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Chapter

Neuropsychological Functions and Cognitive Neurorehabilitation in Multiple Sclerosis

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Abstract

Although cognitive difficulties are not frequently reported by patients among the initial symptoms of Multiple Sclerosis (MS), there is sufficient evidence that cognitive impairment is present from the early stage of the disease. Today it is commonly accepted that roughly one-half of individuals with MS will experience cognitive dysfunction over the course of the disease. Though MS was originally considered a disease of white matter, more recent investigations with advanced immunohistochemistry techniques have revealed that demyelination of gray matter is a common neuropathological feature in MS contributing significantly to cognitive impairment. However, despite now been recognized as a core symptom of MS, evidence up till now is only modest regarding the efficacy of pharmacological agents on cognitive dysfunction and non-pharmacological interventions such as cognitive rehabilitation also provide incomplete evidence on whether they might improve or stabilize cognitive impairment and especially over long follow up periods. Despite this general consensus, there are studies that have reported the efficacy of cognitive neurorehabilitation in reducing MS associated cognitive deficits. In this chapter we provide a selective review of the most relevant features related to this topic.

Keywords: multiple sclerosis, neuropsychological functions, cognition, cognitive neurorehabilitation

1. Introduction

Historically the disease today known as multiple sclerosis (MS) has been referred to in the historical medical literature with a variety of terms, including, disseminated sclerosis and sclerose en plaque [1]. Lidwina van Schiedam, was the first potential case of MS dating as far back as 1421, when Jan van Berieren commented on her illness. Records showed that she had difficulties walking, paralysis of the right arm, decreased sensation and visual difficulties [2].

Today we know that MS is a chronic inflammatory autoimmune degenerative disease of the central nervous system (CNS). It is the most common non-traumatic neurological disorder among young adults leading to disability. The etiology of MS involves white matter pathology, cortical atrophy, cortical lesions, and microstructural abnormalities in deep gray matter that impact structural and functional

connectivity [3]. Cognitive impairment in MS appears to be a result of this diffuse disruption in brain networks [4]. These patients may also present sensorimotor [5], visual [6], bladder, cerebellar [7] and emotional difficulties leading to functional disability [8] and poorer quality of life [9].

Environmental factors and especially geographical latitude may significantly influence the development of MS. However, genetic susceptibility as is evident from twin studies and familial cases, suggests that MS disease causality is due to a complex interaction between multiple genes and environmental factors, eventually leading to inflammatory-mediated central nervous system deterioration [10]. Genomic studies, with specific HLA antigens (HLA-DR2), have confirmed the genetic susceptibility of MS [10]. Numerous other environmental factors have been evaluated that may be associated with MS, but methodological caveats have casted doubts on their validity. On average, MS patients contracted common childhood illnesses at later ages than healthy controls [11]. A biomarker of Epstein-Barr virus (anti-EBNA IgG seropositivity), infectious mononucleosis, and smoking have shown the strongest consistent evidence of an association. However, additional data and better-designed studies are needed to establish robust evidence [12].

MS disease course is heterogeneous in nature and several types have been described: Relapsing remitting MS (RRMS), Active (with relapses and/or new lesions on MRI), Not Active (no relapses or MRI activity), Progressive MS (Secondary Progressive MS (SPMS) and Primary Progressive MS (PPMS), Active with Progression (relapses/MRI activity and clinical deterioration not due to relapses), Active but without Progression (relapses but no clinical deterioration), Not Active but with Progression, Not Active and without Progression (stable disease) [13]. The use of these terms is primarily for descriptive purposes and for setting reasonable expectations for treatment.

This chapter is not a comprehensive review of the extensive literature on neuropsychological functions and cognitive rehabilitation in multiple sclerosis, but rather a selective review of the most relevant features related to this topic.

2. Neuropsychological functions in multiple sclerosis

Dating back to the seminal writings on MS, Charcot's observations of the adverse effects that MS exerts on memory, concept formation, and the intellect [14], were underestimated for many decades in the neurology literature. It was only with the emergence of the comprehensive care model in the early 1980s, that the nature and significance of cognitive dysfunction in MS became appreciated. 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 MS. Instead, they believed that cognitive impairment was a relatively rare entity in MS, occurred only in advanced cases with a high level of physical disability and was associated with subcortical dementia [15].

