demented patients in Greece based on age- and education-corrected norms. An MMSE score of ≥24 was one of the stipulated study inclusion criteria.

2.3.3. Neuropsychological Assessment. Both groups of patients were administered a comprehensive flexible battery of neuropsychological tests at baseline and within one week of completing the RehaCom treatment phase. The RehaCom-treated group was also assessed 6 months following the completion of the rehabilitation intervention after receiving only the usual clinical care for this period. The main criterion for selecting the cognitive measures to be utilized in this study were their use specifically for this population in routine clinical care and for research purposes, see for example [20–23]. Moreover, the selected cognitive measures assess domains that are normally impaired in MS individuals, independent of disease duration and disability status. This included tests of attention, mental processing speed, verbal fluency/language, verbal and visuospatial memory, and executive functions. All neuropsychological tests were administered using standard procedures in single sessions. To minimize retest effects, alternative forms of the tests were used when available. Table 2 provides a summary of the utilized neuropsychological test battery arranged by cognitive function/domain assessed.

2.3.4. Assessment of Mood. The Beck Depression Inventory-Fast Screen for Medical Patients (BDI-Fast Screen) [31, 32] was administered in order to assess the severity of depression. The BDI-Fast Screen is a 7-item self-report case-finding instrument that screens for severity of depression that corresponds to the psychological or nonsomatic criteria for diagnosing major depression disorders as listed in the DSM-IV [33] in adults and adolescents. It consists of seven items extracted from the 21-item Beck Depression Inventory-II [34]. The administration procedure used was the one suggested by Beck et al. and Strauss et al. [31, 35], using a Greek-translated and adapted version [32], with Cronbach's internal reliability coefficient ($a = 0.82$). The dependent variable in this study included the sum of the highest ratings for each of the seven items (maximum score = 21). The BDI-Fast Screen has been validated in multiple sclerosis patients [36]. More specifically, it discriminated individuals with MS that were receiving treatment for depression from untreated MS patients with neurological symptoms. Moreover, the authors with their findings support its concurrent and discriminative validity in the MS population [36].

2.3.5. Assessment of Fatigue. Fatigue was assessed with the Fatigue Severity Scale (FSS), a 9-item self-assessment scale [37]. The scale was recently adapted and validated in Greek MS patients and found to be reliable and valid for this population [16]. Respondents indicate the fatigue level they experienced throughout the last two weeks. The questions are related to how fatigue interferes with certain activities and rates its severity. The items are scored on a 7-point scale with 1 = strongly disagree and 7 = strongly agree. The scoring is done by calculating the average response to the questions (adding up all the answers and dividing by nine). The minimum score = 1 and maximum score possible = 7. A higher score is indicative of greater fatigue severity. In a recent validation study by Learmonth et al. [38], a mean FSS score ≥ 4 was indicative of substantial fatigue in 77% of the MS patients.

2.3.6. Treatment Intervention. As noted previously, MS patients that were eligible to take part in the study were randomized to either receive specific-computerized cognitive remediation training-cognitive rehabilitation ($n = 32$), over a period of 10 weeks, with 2 weekly 60-minute sessions on an individual basis or usual clinical care standard treatment ($n = 26$) for the same time period. The study is a multicentric (2 centers), randomized controlled trial investigating the efficacy of cognitive functional training in RRMS patients. This approach aims to improve cognitive functioning by restoring or improving network efficiency in the brain

(1) Treatment Intervention: Computer-Assisted Cognitive Rehabilitation (RehaCom modules). The treatment consisted of 20 individualized one-hour sessions over a 10-week period, with a frequency of two sessions per week. The rehabilitation program was conducted by trained clinicians, either speech and language therapists or psychologists, and supervised by a clinical neuropsychologist (LM), on a desktop computer with a large screen. The computer was connected with a special input panel using the commercially available RehaCom software package (RehaCom Cognitive

Table 2: Comprehensive neuropsychological battery that was administered and arranged by cognitive function/domain assessed.

Cognitive functions/domain assessed	Neuropsychological test used
Verbal memory	Selective Reminding Test (SRT)
Visuospatial memory	Brief Visuospatial Memory Test-Revised (BVMT-R)
Verbal fluency/expressive language	Greek Verbal Fluency Test (phonemic and semantic fluency)
Attention/processing speed	Symbol Digit Modalities Test (SDMT) Trail Making Test Part A
Executive functions	Response inhibition Stroop Neuropsychological Screening Test (SNST)-(colour word task) Set-shifting Trail Making Test Part B (TMT-B)

Note: All measures utilized in the study have been adapted for native Greek speaking adults and demographically corrected normative data have been published (with the exception of the BVMT-R that has been adapted in Greece but normative data are not yet available). The BVMT-R and SDMT have been validated in Greek MS patients. SRT: Selective Reminding Test [24] normative study; BVMT-R: Brief Visuospatial Memory Test-Revised [25] validated in the Greek BICAMS study; SDMT: Symbol Digit Modalities Test [26] normative study and [25] validated in the Greek BICAMS study; Greek Verbal Fluency Test (phonemic and semantic fluency) [27] normative study; SNST: Stroop Neuropsychological Screening Test [28] normative study; TMT-A and TMT-B: Trail Making Test Parts A and B [29, 30] normative studies.

Therapy Software. https://www.rehacom.co.uk), which has been utilized extensively in Europe over the last couple of years for the purpose of providing computer-assisted cognitive rehabilitation. The panel keyboard that is utilized limits the interference of motor and coordination impairments. Moreover, the software which has over 20 modules is available in many languages, including Greek. In Greece, the software is available commercially at Ostracon. For more details about this product see the Ostracon website at http://ostraconmed.com/ostracon-proionta/gnostiki-apokatastasi/rehacom/gia-ton epaggelmatia/.

It provides the opportunity to train patients on several levels of difficulty and length of sessions, and according to whether the patient succeeds or fails the task, the difficulty levels are automatically adjusted to meet the patient's needs. Once the training is completed, the therapist can review the session from the results screen. The data can be presented in a variety of ways including charts, graphs, and comparisons. The most common format results are level of progression, number of mistakes, and time utilized for each cognitive task. By analyzing the data thoroughly, the therapist is able to identify particular weaknesses of the patient and address this further in the training. For this specific study, as most of our MS patients that took part in the intervention were impaired in more than one cognitive domain but mostly on episodic memory, information processing speed/attention, and executive functions, the intervention was balanced over the 10-week period in order to train all domains equally. A detailed description of the RehaCom modules used in the cognitive rehabilitation intervention is provided in the Appendix.

(2) Control Group: Standard Clinical Care. MS patients that were randomized to receive standard or usual clinical care continued taking their prescribed medication and all other related treatments (e.g. physiotherapy, psychotherapy), and all other clinical or referral services were available to them as usual for the entire 10 weeks that the intervention group received cognitive training. As in the University Hospital of Patras or the laboratory of audiology, neurotology, and neurosciences of the Higher Educational Institute of Epirus, specific interventions for cognitive difficulties in MS patients are not offered on a standard basis, these patients did not receive any specific cognitive rehabilitation for their cognitive problems. This group of patients for ethical reasons was offered the opportunity to undertake cognitive rehabilitation after completion of the study period.

2.4. Statistical Analysis. We initially computed the basic descriptive statistics and the 95% confidence intervals of the demographic (age, education level, gender, and Wechsler Abbreviated Scale of intelligence: full 2 scale IQ and Vocabulary subscale *T*-score), clinical (Expanded Disability Status Scale, Mini-Mental State Examination, Beck Depression Inventory-Fast Screen, duration of illness, medication regimen at enrolment, and Fatigue Severity Scale), and neuropsychological variables (Trail Making Test parts A and B, Selective Reminding Test, Brief Visuospatial Memory Test-Revised, Symbol Digit Modalities Test, Greek Verbal Fluency Test (semantic and phonemic), and Stroop Neuropsychological Screening Test-colour word task). Next, the normality assumption of the data was tested using the Shapiro-Wilk test since it is more powerful than the most commonly used in practice Kolmogorov-Smirnov test [39]. When the hypothesis of normality was rejected, the nonparametric Mann–Whitney *U* test was used to examine the differences between our two groups (intervention and control group); otherwise, the standard independent sample *t*-test was used. For the comparison of dependent populations, the nonparametric Friedman test was used whenever the normality assumptions were rejected and the paired samples *t*-test in all other cases. The Pearson correlation coefficient was used in order to measure correlations between neuropsychological and disease variables, depression, and fatigue. Furthermore, due to the use of multiple cognitive measures to assess cognitive functions, we decided to calculate composite scores and formulate composite variables (cognitive domains) for verbal episodic memory, attention, verbal fluency, and processing speed, by

transforming raw neuropsychological test scores obtained from the neuropsychological assessment to form composite domain z-scores. In order to extract the new composite variables, the internal consistency of these variables was measured using Cronbach's alpha. As the internal consistency of all extracted composite domains was considered acceptable ($\alpha > 0.60$), the new variables were derived as a weighted sum of the z-scores of the initial neuropsychological variables. We also applied a mixed effect ANOVA in order to compare the mean cognitive domain performance difference between the intervention and control group (between subject's factor) and the time points (baseline and posttreatment) that patients were cognitively evaluated (within subject's factor). Moreover, the interaction of these two factors was evaluated by a two-way mixed ANOVA. Statistical analyses were conducted using the statistical package SPSS 22.0 for Windows.

3. Results

3.1. Comparison of Demographic and Clinical Characteristics at Baseline (Pretreatment). In general, there was a higher proportion of females compared to males that took part in the study. The percentage of females was higher in both groups (68.75% for the rehabilitation and 69.23% for the control group), something that was expected due to the higher female to male ratio in the MS population in general. However, the proportion/ratio of females between the two groups was not significantly different, $[x^2(1) = 0.002,\ p = 0.969]$. We then investigated the normality distribution of our data with the *Shapiro-Wilk normality test*. For the variables age and BDI-FS (depression level), the null hypothesis could not be rejected; therefore, we used the parametric independent samples t-test to test group differences on this variable. In contrast for the variable level of education, WASI (full IQ 2 scale; intelligence level), WASI vocabulary scale T-score (estimated premorbid intelligence level), FSS (fatigue severity), EDSS (disability level), MMSE, and duration of illness, we rejected the null hypothesis and used the nonparametric Mann–Whitney U test to compare these variables. We did not find significant differences between the two groups on baseline (pretreatment) assessment for the variables age $[t(56) = 379,\ p = 0.706]$, educational level $[z = -0.945,\ p = 0.345]$, intelligence level (WASI 2 scale full IQ) $[z = -0.959,\ p = 0.338]$, estimated premorbid intelligence (WASI vocabulary scale) $[z = -0.959,\ p = 0.338]$, depression level (BDI-FS) $[t(56) = 0.179,\ p = 0.859]$, fatigue severity level (FSS) $[z = -0.697, p = 0.486]$, $[z = -0.959, p = 0.338]$, disability level (EDSS) $[z = -0.126,\ p = 0.899]$, general cognitive status $[z = -0.1578,\ p = 0.115]$, and duration of illness $[z = -0.1515,\ p = 0.130]$ (see Table 1 for a detailed description of baseline demographic and clinical characteristics). From the above analysis, we conclude that our two groups were well matched on baseline demographic variables and premorbid intelligence level that may significantly influence outcome measures posttreatment. They also did not differ on important disease-related variables such as duration and course (all had a relapsing-remitting course), neurological disability (EDDS scale), depression (BDI-FS), and fatigue (FSS) severity that have also been reported to negatively impact cognitive performance in MS patients.

3.2. Comparison of Neuropsychological Test Scores at Baseline (Pretreatment). We did not find significant differences between the two groups on baseline (pretreatment) assessment for the variables SRTLR $[t(56) = 0.201,\ p = 0.842]$, TMT-B $[t(56) = 0.201,\ p = 0.604]$, VFT (semantic) $[z = -478,\ p = 0.633]$ and phonemic $[z = -0.335,\ p = 0.520]$, SDMT $[z = -0.916,\ p = 0.360]$, and BVMT-R $[z = -0.989,\ p = 0.578]$. On the contrary, patients randomized to the intervention group verbally recalled significantly less words ($M_{\text{intervention group}} = 6.09$ words versus $M_{\text{control group}} = 7.15$ words) after a 20-minute delay period, SRT delay score $[z = -2.289,\ p = 0.022]$, and required significantly longer duration ($M_{\text{intervention group}} = 73.50$ seconds versus $M_{\text{control group}} = 69.27$ seconds) to correctly complete the Trails A test $[z = -2.294,\ p = 0.020]$, relative to the control group. These findings imply that the intervention group was marginally more cognitively impaired at baseline assessment (see Table 3 for raw cognitive test performance scores of both groups at baseline, posttreatment, and at 6-month follow-up).

3.3. Comparison of Neuropsychological Test Performance for the RehaCom MS-Treated Group between Baseline, Posttreatment, and at 6-Month Follow-Up. We found significant time effects for most of our variables from baseline to posttreatment. Post hoc pairwise comparisons showed that the patients who received functional cognitive training had improved cognitive performance between baseline and posttest on the SRTLR (verbal memory, long-term storage) ($p = 0.000$; with a large effect size; $r = 0.539$), SDMT (processing speed, working memory) ($p = 0.000$; with a large effect size; $r = 0.522$), SRTLR (verbal memory, delay recall) ($p = 0.000$; with a medium effect size; $r = 0.481$), BVMT-R (visuospatial memory, total recall) ($p = 0.000$; with a medium effect size; $r = 0.469$), VFT (semantic) ($p = 0.003$; with a medium effect size; $r = 0.417$), TMT-A (attention, processing speed) ($p = 0.000$; with a large effect size; $r = 0.573$), TMT-B (executive function, set shifting) ($p = 0.000$; with a large effect size; $r = 0.506$), and SNST-colour word task (executive function, response inhibition) ($p = 0.000$; with a medium effect size; $r = 0.460$). In contrast to the positive time effects of the intervention shown for most of our variables, cognitive training did not significantly improve phonemic fluency even though patients improved their mean phonemic production rate from $M_{\text{baseline}} = 31.88$ words versus $M_{\text{posttreatment}} = 33.13$ words.

In order to establish whether the treated patients differed in terms of their baseline versus the 6-month follow-up performance, we compared their cognitive measure scores at these time points. The results revealed that treated patients differed significantly on the SRTLTS ($p = 0.000$; with a medium effect size; $r = 0.469$), SRTDR ($p = 0.001$; with a medium effect size; $r = 0.454$), BVMT-R ($p = 0.001$; with a medium effect size; $r = 0.436$), TMT-A ($p = 0.000$; with a large effect size; $r = 0.509$), TMT-B ($p = 0.000$; with a medium effect size; $r = 0.475$), and SNST ($p = 0.000$; with a

Table 3: Performance on neuropsychological measures for the RehaCom and control group at baseline, posttreatment, and at 6-month follow-up.

		MS RehaCom group ($n = 32$) Mean (95% CI)	SD	MS control group ($n = 26$) Mean (95% CI)	SD
SRTLTS	T0	36.72 (34.57–38.86)	5.94	36.42 (34.37–38.48)	5.08
	T1	43.47 (40.55–46.39)	8.09	36.38 (34.34–38.43)	5.06
	T2	43.00 (40.04–45.96)	8.21	—	—
SRTDR	T0	6.09 (5.44–6.75)	1.82	7.15 (6.65–7.66)	1.25
	T1	8.22 (7.59–8.85)	1.75	7.12 (6.73–7.50)	7.12
	T2	7.75 (7.11–8.39)	1.77	—	—
BVMT-RT	T0	21.40 (17.10–24.30)	5.85	22.50 (17.80–25.20)	7.80
	T1	24.50 (19.50–26.30)	6.02	20.80 (17.50–24.60)	6.85
	T2	23.10 (18.90–25.20)	6.40	—	—
VFT phon	T0	31.88 (28.92–34.83)	8.20	29.81 (23.39–30.23)	8.46
	T1	33.13 (30.60–35.65)	7.01	29.95 (24.16–30.53)	7.88
	T2	31.47 (29.20–33.74)	6.29	—	—
VFT sem	T0	41.03 (38.09–43.97)	8.16	40.50 (36.69–44.31)	9.44
	T1	43.56 (40.55–46.57)	8.34	39.58 (35.60–43.55)	9.83
	T2	42.06 (39.05–45.08)	8.35	—	—
SDMT	T0	36.91 (33.89–39.92)	8.36	37.42 (33.03–41.82)	10.87
	T1	40.03 (37.48–42.58)	7.08	37.43 (33.44–41.40)	9.85
	T2	37.50 (35.25–39.75)	6.25	—	—
TMT-A	T0	73.50 (65.08–81.92)	23.35	69.27 (52.05–68.48)	20.30
	T1	59.53 (52.86–66.20)	18.49	68.88 (52.67–69.10)	20.32
	T2	60.31 (53.28–67.34)	19.49	—	—
TMT-B	T0	145. 81 (129.12–162.50)	46.29	111. 54 (96.23–126.84)	37.89
	T1	113.28 (94.72–131.84)	51.47	110.96 (96.18–125.75)	36.60
	T2	115.78 (97.40–134.16)	50.98	—	—
SNST	T0	59.80 (53.30–64.50)	15.50	58.70 (52.60–63.80)	17.30
	T1	63.50 (57.40–68.10)	13.25	57.60 (52.90–62.70)	14.20
	T2	62.10 (56.90–66.20)	14.20	—	—

Notes: All values are raw scores. T0: baseline assessment; T1: posttreatment assessment; T2: 6-month follow-up assessment. MS control group was not assessed at 6-month follow-up. SRTLTS: Selective Reminding Test Long-Term Storage; SRTDR: Selective Reminding Test-Delayed Recall; BVMT-RT: Brief Visuospatial Memory Test-Revised Total Recall; VFT phon: Greek Verbal Fluency Test-Phonemic Fluency; VFT sem: Greek Verbal Fluency Test-Semantic Fluency; SDMT: Symbol Digit Modalities Test; TMT-A and TMT-B: Greek Trail Making Test Part A, Greek Trail Making Test Part B; SNST: Stroop Neuropsychological Screening Test.

medium effect size; $r = 0.448$). On three of our outcome variables, nonsignificant differences were established between baseline and follow-up performance on the VFT (semantic) ($p = 0.424$), phonemic (ns), and SDMT ($p = 0.222$). Although patients improved their mean semantic fluency production rate from $M_{\text{baseline}} = 41.03$ words versus $M_{\text{follow-up}} = 42.06$ words and their mean digit symbol substitution rate in 90 seconds from $M_{\text{baseline}} = 36.91$ correct substitutions versus $M_{\text{follow-up}} = 37.50$ correct substitutions, this was insufficient to produce statistically significant changes. To examine the long-term effect of the intervention over time, we compared cognitive outcome performance between posttreatment and 6 months' follow-up. Our findings showed that for most of our variables, there were nonsignificant differences between the positive cognitive gains found on posttreatment and follow-up. In contrast, the mean semantic fluency production rate was reduced from $M_{\text{posttreatment}} = 43.56$ words versus $M_{\text{follow-up}} = 42.06$ words and mean digit symbol substitution rate in 90 seconds from $M_{\text{posttreatment}} = 40.03$ correct substitutions versus $M_{\text{follow-up}} = 37.50$ correct substitutions, producing statistically significant changes over this time period (see Table 4).

3.4. Comparison of Neuropsychological Test Performance for the MS Standard Care Control Group between Baseline and Posttreatment. Our results revealed that in the majority of measures there we no significant changes between pre- and postassessments. An exception was the performance on the mean phonemic fluency production rate that increased from $M_{\text{baseline}} = 29.81$ words versus $M_{\text{posttreatment}} = 29.95$ words [$z = -2.365$, $p = 0.018$], the mean semantic fluency production rate that decreased from $M_{\text{baseline}} = 40.50$ words versus $M_{\text{posttreatment}} = 39.58$ words [$z = -2.874$, $p = 0.004$], and Trails A completion time that increased from $M_{\text{baseline}} = 60.27$

Table 4: Comparison of neuropsychological test scores for the RehaCom MS-treated group at baseline, posttreatment, and at 6-month follow-up.

	Baseline		Posttreatment		6-month follow-up		Baseline versus posttreatment p values	Effect size (r)	Baseline versus follow-up p values
	Mean	Median	Mean	Median	Mean	Median			
SRTLTS	36.72	36.50	43.47	41.00	43.00	41.00	0.000***	0.539	0.000***
SRTDR	6.09	6.50	8.22	8.00	7.75	7.00	0.000***	0.481	0.001**
BVMT-RT	21.40	21.00	24.50	23.90	23.10	23.00	0.000***	0.469	0.001**
VFT phon	31.88	32.00	33.13	33.50	31.47	31.50	ns	—	ns
VFT sem	41.03	40.00	43.56	42.00	42.06	40.50	0.003**	0.417	0.424
SDMT	36.91	36.00	40.03	39.00	37.50	37.00	0.000***	0.522	0.222
TMT-A	73.50	70.00	59.53	62.50	60.31	66.00	0.000***	0.573	0.000***
TMT-B	145.81	32.50	113.28	106.50	115.78	107.50	0.000***	0.506	0.000***
SNST	59.80	58.50	63.50	62.90	62.10	60.40	0.000***	0.460	0.000***

Notes: All values are raw scores (***$p < .001$ and **$p < .01$). Friedman's nonparametric test used for comparison of medians between baseline, posttreatment, and follow-up. Wilcoxon test with Holm-Bonferroni correction used for pairwise comparisons. Effect size (r) for Wilcoxon test calculated as follows: $r = z/\sqrt{N}$(N = total number of samples); abs (r) 0.1 small size; 0.3 medium size; 0.5 large size; ns: Friedman's test indicated no significant group effect for VFT phon. SRTLTS: Selective Reminding Test Long-Term Storage; SRTDR: Selective Reminding Test-Delayed Recall; BVMT-RT: Brief Visuospatial Memory Test-Revised Total Recall; VFT phon: Greek Verbal Fluency Test-Phonemic Fluency; VFT sem: Greek Verbal Fluency Test-Semantic Fluency; SDMT: Symbol Digit Modalities Test; TMT-A and TMT-B: Greek Trail Making Test Part A and Greek Trail Making Test Part B; SNST: Stroop Neuropsychological Screening Test.

second versus $M_{\text{posttreatment}} = 60.88$ seconds [$z = -2.117$, $p = 0.034$]. These findings although marginally different in some cases produced statistically significant changes over time, albeit mostly with a negative direction. These results imply that this group did not show improvements over time; on the contrary, there were trends of a possible further cognitive decline in the 10-week period between baseline and posttreatment assessments (see Table 5).

