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Ciclo XXXV

How cognitive rehabilitation can affect motor cognition, fatigue perception and fatigability. Hypothesis of early assessment and intervention.

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The aim of this PhD project is the proposal of a detailed cognitive assessment and thus an early cognitive rehabilitation treatment protocol for both motor control and cognitive function. The project is divided in two phases: 1) considering existing literature, we identified the most ecological clinical tests and potentially effective strategies for cognitive interventions in people with Multiple Sclerosis (PwMS); 2) we built a multidisciplinary cognitive rehabilitation protocol and finally we applied the intervention into the clinical practice.

Chapter 1

Multiple Sclerosis and cognition

Multiple sclerosis (MS) is an autoimmune inflammatory disorder of central nervous system (CNS) of unknown aetiology, characterized by demyelination and variable degrees of axonal loss. The aetiology of MS remains unknown; however, it is believed to be caused by immune dysregulation triggered by genetic and environmental factors.

MS is the main neurological disease of young adults, affecting approximately 2.3 million people worldwide. The clinical symptoms and signs of MS are variable and may result from involvement of sensory, motor, visual, and brainstem pathways; optic neuritis (inflammation of the optic nerve), Uhthoff's phenomenon (transient fluctuation or worsening of MS symptoms with a rise in body temperature) and Lhermitte's phenomenon (an abnormal electric-shock like sensation down the spine or limbs on neck flexion) are characteristic of MS. Common physical impairments in MS include problems with balance, mobility and spasticity. Cognitive impairment will occur in 43–70% of people with MS (PwMS) (Chiaravalloti & DeLuca, 2008).

Even though cognitive impairment is not a core symptom of MS and the McDonald criteria do not require it for diagnosis, patients may have cognitive impairment in the early stages of the disease, even before the first physical symptoms appear. Indeed, a 2013 survey (Achiron et al., 2013) estimated that cognitive impairments could precede other symptoms by 1.2 years. Clinically isolated syndrome (CIS), the mildest form of MS, can be a precursor to a more severe form. Reuter et al (F. Reuter et al., 2011) found early cognitive dysfunction in patients with CIS. In general, patients with CIS have cognitive problems similar to those in patients with the more severe forms of MS, although with relatively intact verbal learning and memory capacity (Potagas et al., 2008). Cognitive dysfunction affects patients with all MS subtypes. The highest frequency of cognitive dysfunction is in secondary progressive PwMS, whereas a lower rate is found in primary progressive course and relapsing-remitting MS, and the lowest in CIS (Achiron et al., 2013).

Amato et al (Amato et al., 2006) reported that cognitive decline in MS is unlikely to subside over time; rather, it progresses slowly. Borghi et al (Borghi et al., 2013) found that the frequency of impaired cognition gradually increases with disease evolution, and progressive forms have more severe cognitive impairments than relapsing-remitting subjects. In a survey of 1500 PwMS, Achiron et al. (Achiron et al., 2013) found that those with the secondary progressive form showed greater cognitive decline than those with the other forms, in all domains except the visuospatial. In a 6-year follow-up study of newly diagnosed patients with MS, Hankomaki et al (Hankomäki et al., 2014) observed quite stable overall cognitive function, but deterioration in attention and processing speed. Borghi (Borghi et al., 2013) looked also at each subtype of MS but were unable to discern subtype-specific patterns of cognitive impairment. This finding suggests a global pattern of cognitive dysfunction independent of disease course.

Cognitive impairment correlates strongly with brain lesions. Brain imaging have identified several potential sources of cognitive impairment in PwMS. Tsolaki et al (Tsolaki et al., 1994) used magnetic resonance imaging and nine neuropsychological tests, and found that cognitive dysfunction correlated with lesions in hippocampus and enlarged third ventricle. Cognitive impairment is also related to brain atrophy with specific involvement of thalamic atrophy and hippocampal damage (Sicotte, 2011), as well as atrophy of the basal ganglia and cerebral cortex (Batista et al., 2012). Furthermore, elevated volume of the third ventricle is a strong biomarker of cognitive decline (Houtchens et al., 2007). Riccitelli et al (Riccitelli et al., 2011) reported that progressive PwMS lost gray matter in cortical regions, while relapsing-remitting patients lost deep gray matter structures. Specifically for the relapsing-remitting form, however, Papadopoulou et al (Papadopoulou et al.,

2013) found that white matter lesions seemed to be an essential factor for cognitive problems. No significant relationship has been found between overall cognitive impairment and physical disability in MS, duration of the disease or education or age (Chiaravalloti & DeLuca, 2008). However, a recent survey reported a connection between cognitive problems and patients' levels of education and physical disability (Ben Ari Shevil et al, 2014).

The most common cognitive impairment reported by PwMS include deficits in memory, attention, concentration and executive functions such as multitasking, problem solving and self- monitoring. Information processing speed, a basic elemental function that may influence other cognitive processes is often the first cognitive deficit to emerge in MS (Bobholz & Rao, 2003; Grzegorski & Losy, 2017).

Cognitive domain impaired	Prevalence in MS (%)
Information processing speed	20–50
Memory	33–65
Attention	12–25
Executive functions	17–19
Visual perceptual functions	Up to 25

Figure 1 Prevalence of impairment of main cognitive domains.(Grzegorski & Losy, 2017)

Fatigue and mood influences on cognition

Often, PwMS perceive to be cognitively impaired more than they perform in cognitive tests; this underestimation of their cognitive abilities is usually believed to be related to two other common MS symptoms: mood disorder and fatigue (Walker et al., 2012).

Research has shown discrepancies between subjective and objective measures of cognitive function in PwMS; indeed, some individuals underestimate and others over-estimate their cognitive functioning. Such discrepancies pose challenges for providers with regard to selecting valid screening measures of cognition and determining the need for more accurate neuropsychological evaluations and more effective interventions (Colbeck, 2018; Tur, 2016).

