Can we define a rehabilitation strategy for cognitive impairment in progressive multiple sclerosis? A critical appraisal

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Abstract: Cognitive impairment (CI) has been shown to be severe in patients with progressive forms of multiple sclerosis (MS), and the most frequently impaired domains are sustained attention, information processing speed, memory, and executive functions. In contrast to relapsing forms of MS, where studies have shown favorable results from cognitive rehabilitation, there is a lack of data on cognitive rehabilitation in progressive forms of MS. A specific approach in assessing CI and in designing and administering rehabilitation training for patients with progressive forms of MS is needed.

Keywords: Primary progressive MS, cognitive impairment, cognitive rehabilitation

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) which is characterized by a broad range of symptoms, including cognitive impairment (CI) and neuropsychiatric disorders. MS typically starts as an episodic, relapsing-remitting multiple sclerosis (RRMS) disease with complete or partial recovery between relapses. Over time, it evolves in many affected individuals into a secondary progressive multiple sclerosis (SPMS) phase characterized by the irreversible deterioration of both motor and cognitive functions. However, up to 15% of MS patients show a progressive course without relapses and remissions from the onset of clinically overt disease, defined as primary progressive multiple sclerosis (PPMS). Despite early uncertainty as to whether PPMS and SPMS are etiologically distinct from relapse-onset disease, recent evidence points toward common disease mechanisms, with no major differences in gene expression among the different MS subtypes. Pathological studies have reached the same conclusions. For this review, except where defined, SPMS and PPMS will be grouped as progressive multiple sclerosis (PMS).

Overall, CI is present in 40%–70%, and the most frequently impaired domains are sustained attention, information processing speed, memory, and executive functions. The relationships between CI and physical disability and between CI and disease duration are still not fully explained. Some studies have found only a weak or no relationship between the incidence of CI and physical disability or disease duration, while others have shown progression of cognitive deterioration correlated with disease progression and physical disability. Amato et al. performed a neuropsychological (NPS) reappraisal (after a follow-up of about 9 years) of 44 people with RRMS, of whom 18 had evolved to SPMS, showing that the degree of physical disability, progressive disease course, and increasing age predicted the extent of CI.

Several NPS batteries are available to assess cognitive status in MS, but none is specific to PMS. To date, the most widely used NPS instruments are the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) and The Brief Repeatable Battery (BRB) of Rao with or without the Stroop Test (ST). However, both require considerable time and resources, and expert personnel. In response to this, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) has been developed as a new shorter battery. It is already validated in some countries (United States, United Kingdom, Italy) and is being validated in a number of other countries.

Epidemiologic data have shown CI in early-stage MS and among the different phenotypes of the disease,
even in people with clinically isolated syndrome (CIS). Although no consensus has been reached yet regarding CI profiles in MS patients based on the MS phenotype and disease duration,15 several studies have been conducted in order to identify whether patients with PMS have a specific profile of cognitive deficits. The frequency of CI in patients with PMS has been variously quoted as 7%,16 29%,17 and up to 50%.18 CI has been shown to be more frequent and severe in patients with PMS compared to those with RRMS.19 In this study, patients with PMS presented with a wide range of cognitive deficits in information processing speed, attention, working memory, executive function, and verbal episodic memory, and furthermore, they were more impaired in cognitive domains than patients with RRMS, even after controlling for Expanded Disability Status Scale (EDSS) score.19

Some domains are consistently reported to be spared in PPMS compared to RRMS/SPMS including spatial perception and word definition,20 as well as verbal reasoning.17 Deficits in attention and working memory,17,21 verbal memory,17,20,21 spatial memory,21 spatial reasoning,17 and verbal fluency17,21 are frequently reported. It is frustrating that studies to date have failed to confidently identify patterns of CI unique to any disease phenotype. Efforts to define distinct CI profiles between SPMS and PPMS have revealed only subtle differences. It should be noted, however, that there is rarely good matching of the MS populations enrolled in different studies. Separate studies have shown that patients with PPMS performed slightly better than patients with SPMS on a spatial working memory task involving planning22 and a spatial memory task.20 In contrast, another study demonstrated that patients with PPMS have poorer spatial recall and verbal fluency than patients with SPMS.21 Other deficits which were more prominent in PPMS include a specific deficit in word fragment completion, that was not present in RRMS or SPMS,23 and impaired complex attention skills, verbal memory, and verbal fluency, compared with RRMS patients.20,21 Patti et al.24 showed that patients with PMS, when compared with RRMS, had worse scores in Semantically Related Word List Test, for both immediate and delayed recall.