3.5. Comparison of Composite Cognitive Domain Performance in the RehaCom Group at Baseline, Posttreatment, and Follow-Up. As is evident from Figure 2, we noted a significant reduction ($p = 0.046$) in processing speed from baseline to posttreatment assessment and a slight nonsignificant increase ($p = 0.067$) from posttreatment to follow-up but without dropping to baseline levels of processing speed capacity. Verbal fluency output on the other hand improved significantly from baseline to posttreatment ($p = 0.034$) but showed significant deterioration from posttreatment to follow-up ($p = 0.020$). Attention which was a composite of timed scored measures showed a significant reduction in completion time from baseline to posttreatment ($p = 0.018$) and remained relatively stable over time from posttreatment to follow-up ($p = 0.290$). Verbal episodic memory which reflects total word learning capacity and delayed recall of words showed a significant increase ($p = 0.002$) from baseline to posttreatment and a nonsignificant decrease ($p = 0.702$) from posttreatment to follow-up, but without dropping to baseline levels.

3.6. Comparison of Composite Cognitive Domain Performance between the RehaCom Intervention and Control Group at Baseline and Posttreatment. As is evident from Figure 3, we found significant composite domain performance differences favoring the intervention group, as an interaction of patient group by time. Specifically, on the verbal episodic memory domain, the rehabilitation group demonstrated a significant increase in the estimated marginal mean over time, indicative of improved encoding, consolidation, acquisition, and delayed recall of verbally learned material, relative to the control group that demonstrated a significant reduction in this domain over the ten-week period. On the attention domain, a composite of timed scored measures and a significant reduction in the estimated marginal mean completion time from baseline to posttreatment were noted, relative to the control group's performance which showed an increase in the estimated marginal mean completion time from pre- to post assessment. A significant reduction was also noted in the estimated marginal mean mental processing speed, from pre- to posttreatment assessment for the intervention group, relative to the control group that demonstrated an increased mental processing speed capacity over this time period. The verbal fluency domain, a composite of phonemic and semantic fluency output, improved significantly for the group that received cognitive treatment, over the 10-week period, from baseline to posttreatment, relative to the control group whose combined fluency output decreased over this time period (see Table 6).

3.7. Relationships between Disease Parameters, Depression and Fatigue Level, and Neuropsychological Performance in MS Patients at Baseline. We found significant negative weak correlations between neurological disability status (EDSS) and performance on the SRTLTS ($r = -0.387$, $p = 0.004$), BVMT-R ($r = 0.305$, $p = 0.010$), and SNST ($r = -0.312$, $p = 0.009$) and between disease duration and SRTLTS ($r = -0.286$, $p = 0.012$). We further established a negative relatively large correlation between disability status (EDSS)

Table 5: Comparison of neuropsychological test scores for the standard care MS control group at baseline and posttreatment.

	Baseline		Posttreatment		Baseline versus posttreatment z-score	p values	Effect size
	Mean	Median	Mean	Median			
SRTLTS	36.42	36.50	36.38	37.00	0.187	0.852	0.026
SRTDR	7.15	7.00	7.12	7.00	0.302	0.763	0.042
BVMT-RT	22.50	22.00	20.80	21.10	0.304	0.675	0.034
VFT phon	29.81	28.00	29.95	28.50	−2.365	0.018*	0.328
VFT sem	40.50	39.50	39.58	38.50	−2.874	0.004**	0.399
SDMT	37.42	38.50	37.43	39.00	−0.069	0.945	0.010
TMT-A	60.27	57.00	60.88	58.50	−2.117	0.034*	0.294
TMT-B	111.54	110.00	110.96	107.50	1.042	0.298	0.144
SNST	58.70	57.40	59.10	57.60	0.348	0.780	0.035

Notes: All values are raw scores. $^{**}p < 0.01$ and $^{*}p < 0.05$. Wilcoxon signed-ranked nonparametric test used for comparison of medians between baseline and posttreatment. SRTLTS: Selective Reminding Test Long-Term Storage; SRTDR: Selective Reminding Test-Delayed Recall; BVMT-RT: Brief Visuospatial Memory Test-Revised Total Recall; VFT phon: Greek Verbal Fluency Test-Phonemic Fluency; VFT sem: Greek Verbal Fluency Test-Semantic Fluency; SDMT: Symbol Digit Modalities Test; TMT-A and TMT-B: Greek Trail Making Test Part A and Greek Trail Making Test Part B; SNST: Stroop Neuropsychological Screening Test.

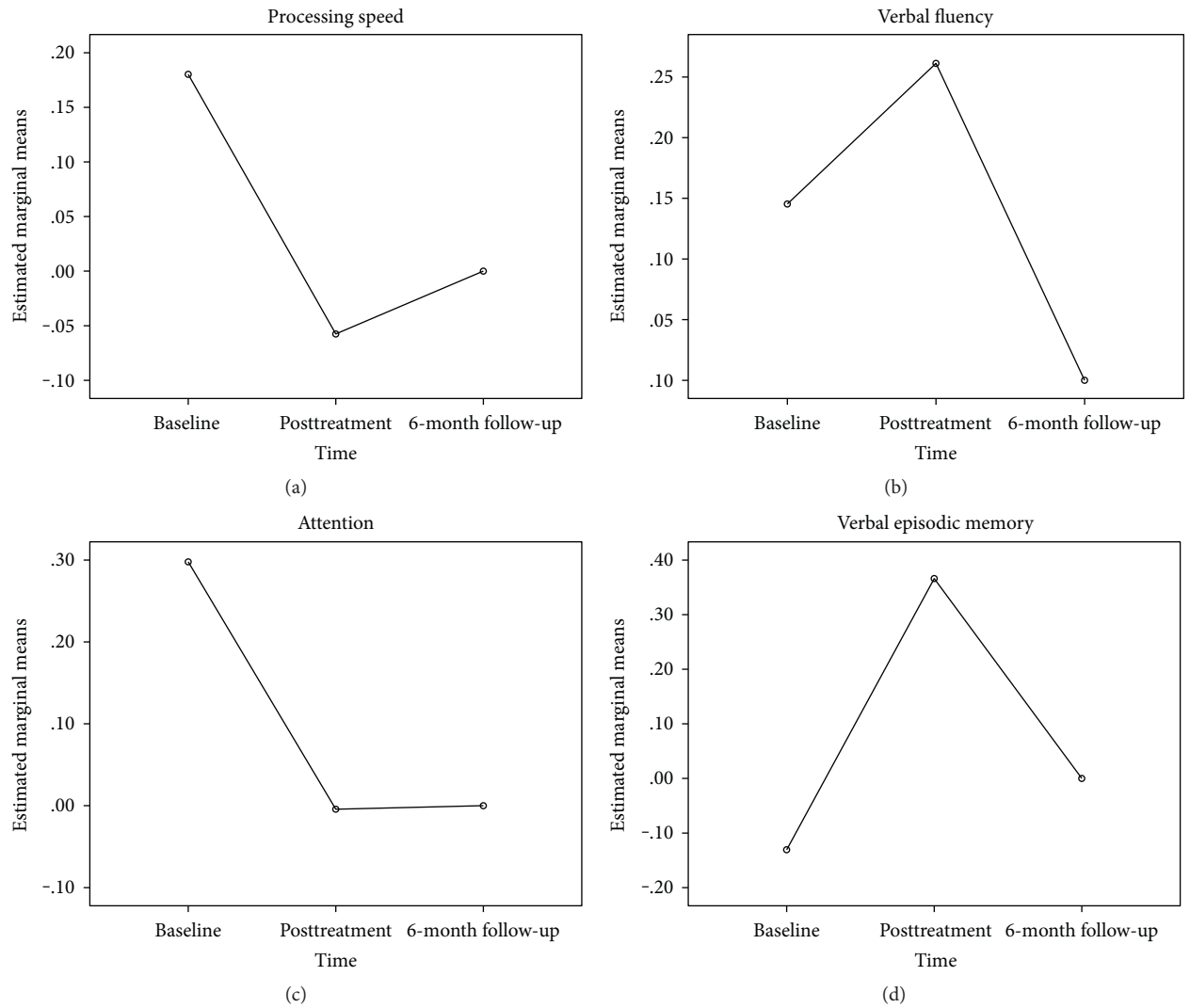

Figure 2: Composite cognitive domain performance (z-scores) in the RehaCom group at baseline, posttreatment, and follow-up.

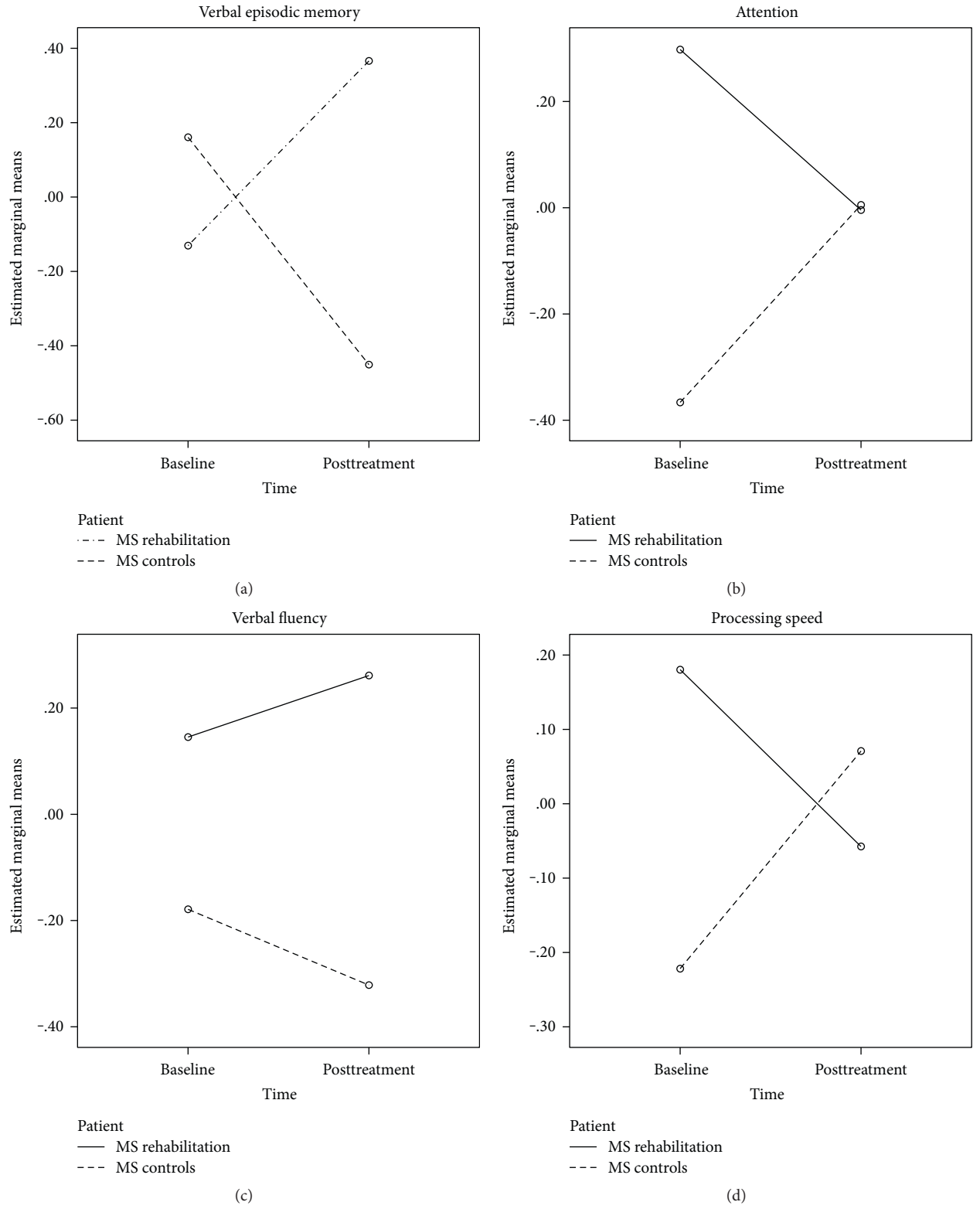

Figure 3: Composite cognitive domain performance (z-scores) in the RehaCom intervention and control group at baseline and posttreatment.

and performance on the SDMT ($r = -0.622$, $p = 0.011$). Depression and fatigue did not correlate significantly with any of the variables. No other significant correlations were noted between any of the variables.

3.8. Satisfaction of Participants Who Completed the Cognitive Rehabilitation Intervention. As mentioned previously in Section 2, we informally asked only cognitively treated patients to provide feedback on a Likert-type Scale ranging

Table 6: Two-way mixed effect ANOVA for cognitive domain performance: time (within subjects' factor) and patient group: (between subjects' factor).

	Verbal episodic memory	Attention	Verbal Fluency	Processing Speed
Time	0.628	0.727	0.767	0.662
Group	0.171	0.099	0.047	0.522
Time × group	<0.001	<0.001	0.006	<0.001

from 1 (no benefit) to 5 (large benefit), regarding the personal benefit gained from the intervention on four verbal questions at the posttreatment assessment. All participants who completed the cognitive rehabilitation intervention in the study (IG group; $n = 32$) also responded to the four verbal questions; 93.7% ($n = 30$) of the participants reported large personal benefits gained from the cognitive intervention, improvement of their cognitive abilities, and further noted that they would recommend the intervention to another MS patient; 87.50% ($n = 28$) of the intervention completers reported that the rehabilitation provided large benefits in terms of everyday life activities. Only a minor proportion of the treated patients, 12.50% ($n = 4$), noted gaining a moderate benefit in everyday life activities from the intervention. Satisfaction of the intervention was also evident by the fact that all 32 participants who were randomly allocated to receive cognitive rehabilitation completed the 10-week duration intervention.

4. Discussion

In the present study, we conducted a 10-week multicenter randomized controlled trial by utilizing therapeutic modules from the RehaCom software in order to restore the most frequent cognitive domains affected in MS patients. Results revealed that the two groups taking part in the study (IG; intervention and CG; control) were well matched at baseline assessment on demographic and clinical characteristics that could negatively impact the outcome measures and made biased the study results. Moreover, patients' medical therapeutic scheme was well balanced between the two groups.

Following treatment, MS patients showed significant improvement on verbal episodic and visuospatial memory, semantic fluency, processing speed/working memory, response inhibition, attention/visuomotor scanning speed, and set-shifting ability. On follow-up assessment, results revealed a significant reduction on semantic verbal fluency and processing speed performance. All other measures remained relatively stable.

When we compared derived-composite cognitive domain scores in the intervention group, our results revealed a significant decrease in processing speed ability from pre- to posttreatment, which was not retained at follow-up, but also did not drop to pretreatment levels of processing speed capacity. Verbal fluency generation improved significantly from before to after treatment, but this gain was not retained to follow-up. The treatment procedure also produced positive changes in the attention domain, with improved performance been evident at posttreatment, and remaining relatively stable over time for six months. Verbal episodic memory delay-recall domain increased after treatment but decreased marginally in the following 6 months without dropping to pretreatment levels. When cognitive domain performance between the RehaCom intervention group and standard treatment control group was compared over time, we noted that the intervention group outperformed the control group on all derived domains from pre- to posttreatment assessment.

Regarding our hypothesis that control participants who receive standard treatment over the 10-week intervention duration will show either further cognitive decline or remain cognitively stable, we found that performance remained relatively stable over this short duration in most measures, possibly implying that the period of the intervention may be inadequate to produce significant cognitive changes in these patients. An exception to this was the score on the semantic fluency task that deteriorated significantly and the time required to complete Trails A, which increased. Moreover, when composite cognitive domain scores were compared from pre- to posttreatment between the two groups, the control group showed reduced performance relevant to the intervention group. These results indicate a possible trend towards further cognitive decline, suggesting that patients on standard available immunomodulatory treatments are possibly not sufficiently protected against ongoing cognitive decline, although other confounding factors such as depression severity or fatigue changes during this period may have also contributed to these findings. However, as our groups were well matched on possible demographic and clinical confounding variables, these findings are less likely to have been biased by such factors.

The positive findings regarding the amelioration of attention, processing speed, and executive function reported in the present study are in concordance with several other studies that have utilized the RehaCom software in cognitively impaired patients with multiple sclerosis. More specifically, Mattioli et al. [40] reported the effectiveness of a 3-month intensive neuropsychological rehabilitation intervention with the assistance of the RehaCom software on attention, information processing, and executive functions. The same group, Mattioli et al. [9] reported that the cognitive benefits experienced by their MS patients after 3 months of intensive neuropsychological rehabilitation with the assistance of the RehaCom software persisted for 9 months after the rehabilitation onset and also generalized to an amelioration of depression and quality of life. In our study, similar long-term benefits of a shorter, however, duration (6 months) were noted in attentional capacity. In addition to their cognitive and behavioral outcome variables, the authors of the previously mentioned studies provide functional MRI data, suggesting that possible neural correlates of the functional cognitive intervention are training-induced activations of the prefrontal and cingulate cortices, brain structures known to be involved in attention and executive functions. The persistence of cognitive gains over the 9-month period made them believe that it may be related to persistent brain plasticity mechanisms [41].

A structural and functional imaging study by Fillipi et al. [42], which evaluated brain changes and neuropsychological functions in RRMS patients after undergoing computer-assisted cognitive rehabilitation of 12-week duration, utilizing the RehaCom software, with an emphasis on attention, information processing, and executive functions, reported similar positive pre- to posttreatment outcomes on the neuropsychological variables to our study. In addition to providing evidence regarding the efficacy of cognitive training with this software on neuropsychological measures, Fillipi et al. [42] also recorded modifications in the activity of the posterior cingulate cortex (PCC) and dorsolateral prefrontal cortex (DLPC) during the Stroop task, as well as modifications of the activity of the anterior cingulum (AC) and PCC at rest, in the RehaCom-treated group. This study showed that functional cognitive training has the potential to modify the activity of trained neuronal system areas in patients with RRMS, and due to its plasticity mechanisms may recruit additional regions to compensate for cognitively demanding tasks.

Other studies utilizing the RehaCom software have placed emphasis on verbal or visual learning and memory with relatively improved pre- to posttreatment performance differences, similar to the findings noted in our study. In one such study [43], utilizing computer-aided (RehaCom modules) of memory and attention, in a randomized, double-blind controlled trial, noted an improvement in 45% of the studied patients receiving treatment, on a word-list generation task. Another study [44], utilizing the RehaCom software, provided computer-assisted cognitive training for 6 weeks (once weekly) and reported significant improvements of autobiographical memory that were associated with increased cerebral activity in posterior cerebral regions. More recently [45], utilizing the RehaCom package and more specifically similar training modules to the ones utilized in the present study (i.e., attention and concentration, divided attention, logical thinking, and verbal memory) found improved cognitive performance after the training on visual and verbal memory and processing speed. These improvements in cognition were associated with increased functional connectivity in the posterior cingulate cortex (PCC) and inferior parietal cortex (IPC) of the default mode network (DMN), implying training-induced adaptive cortical reorganization in the DMN. This network is considered highly relevant for human cognition under physiological conditions and is the most consistent and commonly reported resting-state network in functional MRI studies of functional connectivity (FC) [46].

Most of the studies mentioned previously had no or relatively short follow-up periods ranging from 3 to 9 months after completion of the training intervention. The long-term persistence of a 15-week domain-specific cognitive training intervention with the RehaCom was reported in a recent two-year follow-up study [47]. The authors report that patients treated with specific cognitive modules aimed at ameliorating the related cognitive domains showed significantly less impaired tests both at one and two-year follow-up assessments relative to a specific group (that received generic psychological intervention). These results further strengthen the available evidence regarding the long-term benefits of relatively short duration (15 weeks in this case) domain-specific functional restorative training with the previously mentioned software program.

Other functional neuroimaging studies have revealed changes in brain activation on task-based functional magnetic resonance imaging (fMRI), change in functional connectivity and, for one study, microstructural changes by diffusion tensor imaging after cognitive rehabilitation [48–50]. These results suggest that restorative or functional training could modify brain functioning and improve network efficiency. The characteristics of change in brain activation and connectivity observed after cognitive rehabilitation interventions (homologous region adaptation, local activation expansion, and extraregion recruitment) and the observed association with neuropsychological improvement suggest that adaptive neuroplasticity may occur after restorative training [51].

Regarding the personal benefit gained from the intervention as rated informally on a Likert-type Scale by the treated patients, the majority reported large benefit and were objectively feeling more confident about their cognitive difficulties and everyday functioning ability. Most patients made special reference to their improved concentration and memory capacity and reduced forgetting rate. They generally felt more confident in performing everyday functional tasks and noted appreciable speed ameliorations in performing tasks that require more rapid actions. As the program was very well received from most patients (this is also evident from the fact that there were no dropouts in the treatment group), they said that they would gladly recommend it to other MS patients.

Although our study has several strengths, including its multicenter randomized controlled design, the well-matched baseline clinical, demographic, and cognitive characteristics of the two groups; the strict inclusion criteria; the absence of comorbid conditions that may have biased the study outcome measures; the ecologically valid treatment intervention modules that were utilized from the RehaCom software; and the noninvasive nature of the intervention do have several potential limitations. Firstly, the present study was not blinded.

Secondly, the control group received only standard clinical care, whereas a placebo intervention applied to this group might have restricted the differentiation of the positive cognitive effects caused by the cognitive rehabilitation intervention. Thirdly, depression and fatigue were assessed only at baseline, and we did not ascertain whether our two groups presented a different evolution of these variables over the intervention period. As our study was not blinded and patients receiving the intervention were offered increased attention, clinical care, and individualized contact on a frequent basis, this may have contributed to the treated patients' general well-being and possibly influenced the positive cognitive outcomes in this group. Finally, we did not utilize formal healthy related quality of life or activity of daily living questionnaires as primary outcome measures. However, in order to evaluate the personal benefit of each patient gained from the intervention, we informally asked treated patients to provide feedback regarding the

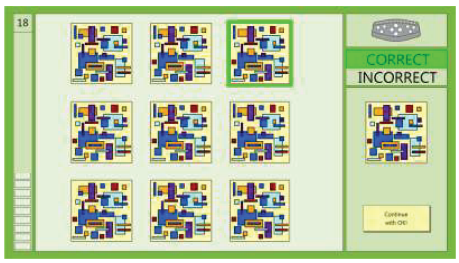

Figure 4: Example of a screen with a 3 by 3 matrix on level 18 of the attention and concentration RehaCom module.

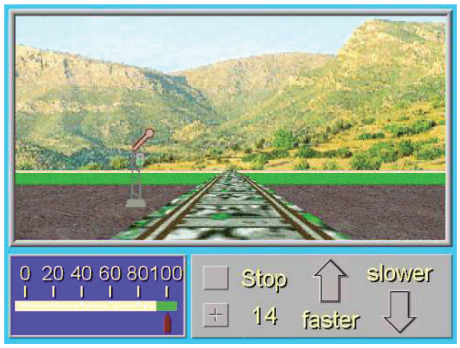

Figure 5: Example of the divided attention task on level 14 of the RehaCom module.

intervention on four verbal questions at the postintervention assessment.