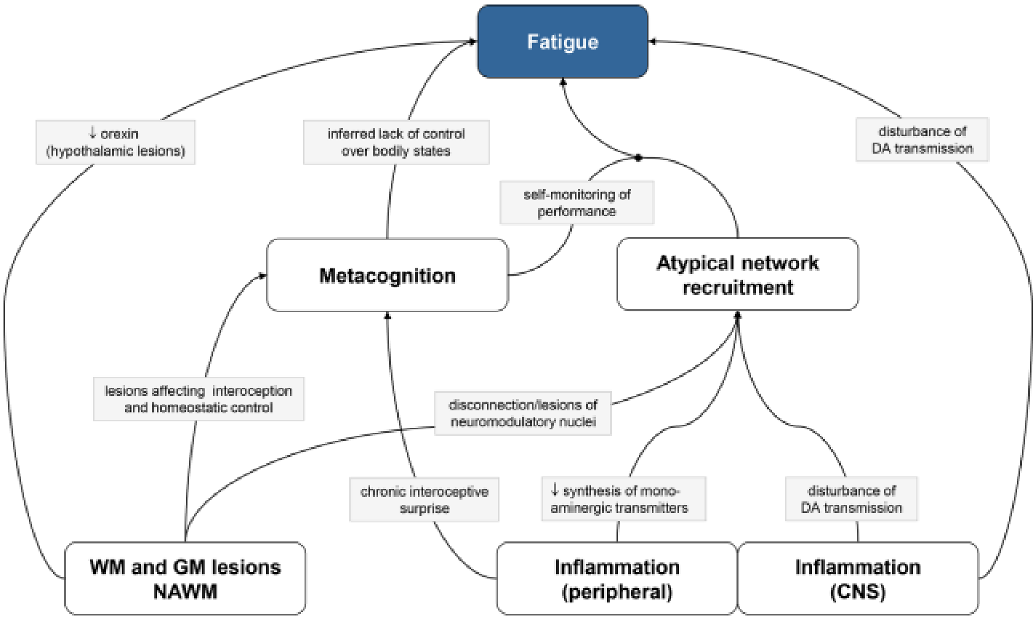

Figure 2. From Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. By Manjaly et al.White and grey boxes represent classes of mechanisms and specific mechanism respectively; directed arrows and circle-ended arrows represent direct and mediating effects, respectively. Due to space limitations, only one mechanism per arrow is shown. CNS, central nervous system; DA, dopamine; GM, grey matter; NAWM, normally appearing white matter; WM, white matter.(Manjaly et al., 2019)

Descriptions of fatigue vary remarkably in the literature. For example, fatigue has been described as 'a feeling arising from difficulty in initiation of or sustaining voluntary effort', 'an overwhelming sense of tiredness that is out of proportion (in relation to the performed activity)' or as a 'feeling that relates to the lack of motivation to deploy resources and engage in high effort performance to cope with their situation'. A recent taxonomy distinguished two major dimensions of fatigue: perception of fatigue and performance fatigability.

Fatigue is one of the most disabling symptoms in MS and needs an accurate diagnosis and a rapid intervention. The assessment and treatment of MS-related fatigue may be complex, and it is mandatory to rule out potential causes or triggers of fatigue. It is important to bear in mind that these causes may or may not be directly related to MS; therefore, careful evaluations are mandatory. Thus, more research into this disabling symptom of MS is needed(Hu et al., 2019) (Tur, 2016).

Among all non-pharmacological approaches, the mixed physical and psychological approaches deserve especial attention. They are naturally comprehensive, and their corresponding clinical trials have shown promising results, which may translate into excellent results if applied into clinical practice. These mixed approaches emphasise the need for multidisciplinary teams and assessments (Amatya et al., 2019).

Besides, the newly appeared mixed approaches promote other important aspects of MS care, such as the performance of regular exercise, which can have benefits potentially beyond the improvement of MS-related fatigue.

Moreover, depressive symptoms are thought to affect PwMS more often than the general population and other chronic diseases (Patten et al., 2003; Siegert & Abernethy, 2005). The prevalence of depressive symptoms in MS range from 26% to 42%, and about half of PwMS have depression (Marrie et al., 2009)(Sadovnick et al., 1996) with 25.7% of all patients suffering from major depression (Patten et al., 2003). Anxiety has been reported in 23.5% to 41% of PwMS (Wood et al., 2013). Anxiety has been shown to interfere with cognitive performance in PwMS (Goretti, Viterbo, et al., 2014). On the contrary, researchers are divided on the interference between depression and cognitive deficits. Indeed, the COGIMUS study found no significant correlation between depression and cognitive dysfunction in PwMS (Patti et al., 2009), but Borghi et al. (Borghi et al., 2013) reported that impaired cognitive performance and depression might be linked in MS, and Sundgren et al (Sundgren et al., 2013) found that even mild depressive symptoms affected cognition in MS. Some evidence suggested that it influences their subjective perception of cognitive impairment (Kinsinger et al., 2010). According to Brassington and Marsh (Brassington & Marsh, 1998), however, other researchers claimed that depression does not affect neuropsychological efficiency and that objective cognitive function and depression vary according to an individual patient’s coping strategies. Kinsinger et al (Kinsinger et al., 2010) concluded that specific domains, such as information processing speed, may be related to depressive symptoms in MS. According to recent manuscripts, their presence has a significant effect on cognitive performance in PwMS.

However, there is still a significant amount of unexplained variance in the prediction of depression and anxiety in MS. It is possible that social cognitive deficits are a contributing factor: for instance, alexithymia (the inability to recognize emotions in oneself) is a significant predictor of depression in MS (Gay et al., 2010), indicating that deficits involved in the perception of emotions may be associated with depressive symptoms. However, the relationship between social cognition and depression/anxiety has not been well studied in MS, and the few studies examining this aspect have resulted in inconsistent findings. Complicating matters is the periodic utilization of self-reported deficits of social cognition, which may be confounded by the fact that some individuals with MS are unaware of the existence or pervasiveness of their own cognitive deficits (Genova et al., 2019).

To overcome the current limitations of neuropsychological testing, future research should focus on constructing a battery that will identify cognitive impairment as early as possible and will not be confounded by depression, anxiety, or other psychiatric disorders. Therefore, disposing of a test able to differentiate the somatic symptoms of MS from anxiety and depressive disturbances is of utmost relevance; it could help to identify patients in whom anxiety and depression may affect cognitive evaluation.

Cognitive fatigability

Fatigability refers to objectively measurable aspects of fatigue, for example, the observable decrease in performance during a cognitive or motor task. It is still debated whether cognitive fatigability may represent an aspect of cognitive impairment rather than a distinct phenomenon. While several studies aimed at quantifying motor fatigability by means of the decrease in the upper limb muscular strength or the reduced walking speed (Severijns et al., 2017), cognitive fatigability has been more difficult to assess (Tommasin et al., 2019). The first attempt defined fatigability as the reduction in performance following the prolonged repetition of a cognitive task. Alternatively, it has been proposed to measure fatigability as the decline in a specific task after inducing fatigue by mental or physical effort (Linnhoff et al., 2019). Finally, a promising approach seems to compare the performance at the beginning with the performance at the end of a demanding task (Linnhoff et al., 2019). One of the most relevant problem in assessing cognitive fatigability (Harrison et al., 2017) is the learning effect, that is, the increased ability of executing a specific task due to experience, which interferes with the tendency of subjects to worsen the performance along the test .

Chapter 2

Cognitive Assessment

Cognitive assessment should constitute a consistent part of the clinical examination in MS, especially when cognitive impairments seem to be present (Weber et al., 2019).

It's hard to find cognitive evaluations taking a multidimensional view of assessing human function and highlighting the complexity of participation, specifically among populations living with a chronic condition that involves the daily management of a varying and unpredictable condition.

Research has clearly shown that such tests have significant predictive value regarding everyday life activity. However, as with any test, neuropsychological tests alone cannot provide absolute clinical predictability. The real question is how can neuropsychological tests be used in the clinical setting as one of several measures to help the clinician understand the impact of MS disease on everyday functioning. When viewed from this perspective, neuropsychological testing plays an invaluable role in the real-world assessment of the patient with MS.

A correct assessment of cognitive functioning goes through the combination of self-reported outcomes and objective testing (not only for the scores but also for the way people conduct the examinations). This is way it's important to create cognitive evaluation team with different professionals.