Cognitive difficulties are not frequently reported by patients among the initial symptoms of MS, although there is sufficient evidence that cognitive impairment is present from the early stage of the disease (see for e.g., the study by [16], which assessed MS patients neuropsychologically, not more than 2 years after experiencing their first neurological symptoms, and [17], who presents three cases evaluated at different stages of the disease). Moreover, cognitive impairment may be present in the early stages of the disease in patients with relatively low or mild physical disability (see for e.g. the studies by [18, 19] who found cognitive deficits in patients with an EDSS disability score of ≤3.5, that had not yet been influenced

significantly in their daily functional abilities and employment status). A recent anatomofunctional study utilizing diffusion imaging and resting state functional MRI, revealed that disconnection in the default mode network (DMN) and attentional networks (ATT), may deprive the brain of the necessary compensatory mechanisms required to face the widespread structural damage during the early course of MS, providing a possible explanation for the cognitive dysfunction in these early stages of the disease [20].

Although it is now commonly accepted that roughly one-half of individuals with MS [21, 22], will experience clinical 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. A recent study that included RRMS and SPMS patients attending an outpatient neurology clinic reported an overall cognitive dysfunction prevalence rate of 53.7% [23]. Moreover, the study by [22], reported that 47% of their MS patients recruited from an outpatient clinical setting, diagnosed with the revised McDonald criteria [24], the majority with RRMS and mean duration of illness at 9.6 years, assessed with a brief cognitive measure (BICAMS), performed below the 1SD cutoff set for impairment on at least one of the three tests that comprise this brief neuropsychological battery. In an interesting cross-sectional study that evaluated the patterns of cognitive impairment in patients with disease duration of up to 30 years, 20.9% performed below the 1SD cutoff for impairment by the 5th year from disease onset, by 10 years this had reached 29.3%. By utilizing regression modeling the authors suggested that cognitive impairment may precede MS onset by 1.2 years [25].

Most of the evidence suggests that cognitive impairment in MS patients is present during all disease stages and across all disease clinical subtypes [26–28], including, RRMS, PPMS, SPMS, Clinically Isolated Syndrome (CIS) and "benign MS" [29, 30], and even Radiologically Isolated Syndrome—(RIS) [31]. Based on the majority of studies that have compared cognitive functions across disease subtype, deficits appear to be more frequent and more widespread in the progressive type rather than in the relapsing form of the disease [23, 29, 31–32].

The dissemination of lesions in cerebral white matter including their affinity for periventricular regions provides the basis for some cognitive dysfunction commonalities [33]. In this respect, some cognitive domains appear to be more commonly compromised than others. Information processing efficiency, episodic memory, attention, and executive functioning are the domains found predominantly to be detrimentally affected in MS [21, 34, 35]. Among these domains the most common pattern involves circumscribed deficits as a combination of one or two of the above-mentioned domains (e.g., attention/processing speed, learning/memory, and or executive functions [11, 15, 21].

Symptoms like cognitive and physical fatigue, which are often accompanied by depression and anxiety, may negatively influence cognition in MS patients. This is especially true when extended periods are required to complete and appear more relevant for the patient's daily life than what may be assumed by many physicians treating MS patients [11].

Although cognitive impairment is highly prevalent among MS patients, some have a tendency to withstand severe disease burden (e.g., white matter lesions and cerebral atrophy), and present with overall lower levels of cognitive decline. One possible explanation for this protective mechanism is the brain reserve hypothesis and the cognitive reserve theory [36]. Recently, it has been verified that highly significant protection for cognitive impairment is provided by brain reserve, defined as the maximal lifetime brain growth (MLBG), and estimated with intracranial volume or head circumference. Larger MLBG a proxy for neuronal and

synaptic count has been linked to lower risk for cognitive impairment in MS [37]. This larger MLBG appears to be associated with more robust neural networks resistant to disease-related disruption and also provides more potential degrees of freedom for the brain to plastically reorganize in the face of MS disease related challenges.