Controlled, cross-sectional, NPS studies of MS patients have demonstrated that cognitive deficits may occur early in the disease process, but are seen more frequently in later disease.25 Less is known about the longitudinal progressive deterioration of NPS skills in individuals with MS. Correlations between CI and indicators of disease progression, such as disability and disease duration, are inconsistent, with some reports showing a significant correlation between CI and physical disability,13,26 while others have recorded no significant relationship.25–28 Several data show preservation of the cognitive skills of MS patients over time,26,28 while others show cognitive deterioration over time.9,10 Recent longitudinal studies of cognition and magnetic resonance imaging (MRI) variables have struggled to demonstrate significant links over time29–31 and future longitudinal studies are warranted.

Identifying specific cognitive deficits may have important clinical implications in terms of tailoring specific rehabilitative interventions.

Across the spectrum of MS phenotypes, there have been a number of studies on cognitive rehabilitation in MS, with many of these studies suffering from significant methodological weaknesses. More recent, well-designed studies, however, have been more promising and have provided evidence of improved objective cognitive performance, as well as improvement in everyday life activities.32–35 Despite this, no specific studies have been carried out to investigate whether patients with PMS might change cognitive performance after cognitive rehabilitation. Only a few studies have sought to investigate the effect of cognitive rehabilitation in cohorts which have included people with PMS, and even here they have not reported results at the sub-group level to isolate the effects in people with PMS. We aim to give an overview of the state-of-the-art of cognition in PMS, highlighting existing shortcomings in assessing and treating cognitive deficits.

**NPS evaluation in different MS phenotypes**

Several studies have reported conflicting results when reporting differences in cognitive profiles among the MS phenotypes. Most of the evidence at present suggests that cognitive deficits are more frequent and widespread in patients with PMS. In the few studies where patients with PPMS and SPMS have been distinguished, some investigators have reported greater CI in those with SPMS,16,20,21 while others have reported essentially no differences between these two forms of PMS.22,36

Patients with PPMS37 were found to have less slowing on measures of information processing speed than those with RRMS, these findings being confirmed by a subsequent study38 which compared CI among PPMs, SPMS, and RRMS. In this study, the authors found that slowing of information processing was more pronounced in SPMS patients and somewhat
less pronounced in PPMS patients. Furthermore, the slowing was unrelated to patients’ disability status or level of depression.

Ruet et al.\textsuperscript{19} showed that patients with PPMS had a wide range of cognitive deficits affecting information processing speed, attention, working memory, executive function, and verbal episodic memory, whereas the impairment in patients with RRMS was limited to information processing speed, attention, and working memory when compared with their respective matched healthy controls. Recently, a retrospective analysis of cognitive testing from the database of a French program for MS care compared 41 late RRMS (more than 10 years of disease duration) with 37 SPMS and 23 PPMS patients.\textsuperscript{39} In all, 63\% had significant CI. After controlling for age, sex, disability level, disease duration, and education level, patients with SPMS were at least twofold more frequently impaired than patients with late RRMS in information processing speed ($p=0.005$), executive functions ($p=0.04$), verbal fluency ($p=0.02$), verbal episodic memory ($p=0.04$), working memory ($p=0.02$), and visuospatial construction ($p=0.01$). SPMS and PPMS groups differed only for visuospatial construction ($p=0.02$).\textsuperscript{39}

Connick et al.\textsuperscript{40} described that in addition to a prominent global influence on cognitive performance, patients with PMS commonly exhibit language and visuospatial deficits, raising the question as to whether cognitive dysfunction in PMS always reflects a universal deficit of all functions, or whether impairment of specific functions can occur independently. The question is not purely speculative but could have practical implications for the choice of appropriate assessment instruments. Therefore, it has been suggested that the evaluation of these abilities (language and visuospatial function) should be included in clinical assessment of cognition in PMS.\textsuperscript{40}

In conclusion, only a few studies have investigated the differences in cognitive skills between PPMS, SPMS, and RRMS, and results are inconsistent. Age and disease duration were often different between groups or simply not reported.\textsuperscript{13,19,36} It seems that defining a specific cognitive profile to discriminate PPMS and SPMS based on the most used and validated NPS evaluations is not possible.