	Driving	Employment	Internet shopping	Financial/medical decision-making
Processing speed	●	●	●	
Executive functions	●	●	●	
Visuospatial functions	●			
Learning and memory	●	●	●	●
Working memory				●
Verbal fluency				●

Sections with black circles indicate significant relationships between these factors in the research literature.

Figure 3 Summary of findings depicting the primary relationships between neuropsychological and functional domains in MS. (Weber et al., 2019)

Currently, cognitive impairments in MS are often assessed through the Brief International Cognitive Assessment for MS (BICAMS) (Benedict et al., 2012; Goverover et al., 2016), a tool easy to administer in daily practice. It includes the Symbol Digit Modality Test (SDMT), the California Verbal Learning Test-II (CVLT-II) and the Brief Visuospatial Memory Test-Revised (BVMTR). The approximate time of completion is 15 min (Benedict et al., 2012; Langdon et al., 2012). The BICAMS has been found to be a promising method to predict performance of daily living activities (Goverover et al., 2016). This sensitive neuropsychological tool can also be effectively used to evaluate cognitive performance in terms of monitoring treatment with disease-modifying drugs (DMDs). Specifically:

- **SDMT** is a reliable and valid test evaluating information processing speed. Indeed, slowed cognitive processing is a very common cognitive symptom of MS. SDMT has demonstrated remarkable sensitivity in detecting not only the presence of brain damage, but also changes in cognitive functioning over time and in response to treatment (Langdon et al., 2012; Van Schependom et al., 2014).
- **CVLT-II** (Goretti, Niccolai, et al., 2014; Stegen et al., 2010) is a comprehensive, detailed assessment of verbal learning and memory deficits in adolescents and adults. It assesses encoding, recall and recognition in a single modality of item presentation (auditory-verbal). The CVLT-II is considered a measure of episodic memory more sensitive than other verbal learning tests. It was designed to not only measure how much a subject learned, but also reveal strategies employed and the types of errors made.

BVMT-R (Goretti, Niccolai, et al., 2014) assesses visuospatial learning and memory. According to Benedict et al.(Benedict et al., 2012), given the same time limit, viewing multiple designs rather than just one figure could result in participants having to rely more on visual memory as opposed to using verbal mediation. However, given the 10 second time restriction for displaying the six figures, poor performances on the BVMT-R may reflect not only visuospatial memory difficulties, but also slower speed of processing as individuals may not be able to fully process all of the figures in the time available.

Moreover, we identified the **Perceived Deficits Questionnaire (PDQ)** (Strober et al., 2016) as measure for self-reported cognitive impairment in PwMS. The PDQ has been developed specifically for MS in order to provide a self-report measure of cognitive dysfunction. This instrument provides an assessment of the most affected cognitive domains in MS: attention, retrospective memory, prospective memory, and planning and organization. The full-length PDQ is of 20 items.

Cognitive Rehabilitation

Cognitive dysfunction in patients with MS affects a range of activities, such as work, driving, social integration, and adherence to medication regimens. As a consequence, the development of strategies to alleviate such deficits is of paramount importance (DeLuca et al., 2020). Potential treatment strategies include disease- modifying treatments, symptom-modifying agents, and cognitive rehabilitation. Cognitive problems are sometimes invisible but difficult for PwMS. Rehabilitation is recommended for all stages of MS, but the best results were observed at the early stage. PwMS have individual and wide-ranging needs and, for these reasons, rehabilitation is usually provided by a multidisciplinary team. Pharmacological therapies for reducing disease activity in MS significantly expanded over the last year. However, no effective treatment has been established in the case of cognitive problems. Therefore, there is a need of new strategies, which can be used specially at an early stage of MS to prevent cognition decline.

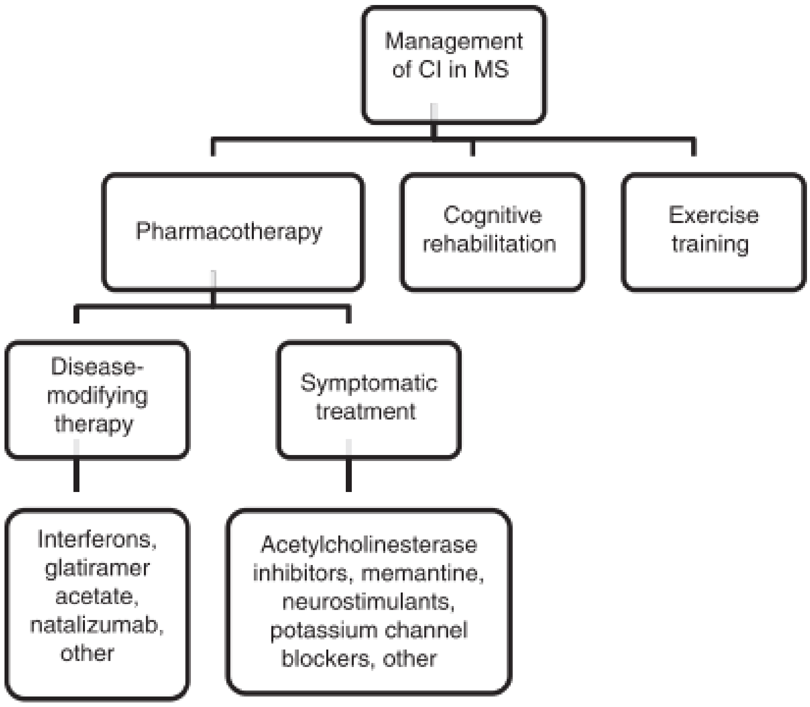

Figure 4 Therapeutic manegement of CI (Grzegorski & Losy, 2017)

The possible options of managing cognitive dysfunction are pharmacologic interventions, cognitive rehabilitation and exercise training (Figure 3) (Kalb et al., 2018; Grzegorski & Losy, 2017). Despite its high prevalence, there are no disease modifying therapies (DMT) effective for treating cognitive dysfunction so alternative treatment approaches (e.g. cognitive remediation, exercise strategies, symptomatic drugs for the management of mood, fatigue and sleep) are needed for mitigating this symptom and its impact on daily living skills.

Appropriate management of cognitive disturbances mainly relies on rehabilitative strategies, which have been reported to be effective and to mitigate the impact on daily living activities (Goverover et al., 2018) (Amatya et al., 2019; DeLuca et al., 2020).

Cognitive rehabilitation (CR) aims to improve cognitive impairments through using compensatory and restorative approaches. CR could be a part of a global approach that takes into account the abilities and disabilities of an individual, as well as the personal and social factors affecting function. It is more than just dealing with cognitive factors, rather, it is a holistic approach and process (Grzegorski & Losy, 2017; Miller et al., 2018). Nevertheless, the cognitive symptoms management in MS is usually based on neuropsychological treatment, exercise training and computer based interventions (Grzegorski & Losy, 2017).