2.1 Assessment of neuropsychological functions in MS

The multidimensional nature of cognitive dysfunction in MS necessitates an assessment of numerous cognitive domains. The challenge until recently was to find the optimal combination of cognitive tests that would provide an accurate picture of the deficits whilst avoiding the use of unnecessary and time-consuming measures [15].

In order to overcome some of the limitations in assessing cognition in MS, and considering the fact that not all neuropsychological measures are appropriate for the MS population, a number of neuropsychological assessment tools (brief screening batteries and comprehensive neuropsychological batteries), have been utilized specifically for this population in routine clinical care and for research purposes. **Table 1** provides a summary of the most important neuropsychological tools utilized in MS patients.

2.2 Neuropsychological functions and neuroimaging

Although MS was originally considered to be a disease of White Matter (WM), more recently with the development and utilization of advanced immunohisto-chemistry techniques investigators have begun to appreciate that demyelination of gray matter (GM) is a common neuropathological feature in MS patients. Demyelination of GM appears to be more common in the cerebellum, spinal cord and hippocampus. Essentially, however, no areas within the CNS are actually spared [38]. The thalamus is considered the most frequently affected subcortical

Cognitive domain	Rao brief repeatable neuropsychological battery (BRB)	Minimal assessment of cognitive function in MS (MACFIMS)	NINDS common data elements	Brief assessment of multiple sclerosis (BICAMS)
Cognitive processing speed	SDMT	SDMT	SDMT	SDMT
	PASAT	PASAT	PASAT	—
Language	COWAT	COWAT	COWAT	—
Visual/spatial	—	JLO	—	—
Memory	SRT	CVLT2	CVLT2	CVLT2
	10/36 Spatial Recall Test	BVMTR	BVMTR	BVMTR
Executive function	—	D-KEFS	D-KEFS	—

SDMT: Symbol Digits Modalities Test; PASAT: Paced Auditory Serial Addition Test; COWAT: Controlled Oral Word Association Test; CVLT2: California Verbal Learning Test 2nd edition; BVMTR: Brief Visuospatial Memory Test Revised; DKEFS: Delis Kaplan Executive Function System Sorting Test.

Table 1.
Neuropsychological batteries utilized in MS patients.

GM structure, but lesions have been identified within the putamen, pallidum, caudate, amygdale, substantia nigra and hypothalamus [39].

Considering the above, clinicians and researchers investigating neuropsychological functions in MS patients have realized that cognitive dysfunction in this population cannot be explained by WM pathology alone. GM pathology appears to have a significant impact on cognitive impairment, but requires novel neuroimaging technology in order to detect and visualize these types of lesions. Due to these visualization difficulties in current imaging technologies, research in MS has shifted its focus primarily to comparing WM and GM measures of atrophy [39]. In this respect, [40], noted a similar increase in WM atrophy across disease stages (three-fold), whereas, atrophy of the GM increased proportionally according to disease stage, i.e. three-fold in CIS converting to RRMS, versus 14-fold in SPMS patients.

Another important issue is that GM atrophy has been reported to be regionally specific, involving early volume loss of the basal ganglia, corpus callosum and thalamus. Recent studies have outlined the significance of thalamic volume in relation to cognitive impairment. One such report by [41] found lower thalamic volumes in MS patients compared to healthy participants, with the lowest volumes found in severely cognitive impaired patients. In one of our recent studies, we provide evidence that thalamic atrophy was the best predictor of cognitive dysfunction in RRMS patients and was also highly associated with activities of daily living and employment status [42]. Moreover, in a similar study that recruited late stage SPMS patients, we found that corpus callosum atrophy was associated with deficits in cognitive flexibility, processing speed, episodic memory, executive functions, reaction time and phonological verbal fluency. Processing speed and composite memory were the most sensitive markers for predicting employment status. Corpus callosum atrophy was the most sensitive MRI marker for episodic memory and processing speed deficits. Moreover, corpus callosum atrophy predicted a clinically meaningful cognitive decline, affecting employment status in our SPMS patients [43]. Thus, it appears that irreversible tissue loss, as measured by brain atrophy of the white and gray matter, is strongly associated to cognitive function in the MS population. While white matter atrophy has also been reported to contribute significantly to impairment in mental processing speed and working memory, gray matter atrophy was highly predictive for verbal memory status, but additionally predicted neuropsychiatric symptoms such as disinhibition and euphoria [44].