**Cognitive rehabilitation in PMS: state-of-the-art**

Generally, cognitive rehabilitation is a set of therapeutic services designed to improve cognitive functioning and participation in activities that may be affected by difficulty in one or more cognitive domains. It is often part of a multidisciplinary comprehensive program and it is a continuous process which begins with the NPS assessment (see the available batteries above), followed by project planning and then the execution of specific exercises or other kinds of cognitive training which need to be checked for efficacy, adherence, and tolerance during the entire period of scheduled treatment.

Despite cognitive rehabilitation being widely used in clinical practice,\textsuperscript{41} a recent Cochrane review\textsuperscript{42} concluded that there was low level of evidence for the positive effects of NPS rehabilitation in MS, mainly due to methodological limitations of the currently available studies and subjects’ heterogeneity.

Promising data come from more recent studies. Targeted training interventions on specific cognitive domains (i.e. memory, executive function, attention) have been shown to improve the trained function.\textsuperscript{33,35,43–46}

A number of studies using the software RehaCom have demonstrated that patients who underwent tailored, specific training improved performance in previously impaired cognitive domains when compared with patients who underwent a generic training program. These findings suggest that targeted cognitive rehabilitation may improve specific cognitive functions.\textsuperscript{47} One study, randomizing 86 patients, demonstrated that an intensive and domain-specific cognitive approach was more effective than a non-specific psychological intervention in patients with MS.\textsuperscript{46} In contrast, results of another study, carried out on over 100 patients, showed that strategy-oriented NPS rehabilitation, although it reduced perceived cognitive deficit, did not actually improve objectively measured cognitive performance.\textsuperscript{48} The authors introduce the idea that the ultimate goal of cognitive rehabilitation might be to enable people with disabilities to function as adequately as possible in their environment, even if this appears to be independent of any measured amelioration in specific cognitive testing.\textsuperscript{48}

Overall, studies investigating the effects of cognitive rehabilitation have been conducted in RRMS or in mixed MS populations, without subgrouping SPMS and PPMS.

Regarding the domain on which the overall intervention was focused, rehabilitation of learning and working memory, attention, and executive functions were most frequently reported. The length of all cognitive rehabilitation treatments has been extremely heterogeneous, ranging from 1 day to 6 months, with the number of intervention sessions varying from 1 to 36...
and the frequency from twice per month to five times per week. Some studies tested the long-term effects of cognitive rehabilitation at follow-up. In addition to the heterogeneity of the interventions between the various studies, within-study variations were also noted (a tailoring of rehabilitation intervention according to each patient’s individual symptoms), thereby making direct comparison of the interventions impossible. Furthermore, in some studies, the cognitive rehabilitation treatments were not homogeneously compared.

In a study by Vogt et al.,49 two different cognitive rehabilitation schedules, a high-intensity program (four times per week for 4 weeks) versus low-intensity program (twice a week for 8 weeks), were compared. The results showed that cognitive rehabilitation significantly improved working memory and mental speed performance with no difference between the high- and low-intensity groups.

Mattioli et al.46 highlighted the importance of the time schedule (high frequency and long duration of treatment) in facilitating learning strategies during an intensive cognitive rehabilitation program.

To date, therefore, there is no definite evidence of a positive effect of cognitive rehabilitation programs for patients with PMS.

Considering PPMS specifically, so far only one study has been conducted exclusively in this group.51 This interventional study investigated the effect of three endurance-training interventions on physical fitness, walking ability, and cognitive function. The authors found an improvement in verbal learning and memory and decreased AD and increased RD are considered as markers of axonal damage and demyelination, respectively, thus representing parameters that are sensitive to underlying pathological processes of MS.61