1. Rigorous research designs are required to produce higher levels of evidence for cognitive rehabilitation research, including multicenter double-blind randomized controlled trials, with clear and specific a priori outcomes. Essential guidelines for the conduct of high-quality cognitive intervention trials have been discussed by Simons and colleagues.[47] Adherence to these recommendations by investigators, post hoc reviewers, and journal editors will greatly improve trial quality and the science of MS cognitive rehabilitation.
2. We require theoretical frameworks to build a science of cognitive rehabilitation in MS, with biologically plausible mechanisms of action, and clear delineation of rehabilitation approaches (e.g., restorative vs compensatory). Models will be informed by greater understanding of neural bases of cognitive function. The goal of changing brain structure and function in plausible and lasting ways likely requires greater "doses" (duration and intensity) of interventions, or combined therapies with synergistic effects.
3. Structural and functional neuroimaging outcomes may explore mechanisms of action for interventions; however, when used as trial endpoints, specific hypotheses of treatment effects on neuroimaging outcomes should be stated a priori. Otherwise, such outcomes should be considered exploratory evidence requiring confirmation in a subsequent trial.
4. Observational research has identified candidate modifiable lifestyle factors that may protect against cognitive decline, including mental activity, physical exercise, and stress management. Research is needed to (1) establish causal relationships between protective factors and outcomes, including utilization of RCTs, (2) examine the unique and possibly differential contributions of each protective (or risk) factor to each individual cognitive outcome (speed, memory), as well as potential synergistic effects (interactions) among protective factors, and (3) explore mechanisms of action for different protective (or risk) factors (e.g., moderating MS disease activity itself vs building/preserving reserve).
5. Any promising cognitive interventions must be implemented in the context of a patient's life. A holistic approach to match treatment with a patient's unique circumstances, priorities, and abilities is necessary in future translational research and practice. That is, interventions will only be effective if they are clinically feasible for an individual patient.
6. Cognitive rehabilitation interventions may be most effective when tailored to a patient's specific deficit, which may differ within the same cognitive domain (e.g., memory deficit secondary to diffuse white matter lesions vs focal hippocampal lesion). Consideration of distinct subtypes/etiologies of deficits requiring distinct treatment approaches (i.e., precision medicine) is both a challenge and a potential opportunity for rehabilitation.
Abbreviations: MS = multiple sclerosis; RCT = randomized controlled trial.

Figure 5 Key priorities for treatment and prevention of cognitive deficits (Sumowski et al., 2018)

To date, few studies examined the impact of the multidisciplinary approach (Bobholz & Rao, 2003; Goverover et al., 2018) on the effectiveness of the cognitive functions treatment. Underlining this need of more evidence is of utmost relevance; in fact, the cognitive functions are stimulated also in the care process of other disciplines of the rehabilitation, such as occupational therapy and speech and swallow therapy (Cheng et al., 2012; George & Rampling, 2018). Bagert et al. (2002) (Bagert et al., 2002), for example, described strategies for dealing with cognitive problems provided by occupational therapists, speech- language therapists, psychologists and CR specialists. However, more evidence of effectiveness for cognitive multidisciplinary rehabilitation is needed to enforce its use as gold standard in clinical practice (Amatya et al., 2019). In this scenario, it is important to consider also the relationship between cognitive impairments and fatigue, depression, and participation in activities of daily living (ADL), which could have a key role to ameliorate the compensative part of CR approach through ecological evaluations and ecological intervention from different professional points of view and consequent tailored interventions. The goals of occupational therapy and neuropsychological interventions, for example, are not only the improvements of cognitive test performances, but facilitating coping strategies and maximising self-perceived function.

At this moment the efficiency of multidisciplinary CR in managing cognitive dysfunction MS-related is speculative due to methodological variability, lack of ecologically valid outcome measure and investigation over long follow-up periods but research for the management of others neurological chronic disorders, related with cognitive dysfunction, such as Parkinson disease, has shown a positive trend toward multimodal approaches. (Ferrazzoli et al., 2018; I. Reuter et al., 2012)

To build a multidisciplinary CR protocol is important to consider different strategies applicable in multiple setting and theoretical models focusing the integration of different professional expertise (Fleeman et al., 2015). Recent studies have also underlined the importance of attentional states in delivering effective cognitive treatments. Benso et al. (Benso et al., 2021) reported that the efficacy of a cognitive treatment increases in presence of the activation of the executive attentive system and identified some essential criteria of integrated cognitive treatment that could be used not only by psychologist but also by other professionals of the rehabilitation. Specifically, adaptivity, empathy, customization, avoidance of automatism and stereotypes, and alertness activation are considered fundamental to increase the training efficacy.

In this context could be useful to build CR programs, according to these suggestions, including physiotherapy, speech and swallow therapy, neuropsychological therapy and occupational therapy to face the impact on every aspect of daily living of cognitive impairment and study the effectiveness of these programs.

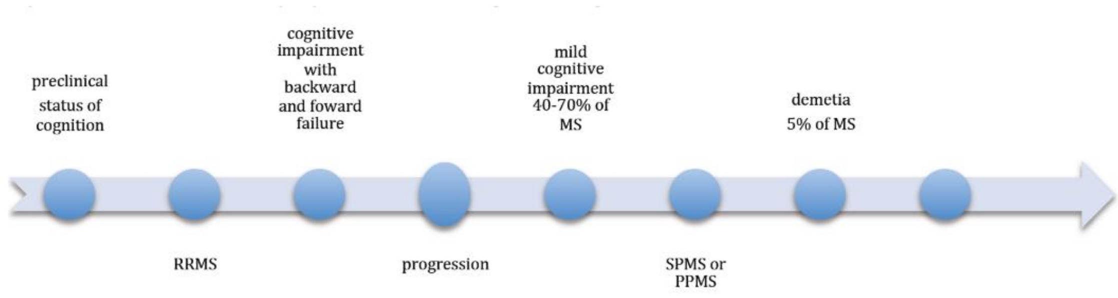

Figure 6: Development of cognitive impairment in MS. From pharmacological and Non-pharmacological Therapies of Cognitive Impairment in Multiple Sclerosis. (Miller et al., 2018)

Non-pharmacological treatments

Here some examples of non-pharmacological treatments to manage cognitive impairment in MS.

Neuropsychological Rehabilitation

The aim of neuropsychological rehabilitation is reducing cognitive impairment (Cheng et al., 2012; Hiele et al., 2020) as well as increase patient awareness of cognition deficits in everyday activities. Neuroplasticity due to remyelinisation processes may reduce the cognitive decline. Cognitive rehabilitation is typically a combination of various methods, tailored to the patient’s needs. Therefore, the effectiveness of a multifactorial intervention is difficult to evaluate. High-quality studies on a relationship between rehabilitation and improvement of cognition in PwMS are scarce. A recent meta-analysis of randomized and quasi-randomized trials showed that cognitive training could increase memory span and working memory. It indicated that cognitive training, combined with other neuropsychological methods, can improve attention, immediate verbal memory, and delayed memory. A recent randomized controlled trial, conducted by Hanssen et al. (2016), found positive effects of multicomponent cognitive rehabilitation in a group of 120 PwMS with cognitive complaints on psychological aspects of health-related quality of life (HRQoL). In a recent Cochrane review the impact of psychological therapies on cognition improvement in MS was reported. However, it was found that published literature show only low-level of evidence.