5. Conclusions

In this multicenter randomized controlled trial, we implemented a computer-assisted functional training cognitive rehabilitation intervention of 10-week duration (twice weekly), on cognitively impaired RRMS patients, with low disability status. Our data showed that this relatively short period of domain-specific cognitive training (attention, processing speed, executive functions, and episodic memory) can be helpful in ameliorating the trained functions and that effectiveness persisted at 6-month follow-up for the attention domain. For the other trained domains, performance did not deteriorate to pretreatment levels after 6 months, implying a possible protective long-term effect of the intervention in terms of cognitive deterioration rate. The RehaCom software appears to have sufficient flexibility, dynamics, objectivity, and ecological validity, to make a useful contribution to the clinical practice of cognitive rehabilitation in the MS population. Recent explorative functional neuroimaging studies have reported findings suggesting that cognitive rehabilitation interventions, including those that incorporated the RehaCom software, may induce an increase in the brain activation of treated patients. The contribution of these studies, however, in assessing the impact of cognitive rehabilitation in MS warrants further investigation. Well-designed studies, with clearly defined MS patient populations (e.g., the investigation of cognitive rehabilitation efficacy in progressive MS), and utilization of longer duration and frequency of treatment

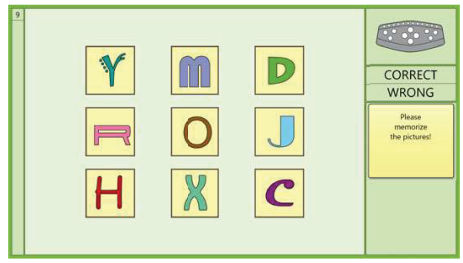

Figure 6: Example training on level 9, of the topological memory task RehaCom module.

interventions, with longer follow-up periods, are required in order to elucidate the functional correlates of cognitive amelioration in MS individuals and to make further progress in this rapidly advancing field of cognitive rehabilitation in MS.

Appendix

Detailed Description of the RehaCom Modules Used in the Cognitive Rehabilitation Intervention

As noted previously, in this specific study, as most of our MS patients that took part in the intervention were impaired in more than one cognitive domain but mostly on episodic memory, information processing speed/attention and executive functions, the intervention was balanced over the 10-week period in order to train all domains equally.

In order to train attention, we used two modules. The first module is called *attention and concentration*, training mainly selective attention, and in this procedure, a separately presented picture is compared to a matrix of pictures. The patient has to recognize a picture (symbols, items, animals, or abstract figures) and respond by selecting it from a matrix. This activity trains the ability to differentiate and concentrate simultaneously. The matrices are either 3 pictures (1×3 matrix), 6 pictures (2×3 matrix), or 9 pictures (3×3 matrix) depending on the level of difficulty that we want to train (see Figure 4).

The second module used to train attention is a more naturalistic or ecologically valid cognitive task called *divided attention.* In this task, the patient works through the cognitive training as the driver of a train shown on the lower part of the screen. He sits in the steeple cab (or driver's cab) of the train and can observe the railway like looking through the windscreen of the driver's cab and has the following task: he must carefully observe the control panel of the train and the countryside, as it flashes past, and react to different events as they occur. At first, only the acceleration of the train is to be regulated. Later, and with increasing levels of difficulty, more tasks are added, in which different levels of attention and particular reactions are expected from the trainee. The driver's panel contains a speedometer, a so-called "Deadman's lamp" and the "emergency stop lamp." On the speedometer, a "target speed" is set that the patient must retain. As soon as a lamp lights up, the patient has to press the corresponding button on the RehaCom Panel

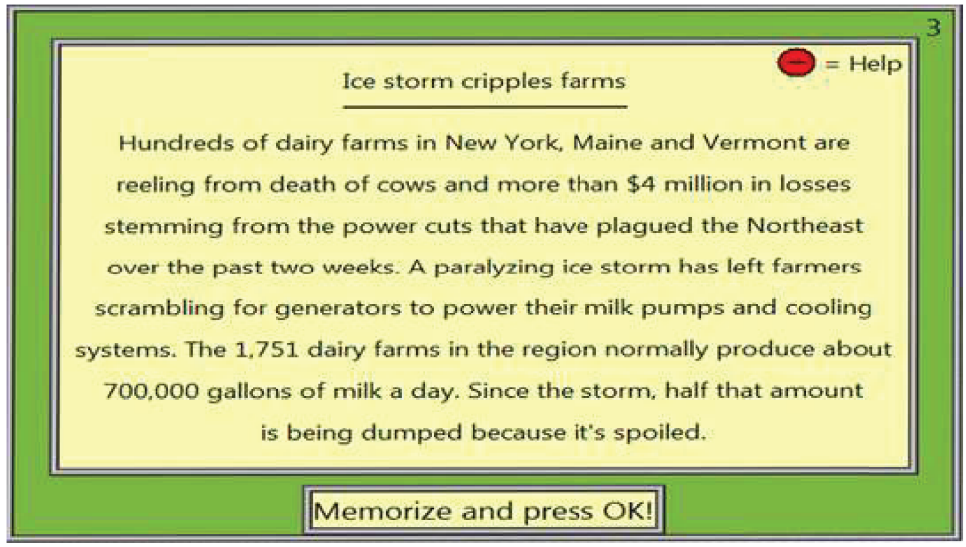

Figure 7: Example of training on level 3, of the verbal memory RehaCom module.

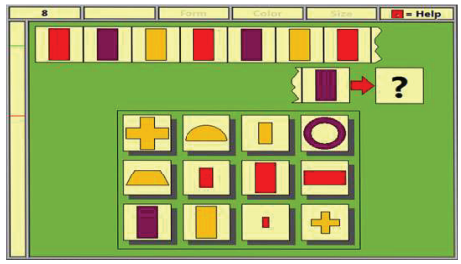

Figure 8: Example of training on level 8, on the logical reasoning RehaCom module.

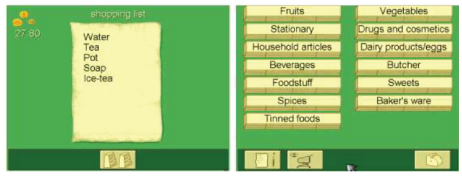

Figure 9: Example of a shopping list on level 14, of the Shopping RehaCom module (from level 11 onward, an amount of money the patient has at his/her disposal is displayed in the upper left of the screen).

(e.g., the stop button). If a relevant object appears on the railway, the patient also has to react to it (e.g., stopping at a red signal) (see Figure 5).

In order to train memory, we also used two different modules. For training visuospatial memory, we used the *topological memory* module. In the so-called "memorizing phase," a variable number of cards (depending on the level of difficulty) with concrete pictures or geometric figures are displayed on the screen. The patient has to memorize the position of the pictures. After a preset time—or manually by pressing the OK button—the pictures of the matrix are hidden (turned face down). The patient must find the picture matching the one indicated on the right side of the screen. Altogether, 464 pictures of concrete objects, geometric figures, and letters are available. The number of simultaneously displayed cards varies from 3 to a maximum of 16 (see Figure 6).

In order to train verbal episodic memory, we used the *verbal memory* module. In this task, a short story is presented on the screen. The patient has to memorize as many details of the story as possible (names, numbers, events, and objects). The learning phase is completed by pressing the OK button. After that, the patient must answer questions about the content of the story. More than 80 short stories are available. Depending on the setting, either the computer or the therapist selects a story for the patient (see Figure 7).

Executive functions were trained with two respective modules. The first module called *logical reasoning* trains abstract logical thinking ability and conclusive thinking. The task requires that from several symbols (pool of answers), the client has to find out the one that correctly continues a given sequence of symbols. A sequence of symbols (circles, triangles, squares, etc.) of different shape, color, and size is displayed on the screen being in a regular relation to each other. If the answer is wrong, special pieces of information about the type of error (shape, color, and/or size) are provided. The principle behind the training is that the problem-solving tasks are graphic and vivid. The patient learns to recognize the concepts underlying each problematic situation and uses these concepts to find a solution to the logic problem (see Figure 8).

The second module used to treat executive function is a more ecologically valid highly realistic training exercise called *shopping*. The patient performs the same tasks on the computer that he would have to do while going shopping in a supermarket. Specifically, the trainee gets a shopping list of articles that he has to look for in a supermarket and put into a trolley. When all articles are in the trolley, the trainee can leave the supermarket by using the "cash" button. Beyond a certain level of difficulty, additional demands are made on the trainees' mathematical abilities (a certain amount of money is specified, the products are marked

with prices, etc.). This training module currently uses more than 100 articles illustrated photorealistically (food, household objects, etc.). These articles appear on shelves from which the client must choose them. The training programme disposes of a voice output, which means all articles are named when selected (see Figure 9).

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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References

[1] C. Potagas, E. Giogkaraki, G. Koutsis et al., "Cognitive impairment in different MS subtypes and clinically isolated syndromes," *Journal of the Neurological Sciences*, vol. 267, no. 1-2, pp. 100–106, 2008.

[2] L. Messinis, M. H. Kosmidis, E. Lyros, and P. Papathanasopoulos, "Assessment and rehabilitation of cognitive impairment in multiple sclerosis," *International Review of Psychiatry*, vol. 22, no. 1, pp. 22–34, 2010.

[3] N. Putzki, J. Fischer, K. Gottwald et al., "Quality of life in 1000 patients with early relapsing-remitting multiple sclerosis," *European Journal of Neurology*, vol. 16, no. 6, pp. 713–720, 2009.

[4] C. Engel, B. Greim, and U. K. Zettl, "Diagnostics of cognitive dysfunctions in multiple sclerosis," *Journal of Neurology*, vol. 254, supplement 2, pp. 1130–1134, 2007.

[5] A. Papathanasiou, L. Messinis, P. Zampakis et al., "Thalamic atrophy predicts cognitive impairment in relapsing remitting multiple sclerosis. Effect on instrumental activities of daily living and employment status," *Journal of the Neurological Sciences*, vol. 358, no. 1-2, pp. 236–242, 2015.

[6] S. Roy, R. H. Benedict, A. S. Drake, and B. Weinstock-Guttman, "Impact of pharmacotherapy on cognitive dysfunction in patients with multiple sclerosis," *CNS Drugs*, vol. 30, no. 3, pp. 209–225, 2016.

[7] A. M. Plohman, L. Kappos, W. Ammann et al., "Computer assisted retraining of attentional impairments in patients with multiple sclerosis," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 64, no. 4, pp. 455–462, 1998.

[8] N. D. Chiaravalloti, N. B. Moore, O. M. Nikelshpur, and J. DeLuca, "An RCT to treat learning impairment in multiple sclerosis," *Neurology*, vol. 81, no. 24, pp. 2066–2072, 2013.

[9] F. Mattioli, C. Stampatori, C. Scarpazza, G. Parrinello, and R. Capra, "Persistence of the effects of attention and executive functions intensive rehabilitation in relapsing remitting multiple sclerosis," *Multiple Sclerosis and Related Disorders*, vol. 1, no. 4, pp. 168–173, 2012.

[10] M. Mitolo, A. Venneri, I. D. Wilkinson, and B. Sharrack, "Cognitive rehabilitation in multiple sclerosis: a systematic review," *Journal of the Neurological Sciences*, vol. 354, no. 1-2, pp. 1–9, 2015.

[11] E. M. Rosti-Otajarvi and P. I. Hamalainen, "Neuropsychological rehabilitation for multiple sclerosis," *Cochrane Database Systemic Review*, no. 2, article CD009131, 2014.

[12] W. I. McDonald, A. Compston, G. Edan et al., "Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis," *Annals of Neurology*, vol. 50, no. 1, pp. 121–127, 2001.

[13] A. Papathanasiou, L. Messinis, L. V. Georgiou, and P. Papathanasopoulos, "Cognitive impairment in relapsing remitting and secondary progressive multiple sclerosis patients: efficacy of a computerized cognitive screening battery," *ISRN Neurology*, vol. 2014, Article ID 151379, 7 pages, 2014.

[14] L. Messinis and P. Papathanasopoulos, *Wechsler Abbreviated Scale of Intelligence (WASI) [Greek Adaptation and Preliminary Normative Data] (Unpublished Data)*, Neuropsychological laboratory, Department of Neurology, University of Patras Medical School, Greece, 2012.

[15] J. F. Kurtzke, "Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS)," *Neurology*, vol. 33, no. 11, pp. 1444–1452, 1983.

[16] D. Bakalidou, E. K. Skordilis, S. Giannopoulos, E. Stamboulis, and K. Voumvourakis, "Validity and reliability of the FSS in Greek MS patients," *SpringerPlus*, vol. 2, no. 1, p. 304, 2013.

[17] D. Wechsler, *Wechsler Abbreviated Scale of Intelligence (WASI)—Manual*, Psychological Corporation, San Antonio, TX, USA, 1999.

[18] K. N. Fountoulakis, M. Tsolaki, H. Chantzi, and A. Kazis, "Mini Mental State Examination (MMSE): a validation study in Greece," *American Journal of Alzheimer's Disease and Other Dementias*, vol. 15, no. 6, pp. 342–345, 2000.

[19] A. Solias, P. Skapinakis, N. Degleris, M. Pantoleon, E. Katirtzoglou, and A. Politis, "Mini Mental State Examination (MMSE): determination of cutoff scores according to age and educational level," *Psychiatriki*, vol. 25, no. 4, pp. 245–256, 2014.

[20] S. M. Rao, G. J. Leo, L. Bernardin, and F. Unverzagt, "Cognitive dysfunction in multiple sclerosis: I. frequency, patterns, and prediction," *Neurology*, vol. 41, no. 5, pp. 685–691, 1991.

[21] R. H. B. Benedict, J. S. Fischer, C. J. Archibald et al., "Minimal neuropsychological assessment of MS patients: a consensus approach," *The Clinical Neuropsychologist*, vol. 16, no. 3, pp. 381–397, 2002.

[22] D. W. Langdon, M. P. Amato, J. Boringa et al., "Recommendations for a brief international cognitive assessment for multiple sclerosis (BICAMS)," *Multiple Sclerosis Journal*, vol. 18, no. 6, pp. 891–898, 2012.

[23] National Institute of Neurological Disorders and Stroke, "NINDS multiple sclerosis common data elements (CDE) recommendations," April 2017, https://commondataelements.ninds.nih.gov/Doc/MS/Neuropsychology_Cognition_Recommendations-Adult_and_Pediatric.pdf.

[24] I. Zalonis, E. Kararizou, F. Christidi et al., "Selective Reminding Test: demographic predictors of performance and normative data for the Greek population," *Psychological Reports*, vol. 104, no. 2, pp. 593–607, 2009.

[25] E. Polychroniadou, C. Bakirtzis, D. Langdon et al., "Validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) in Greek population with multiple

sclerosis," *Multiple Sclerosis and Related Disorders*, vol. 9, pp. 68–72, 2016.

[26] E. Argirokastritou, T. Samanda, and L. Messinis, "Normative data for the Symbol Digit Modalities Test (SDMT) in Greece," in *Paper presented at the 10th Pan-Hellenic Congress of Psychology*, Ioannina, Greece, 2005.

[27] M. H. Kosmidis, C. H. Vlahou, P. Panagiotaki, and G. Kiosseoglou, "The verbal fluency task in the Greek population: normative data and clustering and switching strategies," *Journal of the International Neuropsychological Society*, vol. 10, no. 2, pp. 164–172, 2004.

[28] I. Zalonis, F. Christidi, A. Bonakis et al., "The Stroop effect in Greek healthy population: normative data for the Stroop Neuropsychological Screening Test," *Archives of Clinical Neuropsychology*, vol. 24, no. 1, pp. 81–88, 2009.

[29] C. H. Vlahou and M. H. Kosmidis, "The Greek Trail Making Test: preliminary normative data for clinical and research use," *Psychology: The Journal of the Hellenic Psychological Society*, vol. 9, pp. 336–352, 2002, (In Greek).

[30] I. Zalonis, E. Kararizou, N. I. Triantafyllou et al., "A normative study of the trail making test a and B in Greek adults," *The Clinical Neuropsychologist*, vol. 22, no. 5, pp. 842–850, 2008.

[31] A. T. Beck, R. A. Steer, and G. K. Brown, *BDI – FastScreen for Medical Patients*, Psychological Corporation, San Antonio, TX, USA, 2000.

[32] L. Messinis and I. Tsakona, *BDI – FastScreen for medical patients (Greek translation and adaptation). Unpublished data*, Neuropsychological laboratory, Department of Neurology, University of Patras Medical School, Greece, 2004.

[33] American Psychiatric Association, *Diagnostic and Statistical Manual*, APA, Washington, DC, USA, IV edn edition, 1994.

[34] A. T. Beck, *Beck Depression Inventory-II: Manual*, The Psychological Corporation, San Antonio, TX, USA, 1996.

[35] D. L. Strauss, O. Spreen, and E. M. Sherman, *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*, Oxford University Press, New York, NY, USA, 2006.

[36] R. H. B. Benedict, I. Fishman, M. M. McClellan, R. Bakshi, and B. Weinstock Guttman, "Validity of the Beck Depression Inventory-Fast Screen in multiple sclerosis," *Multiple Sclerosis*, vol. 9, no. 4, pp. 393–396, 2003.

[37] L. B. Krupp, N. G. LaRocca, J. Muir Nash, and A. D. Steinberg, "The Fatigue Severity Scale: application to patients with multiple sclerosis and systemic lupus erythematosus," *Archives of Neurology*, vol. 46, no. 10, pp. 1121–1123, 1989.

[38] Y. C. Learmonth, D. Dlugonski, L. A. Pilutti, B. M. Sandroff, R. Klaren, and R. W. Motl, "Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact cale," *Journal of the Neurological Sciences*, vol. 331, no. 1-2, pp. 102–107, 2013.

[39] H. J. Thode, *Testing for Normality*, Marcel Dekker, New York, NY, USA, 2002.

[40] F. Mattioli, C. Stampatori, D. Zanotti, G. Parrinello, and R. Capra, "Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis," *Journal of the Neurological Sciences*, vol. 288, no. 1-2, pp. 101–105, 2010.

[41] F. Mattioli, C. Stampatori, F. Belloni, R. Capra, M. Rocca, and M. Fillipi, "Neuropsychological rehabilitation in adult multiple sclerosis," *Neurological Sciences*, vol. 31, no. supplement 2, pp. S271–S274, 2010.

[42] M. Fillipi, G. Riccitelli, F. Mattioli et al., "Multiple sclerosis: effects of cognitive rehabilitation on structural and functional MR imaging measures—an explorative study," *Radiology*, vol. 262, no. 3, pp. 932–940, 2012.

[43] A. Solari, A. Motta, L. Mendozzi et al., "Computer-aided retraining of memory attention in people with multiple sclerosis: a randomized, double-blind controlled trial," *Journal of Neurological Sciences*, vol. 222, no. 1-2, pp. 99–104, 2004.

[44] A. Ernst, A. Botzung, D. Gounot et al., "Induced brain plasticity after a facilitation programme for autobiographical memory in multiple sclerosis: a preliminary study," *Multiple Sclerosis International*, vol. 2012, Article ID 820240, 12 pages, 2012.

[45] S. Bonavita, R. Sacco, M. Della Corte et al., "Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study," *Journal of Neurology*, vol. 262, no. 1, pp. 91–100, 2015.

[46] F. Esposito, A. Bertolino, T. Scarabino et al., "Independent component model of the default-mode brain function: assessing the impact of active thinking," *Brain Research Bulletin*, vol. 16, pp. 263–268, 2006.

[47] F. Mattioli, F. Bellomi, C. Stampatori et al., "Two years follow up of domain specific cognitive training in relapsing remitting multiple sclerosis: a randomized clinical trial," *Frontiers in Behavioral Neuroscience*, vol. 10, p. 28, 2016.

[48] N. D. Chiaravalloti, H. M. Genova, and J. DeLuca, "Cognitive rehabilitation in multiple sclerosis: the role of plasticity," *Frontiers in Neurology*, vol. 6, p. 67, 2015.

[49] L. De Giglio, F. Tona, F. De Luca et al., "Multiple sclerosis: changes in thalamic resting-state functional connectivity induced by a home-based cognitive rehabilitation program," *Radiology*, vol. 280, no. 1, pp. 202–211, 2016.

[50] L. De Giglio, N. Upadhyay, F. De Luca et al., "Corpus callosum microstructural changes associated with Kawashima Nintendo Brain Training in patients with multiple sclerosis," *Journal of the Neurological Sciences*, vol. 370, pp. 211–213, 2016.

[51] B. Brochet, "Functional training is a senseless strategy in MS cognitive rehabilitation: strategy training is the only useful approach – commentary," *Multiple Sclerosis Journal*, vol. 23, no. 7, pp. 932-933, 2017.

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Review Article

Pediatric Multiple Sclerosis and Cognition: A Review of Clinical, Neuropsychologic, and Neuroradiologic Features

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Multiple sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disease. Although cognitive impairment has been well established in adult patients with MS, its occurrence in patients with pediatric-onset MS has recently been reported. In this review, I discuss the main features of cognitive impairment in pediatric MS as determined by long-term follow-up studies, neuropsychiatric test batteries, and the results of neuroradiological imaging studies that investigated the pathogenesis of pediatric MS. The most commonly affected cognitive domains in adults are attention, processing speed, and visuomotor skills; language and intelligence are also affected in pediatric MS. A young age at disease onset is the strongest risk factor for these impairments, which may be due to the effect of inflammatory demyelination and neurodegeneration on the developing central nervous system and neural networks in children. Cognitive impairment has long-term effects on patients' academic life and the quality of their social life. Therefore, all patients with pediatric MS should be screened and monitored for cognitive impairment. This review also highlights the need for neuropsychological test batteries that assess different cognitive domains in children and adolescents with multiple sclerosis and for cognitive rehabilitation programs to improve the quality of their academic and social life.

1. Introduction

Multiple sclerosis (MS) is an autoimmune-mediated neurodegenerative and demyelinating disorder of the central nervous system primarily affecting young adults. Approximately 2–5% of MS patients have onset before age 18 [1, 2]. The International Pediatric Multiple Sclerosis Study Group defined diagnostic criteria for pediatric MS [3]. MS can cause both physical and cognitive disability. The occurrence of cognitive impairment is well established in adult patients with MS, occurring in approximately 45–65% of these patients [4]. The cognitive domains that are most commonly affected in adult MS patients are complex attention, information processing speed, episodic memory, visuospatial abilities, and executive functions [5]. Cognitive impairment in pediatric MS patients has been described with different studies reporting cognitive impairment in 30–50% of cases [5–8]. Cognitive impairment in pediatric multiple sclerosis differs from that in adults in terms of the cognitive domains involved. Factors such as age, maturation of the central nervous system, and cognitive reserve have different effects on cognition in childhood. The maturation status of the central nervous system at the time of MS onset is a long-term prognostic factor, and it is crucial to develop appropriate neuropsychological test batteries that assess different cognitive domains in children and adolescents with MS. Moreover, cognitive rehabilitation to improve the quality of academic and social life in pediatric MS patients has not yet been well studied. In this review, I discuss the main features of cognitive impairment in pediatric MS, long-term follow-up findings, neuropsychiatric test batteries, and the result of neuroradiological imaging studies that investigated the pathogenesis of pediatric MS.