Cognitive rehabilitation in PMS: the role of neuroimaging

The relatively recent introduction of more objective surrogate neuroimaging measures of cognitive rehabilitation (e.g. functional MRI (fMRI), diffusion tensor imaging (DTI)) in MS studies has suggested that effects of cognitive rehabilitation strategies may be mediated by neuroplasticity activation, which can provide a functional as well as structural basis for any clinical findings. The term neuroplasticity refers to “the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function, and connections.”53 That is, the brain is able to reorganize its structural and functional connections in an effort to maximize functional capacity and “adjust” its resources to cope with CI. Changes in functional activation in persons with MS revealed after cognitive rehabilitation have been interpreted as showing neuroplasticity to have a positive or “adaptive” outcome.34,54 However, it is important to recognize that such plasticity may also be “maladaptive.” The term “maladaptive plasticity” may be used to refer to cerebral inefficiency in situations in which neuroplasticity is correlated with CI or decline.55,56 Several studies in MS have looked at the structural effects of cognitive rehabilitation on the brain and have demonstrated changes in specific brain regions,34,43–45,54,57,58 with numerous researchers noting induced neural plasticity in response to cognitive rehabilitation.

As expected, the specific brain regions vary with the treatment protocol investigated, the specific cognitive function targeted for treatment, as well as the imaging protocol applied. Studies have also shown different relationships recorded between these changes in patterns of cerebral activation and changes in behavior documented via NPS testing. Some studies found that the changes in fMRI correlated with improvement in NPS assessment in the targeted domain,34,54 while others failed to show such a relationship.54

The most promising advanced MRI techniques for investigating brain plasticity are fMRI and DTI.59 fMRI is based on the detection of changes in the blood oxygenation level–dependent (BOLD) signal, which is in turn affected by changes in neural activity in a specific brain region and the underlying physiology or pathology. Changes in BOLD signals can be investigated during the execution of a specific task (e.g. simple motor activity, sensory stimulation, and cognitive effort)60 or at rest, to explore the functional connectivity (FC), that is, the functional interaction between different brain regions.61 DTI is a method to assess myelin in vivo, providing information on the integrity of the myelin-axon unit based on the directional asymmetry of water diffusion, that is, the so-called fractional anisotropy (FA).62 The FA value is determined by the ratio of axial diffusivity (AD) and radial diffusivity (RD), and decreased AD and increased RD are considered as markers of axonal damage and demyelination, respectively.
Using these advanced MRI techniques, it has been recently demonstrated that rapid-onset plasticity and functionally relevant chronic reorganization processes are preserved even in PMS and that these phenomena are functionally relevant to maintain motor and cognitive functions. Therefore, fMRI may provide a powerful tool to investigate functional and structural brain changes related to recovery (or not) of function after rehabilitation.64

Application of fMRI techniques to the PMS population is scarce in literature, probably due to the difficulty in recruiting patients with PMS with relatively preserved cognition, which is a critical requirement for having interpretable fMRI results.

Nevertheless, the results of the available fMRI studies seem to indicate that the inefficiency of brain adaptive mechanisms might be among the factors responsible for the unfavorable disease evolution of PMS.65–66 A study enrolling 16 right-handed patients with PPMS and 17 matched controls showed six PPMS patients with CI.67 Structural MR imaging measures did not differ between patients with and without CI, while functional changes were detected between patients who were cognitively preserved and those with CI. Compared with patients with CI, those cognitively preserved had increased activation of the left caudate nucleus, the prefrontal cortex, and the inferior parietal lobule. Compared with controls and patients who were cognitively preserved, patients with CI had increased activation of the secondary sensorimotor cortex, cerebellum, and insula. Compared with controls, they also had increased activation of the right precentral gyrus and a reduced recruitment of the left prefrontal cortex.67 In patients with PPMS, a decreased composite cognitive score (comprising attention and information processing, verbal and visuospatial memory, abstract reasoning, executive skills, linguistic abilities, lexical access, and spatial cognition) correlated with increased activity of the cerebellum, insula, and secondary sensorimotor cortex, as well as decreased prefrontal cortex activity.67 The authors speculated that in PPMS an increased recruitment of cognitive-related networks might represent a functional reserve with the potential to limit the severity of the CI, while the accumulation of T2 lesions and the consequent exhaustion of frontal lobe plasticity might contribute to the CI in PPMS.67

An important issue is to verify whether measures of behavioral change relate to corresponding functional and/or structural brain changes, and whether they are beneficial adaptive or maladaptive mechanisms which we should aim to either stimulate or prevent. Maladaptive plasticity may be hypothesized when looking at several results with resting state FC in SPMS. In these patients, we can observe more extra-regional activation which is to be considered as maladaptive. In other words, activation in CIS and RRMS seems to be adaptive and beneficial, while extra-regional activation in progressive patients seems maladaptive.68 Studies to confirm these suggestions in PMS are needed.