Breathing rehabilitation

Yogic philosophy clearly states that the breath and the mind are closely related. This constitutes a foundational premise of many ancient techniques of breath control known collectively as pranayama. A primary goal of these practices is to stabilize the attention, or calm the fluctuations of the mind (citta vritti in Sanskrit), in order to prepare the mind for deep meditative practice. Yogic teachings suggest that the characteristics of breath and mental state are correlated, and by consistent observation and training of the breath, stability of attention and a focused mind can be achieved. It agrees that respiratory activity is involved in regulating neuronal activity; however, how this relationship occurs remains an open question.

Therapeutic uses of breath practices should also be considered. Disorders of anxiety and depression may particularly benefit of self-modulation Locus Coeruleus/noradrenergic system and frontal-attentional dynamics with the breath. Given the known involvement of the LC in stress-resilience and cognitive control, and that individual self-regulation has been successfuly indexed by measures of pupil dilatation Application of breath-focused practices to changes in brain plasticity and neurogenesis might also be a fruitful field of study, as both synaptic remodelling and brain-derived neurotrophic factor (BDNF), particularly in the hippocampus, are modulated by LC activity and NA signalling pathways. It seems plausible that by controlling the breath, NA levels could be optimized to facilitate the formation of neuronal connectivity, and encourage BDNF expression and neurogenesis, given our findings of NA-respiratory coupling (Melnychuk et al., 2021b).

Aerobic Training

PwMS show a lower level of physical activity than healthy people. Therefore, aerobic training (AT) can be a very important factor preventing decondition, osteoporosis, cardiovascular problems, obesity and other MS specific symptoms. Obtained data, suggest that exercises, mainly aerobic ones, can improve cognitive functioning. Cognition-enhancing effects of AT were studied in both in vivo and animal experiments. Positive effect of AT on physiological processes such as glucoregulation and cardiovascular health is well known. Several clinical studies revealed some benefits for executive control including planning, selective attention, multitasking work, and inhibition, working memory, particularly in women. Brain imaging studies show that AT might be associated with reduced age-related atrophy and more effective perfusion in brain regions responsible for executive control and memory. Finally, clinical studies showed that AT may increase hippocampal volume due to an increased level of BDNF which is one of the most important molecules affecting neurogenesis and stimulating dendritic network.

Occupational Therapy

The reviews of CR in MS usually do not mention occupational therapy (OT). However, Deluca et al. (2020) (DeLuca et al., 2020) reported that the substantial real life impact of cognitive deficits in MS underlines the importance of effectively managing MS-related cognitive impairment. The National MS Society has recommended remedial interventions and accommodations that can be made to manage cognitive impairment and improve everyday functioning in both adult and paediatric MS populations.

Everyday functioning and occupational role are strictly connected with the OT focus of intervention. Yu & Mathiowetz (Yu & Mathiowetz, 2014) reported that multidisciplinary rehabilitation programs acknowledge the role of OT in rehabilitation for PwMS. OT interventions within multidisciplinary programs focused mainly on activity and participation and ranged from ADL training to fatigue and stress management. However, the specific contribution of OT is difficult to be determined from these studies because the effects of these interventions cannot be separated from the effects of the program as a whole.

The correlation between cognitive impairments and fatigue management, depression, participation in ADL could have the key role to ameliorate the CR approach (through ecological evaluations and ecological intervention). There are some work about the differences between objective and self-perceived cognitive performance: the existing discrepancy provides justification to consider both aspects, the goals of OT interventions may not be only the improvement of cognitive test performances, but facilitating coping strategies and maximising self-perceived function. Some authors contend that research has shown correlations between psychological factors and biological disease progression, suggesting that a reduction in stress levels through improved perceptions of cognitive performance is crucial (George & Rampling, 2018).

The lack of OT efficacy studies in PwMS should be of great concern. It is known that MS is a progressive disease with a high impact on functional ability and participation. In multidisciplinary rehabilitation, the role of OT is well recognized. OT aims at consolidating functional abilities and participation despite the expected decline in physical functions and abilities which is often seen in progressive diseases.

The key to combine different professional with as common aim to ameliorate cognitive functioning could be the model of integrated cognitive treatment.

Integrated Cognitive Treatment

Integrated Cognitive Treatment (ICT) is an adaptive rehabilitative treatment. It is defined as integrated because it aims to strengthen not only the attentive-executive system, but also specific systems that are underdeveloped or deteriorated (reading, for example) and their underlying functions (e.g., language and visual-perception).

Fundamental and essential elements that are required to create an effective treatment protocol, and which thus constitute the ICT structure. The essential ICT criteria identified are as follows:

a. Considering what cognitive neuroscience has revealed about the theoretical models of learning, different aspects of attention and some executive functions are expressed in working memory capacity. Moreover, it is necessary to understand the functional architectures to integrate the underlying trigger to the servo- systems of deteriorated or underdeveloped modular circuits.

b. An empathic and motivating operator administering the treatment, who can also control computer software

c. A trainer who has the following skills:

- the ability to vary and recognize attentional states (with targeted exercises that aim to activate, maintain, change, and strengthen each state), and understanding the different levels of attention (which allows for the creation ofoptimal "flow states" during learning and enables the phase of activation; see section Attentional Networks;

- the capacity for empathic bonding with the trainee;

- the ability to calibrate items and exercise difficulty according to the skills of individual subjects, and to carefully evaluate the development of skills during the training (adaptivity of the training).

Trainers should also avoid interventions that are involve repetitive, stereotyped, and automated loops.

Aim

Current work aims to incorporate the cognitive assessment into MS clinics and clinical trials, to utilize state-of-the-art neuroimaging to explicate neural bases of deficits, and to develop effective symptomatic cognitive treatments. However, some knowledge gaps are present and methodologic approaches need to be improved, with the final goal to dispose of more effective, evidence-based, clinically feasible interventions to prevent and treat cognitive deficits. Literature typically emphasizes what is known, but awareness of what is unknown should prompt professionals and researchers towards more reliable approaches.

Chapter 3

In this part we described the application of the protocol in the clinical practice and the way we decided to combine what we found effective in literature review.

Protocol description

Both ReBrain protocol and standard care has been ran by psychologists, physiotherapists, occupational therapists and speech and swallow therapists of the Italian MS Society Rehabilitation Center of Genoa (Italy) who have a strong expertise in MS rehabilitation. Therapists involved in ReBrain treatments have an additional expertise in CR and cognitive dysfunction management (through the participation to webinars, courses and events focused on cognitive impairment and cognitive rehabilitation).

Rebrain protocol is a CR multidisciplinary protocol which consist of 20 physiotherapy, 12 occupational therapy, 4 speech and swallow therapy, 12 neuropsychological treatments in 2 hour twice a week sessions to maximize the effects of interventions in retaining memory of what they do during treatments. The multidisciplinary team was constituted considering each discipline's unique contribution to cognitive rehabilitation as well as the cumulative benefits of combining these roles for optimizing rehabilitation outcomes (Fleeman et al., 2015).

Content of the session has been organized as follow:

- First and second week: Speech and swallow therapy 1 h and 1 h neuropsychological (or occupational therapy) training (twice a week)
- From 3rd to 6th week 1 h neuropsychological training (or occupational therapy) and 1 hour physiotherapy (twice a week)

- From 7th to 12th week 1 h occupational therapy (or neuropsychological training) and 1 hour physiotherapy (twice a week)

ReBrain session contents

All the treatments are characterized by the presence of customization, avoidance of automatism and stereotypes and alertness activation. They have been built following the main principle of integrated cognitive treatment.