2. The Main Features of Cognitive Impairment in Pediatric MS Patients

Banwell and Anderson were the first to use a neuropsychological battery to systematically investigate a cohort of patients with pediatric MS. They assessed cognitive functions in 10 children with MS and identified deficits in general cognition, language, visuomotor integration, and verbal and visual memory. Children with longer disease duration demonstrated

deficits in executive functions, information processing speed, and working memory, suggesting that children with longer disease duration and a younger age at onset are at higher risk for cognitive impairment [6].

MacAllister et al. evaluated 37 children and adolescents with MS and reported significant cognitive impairment in 35% of these patients. The most common impairment was in complex attention. They also found receptive language problems and poor naming in many patients, whereas verbal fluency was unaffected. Immediate verbal memory was impaired in only one patient; however, delayed recall was impaired in seven patients. The researchers suggested that, in these patients, the effect of MS on attention and memory was similar to that in adults with MS, but visuospatial functions were less affected. They found a strong relationship between cognitive impairment and Expanded Disability Status Scale (EDSS) score, total number of relapses, and disease duration [7].

In a multicenter study, Amato and colleagues assessed the frequency, pattern, and clinical correlates of cognitive impairment in childhood and adolescent MS cases and compared these characteristics with those in healthy controls. The researchers used a neuropsychological battery to assess intelligence quotient (IQ), memory, attention/concentration, executive functions, and language. They found significant cognitive impairment in 31% of the patients with MS, and 53% of the cases failed at least two tests. Both verbal and performance IQ scores were lower in MS patients than in healthy controls. The most frequently affected cognitive domains were memory, particularly visuospatial memory, complex attention, verbal comprehension, and executive functions. In this study, EDSS and number of relapses were not adequate descriptors of cognitive condition; cognitive impairments were found also in patients with low disability levels. In this cohort, there was a significant correlation between cognitive impairment and low IQ scores. Low IQ score was also significantly associated with younger age at disease onset [8].

In a study of the magnetic resonance imaging (MRI) correlates of cognitive impairment in pediatric MS patients, Till et al. found impairments in attention and processing speed, visuomotor integration, and expressive language. They observed cognitive impairment in 29.4% of the MS patients. Full-scale IQ and verbal IQ were significantly reduced in children with MS and a higher IQ was associated with a shorter disease duration and an older age at disease onset. Moreover, a higher full-scale IQ was correlated with a lower EDSS score, and patients with cognitive impairment tended to be male. Finally, cognitive impairment was associated with a longer disease duration and a younger age at onset [9].

In a large multicenter study, Julian et al. examined cognitive function in 231 pediatric patients with MS ($n = 187$) or clinically isolated syndrome ($n = 44$). The cognitive impairment was noted in 35% of patients with MS and 18% of patients with clinically isolated syndrome. The cognitive areas that were most frequently affected were fine motor coordination (54%), visuomotor integration (50%), and information processing speed (35%). EDSS score was the only variable that was significantly and independently associated with reduced cognitive function [10].

The methods and results of these cross-sectional studies are shown in Table 1. Although these studies used different neuropsychological tests and different definitions of cognitive impairment, they found similar rates of cognitive impairment. The rate of cognitive impairment in pediatric MS ranged from 29.4% to 35%. Full-scale IQ and verbal and performance IQ were lower in children with MS. Low IQ scores were associated with higher EDSS score and young age at disease onset [8, 9]. The relationship of cognitive impairment with young age at onset and disease duration was similar in many studies [6–9]. However, the relationship between EDSS score and cognitive impairment varied between these studies. For example, Julian et al. and Banwell and Anderson found that EDSS score was associated with cognitive impairment but other studies did not [6, 10]. These studies suggested that cognitive impairment affected academic and social activities negatively and impaired the quality of life [6–8].

In summary, similar to adult patients, pediatric MS patients experience deficits in attention, information processing speed, memory, executive functions, and visuomotor integration. Additionally, unlike in adults, MS affects language functions and intelligence occurs in particularly young children. The relationship between cognitive dysfunction and disease duration, disability scores, and relapse frequency is unclear. The strongest predictor is a younger age at disease onset. Although the relationship between motor disability and cognitive disability is controversial, cognitive impairment could occur independently from motor disability. Cognitive impairment affects academic and social activities and quality of life. Monitoring of cognitive impairment in pediatric MS patients is important to enable optimal treatment and rehabilitation for prevention of further cognitive disability.

Another factor affecting MS-induced cognitive functions is cognitive reserve. The cognitive reserve theory states that individual differences in how tasks are processed or neural networks are used can allow some people to cope better with brain pathology than others [11]. It has been shown that both heritable (brain reserve) and environmental (greater intellectual enrichment) factors may attenuate the negative effects of MS on cognitive status in adults [12]. The role of cognitive reserve in pediatric MS is unclear. Pastò et al. assessed the potential impact of cognitive reserve on cognition in a cohort of pediatric MS patients. A total of 48 pediatric MS patients and 57 healthy controls were included in this study, and patients were followed up for 4.7 ± 0.4 years. Cognitive reserve was estimated by measuring the IQ at baseline, and cognitive impairment was defined as failure in $\geqslant 3$ tests of an extensive neuropsychological battery that included the Selective Reminding Test (SRT) and Selective Reminding Test-Delayed (SRT-D), the 10/36 Spatial Recall Test (SPART), the 10/36 Spatial Recall Test-Delayed, the Symbol Digit Modalities Test (SDMT), the Trail Making tests (TMT-A and TMT-B), a Semantic and Phonemic Verbal Fluency Test, an Oral Denomination Test from the Aachener Aphasia Test, the Token Test, the Indication of Pictures from the Neuropsychological Examination for Aphasia, and Phrase Comprehension Test from the Battery for the

Table 1: Methods and results of cross-sectional studies.

Authors	MS sample size	Control sample size	Cognitive impairment definition	Neuropsychological tests	Impaired cognitive domains	Impairment rate
Banwell and Anderson [6]	10	—	Each individual's performance on each measure was scored relative to age norms.	Full-Scale IQ, Verbal IQ, Performance IQ, Verbal Comprehension Index, Perceptual Organization Index, Freedom from Distractibility Index, Processing Speed Index, CELF, COWAT, CELF formulated sentences, TLC Ambiguous sentences, VMI, Rey-O Figure, Grooved Pegboard, Vigilance subtest, CMS, CAVLT, WJRTA, WRAT	Language, visuomotor integration, verbal and visual memory, information processing speed, working memory and executive functions, general cognition	
MacAllister et al. [7]	37	—	Scores > 1.5 SDs below the published normative means on least 2 cognitive tasks	TMT, COWAT, Boston Naming Test, CELF-3rd edition, two subtests of the WRAML: Verbal Learning and Visual Learning, VMI	Complex attention receptive language, naming, memory	35%
Amato et al. [8]	63	57	Scoring less than the 5th percentile of healthy control performance on least 3 tests	WISC-R, SRT and SRT-D from the Rao's BRB, SPART and SPART-D from the BRB, SDMT from the BRB, TMT A and B, Modified Card Sorting Test, Semantic and Phonemic Verbal Fluency Test, and Oral Denomination Test from the Aachener Aphasia Test	Complex attention, visual and verbal memory, executive functions, language function	31%
Till et al. [9]	35	33	Three or more test scores 1.5 SDs below the normative values on the test battery	WASI, TMT-A and B, SDMT-Oral version, Visual Matching from the Woodcock–Johnson III (WJ-III) Test of Cognitive Abilities, Rapid Picture Naming from the WJ-III Test of Cognitive Abilities, Conner's Continuous Performance Test—5th edition, WSR, WMI-5th edition, Verbal Fluency subtest from the Delis–Kaplan Executive Function System, Picture Vocabulary from WJ-III Tests of Academic Achievement, Vocabulary and Similarities subtests from the WASI, WCST	Attention, information processing speed, expressive language, visuomotor integration	29.4%

Table 1: Continued.

Authors	MS sample size	Control sample size	Cognitive impairment definition	Neuropsychological tests	Impaired cognitive domains	Impairment rate
Julian et al. [10]	187 (MS) 44 (CIS)	—	≥33% of test scores < 1 SD below normative data	WASI Full 2, Wechsler Individual Achievement Test II Pseudoword Decoding, Expressive One-Word Picture Vocabulary Test, Digit Span test, Wechsler Intelligence Scale for Children Coding Test, Contingency Naming Test, Delis Kaplan Executive Function System Trail Making Test, California Verbal Learning Test-Child version or II, WMI-6th edition, Wechsler Abbreviated Scale of Intelligence Matrix Reasoning, Grooved Pegboard Test	Fine motor speed, visuomotor integration, information processing speed	35% (MS) 18% (CIS)

BRB: Rao's Brief Repeatable Battery; CAVLT: children's auditory verbal learning test; CELF: clinical evaluation of language fundamentals; CMS: children's memory scale; COWAT: controlled oral word association test; Rey-O: Rey–Osterreith complex figure; SDMT: Symbol Digit Modalities Test; SRT: Selective Reminding Test; SRT-D: Selective Reminding Test-Delayed; SPART: Spatial Recall Test; SPART-D: Spatial Recall Test-Delayed; TMT: Trail Making Test; TLC: test of language competence; VMI: Beery–Buktenica visual motor integration test; WASI: Wechsler Abbreviated Scale of Intelligence; WCST: Wisconsin card sorting test; WISC-R: Wechsler Intelligence Scale for Children-Revised; WJ: Woodcock Johnson; WJRTA: Woodcock Johnson-revised tests of achievement; WRAML: wide range assessment of memory and learning test; WRAT: wide range achievement test; WSR: word selective reminding.

Analysis of Aphasic Deficits. The reliable change index (RCI) method was used to assess changes in neuropsychological performance. Cognitive impairment was found in 29.2% of patients with pediatric onset MS at baseline. Deterioration in cognitive performance was detected using the RCI method in 37.6% patients with pediatric onset MS. A higher cognitive reserve predicted stable or improving performance, whereas a lower reserve was associated with deteriorating performance at follow-up [13]. In other studies, on traumatic brain injury, higher cognitive reserve was associated with higher performance and a greater resistance to the development cognitive deficits [13–15]. Thus, measurement of cognitive reserve can be used to identify patients at high risk for cognitive impairment. Alternatively, cognitive reserve can be used to develop cognitive-protective approaches and cognitive rehabilitation programs.

Compared to adults, children are better able to compensate for brain damage because of the greater neural plasticity of the developing brain. Pediatric MS occurs during periods of brain growth, myelination, and neural network maturation; therefore, longitudinal follow-up studies are important to understanding the interactions between progressive brain pathology and maturation, neural plasticity, and compensatory abilities. During 2- and 5-year follow-ups of childhood and adolescent MS cases in their multicenter study, Amato et al. used the same neuropsychological battery as that used at baseline, with alternative versions of the tests to assess memory, attention/concentration, executive functions, and language. At the 2-year follow-up, 70% of patients failed at least three tests, and overall, 75% of the cases were classified as having deteriorating cognitive performance. Failure was more prominent in tests of verbal memory, complex attention, verbal fluency, and receptive language. An individual cognitive change index was also calculated to assess the direction of change in cognition over the follow-up period. At the 2-year follow-up, cognitive deterioration was observed in 75% of the patients, while 25% of the cases were classified as stable or improving. At the 5-year follow-up, the cognitive impairment index decreased in 56% of the patients, improved in 25%, and remained stable in 18.8%. Cognitive deterioration was associated with male sex, younger age at disease onset, and lower educational level. The cognitive domains with the most tendencies toward deterioration were visuospatial learning and expressive language [16, 17].

In a small cohort of patients with pediatric MS, MacAllister et al. assessed cognitive function longitudinally and found deficits in attention, executive functions, and memory. Their findings suggested that neurological impairment early in the course of the disease was predictive of cognitive decline over time. There was no strong association between duration of disease and cognitive decline. The results suggested that, in patients with pediatric MS, cognition might deteriorate over time relative to that of their peers and their baseline performance [18].

In a longitudinal study, Charvet et al. evaluated cognitive function in 62 patients with pediatric MS and five with clinically isolated syndrome. The researchers evaluated cognition at baseline and at follow-up, with a mean follow-up time of 1.64 ± 0.63 years. Cognitive impairment was detected in 37% of patients at baseline and 33% of patients at follow-up. The most commonly impaired cognitive functions included visuomotor integration, information processing speed, and attention. The researchers indicated that cognitive performance might remain stable, or even improve, over a short period of time [19].

In another longitudinal study, Hosseini et al. investigated how the age at disease onset and cognitive reserve may affect cognitive maturation in children and adolescents with pediatric MS. They used two standardized and widely used neuropsychological measures (SDMT and TMT) to assess visual scanning, information processing speed, and working memory. Cognitive reserve capacity was assessed using the patient's baseline full-scale IQ and parental social status. They used growth curve analysis to evaluate cognitive maturation over childhood and adolescence. Their results showed that a younger age at disease onset was associated with decreased performance on neuropsychological measures (SDMT and TMT). A younger age of disease onset was also associated with lower developmental gain on the neuropsychological measures. Cognitive reserve, including baseline full-scale IQ and parental social status, did not protect against cognitive deterioration [20].

Till et al. investigated the extent, pattern, and correlates of change in cognitive functioning over an approximately 15-month interval in 28 patients with pediatric MS and compared their findings with data from 26 healthy controls. The RCI was used to determine individual differences on test scores over time in this prospective longitudinal study. Participants were categorized as showing either "decline" or "improvement" if changes in scores exceeded the RCI on three or more tests. They observed that healthy controls were more likely to show improvement across multiple domains of function than patients with pediatric MS were. When cognitive change was examined on an individual basis, cognitive deterioration was observed in seven of 28 patients with pediatric MS and only one of 26 healthy controls. Clinically significant improvement on three or more of the neuropsychological tests was detected in 69.2% of healthy controls compared with only 17.9% of pediatric MS patients. Patients with pediatric MS showed decline mainly on tests of information processing speed and attention, visuomotor integration, verbal fluency, abstract visual memory, calculation, and spelling. An association was found between disease duration and deterioration in visuomotor integration. The results showed that patients who were classified as having declined cognitive function ($n : 7$) did not differ from those with stable/improved cognitive function ($n : 21$) with regard to age at testing, age at disease onset, disease duration, sex, mood-related symptoms, baseline IQ, and EDSS scores. The researchers reported that patients with pediatric MS failed to demonstrate age-expected improvements in several domains of cognitive performance [21].

In a study investigating long-term outcomes in adult patients with pediatric-onset MS, SDMT scores were lower in patients with pediatric onset than adult onset both in unadjusted analysis and after adjustment for disease

duration. The researchers suggested that, in adulthood, pediatric-onset MS may result in greater impairment in processing speed and that further investigation of other cognitive domains was warranted in this group of patients [22].

The methods and results of longitudinal follow-up studies are shown in Table 2. The duration of follow-up in these studies varied between 1 and 5 years. In Amato et al.'s study, most of the patients (75%) showed deteriorating performance between baseline and year 2; however, comparing baseline and 5-year testing, cognitive impairment index deterioration was observed in 56% of the patients, improvement in 25%, and stability in 18.8% [16, 17]. Charvet et al. emphasized that most of the cases had a stable cognitive function in the mean 1.6-year follow-up [19]. Till et al. found that 75% of the cases showed stabilization or improvement in cognitive function at 15 months follow-up, but the improvement rate was less than that of healthy controls [21]. The variations in the results of the studies may be related to the differences in follow-up periods and evaluation methods used.

The reason for the improvements observed in children may be the ongoing development in the brain and neural plasticity. Brain development and neural plasticity may be involved in the success of cognitive rehabilitation and cognitive reserve enhancement approaches. Alternatively, cognitive performance in patients with pediatric MS may deteriorate in the long term relative to their baseline performance and the performance of their peers. This worsening cognitive state can be explained by impairment of the maturation and development of the immature central nervous system by demyelinating and neurodegenerative processes.

3. Social Cognition

Social cognition, a distinct area of cognitive function, refers to "the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others" [23]. The theory of mind is an essential domain of social cognition, defined as the ability to infer other people's mental states, including beliefs, desires, knowledge, and intentions, hence explaining and predicting their behavior [24]. Social cognitive impairment has been studied in autism, psychiatric disorders, and developmental and neurodegenerative diseases. However, studies on social cognition in pediatric MS are very limited, with only one study published in the literature. Charvet and colleagues examined social cognition in 28 patients with pediatric-onset MS and 38 healthy controls. They used the SDMT and all three theories of mind tasks: reading the mind in the eyes test, the faux pas test, and the false-belief task. Patients with pediatric-onset MS performed worse than healthy controls on all theories of mind tasks, including both affective (eyes test) and cognitive (faux pas test and false-belief task) measures. Information processing speed, which was measured by SDMT, was slower in the pediatric-onset MS group (38%) than in the healthy control group (6%). However, when logistic regression analysis was performed to assess the influence of information processing speed on the theory of mind tasks, they suggested that information processing speed had no influence on the theory of mind [25]. Social cognitive impairment has been reported in adult patients with MS who were otherwise cognitively intact [26, 27]. Social cognition is important for the ability to form and maintain personal relationships. The effect of MS on social cognition is particularly important in patients with pediatric-onset MS since their social cognition skills are still undergoing development [25–27]. More studies on social cognition in pediatric MS are needed for the identification and prevention of social adjustment problems in these patients.

4. Neuropsychological Test Batteries for Pediatric MS

The aforementioned studies applied neuropsychological tests developed for adults to pediatric patients with MS. There is a need for a standardized, well-approved neuropsychological battery to detect MS-related deficits in pediatric patients. It is important to establish neuropsychological test batteries for evaluating cognitive domains that appear more frequently in children than adults and for assessing cognitive maturation in this age group. Several studies have attempted to establish such a neuropsychological test battery and to measure the sensitivity of presently available tests.

In an Italian multicenter study, Portaccio et al. validated a brief neuropsychological battery that they derived from the extensive battery used by Amato and colleagues. The researchers aimed to develop a Brief Neuropsychological Battery for Children (BNBC) with MS. The extensive neuropsychological battery involved the Wechsler Intelligence Scale for Children-Revised (WISC-R), the Selective Reminding Test (SRT, SRT-Delayed) from Rao's Brief Repeatable Battery (BRB), the Spatial Recall Test (SPART, SPART-D) from the BRB, the Symbol Digit Modalities Test (SDMT) from the BRB, Trail Making Test (TMT-A and TMT-B), Modified Card Sorting Test, Semantic Verbal Fluency Test (SVFT), Phonemic Verbal Fluency Test (PVFT), the Oral Denomination Test from the Aachener Aphasia Test, Token Test, the Indication of Pictures from the Neuropsychological Examination for Aphasia, and the Phrase Comprehension Test from the Battery for the Analysis of Aphasic Deficits (Table 3). Cognitive functions were assessed in 61 patients with childhood and juvenile MS and in 58 healthy controls. In this study, cognitive impairment was found in 41% of MS patients. Verbal and spatial memory (SRT and SPART), attention and concentration (SDMT and TMT), and language abilities (SVFT and Token Test) were the most frequently affected cognitive domains. Discriminant function analysis showed that the SDMT, the TMT-B, the Selective Reminding Test-Consistent Long-Term Retrieval (SRT-CLTR), and the vocabulary test from the WISC had higher discriminating ability. Therefore, using these tests, the researchers created the BNBC, which had a sensitivity of 96% and a specificity of 76% [28]. (Table 4).

Smerbeck et al. investigated the sensitivity and validity of two visual processing tests in 43 children with pediatric MS and 45 healthy controls: the Brief Visuospatial Memory Test-Revised (BVMT-R) and the SDMT. Previous large cross-sectional studies had demonstrated the sensitivity of

Table 2: Methods and results of longitudinal follow-up studies.

Authors	MS sample size at follow-up	Healthy controls sample size at follow-up	Duration of follow-up	Neuropsychological tests	Rate of decline in MS sample	Impaired cognitive domains
Amato et al. [16]	56	—	2 years	SRT, SRT-D, SPART, SPART-D, SDMT, TMT-A, TMT-B, Tower of London Test, Semantic and Phonemic Verbal Fluency Test, Oral Denomination Test from the Aachener Aphasia Test	70% (failure on at least 3 tests) (change in CCI between baseline and 2 years) Deteriorating: 75% Stable: 11.5% Improving: 13.5%	Verbal memory, complex attention, verbal fluency, receptive language
Amato et al. [17]	48	—	5 years	SRT, SRT-D, SPART, SPART-D, SDMT, TMT-A, TMT-B, Tower of London Test, Semantic and Phonemic Verbal Fluency Test, Oral Denomination Test from the Aachener Aphasia Test	38% (failure on at least 3 tests) (change in CCI between baseline and 5 years) Deteriorating: 56% Stable: 18.8% Improving: 25% (change in CCI between years 2 and 5) Deteriorating: 22.9% Stable: 10.4% Improving: 66.7%	Visual–spatial learning, expressive language
MacAllister et al. [18]	12	—	21.58 ± 9.3 months	TMT, COWAT, Boston Naming Test, CELF 3rd edition, WRAML, WMI	5/12 (cognitive decline assessed using the criteria of more tests showing impaired at the time of the 2nd test than at the baseline) 7/12 (cognitive decline assessed using the criteria of decline in z-score composite from the baseline to the time of the 2nd test)	Attention, executive functions, memory
Charvet et al. [19]	62 (MS) 5 (CIS)	—	1.64 ± 0.63 years	WASI, WASI-II, CVLT-C, CVLT-II, EOWPVT, WIAT-II, VMI, Digit Span subtest from WISC-IV, WAIS-IV, TMT	Rate of impairment was 37% at baseline and 33% at follow-up Most participants showed no change while $n = 4$ (6%) declined on two or more tasks and $n = 6$ (9%) improved on 2 or more tasks	Visuomotor integration, information processing speed, attention

Table 2: Continued.