3. Interventions for cognitive dysfunction in multiple sclerosis

Recent evidence from empirical research has indicated that cognitive dysfunction in MS patients is highly related to everyday functioning abilities [45]. One such study that evaluated associations between cognitive functions and objective performance on measures of everyday functioning in MS, [46], reported that MS patients had significantly more difficulties in simple and more complex cooking abilities, using the phone, taking medication, and paying the bills, compared to healthy participants. An interesting study by O'Brien et al. [47] and a more ecologically valid study by Goverover et al [48], utilizing an actual reality (AR) approach through the use of everyday tasks requiring the internet (e.g. booking an airline ticket, purchasing cookies and ordering pizza), the authors report significant correlations between these tasks and performance on mental processing speed (SDMT), concluding that this measure contributes significantly to predicting everyday functioning capacity in MS. A more recent study, [48], examined the ability of MS patients to manage their finances. The authors found that MS patients demonstrated and reported more difficulties in managing their finances compared

to healthy controls. Moreover, MS patient's difficulties in handling their finances were associated with the severity of cognitive dysfunction. As this important everyday task requires intact mental processing ability and executive-attentional abilities, domains usually impaired in MS individuals, these findings may serve as potential intervention indicators when planning cognitive rehabilitation interventions.

From the findings reported by the studies mentioned previously, it becomes obvious that interventions to alleviate, stabilize, reduce or compensate for cognitive impairment are of an extremely high priority, in order to provide MS individuals with the necessary mechanisms to better handle their everyday functioning disabilities. The evidence up till now is only modest regarding the efficacy of pharmacological agents on cognitive dysfunction [49, 50], and non-pharmacological interventions such as cognitive rehabilitation also provide incomplete evidence on whether they might improve or stabilize cognitive impairment and especially over long follow up periods [51]. Despite this general consensus, there are studies that have reported the efficacy of pharmacological agents [52] and cognitive rehabilitation [28, 53, 54] in reducing MS associated cognitive deficits.

3.1 Cognitive neurorehabilitation in multiple sclerosis

The goals of non-pharmacological treatments for MS-related cognitive deficits are similar to those of the immune-modulating drugs. In other words, these interventions are used with the intent of preventing the progression of cognitive dysfunction and promoting a therapeutic 'milieu' in which optimal cognitive functioning can occur, and include specific approaches which are known to be effective in remediating cognitive disorders of any etiology [15]. Cognitive rehabilitation or 'rehabilitation of individuals with cognitive impairment' [55] include specific approaches designed to assist the MS patient to better cope with existing cognitive impairments or to improve a specific cognitive skill. It focuses on two main approaches: the restorative or functional training approach (i.e. ameliorating patients' deficits in processing and interpreting information—e.g. when cognitive training is used to enhance attention or memory performance). The restorative approach depends on the brains capability of cortical reorganization following injury (i.e. that the brain possesses some degree of plasticity). The second is the compensatory or strategy training approach (e.g. modifying the patient's environment, using a calendar and set phone reminders). These approaches have different goals and limitations, and may be used in isolation or in combination. For example, in patients with extensive tissue loss, neural plasticity might be hampered and no or little effect will result from restorative or functional training. In that particular patient, compensatory or strategy training might help the patient to work around the problems that are present. As for most MS patients, especially those with a relapsing disease course, it is expected that restorative or functional training will lead to improved cognitive functioning on neuropsychological measures, improved functioning in everyday life activities, and ultimately will lead to an improvement in network efficiency [56].

Several studies have investigated the effectiveness of cognitive rehabilitation interventions in patients with MS, including computer-based training and neuropsychological counseling, but with inconsistent results. The majority of studies found improvements in specific cognitive domains, but the evidence provided in the literature remains inconclusive [57]. A significant limitation in providing evidence on the efficacy of studies involving cognitive rehabilitation is the great variability in the methods or strategies utilized for treatment, the measures used to assess cognition and other secondary outcome variables and the lack of ecologically

valid outcome measures in order to assess the efficiency of these interventions in everyday functioning ability.