- Neuropsychological therapy: the psychologist, with a restorative approach, uses Rehacom (Hasomed, Germany), a computerized rehabilitation software for cognitive intervention, paper and pencil exercises (if the patient has a low technology attitude) and mindfulness techniques (Amatya et al., 2019; DeLuca et al., 2020; Genova et al., 2019) to trigger different emotional and attentional states as needed.

Figure 7 Rehacom device

- Physiotherapy: cognitive-motor dual task exercises, techniques for the activation of the executive attention system are conducted by the physiotherapist during the sessions;

they work on balance and strengthening combining cognitive stimulation(Guti et al., 2020; Kirkland et al., 2015)(Jonsdottir et al., 2018). Therapist builds different setting and exercises to enhance executive cognitive attentional circuits, avoiding stereotypical setting. The exercises are tailored according to functional levels of the patients.

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Figure 8 Examples of physiotherapy exercises

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- Occupational therapy: the interventions will be focused mainly on activity and participation and it will range from ADL training to fatigue and stress management. Compensatory strategies, for improving the functional abilities, will be also trained during the session to optimize the cognitive performances at work/home. Techniques for the activation of the executive attention system will be conducted by the occupational therapist, if needed (in case of low arousal), during the sessions(Weber et al., 2019)(Buzaid et al., 2013; Reilly & Hynes, 2018; Tur, 2016).
- Speech and swallow therapy: during the session the therapist focuses the intervention on breathing control to train the patients with proprioceptive exercises. Breathing control has a key role on paying attention (Biskamp et al., 2017; Melnychuk et al., 2021a). An active control on it could be an important tool to face cognitive fatigue and anxiety during cognitive performance and communication.

Standard care

The control condition consists of a standard care protocol based on motor control and compensatory strategies to minimize the impact on participation of Multiple Sclerosis symptoms. The intervention consists of 12 weeks, 2-hour twice a week sessions. This control program matched the study intervention in number of sessions and schedule (but not in session content) in order to control the non-specific effects of ReBrain.

- First and second week: Speech and swallow therapy 1 h and 1 h neuropsychological (or occupational therapy) training (twice a week)
- From 3rd to 6th week 1 h neuropsychological training (or occupational therapy) and 1 hour physiotherapy (twice a week)
- From 7th to 12th week 1 h occupational therapy (or neuropsychological training) and 1 hour physiotherapy (twice a week)

Assessment

Evaluations have been planned at baseline (T0), at the end of the intervention (T1) and 12-week after treatment end (T2). Overall, the visit lasted about 60 minutes.

Measures

Since combining information from different domains (i.e. cognition, mood, quality of life and motor control) could help to increase prediction accuracy over and above what can be achieved at the level of single category markers (i.e. cognition alone), this study aimed to identify distinct and predominant effects of rehabilitation using different outcomes measures (Podda et al., 2021). To evaluate the effectiveness of the ReBrain protocol we used the Italian versions of BICAMS (Benedict et al., 2012; Goretti, Niccolai, et al., 2014) including Symbol Digit Modalities Test (SDMT) California

Verbal Learning Test-II (CVLT-II), Brief Visual-Memory Test-Revised (BVMT-R), Shortened Balance Evaluation System Test (MiniBEST)(Potter et al., 2019), Perceived Deficits Questionnaire (PDQ), Hospital Anxiety and Depression Scale (HADS)(Pais-ribeiro, 2018), Frontal Assessment Battery (FAB) , Multiple Sclerosis Quality of Life 54-items questionnaire (MSQOL-54)(Vickrey et al., 1995).

Primary Outcome Measure

SDMT (see paragraph x for a detailed description of the test)

Secondary Outcome Measures

- Mini-BESTest assesses dynamic balance, a unidimensional construct and includes items addressing anticipatory postural adjustments, reactive postural control, sensory orientation, dynamic gait
- CVLT-II
- BVMT-R
- FAB: it consists of six subtests exploring conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy.
- PDQ: it has been built specifically for MS in order to provide a self-report measure of cognitive dysfunction. This instrument provides an assessment of several domains of cognitive functioning that are frequently affected in MS: attention, retrospective memory, prospective memory, and planning and organization. The full-length PDQ consists of 20 items.
- HADS (Pais-ribeiro, 2018) is a well-validated measure that consists of two seven-item subscales to assess anxiety and depressive levels. Higher scores indicate higher levels of depressive or anxiety symptoms. Unlike many similar measures, the HADS excludes somatic symptoms of anxiety and depression, which may overlap with physical illness.

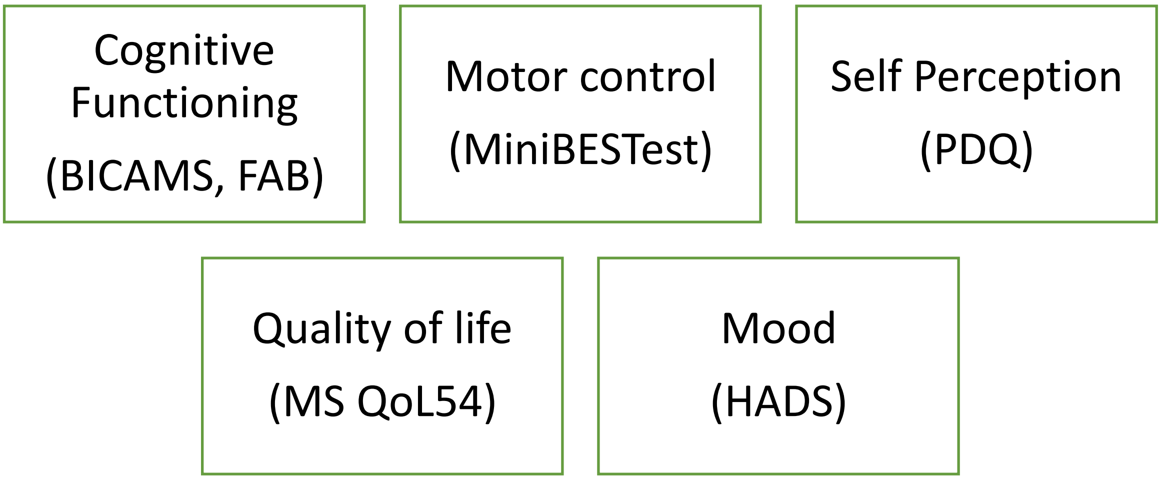

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Figure 9 Overview of the study's primary and secondary outcomes. Stated that MS is a complex condition which requires comprehensive, long-term management, and that rehabilitation programs aim to improve function, well-being and quality of life, for people with MS, we decided to use different outcomes to better understand the cascade effect given by cognitive impairment on other domains and consequently the impact of a multidisciplinary rehabilitation program on them.

Clinical information and measures

The following information has been also provided by the PwMS medical doctor at T0: EDSS score (JF, 1983), MS course (relapsing remitting, primary progressive, secondary progressive), presence/type of co-pathologies, and ongoing treatment. The physiatrist updated occurrence of new relapses at each time-point.