Authors	MS sample size at follow-up	Healthy controls sample size at follow-up	Duration of follow-up	Neuropsychological tests	Rate of decline in MS sample	Impaired cognitive domains
Hosseini et al. [20]	35	—	Neuropsychological evaluations were conducted at baseline and up to four more assessments, with each evaluation separated by a minimum of 1 year.	SDMT, TMT, WASI, WISC-III	This study examined changes in cognitive maturation in a cohort of pediatric-onset MS patients as a function of age at disease onset and cognitive reserve factors (baseline IQ and parental social status) Younger age at disease onset was associated with a greater likelihood of cognitive decline on both the TMT-B ($p = 0.001$) and SDMT ($p = 0.005$)	Younger age at disease-onset increases the vulnerability for disrupted performance on measures of information processing, visual scanning, perceptual/motor speed, and working memory
Till et al. [21]	28	26	13–16 months (mean: 15 months)	WASI, Visual Matching from the WJ Tests of Cognitive Abilities, TMT A-B, SDMT, Conner's Continuous Performance Test (5th edition)–number of omission errors, Vocabulary and Similarities subtests of the WASI, WJ Tests of Achievement, Verbal Fluency Test from DKEFS, VMI, Block Design and Matrix Reasoning subtests from the WASI, TOMAL-2, WSR, Grooved Pegboard test	Improving: 18% in MS group, 86% in control group The RCI method results showed that the majority of patients remained stable or improved over time (21 of 28; 75%), with only seven of 28 patients (25%) demonstrating decline on three or more of the neuropsychological tests. Only 1 of 26 controls (3.8%) showed cognitive deterioration ($p < 0.05$).	Attention, information processing speed, visuomotor integration, verbal fluency, visual memory, calculation, spelling ability

CCI: cognitive change index; CVLT: California Verbal Learning Test; DKEFS: Delis–Kaplan executive function system; EOWPVT: Expressive One-Word Picture Vocabulary Test; RCI: reliable change index; TOMAL-2: test of memory and learning-2nd edition; WAIS-IV: Wechsler adult intelligence scale 4th edition; WIAT-II: Wechsler Individual Achievement Test-2nd edition.

Table 3: Neuropsychological tests.

Neuropsychological test	Cognitive domain
WISC-R (Wechsler Intelligence Scale for Children)	IQ (intelligence quotient)
SRT-LTS (Selective Reminding Test-Long-Term Storage) SRT-CLTR (Selective Reminding Test-Consistent Long-Term Retrieval) SRT-D (Selective Reminding Test-Delayed) SPART (Spatial Recall Test) SPART-D (Spatial Recall Test-Delayed)	Memory
MCST (Modified Card Sorting Test)	Abstract/conceptual reasoning
SDMT (Symbol Digit Modalities Test) TMT-A/ B (Trail Making Test A/B)	Attention/concentration
SVFT (Semantic Verbal Fluency Test) PVFT (Phonemic Verbal Fluency Test) IPT (Indication of Pictures Test) PCT (Phrase Comprehension Test) Token Test ODT (Oral Denomination Test)	Language

Table 4: Brief Neuropsychological Battery for Children (BNBC).

(i) SRT
(ii) SDMT
(iii) TMT
(iv) Vocabulary test from the WISC-R

Duration: 30 minutes. Sensitivity (96%), specificity (76%).

these tests in adults. They found statistically significant differences between children with MS and healthy controls on BVMT-R Total Learning, BVMT-R Delayed Recall, and SDMT. These findings indicated that two relatively brief measures of visual-cognitive processing could be successfully applied to the pediatric population and could be useful in detecting and monitoring significant cognitive impairment [29].

Charvet et al. evaluated the SDMT as a screening tool for identifying pediatric onset MS patients at risk for cognitive impairment. The SDMT showed 77% sensitivity and 81% specificity for detecting neuropsychological impairment when administered within 1 year. Age and EDSS score were negatively correlated with SDMT score. The researchers concluded that these results support the use of the SDMT as a screening tool for cognitive function in pediatric MS [30].

5. Neuroradiologic Studies and Anatomic Correlation of Cognitive Impairment in Pediatric MS Patients

Several neuroradiologic studies have reported a correlation between deficits in executive function and atrophy of the thalamus and frontal lobes, as well as the correlation of a decrease in cognitive speed and mathematical performance with corpus callosum damage [31–33].

To normalize total and regional brain volumes for head size in their MRI correlations, Till and colleagues calculated cortical gray matter, thalamic, and global brain volumes using a scaling factor computed using the normalization of atrophy method. In addition, they also calculated T1- and T2-weighted lesion volumes in MS patients. Thirty-five pediatric-onset MS patients and 33 healthy controls were included in the study. Thalamic volume, corpus callosum area, normalized brain volume, and normalized gray matter volume were significantly lower in patients with MS than in healthy controls. Thalamic volume was strongly and positively correlated with an index global intellectual function in MS patients. MS patients with cognitive impairment did not differ from MS patients without cognitive impairment with regard to T1 or T2 lesion volume, normalized grey matter volume, or normalized brain volume. Neuropsychologic test performance was highly correlated with global and regional brain volume and less strongly correlated with T1 and T2 lesion volumes. The researchers suggested that cognitive impairment was related to the neurodegenerative component of MS [9].

The cerebellum is another anatomical area associated with cognitive function. It is a strategic node in various networks such as coordination and cognitive-behavioral loops [34]. Weier et al. examined associations between cognitive outcomes and cerebellar volume independent of cerebral volume in patients with pediatric MS. Twenty-eight pediatric-onset MS patients and 33 age- and sex-matched healthy controls were included in this study. All subjects underwent structural MRI and neuropsychological evaluation to assess intelligence, attention, information processing speed, language, visuomotor integration, and fine-motor dexterity. Neuropsychological battery included the Wechsler Abbreviated Scale of Intelligence (WASI), the TMT-B, the SDMT-oral version, Beery Visual Motor Integration, the vocabulary subtest of the WASI, and the Grooved Pegboard test. Cognitive performance in patients with MS was reduced relative to that in the healthy controls in the domains of attention, information processing speed, expressive language, visuomotor integration, and fine motor dexterity. Cerebellar volumes did not differ between MS group and healthy controls; however, cerebellar posterior lobe volume and infratentorial

lesion volume accounted for extra variance in cognitive measures of information processing (SDMT) and vocabulary within MS patients in regression analysis. The researchers suggested that in addition to cerebral volume, the cerebellar volume was another correlate of cognitive function in children and adolescents with MS [35].

In a neuroradiologic study, Rocca and colleagues performed a structural and functional MRI examination to investigate the mechanisms responsible for the presence and severity of cognitive impairment in pediatric patients with MS. A total of 35 pediatric patients with MS and 16 sex- and age-matched healthy controls were included in the study. The researchers used voxel-based analysis with advanced structural MRI techniques to determine the patterns of regional involvement of white and gray matter according to patient's cognitive profile. They also used functional MRI to quantify the resting-state functional connectivity of the default mode network (DMN). The BNBC was used to assess participants' cognitive function, and subjects with abnormal performance in two tests were classified as cognitively impaired. Among the patients with MS, 45% were classified as cognitively impaired. Spatial and verbal memory abilities, language, attention, and concentration were the most significantly involved cognitive areas. The results showed that cognitively impaired patients with MS had a higher occurrence of T2 lesions and white and gray matter damage, including atrophy and diffusivity abnormalities in the posterior region of the parietal lobes close to midline (precuneus, posterior cingulum, and corpus callosum). Reduced resting-state functional connectivity in the precuneus was observed in cognitively impaired patients, whereas cognitively preserved patients showed increased resting-state functional connectivity in the anterior cingulate cortex. The researchers concluded that the presence and severity of cognitive impairment were associated with structural and functional abnormalities of the posterior core regions of the DMN in pediatric patients with MS [36].

In these neuroradiological studies, researchers used different parameters such as global brain volume, thalamic volume, gray matter volume, T1-T2 lesion volume, and cerebellar volume. Cognitive impairment has been related to T2 hyperintense lesions, diffuse white matter damage, and cortical and deep gray matter atrophy in adult MS patients [37]. Neuropathologic findings have revealed that MS affects regions that are functionally or anatomically involved in cognitive processes, such as cortical and deep gray matter, hippocampus, white matter, including normal appearing white matter in adult patients [38]. Consistent with the findings in adult patients, studies in pediatric MS patients suggest that a relationship exists between cognitive impairment and gray matter atrophy, white matter atrophy, and global and regional brain volume [9, 36].

6. Conclusions

A third of the pediatric MS patients experience cognitive impairment. In pediatric cases, the influence of demyelination on the developing central nervous system and neural network affects cognitive function negatively; on the other hand, neural plasticity and ability of compensation can have a positive effect on cognitive functions. Unlike in adults, intelligence and language functions are affected in pediatric MS. Young age at disease onset increases the risk of cognitive impairment. Although varying findings have been reported for the relationship between motor disability and cognitive disability, cognitive impairment may also occur independently from motor disability. Cognitive reserve is important both for the detection of patients with high risk and for the development of cognitive-protective approaches and rehabilitation. Knowledge about social cognition is limited in pediatric MS. Cognitive impairment in pediatric MS is a critical problem that has long-term effects on patients' academic and social quality of life; thus, the development of appropriate neuropsychological test batteries is important for screening patients who are at risk. Current studies have shown that SDMT and Brief Neuropsychological Battery for Children (BNBC) could be effectively used for screening cognitive functions in pediatric MS.

MRI studies have suggested that cognitive impairment in pediatric MS can be related to both gray matter atrophy and white matter atrophy and global and regional brain volume. More longitudinal studies with standardized neuropsychological batteries and advanced MRI techniques are needed to explore the mechanism of cognitive impairments and predict high-risk group. Understanding the pathogenesis of impaired cognition and the involvement of specific cognitive areas in pediatric MS will guide the development of treatment and rehabilitation, including cognitive rehabilitation, about which limited data are available in pediatric MS patients.

Assessment of cognitive function is also important for the evaluation of response to treatment. While defining the response to treatment and disease activity in pediatric MS, preservation of age-expected global and regional brain growth and age-expected cognitive maturation and function should be assessed, as well as the number of relapses, disability progression, and MR findings such as new, enlarging, or enhancing lesions.

Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this paper.

References

[1] P. Duquette, T. J. Murray, J. Pleines et al., "Multiple sclerosis in childhood: clinical profile in 125 patients," *The Journal of Pediatrics*, vol. 111, no. 3, pp. 359–363, 1987.

[2] A. Ghezzi, V. Deplano, J. Faroni et al., "Multiple sclerosis in childhood: clinical features of 149 cases," *Multiple Sclerosis Journal*, vol. 3, no. 1, pp. 43–46, 1997.

[3] L. B. Krupp, M. Tardieu, M. P. Amato et al., "International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions," *Multiple Sclerosis Journal*, vol. 19, no. 10, pp. 1261–1267, 2013.

[4] S. M. Rao, "Neuropsychology of multiple sclerosis," *Current Opinion in Neurology*, vol. 8, no. 3, pp. 216–220, 1995.

[5] J. A. Bobholz and S. M. Rao, "Cognitive dysfunction in multiple sclerosis: a review of recent developments," *Current Opinion in Neurology*, vol. 16, no. 3, pp. 283–288, 2003.

[6] B. L. Banwell and P. E. Anderson, "The cognitive burden of multiple sclerosis in children," *Neurology*, vol. 64, no. 5, pp. 891–894, 2005.

[7] W. S. MacAllister, A. L. Belman, M. Milazzo et al., "Cognitive functioning in children and adolescents with multiple sclerosis," *Neurology*, vol. 64, no. 8, pp. 1422–1425, 2005.

[8] M. P. Amato, B. Goretti, A. Ghezzi et al., "Cognitive and psychosocial features of childhood and juvenile MS," *Neurology*, vol. 70, no. 20, pp. 1891–1897, 2008.

[9] C. Till, R. Ghassemi, B. Aubert-Broche et al., "MRI correlates of cognitive impairment in childhood-onset multiple sclerosis," *Neuropsychology*, vol. 25, no. 3, pp. 319–332, 2011.

[10] L. Julian, D. Serafin, L. Charvet et al., "Cognitive impairment occurs in children and adolescents with multiple sclerosis: results from a United States network," *Journal of Child Neurology*, vol. 28, no. 1, pp. 102–107, 2013.

[11] Y. Stern, "Cognitive reserve," *Neuropsychologia*, vol. 47, no. 10, pp. 2015–2028, 2009.

[12] J. F. Sumowski and V. M. Leavitt, "Cognitive reserve in multiple sclerosis," *Multiple Sclerosis Journal*, vol. 19, no. 9, pp. 1122–1127, 2013.

[13] L. Pastò, E. Portaccio, B. Goretti et al., "The cognitive reserve theory in the setting of pediatric-onset multiple sclerosis," *Multiple Sclerosis Journal*, vol. 22, no. 13, pp. 1741–1749, 2016.

[14] S. R. Kesler, H. F. Adams, C. M. Blasey, and E. D. Bigler, "Premorbid intellectual functioning, education, and brain size in traumatic brain injury: an investigation of the cognitive reserve hypothesis," *Applied Neuropsychology*, vol. 10, no. 3, pp. 153–162, 2003.

[15] J. E. Farmer, S. M. Kanne, J. S. Haut, J. Williams, B. Johnstone, and K. Kirk, "Memory functioning following traumatic brain injury in children with premorbid learning problems," *Developmental Neuropsychology*, vol. 22, no. 2, pp. 455–469, 2002.

[16] M. P. Amato, B. Goretti, A. Ghezzi et al., "Cognitive and psychosocial features in childhood and juvenile MS two-year follow-up," *Neurology*, vol. 75, no. 13, pp. 1134–1140, 2010.

[17] M. P. Amato, B. Goretti, A. Ghezzi et al., "Neuropsychological features in childhood and juvenile multiple sclerosis five-year follow-up," *Neurology*, vol. 83, no. 16, pp. 1432–1438, 2014.

[18] W. S. MacAllister, C. Christodoulou, M. Milazzo, and L. B. Krupp, "Longitudinal neuropsychological assessment in pediatric multiple sclerosis," *Developmental Neuropsychology*, vol. 32, no. 2, pp. 625–644, 2007.

[19] L. E. Charvet, E. H. O'Donnell, A. L. Belman et al., "Longitudinal evaluation of cognitive functioning in pediatric multiple sclerosis: report from the US pediatric multiple sclerosis network," *Multiple Sclerosis Journal*, vol. 20, no. 11, pp. 1502–1510, 2014.

[20] B. Hosseini, D. B. Flora, B. L. Banwell, and C. Till, "Age of onset as a moderator of cognitive decline in pediatric-onset multiple sclerosis," *Journal of the International Neuropsychological Society*, vol. 20, no. 08, pp. 796–804, 2014.

[21] C. Till, N. Racine, D. Araujo et al., "Changes in cognitive performance over a 1-year period in children and adolescents with multiple sclerosis," *Neuropsychology*, vol. 27, no. 2, pp. 210–219, 2013.

[22] N. F. Baruch, E. H. O'Donnell, B. I. Glanz et al., "Cognitive and patient-reported outcomes in adults with pediatric-onset multiple sclerosis," *Multiple Sclerosis Journal*, vol. 22, no. 3, pp. 354–361, 2016.

[23] M. F. Green, D. L. Penn, R. Bentall et al., "Social cognition in schizophrenia: an NIMH workshop on definitions, assessment, and research opportunities," *Schizophrenia Bulletin*, vol. 34, no. 6, pp. 1211–1220, 2008.

[24] R. Adolphs, "Cognitive neuroscience: cognitive neuroscience of human social behavior," *Nature Reviews Neuroscience*, vol. 4, no. 3, pp. 165–178, 2003.

[25] L. E. Charvet, R. E. Cleary, K. Vazquez, A. Belman, and L. B. Krupp, "Social cognition in pediatric-onset multiple sclerosis (MS)," *Multiple Sclerosis Journal*, vol. 20, no. 11, pp. 1478–1484, 2014.

[26] M. Jehna, C. Langkammer, M. Wallner-Blazek et al., "Cognitively preserved MS patients demonstrate functional differences in processing neutral and emotional faces," *Brain Imaging and Behavior*, vol. 5, no. 4, pp. 241–251, 2011.

[27] J. Cotter, J. Firth, C. Enzinger et al., "Social cognition in multiple sclerosis, a review and meta-analysis," *Neurology*, vol. 87, no. 16, pp. 1727–1736, 2016.

[28] E. Portaccio, B. Goretti, S. Lori et al., "The brief neuropsychological battery for children: a screening tool for cognitive impairment in childhood and juvenile multiple sclerosis," *Multiple Sclerosis Journal*, vol. 15, no. 5, pp. 620–626, 2009.

[29] A. M. Smerbeck, J. Parrish, D. Serafin et al., "Visual-cognitive processing deficits in pediatric multiple sclerosis," *Multiple Sclerosis Journal*, vol. 17, no. 4, pp. 449–456, 2011.

[30] L. E. Charvet, R. Beekman, N. Amadiume, A. L. Belman, and L. B. Krupp, "The symbol digit modalities test is an effective cognitive screen in pediatric onset multiple sclerosis (MS)," *Journal of the Neurological Sciences*, vol. 341, no. 1-2, pp. 79–84, 2014.

[31] C. Till, C. Ho, A. Dudani, D. García-Lorenzo, D. L. Collins, and B. L. Banwell, "Magnetic resonance imaging predictors of executive functioning in patients with pediatric-onset multiple sclerosis," *Archives of Clinical Neuropsychology*, vol. 27, no. 5, pp. 495–509, 2012.

[32] A. Bethune, V. Tipu, J. G. Sled et al., "Diffusion tensor imaging and cognitive speed in children with multiple sclerosis," *Journal of the Neurological Sciences*, vol. 309, no. 1-2, pp. 68–74, 2011.

[33] C. Till, A. Deotto, V. Tipu et al., "White matter integrity and math performance in pediatric multiple sclerosis: a diffusion tensor imaging study," *NeuroReport*, vol. 22, no. 18, pp. 1005–1009, 2011.

[34] D. Timmann, J. Drepper, M. Frings et al., "The human cerebellum contributes to motor, emotional and cognitive associative learning. A review," *Cortex*, vol. 46, no. 7, pp. 845–857, 2010.

[35] K. Weier, C. Till, V. Fonov et al., "Contribution of the cerebellum to cognitive performance in children and adolescents with multiple sclerosis," *Multiple Sclerosis Journal*, vol. 22, no. 5, pp. 599–607, 2016.

[36] M. A. Rocca, M. Absinta, M. P. Amato et al., "Posterior brain damage and cognitive impairment in pediatric multiple sclerosis," *Neurology*, vol. 82, no. 15, pp. 1314–1321, 2014.

[37] F. Paul, "Pathology and MRI: exploring cognitive impairment in MS," *Acta Neurologica Scandinavica*, vol. 134, Supplement 200, pp. 24–33, 2016.

[38] G. C. DeLuca, R. L. Yates, H. Beale, and S. A. Morrow, "Cognitive impairment in multiple sclerosis: clinical, radiologic and pathologic insights," *Brain Pathology*, vol. 25, pp. 79–98, 2015.

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Research Article

Face-to-Face or Telematic Cognitive Stimulation in Patients with Multiple Sclerosis and Cognitive Impairment: Why Not Both?

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Introduction. Cognitive impairment (CI) affects 40–65% of patients with multiple sclerosis (MS). Few studies address telematic cognitive stimulation (TCS) in MS. The objective of this study is to evaluate the efficacy and impact of telestimulation or distance cognitive stimulation (TCS), with and without the support of face-to-face cognitive stimulation (FCS) in cognitive impairment in MS. *Methods*. Multicentre, prospective, randomised, controlled study. We will include 98 MS patients with EDSS ≤ 6, symbol digit modality test (SDMT) ≤ Pc 25, and Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) > 26 points. Patients will be randomised into 3 groups, a TCS group, a mixed TCS/FCS group, and a control group. CS is performed 3 days a week for 3 months. Processing speed, memory, attention, and executive functions will be rehabilitated. FCS will include ecological exercises and strategies. EDSS and a cognitive evaluation (SDMT, CTMT, PASAT, and TAVEC), MSNQ, psychological impact scales (MSIS), and depression (BDI) will be carried out, baseline, postrehabilitation, and also 6 and 12 months later, to evaluate the effect of CS in the longer term. *Conclusion*. This study could help to establish the usefulness of TCS or, in its absence, TCS with face-to-face help for CI in MS. The interest lies in the clear benefits of remote rehabilitation in the daily life of patients.

1. Introduction

Multiple sclerosis (MS), a chronic demyelinating disease, is characterised by a heterogeneous set of symptoms that can lead to severe disability and have an impact on accessibility to medical services, functional capacity of the patient, and health-related quality of life (HRQOL) [1].

Cognitive impairment (CI) affects 40–65% of patients and mainly involves information processing speed (IPS), attention, executive functions, and memory. It becomes more frequent as the disease evolves, but may appear in early stages and be independent of physical disability. IC correlates mainly with cerebral atrophy estimated by magnetic resonance (MR) volumetric techniques [2–4]. In MS, deficits in concentration, attention, working memory, IPS, and executive functions, predominantly in problem solving and abstract reasoning [5], are more frequently observed. Deficits vary from series to series in relation to, among other factors, the neuropsychological batteries used and the type of patient studied. Two neuropsychological batteries have been widely accepted for the study of CI in MS, the Rao Brief Battery (BRB-N) [6], and the MACFIMS (Minimal Assessment of

Cognitive Function in Multiple Sclerosis) [7]. Both have the inconvenience of administration time, 30 and 90 minutes, respectively, and require qualified personnel. The Symbol Digit Modalities Test (SDMT) (about 2 minutes for execution) has been proposed as a screening test because of its high sensitivity and specificity to discriminate patients with and without CI. It is a good tool in longitudinal studies because of its reproducibility [8]. Recently, the BICAMS (Brief International Cognitive Assessment of Multiple Sclerosis) has been proposed as a new screening battery. This has been validated in 28 countries and supported by different neurological associations. It takes 15 minutes, can be performed by nonspecialised staff, and includes the California Verbal Learning Test-II (CVLT-II), the Brief Visuospatial Memory Test-Revised, and the SDMT [9].

There is no pharmacological treatment for CI in MS [10]. There is a sufficient consensus on the protective role of intellectual enrichment in the development of CI in dementia and aging. In MS, the work is with lower numbers but the results are similar: level of education and the intellectual enrichment maintained by leisure activities such as reading, among others, diminish the deleterious effect of the lesional load and atrophy in cognition [11, 12]. There are few studies that analyse the effect of cognitive rehabilitation on MS's cognitive dysfunction [13]. Recent analyses by Cochrane [14, 15] show that intensive training, specifically in memory, seems to have a clear benefit. Fifteen phase III studies with a total of 989 participants are included, but the risk of bias is low in only 7 of these and heterogeneity is important. The results are more contradictory with attention; there is little work with rehabilitation programmes aimed at treating IPS and executive functions [8, 9, 14, 15]. Functional MRI studies have shown that this CS activates the prefrontal and cingulate cortexes [16].