Applying a technique known as the Story Memory Technique (SMT), [58] provided class 1 evidence that this technique applied for 5 weeks/twice weekly (10 sessions) with an emphasis on teaching context and imagery to facilitate learning, improved episodic memory in MS patients relative to controls and moreover produced increased f-MRI activation during a memory task in frontal and parietal regions. Positive effects were additionally observed for objective measures of everyday memory function, general contentment, and executive functioning. These positive outcomes were sustained for a period of 6 months.

Clinical trials utilizing the RehaCom computerized software in MS patients with cognitive impairments have also shown positive outcomes. Bonavita et al. [59], noted significant pre-to post treatment improvements in a RehaCom treated MS cohort, on mental information processing, executive functions and attention. This and other similar studies have reported positive outcomes in MS patients treated with this software, and moreover, associations between functional neuroimaging (f-MRI) findings with changes in neurocognitive measures have been reported [59–61]. In a multicenter Italian study, RehaCom was utilized to provide specific intensive cognitive training for 12 months. Results showed that MS patients treated with this modality had improved scores post treatment on the SDMT, PASAT, and episodic memory measures relative to MS patients who received aspecific psychological therapy for the same period of time [62].

In 2017, our group, [53], conducted a multicenter randomized controlled trial with 58 clinically stable RRMS patients utilizing computer-assisted (RehaCom) functional cognitive training with an emphasis on episodic memory, information processing speed/attention, and executive functions for 10 weeks. Our findings revealed that only the group that had received functional cognitive training 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. Treated patients rated the intervention positively and were more confident about their cognitive abilities following treatment.

While the previously mentioned positive results regarding the efficacy of cognitive rehabilitation interventions in MS individuals cannot be overstated, it is important to note that a recently published Cochrane Review that included 15 studies and 989 MS participants regarding the efficacy of memory retraining techniques with or without the assistance of computer software, concluded that there is only limited evidence on the effectiveness of memory rehabilitation in this population. The authors further suggest that more RCTs of high methodological quality be conducted with the utilization of ecologically valid outcome assessments [63].

Another Cochrane Review that included 20 studies and 966 MS participants evaluating the effectiveness of neuropsychological rehabilitation in MS [64], reported low-level evidence for the positive effects of neuropsychological rehabilitation in this population. However, the authors reported that the comparability of the 20 studies reviewed was limited due to heterogeneity of interventions and outcome measures. It should be noted however, that the majority of studies included in this review did show some evidence of positive effects on cognitive outcome measures.

Despite the limitations noted by the previously mentioned Cochrane reviews, a growing body of literature supports the efficacy of cognitive rehabilitation for individuals with MS and more randomized controlled trials are needed to support

existing and new rehabilitation techniques. Cognitive rehabilitation appears to be useful for all patients with MS regardless of disease course and level of cognitive impairment, although studies including exclusively MS patients with progressive disease course are limited. Future clinical trials utilizing cognitive rehabilitation interventions in progressive MS patients should become a priority.

4. Conclusions

Cognitive impairment is frequently encountered in MS individuals, irrespective of disease duration, severity of physical disability, and at both the earlier and later disease stages. Moreover, cognitive dysfunction in this population may have a significant negative impact on quality of life, activities of daily living and employment status. Furthermore, past and current pharmacological treatments have shown inconsistent findings in alleviating cognitive impairment in individuals with MS requiring further clarification. 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, prioritizes the need for utilizing potentially more effective non-pharmacological, neurobehavioral 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 MS individual's everyday life functioning ability. In this respect it becomes obvious that there is a need for rigorous new cognitive neurorehabilitation studies that may overcome some of the methodological limitations of older studies, and provide robust evidence regarding the efficiency of such cognitive interventions for the MS population.

Conflict of interest

The authors have no conflict of interest.

Declarations

Parts of this chapter originate from my Doctoral Dissertation entitled: Neuropsychological functions and association with Single Photon Emission Computed Tomography (SPECT) in Greek Multiple Sclerosis patients: Efficacy of a Computerized Cognitive Rehabilitation Intervention (2017). Department of Neurology, University of Patras Medical School, Patras, Greece.

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