Dropout and suspension criteria

Subject had the right to withdraw from the study at any time during the intervention period. Additionally, the subject will be excluded if any unexpected worsening of motor or cognitive symptoms occur.

Participant recruitment and eligibility

For the aim of the projects we defined some eligibility criteria.

Participants has been recruited among those followed as outpatients at the Italian MS Society (AISM) Rehabilitation Service of Genoa (Italy). PwMS were screened if they reported cognitive problems in daily life and/or showed signs suggestive of cognitive dysfunction during clinical routine (i.e. medical visit or rehabilitative interventions).

Inclusion criteria were: diagnosis of MS according to 2017 revised Mc Donald criteria (Thompson et al., 2017), age ≥18 years, Expanded Disability Status Scale (EDSS) < 6, Symbol Digit Modalities Test (SDMT) <38 (Beier et al., 2017), speaking Italian fluently and written informed consent. Exclusion criteria are: Mini Mental State Examination (MMSE) <19 (i.e. severe cognitive deficits), psychosis or other serious psychiatric conditions, MS diagnosis for less than three months, one or more relapses in the previous 3 months, and current pregnancy.

PwMS respecting the eligibility criteria has been randomly allocated into experimental (i.e. ReBrain) or control (i.e. standard therapy) group. The clinical measures and outcomes has been collected by a physiatrist expert in the administration of the outcomes; he/she not attended any rehabilitation intervention.

Allocation has been conducted by staff members responsible for treatments scheduling (blind to assessment and treatments).

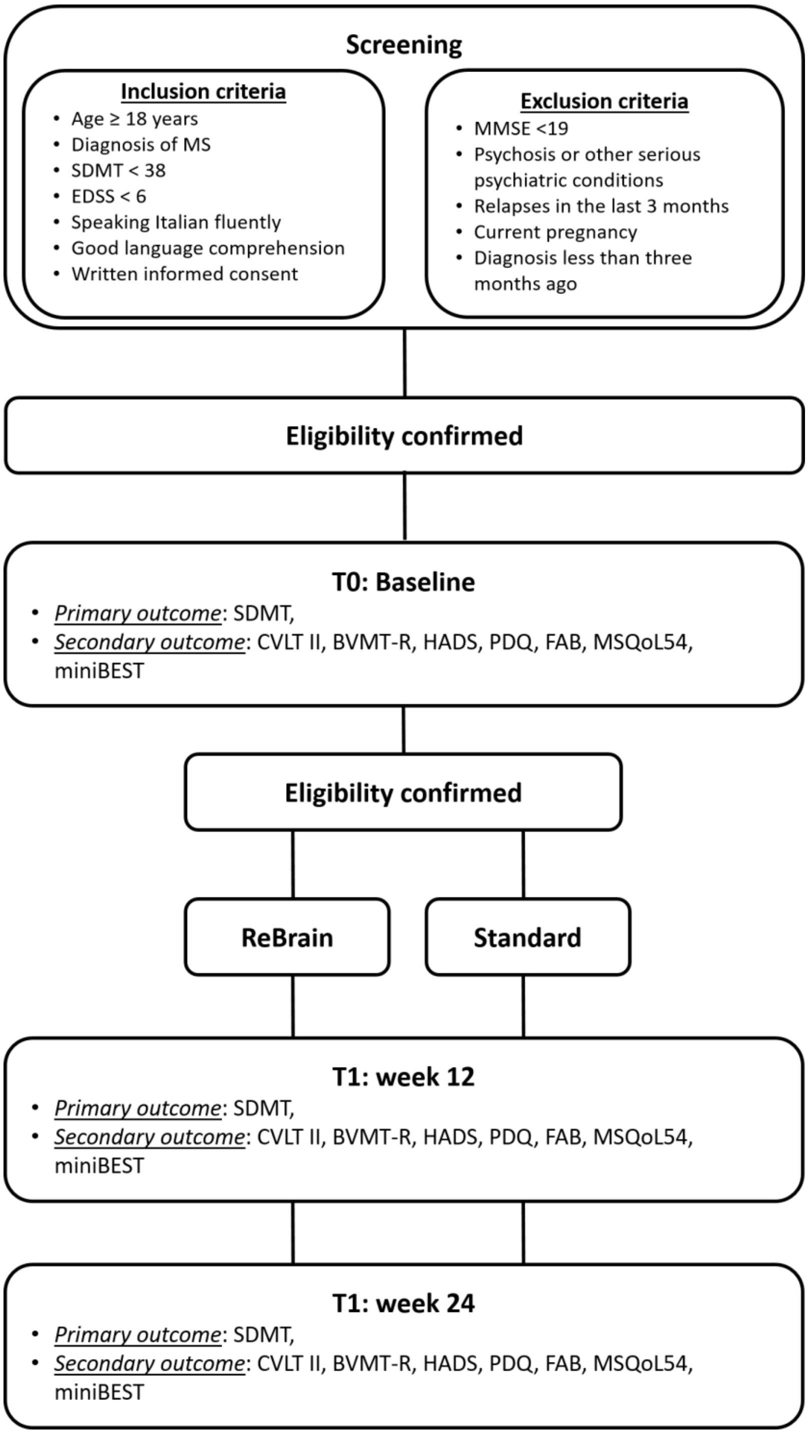

Figure 10 diagram of the study design.

SDMT - Symbol Digit modalities test; CVLT II - California Verbal Learning Test II version; BVMT-R - Brief Visuo-spatial Memory Test-Revised; HADS - Hospital Anxiey and Depression Scale; PDQ - Perceived Deficits Questionnaire; FAB - Frontal Assessment Battery; MSQoL-54 - MS Quality of Life 54 items questionnaire; miniBEST - mini Balance Evaluation System Test.

Results

Screened sample

Between December 2020 and December 2022, 153 PwMS reporting cognitive problems in daily life and/or showing signs suggestive of cognitive dysfunction during clinical routine, underwent medical visit to assess cognitive functioning. During the visit the medical doctor has collected clinical history, demographic data and he/she administered, BICAMS and PDQ as screening tools to assess both objective and subjective perception of functioning.

Screened	**N**	**Min**	**Max**	**Mean**	**SD**
Age	153	28,00	79,00	52,78	9,90
Disease duration (years since diagnosis)	153	0,00	41,00	14,07	10,47
Educational level (years of schooling)	153	5,00	22,00	11,95	3,60
Total	153				

Sex		**Frequency**	**%**	**Valid %**	**Cumulative %**
Valid	1,0	101	66,0	66,0	66,0
	2,0	52	34,0	34,0	100,0
	Total	153	100,0	100,0	

Table 1: Socio-demographic characteristic of the screened sample. In Sex 1= female 2= male

Disease course		Frequency	%	Cumulative %
Valid	**RR**	89	58,2	58,2
	SP	44	28,8	86,9
	PP	20	13,1	100,0
	Totale	153	100,0	

Table 2 Disease course: frequency of presentation in the screened sample. 1: RR, 2: SP. 3:PP

Recruited

24 pwMS met the inclusion and exclusion criteria, of which 16 underwent a multidisciplinary rehabilitation program.