1.1. Justification and Hypotheses. No comparative studies comparing telematic (TCS) and face-to-face stimulation (FCS) with neuropsychologists are currently known. Telestimulation would offer clear advantages for the patient, given its lower interruption in their daily activities, work, social life, and so forth. With the design of this randomised and controlled pilot study, we want to compare individualised training by TCS with face-to-face support, with individualised training only by TCS.

1.2. Objectives of the Study

1.2.1. Main Goal. The main goal is to evaluate the efficacy and impact of TCS with and without FCS support on CI.

1.2.2. Secondary Objectives

(1) Evaluate the degree of patient satisfaction with the TCS programme.

(2) Evaluate adherence to treatment with the TCS programmes.

(3) Evaluate if the changes obtained with the rehabilitation treatment are maintained at 6 and 12 months of the CS.

2. Material and Methods

This is an experimental, prospective, randomised, controlled, minimally interventional, and multicentre study.

The study is being carried out in the following hospitals, with the approval of the Research Ethics Committee of each centre: Hospital Virgen de la Luz (Cuenca), Hospital Universitario Virgen de la Salud (Toledo), Hospital Santa Bárbara (Ciudad Real), Hospital Virgen de Sonsoles (Ávila), Hospital Valdepeñas (Ciudad Real), and Hospital Universitario de Getafe (Madrid).

Patients with MS according to the McDonald Criteria, 2010 (1917) from multiple sclerosis consultations ranging from 18–65 years old, EDSS (Expanded Disability Status Scale, 1983) ≤ 6, with a score of >26 in the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) [17] and/or $\leq$Pc 25 in the SDMT [18], have signed informed consent.

Exclusion criteria are severe cognitive impairment (defined by the Mini-Mental State Examination (MMSE) scores ≤ 26) [19], being free of attacks and/or treatment with corticosteroids 30 days before the first cognitive assessment, presence of other CNS disease, history of vascular or traumatic brain damage, and psychiatric disorder or psychotropic substance abuse that may interfere with the test performance.

The patients included will be randomised into 3 groups: (1) TCS group, patients will receive only telematic intervention for 3 days each week; (2) mixed TCS/FCS group, patients will receive telematic intervention for 2 days more FCS for one day each week; and (3) control group. The face-to-face rehabilitation will be performed with 2 neuropsychologists in groups of five patients. As in the design of another recent clinical trial on cognitive rehabilitation, our control group will be assigned to the waiting list, providing the opportunity to participate in the cognitive rehabilitation programme once the study has been completed [20].

2.1. Neurological and Neuropsychological Evaluation. Patients from all three groups will undergo a neuropsychological evaluation that includes the domains of IPS, attention, memory, and executive functions, before starting CS (baseline visit), at the end of 12 weeks of treatment (visit 2) and at 6 and 12 months.

The neurological and neuropsychological evaluation is detailed as follows:

(1) Disability: EDSS, baseline, and after training

(2) Neuropsychological testing

  (i) Processing speed: SDMT [18], Comprehensive Trail Making Test (CTMT) CTMT 1 [21]

  (ii) Attention: CTMT 2 y 3 [20]

  (iii) Executive functions: PASAT 3 (Paced Auditory Serial Addition Test) [22], CTMT 4 and 5, verbal fluency (phonological and semantic)

(iv) Memory: Spain-Complutense Verbal Learning Test (TAVEC) (Spanish version of the California Verbal Learning Test) [23]

(3) Self-administered questionnaires

(i) Risk for neuropsychological impairment and self-perceived cognitive quality of life: MSNQ [17]

(ii) Fatigue: Fatigue Severity Scale (FSS) and Fatigue Impact Scale (FIS) [24]

(iii) Physical and psychosocial impact of MS: Multiple Sclerosis Impact Scale (MSIS-29) [25]

(iv) Depression: Beck Depression Inventory (BDI) [26]

(v) Satisfaction measure: satisfaction questionnaire

2.1.1. Cognitive Stimulation Programme

(1) Cognitive Telestimulation Programme. A state-of-the-art cognitive stimulation application will be installed on the latest generation devices (computers, tablets, and smartphones). This platform is based on a web resource and mobile applications and uses games, validated [27, 28] and selected by expert neuropsychologists. This computer programme has been validated in fibromyalgia, healthy students and children with attention deficit hyperactivity disorder [27, 28]. It has different training settings ("full brain," "athletes," "students," "drivers," "executives," "over 60," and "children") and allows users to obtain a profile of the advances obtained by cognitive stimulation. In addition, they are sent reminder messages to perform assigned tasks. They have 62 games classified according to the predominant cognitive domain, "perception and speed," "memory," "attention," and "executive functions."

At each training session, patients will perform 4 sets (one from each cognitive domain), with an estimated time of 15 minutes for all four games.

(2) Cognitive Stimulation Face-to-Face in Cognitive Strategies. It will be based on exercises and teach strategies with ecological exercises based on principles of optimisation, compensation, and restoration, to improve cognition (one session), attention (2 sessions), memory (2 sessions), and executive functions (one session on inhibition and another on problem solving). There will be 3 more sessions for presentation and adherence to the programme, feedback on the CS software, and evaluation of the programme.

2.2. Statistical Analysis. We have calculated the sample size with an online platform (http://Fisterra.com). The sample size estimate is based on an analysis of the MSIS. Starting from a population of 450 patients with MS, a sample size of 98 patients with CI and MS representative of MSIS has been calculated.

The SPSS.22.0 program will be used for statistical analysis.

The primary outcome was a cognitive performance measured by improvement in SDMT, PASAT, CTMT and TAVEC, and self-perceived psychosocial impact (MSNQ, MSIS-29).

Continuous variables will be expressed as mean and standard deviation or median and 25th and 75th percentiles and categorical variables as percentages. The normal distribution of the data will be verified by the Kolmogorov–Smirnov test. To compare baseline demographic, clinical, and neuropsychological variables between groups, one-way ANOVA or Kruskal-Wallis will be used for quantitative variables and Chi-square or Fisher's exact test for categorical variables.

The effect of CS on cognitive performance was measured in each group (named "intragroup") comparing cognitive scores before and after treatment using an ANCOVA (analysis of covariance) adjusted by depression level or Friedman test for independent samples. To compare outcomes in cognitive scores between groups, an ANCOVA adjusted by sex, age, education level, baseline cognitive scores, and depression level will be used. The same procedure will be employed to analyse the effect of CS on MSIS and MSNQ as daily life impact measures.

Patients will be stratified in 2 groups: cognitive improvement and no changes/impairment in order to evaluate if age, sex, EDSS, educational level, baseline cognitive status, and FCS support (independent variables) have a capacity of predicting the cognitive improvement (dependent variable) through a logistic regression model. Cognitive improvement is defined as a gain > 1.5 S.D. in the score in at least 2 cognitive tests.

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3. Discussion

Telemedicine (TM) is the exchange of medical information between two different physical locations. The goals of TM are to provide services that cannot be managed face-to-face and improve the efficiency of existing ones. The use of TM to clinically monitor MS patients has been shown to improve Health-related quality of life (HRQOL), reducing the cost of associated medical services [29]. A randomised clinical trial has shown that cognitive behavioural therapy was an effective treatment for fatigue in MS, using an internet-based version programme consisting of eight interactive sessions with clinical psychologists [30]; although studies with a greater number of patients are needed.

A recent Spanish study demonstrated the usefulness of TM to assess gait disability in MS patients, especially in the most disabled. The gait distance evaluation included a video of self-performed neurological examination and specific multimedia questionnaires, together with the measurements of a triaxial accelerometer [31].

Several studies about impact of cognitive rehabilitation in MS, although with methodology limitations [32], show some improvements in attention, IPS, executive functions, and working memory [33, 34]. They have few patients and are

not comparable and thus do not confirm the effectiveness reported. Cochrane has performed a systematic review on TCS in MS patients, including studies using telecommunication technology in their environment [35]. They included nine randomised clinical trials ($N = 531$ participants, 469 patients included) investigating a variety of TCS interventions in adults with MS. These interventions were complex, with more than one rehabilitation component, and included physical activity and management of behavioural and educational symptoms. The methodological quality was considered low. They conclude that there is "low-level" evidence for TCS interventions in reducing short-term disability and fatigue, functional activities, fatigue, pain, insomnia, and long-term psychological symptoms. The data was limited on the evaluation of the process (the satisfaction of the participants and the therapists), and no cost analysis was performed [35]. Despite the paucity of data and the low level of evidence, partly explained by methodological problems, such interventions could be an alternative method of functional and cognitive rehabilitation in MS patients, although more robust trials are needed to prove clinical effectiveness and the cost of these interventions [35, 36].

Several authors have reported that adaptation to these computer programmes is good. Amato et al. observed a benefit only in sustained attention tasks in a randomised trial conducted on 88 patients, using training with specific computerized training and nonspecific training for one hour twice a week. Regardless of the training received, the patients' perception was positive [37]. The same results in adaptation to the programme have recently been published with an application for mobile devices with memory exercises [38].

The main dilemma in this issue is that there are no programmes, computer programme or on-site, that have demonstrated superiority; then, there is no recommendation in this regard. Even more, we do not know what is the therapeutic window for cognitive rehabilitation. The efficacy of CS in neurodegenerative diseases, as MS, today is subject of controversy; maybe, it only allows a better adaptation to cognitive dysfunction.

Nevertheless, a recent Cochrane review of 2016 finds that the benefit of cognitive rehabilitation is clear in MS patients with cognitive impairment, at least in memory [39]. MS is a progressive disease, and CS can, through the neuronal plasticity of a young brain, meet both expectations: functional improvement and cognitive improvement. Other authors believe that CS does not improve cognitive performance but reduces perceived deficit in MS patients [36, 40]. Like other authors [41], we think that both goals can be achieved, as in stroke and brain damage.

This project aims to evaluate whether this type of intervention may be an alternative method in the treatment of patients with MS and cognitive impairment, given the need for more studies that prove the clinical effectiveness and cost of these interventions [30].

4. Conclusion

The design of our study aims to answer the question of the validity of TCS in MS patients with CI, since it has not been shown to have the same ability to maintain cortical functions as is attributed to FCS. The interest lies in the clear benefits of remote rehabilitation for patients' daily lives.

In our opinion, a feasible, cost-effective alternative that could respond to this need would be the combination of both forms of training; since in our experience, patients with CI require supervision and training in the cognitive therapy to be applied, whether face-to-face or remote.

We considered that this study could help to establish the usefulness of TCS; or in its absence, TCS with FCS helps in MS patients with CI.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

C Guijarro-Castro, Y Aladro-Benito, M Cerezo-García, and M. J. Laredo did the conceptualization. All the authors did the resource and data curation. Y Aladro-Benito and M Cerezo-García did the formal analysis. All the authors did the investigation. C Guijarro-Castro, Y Aladro-Benito, and M Cerezo-García did the writing and preparing of the original draft. All the authors did the writing, review, and editing. All authors read and approved the final manuscript.

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References

[1] C. Guijarro-Castro, S. Moreno-García, F. Bermejo-Pareja, and J. Benito-León, "Calidad de vida relacionada con la salud en Esclerosis Múltiple," *Revista Española de Esclerosis Múltiple*, vol. 13, pp. 17–23, 2010.

[2] N. D. Chiaravalloti and J. DeLuca, "Cognitive impairment in multiple sclerosis," *The Lancet Neurology*, vol. 7, no. 12, pp. 1139–1151, 2008.

[3] G. C. DeLuca, R. L. Yates, H. Beale, and S. A. Morrow, "Cognitive impairment in multiple sclerosis: clinical, radiologic and pathologic insights," *Brain Pathology*, vol. 25, no. 1, pp. 79–98, 2015.

[4] C. Guijarro-Castro, M. Muñoz-Pasadas, and A. Martínez-Alvárez, "El Symbol Digit Modality Test no discrimina pacientes de Síndrome Radiológico Aislado de controles sanos," in *Comunicación en la LVXIII Reunión Anual de la SEN*, Valencia, 2015.

[5] B. A. Parmenter, B. Weinstock-Guttman, N. Garg, F. Munschauer, and R. HB Benedict, "Screening for cognitive impairment in multiple sclerosis using the symbol digit modalities test," *Multiple Sclerosis*, vol. 13, pp. 152–157, 2007.

[6] S. M. Rao, *A Manual for the Brief, Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis*, National Multiple Sclerosis Society, New York, 1990.

[7] R. H. B. Benedict, D. Cookfair, R. Gavett et al., "Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS)," *Journal of the International Neuropsychological Society*, vol. 12, no. 4, pp. 549–558, 2006.

[8] M. P. Amato, E. Portaccio, B. Goretti et al., "Relevance of cognitive deterioration in early relapsing-remitting MS: a 3-year follow-up study," *Multiple Sclerosis Journal*, vol. 16, no. 12, pp. 1474–1482, 2010.

[9] D. W. Langdon, M. P. Amato, J. Boringa et al., "Recommendations for a brief international cognitive assessment for multiple sclerosis (BICAMS)," *Multiple Sclerosis Journal*, vol. 18, pp. 891–898, 2012.

[10] M. P. Amato, D. Langdon, X. Montalban et al., "Treatment of cognitive impairment in multiple sclerosis: position paper," *Journal of Neurology*, vol. 260, no. 6, pp. 1452–1468, 2013.

[11] R. H. Benedict, S. A. Morrow, B. Weinstock Guttman, D. Cookfair, and D. J. Schretlen, "Cognitive reserve moderates decline in information processing speed in multiple sclerosis patients," *Journal of the International Neuropsychological Society*, vol. 16, no. 05, pp. 829–835, 2010.

[12] J. F. Sumowski, M. A. Rocca, V. M. Leavitt et al., "Brain reserve and cognitive reserve protect against cognitive decline over 4.5 years in MS," *Neurology*, vol. 82, no. 20, pp. 1776–1783, 2014.

[13] E. M. Rosti-Otajärvi and P. I. Hämäläinen, "Neuropsychological rehabilitation for multiple sclerosis," *Cochrane Database of Systematic Reviews*, vol. 2, 2014.

[14] R. das Nair, H. Ferguson, D. L. Stark, and N. B. Lincoln, "Memory rehabilitation for people with multiple sclerosis," *Cochrane Database of Systematic Reviews*, vol. 3, 2012.

[15] R. das Nair, K. J. Martin, and N. B. Lincoln, "Memory rehabilitation for people with multiple sclerosis," *Cochrane Database of Systematic Reviews*, vol. 3, 2016.

[16] L. Parisi, M. A. Rocca, P. Valsasina, L. Panicari, F. Mattioli, and M. Filippi, "Cognitive rehabilitation correlates with the functional connectivity of the anterior cingulate cortex in patients with multiple sclerosis," *Brain Imaging and Behavior*, vol. 8, no. 3, pp. 387–393, 2014.

[17] R. H. Benedict, F. Munschauer, R. Linn et al., "Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire," *Multiple Sclerosis Journal*, vol. 9, no. 1, pp. 95–101, 2003.

[18] J. C. Arango-Lasprilla, D. Rivera, G. Rodríguez et al., "Symbol digit modalities test: normative data for the Latin American Spanish speaking adult population," *NeuroRehabilitation*, vol. 37, no. 4, pp. 625–638, 2015.

[19] M. F. Folstein, S. E. Folstein, and P. R. McHugh, ""Mini-mental state". A practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[20] O. Rilo, J. Peña, N. Ojeda et al., "Integrative group-based cognitive rehabilitation efficacy in multiple sclerosis: a randomized clinical trial," *Disability and Rehabilitation*, vol. 40, no. 2, pp. 208–216, 2018.

[21] T. N. Tombaugh, "Trail making test A and B: normative data stratified by age and education," *Archives of Clinical Neuropsychology*, vol. 19, no. 2, pp. 203–214, 2004.

[22] D. M. A. Gronwall, "Paced auditory serial-addition task: a measure of recovery from concussion," *Perceptual and Motor Skills*, vol. 44, no. 2, pp. 367–373, 1977.

[23] M. J. Benedet and M. A. Alejandre, *TAVEC: test de aprendizaje verbal España-Complutense: manual*, TEA Ediciones, Madrid, 1998.

[24] L. B. Krupp, N. G. LaRocca, J. Muir-Nash, and A. D. Steinberg, "The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus," *Archives of Neurology*, vol. 46, no. 10, pp. 1121–1123, 1989.

[25] J. Hobart, D. Lamping, R. Fitzpatrick, A. Riazi, and A. Thompson, "The multiple sclerosis impact scale (MSIS-29): a new patient-based outcome measure," *Brain*, vol. 124, no. 5, pp. 962–973, 2001.

[26] A. T. Beck, C. H. Ward, M. Mendelson, J. Mock, and J. Erbaugh, "An inventory for measuring depression," *Archives of General Psychiatry*, vol. 4, no. 6, pp. 561–571, 1961.

[27] M. Fernández-Sanchez, J. Sánchez, J. M. Diago, and J. M. Bescos, "Neuropsychological rehabilitation in fibromialgia patients. Effects of an online cognitive training program," in *Conference on Recent Advances in Neurorrehabilitation (ICRAN2013)*, Valencia, 2013.

[28] P. Fernández-Sanchez Barjola, J. Sánchez, J. M. Diago, and J. M. Bescos, "Evaluación de los efectos de un programa de brainfitness online sobre el rendimiento académico y neuropsicológico de un grupo de estudiantes universitarios," in *IN:X Congreso Andaluz de Neuropsicología: Rehabilitación Neuropsicológica en la Infancia y la Adolescencia*, Cádiz, 2013.

[29] N. Sola-Valls, Y. Blanco, M. Sepúlveda, E. Martinez-Hernandez, and A. Saiz, "Telemedicine for monitoring MS activity and progression," *Current Treatment Options in Neurology*, vol. 17, no. 11, p. 47, 2015.

[30] R. Moss-Morris, P. McCrone, L. Yardley, K. van Kessel, G. Wills, and L. Dennison, "A pilot randomised controlled trial of an internet-based cognitive behavioural therapy self-management programme (MS Invigor8) for multiple sclerosis fatigue," *Behaviour Research and Therapy*, vol. 50, no. 6, pp. 415–421, 2012.

[31] N. Sola-Valls, Y. Blanco, M. Sepúlveda et al., "Walking function in clinical monitoring of multiple sclerosis by telemedicine," *Journal of Neurology*, vol. 262, no. 7, pp. 1706–1713, 2015.

[32] A. M. Plohmann, L. Kappos, W. Ammann et al., "Computer assisted retraining of attentional impairments in patients with multiple sclerosis," *Journal of Neurology, Neurosurgery, & Psychiatry*, vol. 64, no. 4, pp. 455–462, 1998.

[33] A. Vogt, L. Kappos, P. Calabrese et al., "Working memory training in patients with multiple sclerosis - comparison of two different training schedules," *Restorative Neurology and Neuroscience*, vol. 27, no. 3, pp. 225–235, 2009.

[34] F. Mattioli, C. Stampatori, D. Zanotti, G. Parrinello, and R. Capra, "Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis," *Journal of the Neurological Sciences*, vol. 288, no. 1-2, pp. 101–105, 2010.

[35] F. Khan, B. Amatya, J. Kesselring, and M. Galea, "Telerehabilitation for persons with multiple sclerosis," *Cochrane Database of Systematic Reviews*, vol. 9, no. 4, 2015.

[36] N. B. Lincoln, R. das Nair, L. Bradshaw et al., "Cognitive rehabilitation for attention and memory in people with multiple sclerosis: study protocol for a randomised controlled trial (CRAMMS)," *Trials*, vol. 16, no. 1, p. 556, 2015.

[37] M. Amato, B. Goretti, R. Viterbo et al., "Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial," *Multiple Sclerosis Journal*, vol. 20, no. 1, pp. 91–98, 2014.

[38] A. Tacchino, L. Pedullà, L. Bonzano et al., "A new App for at-home cognitive training: description and pilot testing on

patients with multiple sclerosis," *JMIR mHealth and uHealth*, vol. 3, no. 3, 2015.

[39] R. das Nair, K. Martin, and N. B. Lincoln, "Memory rehabilitation for people with multiple sclerosis," *Cochrane Database of Systematic Reviews*, no. 3, 2016.

[40] A. Mäntynen, E. Rosti-Otajärvi, K. Koivisto, A. Lilja, H. Huhtala, and P. Hämäläinen, "Neuropsychological rehabilitation does not improve cognitive performance but reduces perceived cognitive deficits in patients with multiple sclerosis: a randomised, controlled, multi-centre trial," *Multiple Sclerosis Journal*, vol. 20, no. 1, pp. 99–107, 2014.

[41] A. Cerasa, F. Tomaiuolo, and A. Quattrone, "Which is the goal of cognitive rehabilitation in multiple sclerosis: the improvement of cognitive performance or the perception of cognitive deficits?," *Multiple Sclerosis Journal*, vol. 20, no. 1, pp. 124-125, 2014.

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Research Article

Cognitive Impairment in Relapsing-Remitting Multiple Sclerosis Patients with Very Mild Clinical Disability

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Cognitive dysfunction affects 40–65% of multiple sclerosis (MS) patients and can occur in the early stages of the disease. This study aimed to explore cognitive functions by means of the Italian version of the minimal assessment of cognitive function in MS (MACFIMS) in relapsing-remitting MS (RRMS) patients with very mild clinical disability to identify the primarily involved cognitive functions. Ninety-two consecutive RRMS patients with Expanded Disability Status Scale (EDSS) scores ≤ 2.5 and forty-two healthy controls (HC) were investigated. Our results show that 51.1% of MS patients have cognitive dysfunction compared to HC. An impairment of verbal and visual memory, working memory, and executive functions was found in the RRMS group. After subgrouping RRMS by EDSS, group 1 (EDSS ≤ 1.5) showed involvement of verbal memory and executive functions; moreover, group 2 ($2 \leq$ EDSS ≤ 2.5) patients were also impaired in information processing speed and visual memory. Our results show that utilizing a comprehensive neuropsychological assessment, approximately half of MS patients with very mild physical disability exhibit cognitive impairment with a primary involvement of prefrontal cognitive functions. Detecting impairment of executive functions at an early clinical stage of disease could be useful to promptly enroll MS patients in targeted rehabilitation.

1. Introduction

Cognitive impairment (CI) is a common deficit of multiple sclerosis (MS), with prevalence rates ranging from 40 to 65% [1]. It can have a dramatic impact on a patient's quality of life, influencing role fulfilment in work as well as in social life independent of physical disability [2]. The cognitive domains mostly affected are attention, visuospatial abilities, learning and memory, information processing speed, and problem solving, while "simple" attention and essential verbal skills are not usually compromised [3, 4]. To identify cognitive impairment, scores on the single test are usually used. Recently, Migliore et al. [5] considered also the cognitive domains rather than the single tests to better identify patients with multidomain cognitive impairment. This classification may be more specific to identify MS patients with a clear cognitive impairment; in fact, patients with two tests failed in the same domain are not considered multidomain cognitively impaired.