In the attempt to confirm the processes underlying neuroplasticity, some studies have been carried out at a molecular level, investigating long-term potentiation (LTP), as reported in the following section.

Cognitive rehabilitation in PMS: effects at the molecular level
LTP is one of the most important and most studied forms of synaptic plasticity. LTP results in intensified communication between simultaneously excited neurons, leading to enhanced synaptic transmission.69 Thus, it requires the cooperation between pre- and postsynaptic neurons. Results from various studies have pointed to the important role of LTP in the plasticity of synaptic morphology. LTP induction may result in an increased size and shape of dendritic spines, promotion of their clustering, and also the growth of dendrites, potentially restoring the excitation in denervated neurons or in those lacking part of their synaptic input.70 LTP is preserved in RRMS patients and plays an important role in recovery from neurological deficits.71 LTP is present in stable MS patients, while it is ineffective in the progressive form of the disease.71 It has thus been suggested that PMS patients have lost their potential to induce synaptic plasticity and thereby to mask the clinical progression of the disease.72 Of interest, it has been indicated that a single nucleotide polymorphism of the N-methyl-o-aspartate (NMDA) receptor (rs4880213 allele T) is associated with the increased synaptic transmission. This genetic variant exerts opposite effects in PPMS and RRMS patients. In PPMS, it leads to exacerbated excitotoxicity and clinical worsening, while in RRMS it is associated with an improved clinical outcome due to more efficient LTP.73

Conclusion and future perspectives
Data on cognitive dysfunction are still insufficient to define a specific cognitive profile for patients with PMS. Patients with PMS seem to be more impaired in executive function and verbal episodic memory than patients with RRMS.
Although a number of studies have demonstrated that cognitive rehabilitation may be effective in improving cognitive functioning in RRMS and have stimulated ongoing work in this direction, there is a general lack of data on cognitive rehabilitation in PMS.

Data from the overall MS population have shown that cognitive rehabilitation has the potential to improve attention, processing speed and memory performances, and executive functions. There is also weak evidence that the beneficial effect of cognitive rehabilitation extends to fatigue, depression, and quality of life, even several months after treatment termination. However, no specific data can be drawn for PMS population.

A specific cognitive rehabilitation training in patients with PMS is lacking and seems to be far off. Randomized clinical trials to investigate rehabilitation effects are therefore warranted, but before we could speculate on any possibility of cognitive rehabilitation in PMS, we dramatically need uniformity in the inclusion criteria of PMS population included in the clinical studies. They should also include measures of neural plasticity in order to demonstrate whether PMS could have the potential to cognitively improve. We need to verify whether rehabilitation leads to functionally positive plastic changes or to an overloading of cognitive networks through overuse—examining first functionally and then structurally the impact of cognitive training activities (Box 1).

Box 1. The unmeet needs in cognitive rehabilitation of progressive forms of MS.

What are the unmet needs?

Identifying specific NPS profiles of PFMS
- Enrollment of only strictly defined progressive forms of MS;
- Comparison with relapsing-remitting and healthy controls in large sample;
- Construction and validation of new potential NPS tests which are more specific for those deficits identified in progressive forms of MS enrolled from large population and cross-sectional studies.

Developing specific rehabilitative strategies and techniques based on the NPS profiles identified

Measuring neuroplasticity in PFMS and the potential effects of maladaptive brain changes as consequences of rehabilitation

NPS: neuropsychological; MS: multiple sclerosis.

Conflict of interest

Dr Patti has served on the scientific advisory board for Teva, Biogen-Ide, Bayer-Schering, Novartis, and has received honoraria as a speaker for Teva, Biogen, Merck-Serono, Bayer-Schering, Genzyme/Sanofi, and Novartis. Dr Tumani serves on a scientific advisory board, as a consultant for, and/or received funding for research projects and travel from Bayer, Biogen, Genzyme, Merck-Serono, Novartis, Roche, Siemens, and Teva; serves on editorial board for MSI (Multiple Sclerosis international) and NPBR (Neurology, Psychiatry and Brain research); and receives research support from BMBF, University of Ulm, Landesstiftung BW. Dr D’Amico has nothing to disclose. Dr Leone has nothing to disclose.

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