Recruited	N	Min	Max	Mean	SD
Age (years)	24	41	73	55,37	8,42
Disease duration (years since diagnosis)	24	0,00	34,00	13,00	10,00
Educational level (years of schooling)	24	5,00	22,00	12,00	3,55
Total	24				
Sex		**Frequency**	**%**	**Valid %**	**Cumulative %**
Valid	1,0	9	37,5	37,5	37,5,0
	2,0	15	62,5	62,5	100,0
	Total	24	100	100	

Table 3 Socio-demographic characteristics of the recruited patients. In Sex 1= female 2= male

		Frequency	%	Cumulative %
Valid	1,0	10	41,67	41,67
	2,0	8	33,33	75,00

	3,0	6	25,00	100,0
	Totale	24	100,0	

Table 4: Disease course frequency 1: RR, 2: SP. 3:PP

Intervention sample

10 pwMS were allocated to ReBrain group.

ReBrain	**N**	**Min**	**Max**	**Mean**	**SD**
Age (years)	10	41	73	54,90	5,32
Disease duration (years since diagnosis)	10	0,00	34,00	14,00	12,25
Educational level (years of schooling)	10	5,00	18,00	13,00	4,26
Total	10				
Sex		**Frequency**	**%**	**Valid %**	**Cumulative %**
Valid	1,0	5	50,0	50,0	50,0
	2,0	5	50,0	50,0	100,0
	Total	10	100,0	100,0	

Table 5: Socio-demographic characteristics of ReBrain group. In Sex 1= female 2= male

Rebrain-**(Disease Course)**		**Frequency**	**%**	**Cumulative %**
Valid	1,0	6	60,00	60,00
	2,0	3	30,00	90,00
	3,0	1	10,00	100,0
	Totale	10	100,0	

Table 6 : Disease course frequency in ReBrain sample. 1: RR, 2: SP. 3:PP

6PwMSwere allocated to control group

Standard care	**N**	**Min**	**Max**	**Mean**	**SD**
Age (years)	6	41	73	58,17	13,17
Disease duration (years since diagnosis)	6	0	20	9,00	8,71
Educational level (years of schooling)	6	8	12	10	7,99
Total	6				
Sex		**Frequency**	**%**	**Valid %**	**Cumulative %**
Valid	1,0	2	33,33	33,33	33,33
	2,0	4	66,67	66,67	100,00
	Total	6	100	100	

Table 7: socio-demographic characteristics of standard care group. In Sex 1= female 2= male

ReBrain

10 people underwent the ReBrain protocol. Results obtained compairing T0 and T1 evaluations

These are the results obtained:

	T0	T1	t	p
	M (SD)	M (SD)		
FAB	15.44 (1.88)	16.66 ((1.22)	-2.34	0.047
CVLT	50.44 ((15.54)	56.78 ((17.89)	-2.61	0.031
SDMT	34.00 (9.37)	38.11 (12.78)	-2.17	0.062
BVMT-R	17.44 (8.23)	20.22 (9.07)	-1.06	0.321
HADS-A	7.17 (2.79)	6.0 (2.45)	1.56	0.180
HADS-D	5.17 (1.94)	3.17 (1.17)	2.93	0.033
PDQ	36.50 (14.30)	33.7 (11.88)	0.66	0.526

Table 8: Analysis of the comparison between pre and post evaluations paired t test of ReBrain group results. M= mean; SD= Standard deviation, t= test statistics t; p= two-tailed probability. In red significant p results.

Standard care

The standard care group sample was too little to conduct a comparison between the evaluation before and after the treatments.

Discussion

This study primarily aimed to evaluate the efficacy of a multidisciplinary cognitive rehabilitation protocol on improving information processing speed and secondly the impact on other cognitive domains and motor control on balance.

The main finding obtains of the recruitment phase was that the PDQ was significantly higher in patients presenting RR course compaired to patients presenting progressive course, underlining that the impact of CI perceived is higher for the first group. We also noticed that PDQ (in RR course group) was correlated with the CVLT II scores. One speculation could be that in the questionnaire most of the items refer to memory domain. PDQ in patients with RR course could be an useful instrument to assess the self-perception of cognitive functioning and to more clearly understand everyday situations lived by PwMS presenting an altered cognition.

The ReBrain cognitive rehabilitation protocol had an impact mainly on executive functions (evaluated with FAB), on memory (assessed with CVLT II) and in improving the HADS-D results.

These parameters described a little part of the domains affected by cognitive impairments in MS but, considered the number of subjects which underwent the protocol, they could represent a positive impact of the multidisciplinary cognitive rehabilitation protocol on multiple aspects.

Unfortunately, the primary outcome hadn't show a significant modification after the treatments.

Conclusions

According to the preliminary data collected, the newly introduced ReBrain protocol allows a reliable management of PwMS showing cognitive impairment.

Giving to all the rehabilitation professional reliable tools to manage cognitive deficits during the treatments should be a promising approach for the development of a future large-scale RCT.

Furthermore the correlation of PDQ emerged with cognitive functioning suggests that it could be an useful tool to monitor self-perception of cognitive impairment in association with BICAMS. Professionals should take into account both subjective and objective measure in making decision of intervention protocol.

Study limitations

Given its preliminary nature, the present experimental protocol is not free from limitations.

Among these the complexity of the treatments combination and the time required to undergo the protocol concurred to the low number of patients who concluded the study. In both groups, the main reasons for discontinuation were missed sessions for job incompatibility, missed sessions due to absent therapists, other conflicting appointments and noncompliance. Some participants in the groups wished to stop treatment after one session

Among the limitations we have to consider that with regard to assessment, objective cognitive performance was assessed using the BICAMS. Although the BICAMS is among the most commonly used and validated measures for assessing cognition in MS, it is a brief screening tool that does not capture potential deficits in delayed memory, reasoning, problem-solving, or complex attention. It is possible that individuals classified as Underestimators did have cognitive impairment that was not captured by the battery.

Although research has identified a significant relationship between self-efficacy and emotional symptomatology, previous work has failed to examine the role of disease-related characteristics (e.g., time since diagnosis, MS course, and level of physical functioning) in this relationship.

Could be useful consider a tool assessing the Quality of Life of people reporting cognitive impairment.

Importantly, we focused on the multidisciplinary approach to manage MS cognitive impairment, however we know that it is hard to evaluate the impact of every different rehabilitation professional.

Future perspective

In evaluation

To overcome the current limitations of neuropsychological testing, future research should focus on developing a battery able to identify early cognitive impairment and to disambiguate depression, anxiety, or other psychiatric disorders. The need is great for a test that can differentiate the somatic symptoms of MS from anxiety and depressive vegetative disturbances, and help us identify patients in whom anxiety and depression may affect cognitive evaluation.

The ecological validity of new and existing tests is another area that needs further research; any new tests should be designed to evaluate patients' cognitive performance in their everyday activities.

In rehabilitation

The purpose of multidisciplinary cognitive rehabilitation interventions should be substained by new technologies monitoring in an ecological way the patients activities underlying the impact of any intervention. This should be done in order to build more tailored intervention even with the use of consolidated cognitive strategies and facilitators.

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