Cognitive dysfunction can be detected even at the earliest stages of the disease [6, 7]; nevertheless, its prevalence is higher in chronic progressive patients [7]. Longitudinal studies indicate that CI, if present, progresses over time [4, 8, 9]. Moreover, CI has a prognostic value as it indicates a shifting

Table 1: Demographic and clinical characteristics of the study sample.

	MS patients (92)	HC (42)	p
Age years (mean, SD)	41.5 (10.7)	42.0 (9.8)	0.766
Education, years [median (min–max)]	13.0 (5–18)	13.0 (8–18)	0.633
Women—*N* (%)	64 (69.6)	28 (66.7)	0.737
EDSS [median (min–max)]	1.0 (0–2.5)		
(i) EDSS ≤ 1.5: ND—*N* (%)	73 (79.3%)		
(ii) 2 ≤ EDSS ≤ 2.5: VMD—*N* (%)	19 (20.7%)		
Disease duration, years [median (min–max)]	9.5 (0.3–30.1)		

MS = multiple sclerosis patients; HC = healthy control subjects; ND = no physical disability; VMD = very mild disability.

to a progressive phase and motor impairment [8, 10]. The disease course influences cognitive performance profiles: at the very early stage of the disease, that is, in clinically isolated syndrome (CIS) patients, the main domains involved are processing speed and executive functions [7, 9], while in the relapsing-remitting MS (RRMS) course, verbal and visual memory [7, 11] is also affected. Patients with a chronic progressive course, however, tend to exhibit a more frequent, severe, and widespread CI [7, 12].

Many other clinical variables have been explored to determine which one mostly influences cognition in MS patients, and results have been controversial. In particular, CI is scarcely correlated with disease duration [8, 13]. These results may be explained by the difficulty in determining the disease onset. It should be noted, however, that patients with the same disease duration and activity may have completely different levels of physical disability. The evidence of a relationship between CI and level of physical disability is also conflicting [8]. Rao and colleagues [14] reported a slight but significant correlation between physical disability and the presence or degree of CI, whereas other studies failed to find any significant association [15]. More recently, a significant correlation of CI with physical disability was found in a heterogeneous sample of MS patients [7, 16].

Our aim was to explore cognitive function in RRMS patients with very mild clinical disability by means of an ad hoc comprehensive neuropsychological assessment (Italian version of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS)) [5], to identify early affected cognitive domains regardless of disease duration. Moreover, we aimed to evaluate potential correlations among CI and clinical parameters such as Expanded Disability Status Scale (EDSS), disease duration, and neuropsychiatric features.

2. Materials and Methods

2.1. Subjects. Our study included ninety-two patients with a diagnosis of RRMS (according to McDonald's criteria) [17] and forty-two healthy controls (HC) comparable by age, sex, and education. From September 2013 to December 2014, patients were selected at the MS centers of the Neuroscience Department at San Giovanni Calibita "Fatebenefratelli" Hospital (Rome), at the Policlinico "Tor Vergata" (Rome), and at the Neurology Outpatient Clinic of Campus Bio-Medico University (Rome). We contacted the research participants (including all HC) either by mail/telephone or approaching them during their periodic clinical examinations. Considering our patients' study population, about 25% of the RRMS patients were monitored about their cognitive functioning, 25% of them were investigated for specific clinical reasons (i.e., disability evaluation, differential diagnosis of CI versus depressive disorder, suspected cognitive impairment), and about 50% were assessed as research volunteers (i.e., they had no cognitive problems). Our MS sample may be considered representative of the MS population referred to MS centers. Hospital employees (physicians, nurses, clerks, cleaners, and porters) and their relatives were included in the HC group. Table 1 shows demographic and clinical characteristics of the MS and HC groups.

Inclusion criteria were as follows: age 18 or older, fluent in Italian, able to provide informed consent to all procedures, and EDSS ≤ 2.5 (for patients only).

Exclusion criteria were as follows: neurological disorders other than MS; psychiatric disorder other than mood, personality, or behavior change following the onset of MS; medical condition that might influence cognition; history of developmental disorder (e.g., ADHD, learning disability); history of substance or alcohol dependence or current abuse; motor or sensory deficits that might interfere with cognitive test performance; and relapse and/or corticosteroid pulse within four weeks of assessment (for patients only).

We decided not to include or exclude patients on the basis of the medication they were taking. However, none of the participants were under treatment that has a significant impact on their cognitive performance; all patients were under immunomodulant therapy (interferon or glatiramer acetate). A detailed clinical interview was performed to verify the inclusion and exclusion criteria, and each patient underwent complete neurological examinations including EDSS rating. According to Kurtzke's criteria [18], patients were separated into two different subgroups in line with EDSS: in particular, patients with EDSS ≤ 1.5 were not considered to have any disability [group 1, no physical disability (ND)], while patients with EDSS between 2 and 2.5 were considered to have very mild disability (group 2, VMD) (Table 1). We considered EDSS ≤ 2.5 a cut-off in order to investigate only the cognitive function in patients with very mild levels of disability. Each HC and MS patient signed an informed written consent (previously approved by the local ethical committee) to participate in the study.

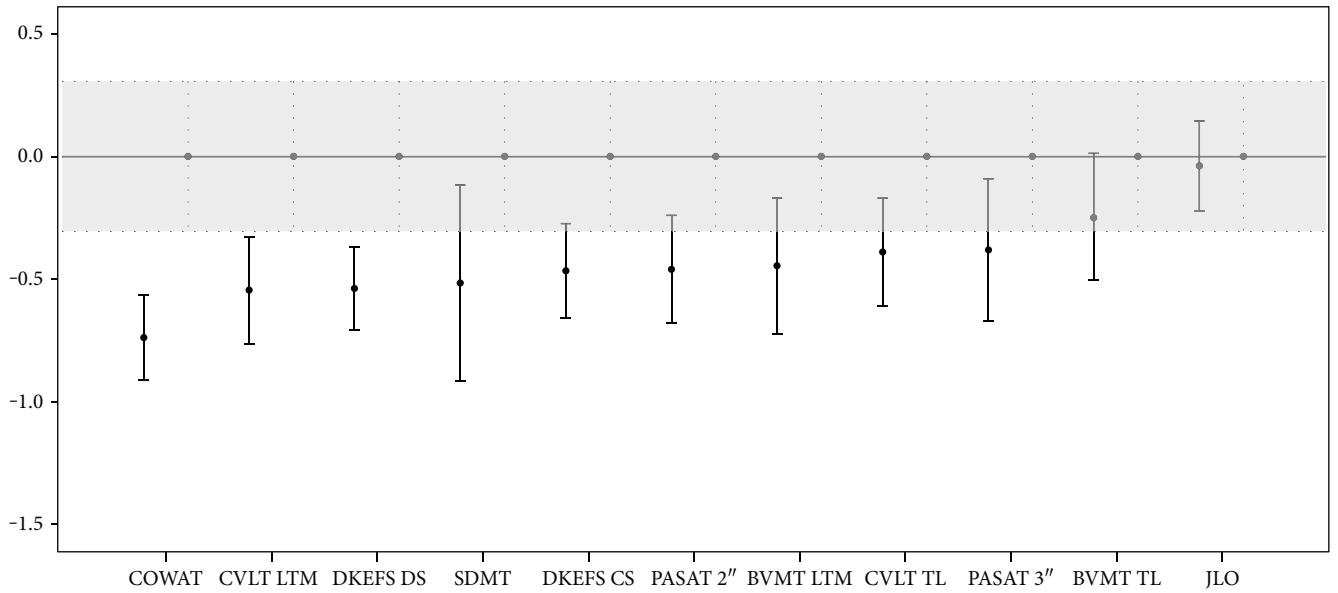

Figure 1: Cognitive performance pattern (z-score mean and 95% confidence interval) in MS patients (closed circles), compared to HC (mean set at 0, with grey band indicating 95% confidence interval). All raw scores, for each scale, were transformed into z-scores using the mean and the standard deviation (SD) of healthy controls. CVLT TL: California Verbal Learning Test total learning; CVLT LTM: CVLT long-term memory; BVMT TL: Brief Visuospatial Memory Test total learning; BVMT LTM: BVMT long-term memory; SDMT: Symbol Digit Modalities Test; PASAT 3″ and 2″: Paced Auditory Serial Addition Test; JLO: Judgment of Line Orientation; DKEFS CS: Delis-Kaplan Executive Function System sorting test correct sort; DEKEFS DS: DEKEFS description score; COWAT: Controlled Oral Word Association Test.

2.2. Neuropsychological Assessment. Both MS patients and HC underwent an Italian version of MACFIMS [5] and neuropsychiatric questionnaires by an expert clinical neuropsychologist. Tests were administered in a standardized manner, during daytime in a quiet room and in a fixed order, in accordance with consensus panel recommendations [3, 19].

Moreover, the participants completed the Beck Depression Inventory (BDI) [20] and State-Trait Anxiety Inventory Form Y (STAI-Y) [21] to check for psychiatric comorbidity. The entire test battery required 90/100 minutes of face-to-face testing time.

Patients were diagnosed as having CI when at least two tests were found to have more than 1.5 standard deviations (SD) below the control mean, according to the proposal of Amato et al. [22]. Moreover, employing 1.5 SD, Benedict et al. [3] found a strong association between MACFIMS tests and vocational outcomes, proving that 1.5 SD is a reliable parameter to detect CI. However, we did a further analysis taking into account the 5th percentile, in order to have a more restrictive parameter for detecting CI [5].

On the basis of the number of test in the CI range, patients were classified as mildly (two tests impaired), moderately (three tests impaired), or severely affected (four or more tests impaired) [5, 12]. This classification reflects different levels of cognitive deterioration in order to highlight different severity degrees of cognitive dysfunction.

In addition to the number of tests failed, we aimed to consider the number of cognitive domains impaired, according to Migliore et al. [5]. More specifically, the domain was considered altered when at least one test in the domain had an impaired result. MS patients were considered multidomain cognitively impaired (mDCI) when at least two domains were found to be altered. In total, five cognitive domains were considered: verbal memory (CVLT total learning—CVLT TL, CVLT long-term memory—CVLT LTM), visual memory (BVMT total learning—BVMT TL, BVMT long-term memory—BVMT LTM), information processing speed (Paced Auditory Serial Addition Task—PASAT 3″ and PASAT 2″, Symbol Digit Modalities Test—SDMT), executive functions (Delis-Kaplan Executive Function System Correct Sort—DKEFS CS, DKEFS description score—DKEFS DS, and Controlled Oral Word Association Test—COWAT), and visuospatial perception (Judgment of Line Orientation—JLO). We also considered the cognitive domains rather than the single tests to better identify those patients showing a multidomain cognitive impairment. This classification may result in a greater specificity in identifying MS patients with a clear cognitive impairment. In fact, patients with two tests impaired in the same domain were not classified as multidomain cognitively impaired (mDCI).

2.3. Statistical Analysis. Group differences regarding demographic and clinical data were assessed using parametric tests (Student's t-test or univariate ANOVA). Correlations among neuropsychological tests and disease duration, BDI and STAI-Y, were evaluated using Spearman's correlation coefficients. Analyses of covariance (ANCOVA) were applied to examine differences in test performance considering diagnosis and sex as factors and BDI as a covariate. To obtain neuropsychological profiles shown in Figures 1 and 2, we transformed all raw scores, for each scale, into z-scores using the mean and the standard deviation (SD) of healthy controls of the present study. Repeated-measures ANOVA were performed on these z-score variables to compare the

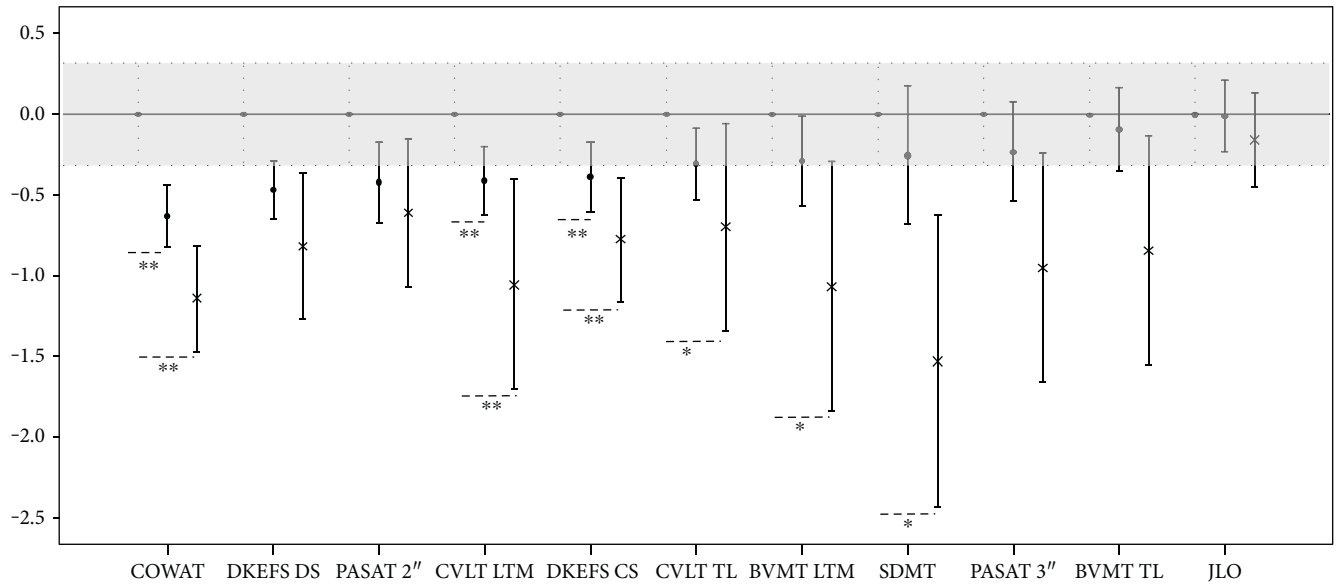

Figure 2: Cognitive performance pattern (z-score mean and 95% confidence interval) in the EDSS subgroups (closed circles for no disability; asterisk for very mild disability), compared to healthy controls (mean set at 0, with grey band indicating 95% confidence interval). All raw scores, for each scale, were transformed into z-scores using the mean and the standard deviation (SD) of healthy controls. CVLT TL: California Verbal Learning Test total learning; CVLT LTM: CVLT long-term memory; BVMT TL: Brief Visuospatial Memory Test total learning; BVMT LTM: BVMT long-term memory; SDMT: Symbol Digit Modalities Test; PASAT 3″ and 2″: Paced Auditory Serial Addition Test; JLO: Judgment of Line Orientation; DKEFS CS: Delis-Kaplan Executive Function System sorting test correct sort; DEKEFS DS: DEKEFS description score; COWAT: Controlled Oral Word Association Test. Post hoc comparisons: $^{*}p < 0.05$; $^{**}p < 0.01$.

performance of each patient group to each neuropsychological test, considering the test type as the within-subjects factor and the group as the between-subjects factor. If the assumption of sphericity was violated, Greenhouse-Geisser correction of degrees of freedom was considered.

To describe the effect size, the "Cohen's d" was calculated; it is the difference between means divided by the pooled SD, and its magnitude is assessed using the thresholds provided by Cohen [23], whereby 0.2 equates to a small effect, 0.5 equates to a medium effect, and effects larger than 0.8 correspond to large effects. Overall, a p value less than 0.05 was considered significant. Tukey's adjustment or, in cases of variance heterogeneity, Dunnett's adjustment was applied for post hoc comparisons. A log transformation was applied to BDI to gain a better fit to Gaussianity, to limit the dangerous effects of extreme values, and to reduce heteroscedasticity in the residuals. All statistical analyses were performed using SPSS 16.

3. Results

3.1. Comparison between MS Group and HC. Neuropsychological test scores for both MS patients and HC are shown in Table 2. According to repeated-measures ANOVA, besides the expected group effect ($F(1,131) = 11.006$; $p = 0.001$), the group X test type interaction ($F(12,1584) = 1.963$; $p = 0.02$) was also significant, indicating that the difference between the two groups changed across tests (Figure 1). Looking separately at each test, we found that the patient group performed significantly worse than HC in verbal memory total learning (CVLT TL), long-term memory (CVLT LTM), visuospatial long-term memory (BVMT LTM), working memory in a subtest with high cognitive load (PASAT 2″), and executive functions (DKEFS CS, DKEFS DS, and COWAT). No significant differences were observed for the other neuropsychological (NP) tests.

According to the definition of CI reported above (at least two tests impaired with 1.5 SD below the control mean), 51.1% of patients were classified as impaired (out of them, 16.3% were mildly, 15.2% were moderately, and 19.6% were severely impaired). Moreover, even when considering the 5th percentile (1.645 SD below the control mean), 40.2% of patients had impaired results (out of them, 10.9% were mildly, 15.2% were moderately, and 14.1% were severely impaired). Detailed data about each NP test are reported in Table 2.

Regarding the number of impaired cognitive domains, according to the cut-off of 1.5 SD below the control mean, 43.5% of MS patients showed at least two domains compromised (out of them, 20.7% were mildly, 9.8% were moderately, and 13.1% were severely impaired). Moreover, if we consider the 5th percentile, 33.7% of patients were found compromised (out of them, 15.2% were mildly, 8.7% were moderately, and 9.8% were severely impaired).

A significant difference was also found on BDI scores comparing MS patients and HC ($p = 0.006$). ANCOVA with diagnosis and sex as factors and BDI (log scale) as a covariate was applied to compare test scores in MS patients and HC. In general, the differences between MS patients and controls still remained significant, with the exception

Table 2: Neuropsychological tests scores.

Test		RRMS ($n = 92$)	HC ($n = 42$)	p	Cohen's d
CVLT TL	Mean (SD)	49.8 (9.6)	54.6 (9.3)	0.008	0.50
	% ± (mean-1.5 SD)	7.6%			
	% ± 5th percentile	5.4%			
CVLT LTM	Mean (SD)	−0.40 (1.06)	0.32 (0.92)	<0.001	0.70
	% ± (mean-1.5 SD)	18.5%			
	% ± 5th percentile	9.8%			
BVMT TL	Mean (SD)	45.6 (13.7)	47.9 (13.3)	0.372	0.17
	% ± (mean-1.5 SD)	27.2%			
	% ± 5th percentile	23.9%			
BVMT LTM	Mean (SD)	49.9 (13.2)	54.9 (10.3)	0.035	0.43
	% ± (mean-1.5 SD)	16.3%			
	% ± 5th percentile	14.1%			
PASAT 3″	Mean (SD)	38.7 (14.1)	41.9 (10.1)	0.187	0.25
	% ± (mean-1.5 SD)	22.8%			
	% ± 5th percentile	20.7%			
PASAT 2″	Mean (SD)	26.3 (14.0)	32.4 (13.2)	0.019	0.45
	% ± (mean-1.5 SD)	23.9%			
	% ± 5th percentile	19.6%			
SDMT	Mean (SD)	42.1 (11.2)	45.2 (6.4)	0.094	0.31
	% ± (mean-1.5 SD)	29.3%			
	% ± 5th percentile	19.6%			
DKEFS CS	Mean (SD)	8.2 (2.2)	9.8 (3.3)	0.001	0.62
	% ± (mean-1.5 SD)	10.9%			
	% ± 5th percentile	10.9%			
DKEFS DS	Mean (SD)	8.17 (2.6)	10.2 (3.3)	<0.001	0.73
	% ± (mean-1.5 SD)	13.0%			
	% ± 5th percentile	13.0%			
JLO	Mean (SD)	23.5 (4.5)	23.6 (5.1)	0.822	0.04
	% ± (mean-1.5 SD)	19.6%			
	% ± 5th percentile	17.4%			
COWAT	Mean (SD)	29.2 (11.1)	39.1 (13.6)	<0.001	0.83
	% ± (mean-1.5SD)	20.7%			
	% ± 5th percentile	17.4%			
BDI	Mean (SD)	13.0 (9.7)	5.1 (5.1)	<0.001	0.92
STAI-Y state	Mean (SD)	0.40 (1.25)	−0.09 (0.77)	0.188	0.44
STAI-Y state	Mean (SD)	−0.09 (1.03)	−0.31 (0.56)	0.474	0.24

CVLT TL: California Verbal Learning Test total learning; CVLT LTM. CVLT long-term memory; BVMT TL: Brief Visuospatial Memory Test total learning; BVMT LTM: BVMT long-term memory; SDMT: Symbol Digit Modalities Test; PASAT 3″and 2″: Paced Auditory Serial Addition Test; JLO: Judgment of Line Orientation; DKEFS CS: Delis-Kaplan Executive Function System sorting test correct sort; DKEFS DS: DKEFS description score; COWAT: Controlled Oral Word Association Test; BDI: Beck Depression Inventory; STAI-Y: State-Trait Anxiety Inventory Form Y; RRMS: relapsing-remitting multiple sclerosis patients; HC: healthy controls. All neuropsychological tests were converted into a standard score using normative data.

of PASAT 2″, where the effect of depression (although marginally significant; $F(1,89) = 3.69$, $p = 0.058$) tempered down the difference between the two groups (see Table 4 in the Supplementary Material available online at https://doi.org/10.1155/2017/7404289). Moreover, a significant effect of sex was observed on the COWAT score ($F(1,89) = 5.15$, $p = 0.026$). STAI-Y did not differ between MS patients and controls. Also, disease duration did not significantly influence NP scores (all p values > 0.2).

3.2. Comparison among EDSS Subgroups and HC. Repeated-measures ANOVA revealed a significant main effect of the groups ($F(2,131) = 8.632$; $p < 0.001$). According to pairwise Tukey's comparisons, the controls' overall estimated mean was not significantly different from that of the ND group ($p = 0.085$) but was significantly higher than that of the VMD group ($p < 0.001$) as expected. Also ND's overall estimated mean was significantly higher than that of the VMD group ($p = 0.015$).

Table 3: Post hoc comparison results. Data are presented as mean (SD); comparisons between VMD and ND are not showed, all p values > 0.2. Tukey's adjustment is applied (∗ indicates Dunnett's adjustment).

CVLT TL	Controls 54.6 (9.3)	Versus	ND 50.2 (9.1) $p = 0.05$
		Versus	VMD 48.2 (11.5) $p = 0.045$
CVLT LTM	Controls 0.3 (0.9)	Versus	ND −0.3 (1.0) $p = 0.007$
		Versus	VMD −0.7 (1.2) $p = 0.001$
BVMT TL	Controls 47.9 (13.3)	Versus	ND 47.1 (12.8) $p = 0.946$
		Versus	VMD 40.1 (15.6) $p = 0.094$
BVMT LTM	Controls 54.9 (10.3)	Versus	ND 51.2 (12.7) $p = 0.265$
		Versus	VMD 45.4 (14.2) $p = 0.016$
PASAT 3″	Controls 41.9 (10.1)	Versus	ND 39.5 (13.7) $p = 0.597$
		Versus	VMD 35.7 (15.8) $p = 0.2$
PASAT 2″	Controls 32.4 (13.2)	Versus	ND 26.5 (14.1) $p = 0.075$
		Versus	VMD 25.6 (14.2) $p = 0.182$
SDMT	Controls 45.2 (6.4)	Versus	ND 43.1 (11.2) $p = 0.474^*$
		Versus	VMD 38.3 (10.6) $p = 0.042^*$
DKEFS CS	Controls 9.8 (3.3)	Versus	ND 8.4 (2.2) $p = 0.014$
		Versus	VMD 7.5 (2.4) $p = 0.005$
DKEFS DS	Controls 10.2 (3.3)	Versus	ND 8.3 (2.6) $p = 0.002$
		Versus	VMD 7.6 (2.6) $p = 0.003$
JLO	Controls 23.6 (5.1)	Versus	ND 23.6 (4.8) $p = 0.999$
		Versus	VMD 22.8 (3.3) $p = 0.813$
COWAT	Controls 39.1 (13.6)	Versus	ND 30.2 (11.5) $p = 0.002$
		Versus	VMD 25.4 (8.7) $p < 0.001$

A significant effect of the group X test type interaction ($F(df1_{\text{Greenhouse-Geisser}} = 12.25$ and $df2_{\text{Greenhouse-Geisser}} = 802.59) = 1.771$; $p = 0.047$) was also found, indicating again that the differences among groups were dependent on the type of test (Figure 2). Separate ANOVAs were conducted for each NP subtest to evaluate intergroup differences, revealing significant differences among groups in verbal memory (CVLT TL: $F(2,131) = 3.95$, $p = 0.022$; CVLT LTM: $F(2,131) = 8.597$, $p < 0.001$), visuospatial long-term memory (BVMT LTM: $F(2,131) = 3.977$, $p = 0.021$), executive functions (DKEFS CS: $F(2,131) = 6.441$, $p = 0.002$; DKEFS DS: $F(2,131) = 8.144$, $p < 0.001$; and COWAT: $F(2,131) = 11.195$, $p < 0.001$), and information processing speed (SDMT: $F(2,131) = 3.220$, $p = 0.043$).

Post hoc comparisons showed that there were significant differences between HC and the ND group in verbal memory (CVLT LTM, $p = 0.007$) and executive functions (DKEFS CS, $p = 0.014$; DKEFS DS, $p = 0.002$; and COWAT, $p = 0.002$) (Table 3). HC and VMD were significantly different in verbal memory (CVLT TL, $p = 0.045$; CVLT LTM, $p = 0.001$), visuospatial long-term memory (BVMT LTM, $p = 0.016$), information processing speed (SDMT, $p = 0.042$), and executive functions (DKEFS CS, $p = 0.005$; DKEFS DS, $p = 0.003$; and COWAT, $p < 0.001$). No significant differences were observed between the ND and VMD subgroups (Table 3).

It should be noted that with such an unbalanced distribution of cases in the two subgroups (73 ND versus 19 VMDP), only large standardized effect sizes (>0.8) have enough probability (power > 80%) to be recognized as statistically significant at the defined significance threshold (0.05).

In Figure 3, for each subgroup considered, percentages of pathological scores (1.5 SD below the control mean) for every NP test are reported, and the VMD, with respect to ND, reflected a greater rate of cognitive impairment in almost every test considered.

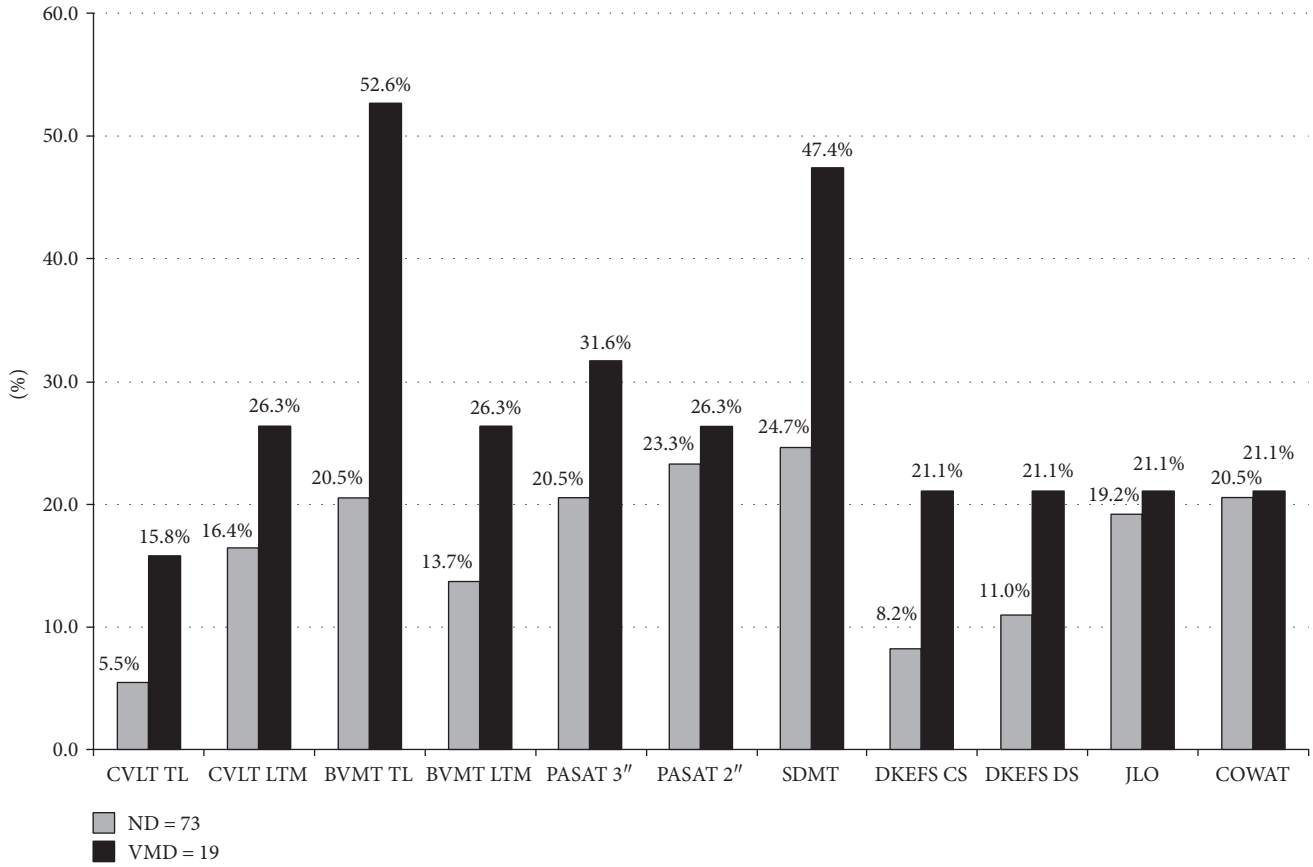

Figure 3: Percentage of impairment in each multiple sclerosis patient subgroup. CVLT TL: California Verbal Learning Test total learning; CVLT LTM: CVLT long-term memory; BVMT TL: Brief Visuospatial Memory Test total learning; BVMT LTM: BVMT long-term memory; SDMT: Symbol Digit Modalities Test; PASAT 3″ and 2″: Paced Auditory Serial Addition Test; JLO: Judgment of Line Orientation; DKEFS CS: Delis-Kaplan Executive Function System sorting test correct sort; DEKEFS DS: DEKEFS description score; COWAT: Controlled Oral Word Association Test. ND: no disability; VMD: very mild disability.

4. Discussion

Our results demonstrate that 51.1% of our MS patients with EDSS ≤ 2.5 have cognitive dysfunction (at least two tests ≤ 1.5 SD); in particular, 16.3% had a mild (two tests failed), 15.2% had a moderate (three tests failed), and 19.6% had a severe (≥four tests failed) level of impairment. Even when we applied a more restrictive cut-off (5th percentile), 40.2% of patients were cognitively impaired. Moreover, considering the number of impaired cognitive domains, we found that 43.5% of MS patients showed at least two compromised domains. Also, by applying the 5th percentile cut-off to the number of impaired domains, we observed that 33.7% of MS patients were significantly altered. Verbal memory (learning and recall), visuospatial long-term memory, working memory, and executive functions (DKEFS and COWAT) were the cognitive functions mostly impaired in MS patients compared to HC. As shown in Table 2, some cognitive tests (namely, COWAT, DKEFS DS, and CVLT LTM) were more sensitive to detect differences between the RRMS and HC groups.

In ND (EDSS ≤ 1.5), an unsatisfactory cognitive performance was limited to verbal memory and executive functions, while VMD patients (2 ≤ EDSS ≤ 2.5) also performed badly in information processing speed and visuospatial long-term memory. Overall, the VMD patients received lower scores than the ND patients in almost every test considered (Figure 3). Finally, MS patient showed higher levels of depression than HC (BDI score). Depression mood can affect cognitive performance; for this purpose, we applied ANCOVA with diagnosis and sex as factors and BDI as a covariate to compare cognitive performance of MS patients and HC. In general, all cognitive differences between MS patients and healthy controls still remained statistically significant.

These findings highlight and confirm that even considering very mildly clinically disabled MS patients, almost half of them experience some degree of cognitive impairment, suggesting that cognitive dysfunction can occur early in the disease. Particularly, executive functions and verbal memory can be impaired even before the onset of significant disability and can remain stable in VMD patients. In addition, information processing speed and visual memory are relatively preserved in ND patients and tend to deteriorate in the VMD group (see neuropsychological profiles shown in Figure 2).

Clinical disability generally progresses over the course of MS [4], although the correlation between cognitive

impairment, clinical disability, and disease duration seems to be weak. Some studies found a neuropsychological performance impairment in recently diagnosed patients [24, 25], in patients with CIS [7, 26, 27], and in RRMS patients at early stages of the disease with little or no disability [7, 22, 26, 28]. Otherwise, many studies reported a poorer neuropsychological performance in patients with chronic progressive or secondary progressive MS [1, 6, 7, 9] than in RRMS patients. These findings imply that the higher the disability in a more advanced stage of MS, the greater the cognitive impairment. However, only a few studies investigated cognitive functioning in very mildly clinically disabled patients so far. Lynch and colleagues [16] showed a significant but slight association between cognitive impairment and clinical disability, independent of disease duration.

In the present study, disease duration ranged from three months to 30 years, but it did not significantly correlate with NP test scores. On the contrary, a significant correlation between clinical disability and CI was observed both in patients without disability and in patients with VMD. These findings, according to the literature [7, 8, 22, 26, 28], emphasize the existence of CI even in patients lacking clinical disability or in cases of VMD and show the progressive impairment of different cognitive domains related to EDSS worsening.

Furthermore, our results confirm the primary engagement of verbal memory and executive functions in very mild levels of clinical disability in accordance with previous studies [7, 29, 30]. Cerezo García and colleagues [29], in a small cohort of patients, found that 24% of very mild RRMS patients had memory deficits and 80% showed information processing speed and executive function impairment, especially in the maintenance of nonautomatic strategies and conceptual/categorization tasks, usually attributed to prefrontal regions. Roca and colleagues [30] showed that MS patients with low physical disability presented a fronto-subcortical pattern with impairment in memory, decision-making, working memory, and planning, as well as in goal-oriented behavior. This pattern correlated with loss of tissue integrity and organization in fronto-subcortical fiber tracts, particularly in the fronto-lateral (FL) areas, as measured with magnetic resonance diffusion tensor imaging. Interestingly, FL areas were specifically linked to executive cognitive dysfunction, such as poor planning, loss of inhibitory control, strategy development, cognitive flexibility, and working memory [31]. Ruano and colleagues [7], in a large Italian multicenter study, show a significant presence of CI since the earlier stages of MS in patients with RRMS and CIS with a more frequent involvement of information processing speed and executive function compared with other cognitive domains. In particular, these studies [7, 29, 30] used a specific executive battery consisting of sensitive tests to detect prefrontal cortex dysfunction.

Memory and executive impairment is relevant functions of the cognitive profile observed in MS and closely linked to prefrontal cortex functions. Memory is the process in which information is encoded, stored, and retrieved. Executive functions refer to the cognitive abilities needed for complex goal-directed behavior and adaptation to environmental changes and include several functions (working memory, reasoning, task flexibility, problem solving, and planning) [32]. Memory and executive function impairment negatively influences a patient's quality of life, as well as their everyday life functioning [33]. Nonetheless, in clinical practice, executive deficits are often misunderstood because their detection and characterization are not easy. Patients do not often complain about them, and the most used NP tests do not include specific executive functioning tests. Our study highlighted that an Italian version of MACFIMS is effective in assessing cognitive functioning in MS patients with very mild disability. This analysis method is specific, reliable, quick, and sensitive for the complete and comprehensive assessment of cognitive function in MS [3].

The high percentage (51.1%) of cognitive impairment in our sample of MS patients with very mild clinical disability could be due to employment of a complete and comprehensive neuropsychological analysis. It would be useful in clinical practice to use reliable and sensitive tools in order to early detect executive function impairment and to suggest an adequate cognitive training. The lack of a significant difference in the cognitive performance of the two patient groups can be attributed to the small VMD sample ($n = 19$). Future studies should therefore take into account the possibility of increasing the sample to evaluate possible differences. Another limitation of this study was the lack of a measure to assess fatigue and nutritional life style, two factors possibly influencing cognitive performance. Moreover, comparing different groups of patients, cognitive reserve is another important variable to be considered in future studies. Finally, another limitation could be the effect of interferon and glatiramer acetate on cognitive functioning; it has been demonstrated that some aspects of cognitive functioning may improve in patients with MS [34–36] and this may have had an impact on our results.

In conclusion, our study showed that half of our MS patients had an impaired performance on at least two cognitive tests, confirming that CI is a common symptom of MS even among patients with very mild or no clinical disability. Furthermore, compared to HC, the very mildly clinically disabled RRMS patients showed impairment of memory and executive functions with a main involvement of prefrontal cognitive functions. These results support the hypothesis that frontal lobes are highly sensitive, even in the early stage of the disease, due to their numerous connections with other cortical and subcortical regions, so that damages in any part of the brain can trigger effects in these areas [37, 38]. Memory impairment is probably related more to a failure in executive functioning, and in particular, organization and use of self-generated strategies to encode and recall new material could be less efficient, reflecting a poor performance of prefrontal functions. Detecting early executive dysfunctions with specific NP tests could be useful in order to promptly enroll MS patients in adequate rehabilitation projects.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

[1] N. D. Chiaravalloti and J. DeLuca, "Cognitive impairment in multiple sclerosis," *The Lancet Neurology*, vol. 7, no. 12, pp. 1139–1151, 2008.

[2] J. H. Kalmar, E. A. Gaudino, N. B. Moore, J. Halper, and J. DeLuca, "The relationship between cognitive deficits and everyday functional activities in multiple sclerosis," *Neuropsychology*, vol. 22, no. 4, p. 442, 2008.

[3] R. H. Benedict, D. Cookfair, R. Gavett et al., "Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS)," *Journal of the International Neuropsychological Society*, vol. 12, no. 04, pp. 549–558, 2006.

[4] S. D. Cook, *Handbook of Multiple Sclerosis*, CRC Press, Boca Raton, FL, USA, 2001.

[5] S. Migliore, A. Ghazaryan, I. Simonelli et al., "Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS) in the Italian population," *Neurological Sciences*, vol. 37, pp. 1261–1270, 2016.

[6] D. R. Denney, L. A. Sworowski, and S. G. Lynch, "Cognitive impairment in three subtypes of multiple sclerosis," *Archives of Clinical Neuropsychology*, vol. 20, no. 8, pp. 967–981, 2005.

[7] L. Ruano, E. Portaccio, B. Goretti et al., "Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes," *Multiple Sclerosis Journal*, 2016.

[8] D. W. Langdon, "Cognition in multiple sclerosis," *Current Opinion in Neurology*, vol. 24, no. 3, pp. 244–249, 2011.

[9] M. P. Amato, G. Ponziani, G. Siracusa, and S. Sorbi, "Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years," *Archives of Neurology*, vol. 58, no. 10, pp. 1602–1606, 2001.

[10] P. Kujala, R. Portin, and J. Ruutiainen, "The progress of cognitive decline in multiple sclerosis. A controlled 3-year follow-up," *Brain*, vol. 120, Part 2, pp. 289–297, 1997.

[11] D. Schulz, B. Kopp, A. Kunkel, and J. H. Faiss, "Cognition in the early stage of multiple sclerosis," *Journal of Neurology*, vol. 253, no. 8, pp. 1002–1010, 2006.

[12] U. Nocentini, P. Pasqualetti, S. Bonavita et al., "Cognitive dysfunction in patients with relapsing-remitting multiple sclerosis," *Multiple Sclerosis*, vol. 12, no. 1, pp. 77–87, 2006.

[13] E. A. Gaudino, N. D. Chiaravalloti, J. DeLuca, and B. J. Diamond, "A comparison of memory performance in relapsing–remitting, primary progressive and secondary progressive, multiple sclerosis," *Cognitive and Behavioral Neurology*, vol. 14, no. 1, pp. 32–44, 2001.

[14] S. M. Rao, G. J. Leo, L. Ellington, T. Nauertz, L. Bernardin, and F. Unverzagt, "Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning," *Neurology*, vol. 41, no. 5, pp. 692–696, 1991.

[15] M. P. Amato, E. Portaccio, M. L. Stromillo et al., "Cognitive assessment and quantitative magnetic resonance metrics can help to identify benign multiple sclerosis," *Neurology*, vol. 71, no. 9, pp. 632–638, 2008.

[16] S. G. Lynch, B. A. Parmenter, and D. R. Denney, "The association between cognitive impairment and physical disability in multiple sclerosis," *Multiple Sclerosis*, vol. 11, no. 4, pp. 469–476, 2005.

[17] C. H. Polman, S. C. Reingold, B. Banwell et al., "Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria," *Annals of Neurology*, vol. 69, no. 2, pp. 292–302, 2011.

[18] J. F. Kurtzke, "Rating neurologic impairment in multiple sclerosis an expanded disability status scale (EDSS)," *Neurology*, vol. 33, no. 11, pp. 1444–1452, 1983.

[19] R. H. Benedict, J. S. Fischer, C. J. Archibald et al., "Minimal neuropsychological assessment of MS patients: a consensus approach," *The Clinical Neuropsychologist*, vol. 16, no. 3, pp. 381–397, 2002.

[20] A. T. Beck, R. A. Steer, R. Ball, and W. F. Ranieri, "Comparison of Beck Depression Inventories-IA and-II in psychiatric outpatients," *Journal of Personality Assessment*, vol. 67, no. 3, pp. 588–597, 1996.

[21] C. D. Spielberger and R. L. Gorsuch, *State-Trait Anxiety Inventory for Adults, Sampler Set: ManualTekst Booklet and Scoring Key*, Consulting Psychologists Press, Palo Alto, CA, USA, 1983.

[22] M. P. Amato, E. Portaccio, B. Goretti et al., "Cognitive impairment in early stages of multiple sclerosis," *Neurological Sciences*, vol. 31, Supplement 2, pp. S211–S214, 2010.

[23] J. Cohen, "A power primer," *Psychological Bulletin*, vol. 112, no. 1, p. 155, 1992.

[24] E. Hankomäki, J. Multanen, E. Kinnunen, and P. Hämäläinen, "The progress of cognitive decline in newly diagnosed MS patients," *Acta Neurologica Scandinavica*, vol. 129, no. 3, pp. 184–191, 2014.

[25] O. Lyon-Caen, R. Jouvent, S. Hauser et al., "Cognitive function in recent-onset demyelinating diseases," *Archives of Neurology*, vol. 43, no. 11, pp. 1138–1141, 1986.

[26] A. Achiron and Y. Barak, "Cognitive impairment in probable multiple sclerosis," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 74, no. 4, pp. 443–446, 2003.

[27] C. Potagas, E. Giogkaraki, G. Koutsis et al., "Cognitive impairment in different MS subtypes and clinically isolated syndromes," *Journal of the Neurological Sciences*, vol. 267, no. 1, pp. 100–106, 2008.

[28] M. P. Amato, V. Zipoli, B. Goretti et al., "Benign multiple sclerosis," *Journal of Neurology*, vol. 253, no. 8, pp. 1054–1059, 2006.

[29] M. Cerezo García, P. Martín Plasencia, and B. Y. Aladro, "Alteration profile of executive functions in multiple sclerosis," *Acta Neurologica Scandinavica*, vol. 131, no. 5, pp. 313–320, 2015.

[30] M. Roca, T. Torralva, F. Meli et al., "Cognitive deficits in multiple sclerosis correlate with changes in fronto-subcortical tracts," *Multiple Sclerosis*, vol. 14, no. 3, pp. 364–369, 2008.

[31] J. L. Cummings, "Frontal-subcortical circuits and human behavior," *Archives of Neurology*, vol. 50, no. 8, pp. 873–880, 1993.

[32] R. Elliott, "Executive functions and their disorders: imaging in clinical neuroscience," *British Medical Bulletin*, vol. 65, no. 1, pp. 49–59, 2003.

[33] J. Kleeberg, L. Bruggimann, J. M. Annoni, G. Mellevan, J. Bogousslavsky, and M. Schluep, "Altered decision-making in multiple sclerosis: a sign of impaired emotional reactivity?," *Annals of Neurology*, vol. 56, no. 6, pp. 787–795, 2004.

[34] M. Lacy, M. Hauser, N. Pliskin, S. Assuras, M. O. Valentine, and A. Reder, "The effects of long-term interferon-beta-1b treatment on cognitive functioning in multiple sclerosis: a 16-year longitudinal study," *Multiple Sclerosis Journal*, vol. 19, no. 13, pp. 1765–1772, 2013.

[35] N. Mokhber, A. Azarpazhooh, E. Orouji et al., "Cognitive dysfunction in patients with multiple sclerosis treated with

different types of interferon beta: a randomized clinical trial," *Journal of the Neurological Sciences*, vol. 342, no. 1, pp. 16–20, 2014.

[36] F. Mori, H. Kusayanagi, F. Buttari, C. G. Nicoletti, G. Bernardi, and D. Centonze, "Glatiramer acetate reverses plasticity and cognitive deficits associated with acute inflammation in MS (P04. 118)," *Neurology*, vol. 78, Supplement 1, pp. P04–118, 2012.

[37] E. Goldberg, "Introduction: the frontal lobes in neurological and psychiatric conditions," *Cognitive and Behavioral Neurology*, vol. 5, no. 4, pp. 231-232, 1992.

[38] E. Goldberg, *The Executive Brain: Frontal Lobes and the Civilized Mind*, Oxford University Press, USA, 2002.