Universidade de Lisboa

Faculdade de Farmácia

Cognitive Impairment as an Invisible Symptom in Multiple Sclerosis

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Monografia orientada pela Professora Doutora Adelaide Maria Afonso Fernandes Borralho, Professora Auxiliar

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Abstract

Multiple Sclerosis is an immune-mediated demyelinating disease of the central nervous system that leads to widespread clinical symptoms, including mainly physical disability among young adults. However, MS patients can experience symptoms that are not, apparently, visible or obvious, to those around them, such as cognitive impairment that is one of the most common and disabling symptoms of MS, occurring in about 40-70% of MS patients. Thus, what appears to be impaired are slowness in information processing, decreased episodic memory, difficulties in executive function, changes in verbal fluency, and reductions in visuospatial analysis. Owing to the heterogeneity of MS, there is no single pathognomonic feature or diagnostic test that can accurately diagnose MS, so the diagnosis is based on the integration of various clinical, imaging and laboratory findings. As for the assessment of cognitive functions, there are several written and oral, and more recently digital, versions of neuropsychological batteries. In this sense, due to its reliability, validity and sensitivity, the Symbol Digit Modalities Test is the most frequently used test to monitor cognitive relapse rates. In recent years, outstanding developments of new Magnetic Resonance Imaging sequences have allowed structural and functional correlates of cognitive impairments to be defined, which appear to be associated with neurodegeneration, brain atrophy and functional network disruption. Although Disease-modifying Therapies have been effective in reducing relapse rates in MS, such treatments, just like symptomatic treatment, are ineffective for the treatment of cognitive impairment in MS. In this sense, alternative treatment approaches for mitigating these symptoms are needed. Hence, cognitive rehabilitation and exercise training are potential candidates for the treatment of MS-related cognitive impairment, though these are still considered to be poorly managed in MS patients. To conclude, future research focusing on cognitive impairment is necessary and crucial to acquire new information and thus improve the quality of life of MS patients as well as their caregivers.

Keywords: Multiple Sclerosis; Cognitive Impairment; Neuropsychological Tests; Resonance Magnetic Imaging; Cognitive Rehabilitation

Abbreviations

^{1}H-MRS	Proton Magnetic Resonance Spectroscopy
ANA	Antinuclear antibodies
APT	Attention Process Training
BBB	Blood-brain-barrier
BHs	Black Holes
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BOLD	Blood Oxygen Level-dependent
BRB-N	Brief Repeatable Battery of Neuropsychological Tests
BVMT-R	Brief Visuo-spatial Memory Test Revised
CBD	Cannabidiol
CIS	Clinical Isolated Syndrome
CNS	Central Nervous System
CVLT-II	California Verbal Learning Test
DIS	Disseminated in Space
DIT	Disseminated in Time
DMN	Default-mode Networks
DMTs	Disease-modifying Therapies
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DTI	Diffusion Tensor Imaging
EBV	Epstein-Barr Virus
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EDSS	Expanded Disability Status Scale
FC	Functional Connectivity
fMRI	Functional Magnetic Resonance Imaging

GAS	Goal Attainment Scales
HLA	Human Leukocyte Antigen
HVLT-R	Hopkins Verbal Learning Test-Revised
MACFIMS	Minimal Assessment of Cognitive Function in Multiple Sclerosis
MLBG	Maximal Lifetime Brain Growth
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
mSMT	Modified Story Memory Technique
MSQLI	Multiple Sclerosis Quality of Life Inventory
MSQoL-54	Multiple Sclerosis Quality of Life-54
MT-MRI	Magnetization Transfer Magnetic Resonance Imaging
MusiQoL	Multiple Sclerosis International Quality of Life
NAA	N-acetylaspartate
NfL	Neurofilaments
NMSS	National Multiple Sclerosis Society
OCBs	Oligoclonal Bands
PASAT	Paced Auditory Serial Addition Test
PET	Positron Emission Tomography
POMS	Pediatric-onset Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
PROs	Patient-reported Outcomes
pwMS	People with MS
QoL	Quality of Life
RCTs	Randomized Controlled Trials
RIS	Radiologically Isolated Syndrome
RRMS	Relapsing-remitting Multiple Sclerosis

RS-fMRI	Resting-state fMRI
SDMT	Symbol Digit Modalities Test
SPMS	Secondary Progressive Multiple Sclerosis
STEM	Strategy-based Techniques to Enhance Memory
THC	Tetrahydrocannabinol
ToM	Theory of Mind
TSPO	Translocator Protein
USPIO	Ultrasmall Superparamagnetic Iron Oxide
WHO	World Health Organization

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1. Introduction

Multiple Sclerosis (MS) is a chronic and inflammatory disease of the central nervous system (CNS), with hallmarks of demyelination and axonal degeneration that is characterized by its heterogeneity in symptoms, disease course, and also outcomes. MS is mainly diagnosed in young adults between the ages of 20 and 40 and is one of the main causes of disability among them (1).

MS is known to predominantly involve physical disability. However, many people with MS experience other types of clinical symptoms that are apparently not obvious to those around them, this can be described as an “invisible symptom”, named precisely because of the lack of external physical indicators. The most frequently reported invisible symptoms may include, but are not limited to: fatigue, pain, spasticity, bowel and bladder dysfunction, sexual dysfunction, vision changes, mood disorders, and cognitive impairment. Which when not properly identified and treated, can have a negative influence on patients' mental health, social roles or interactions, employment, daily life and overall quality of life (QoL). In particular, although a more precise understanding of cognitive impairment still remains elusive, what appears to be most impaired in MS patients is slowness in information processing, decreased episodic memory, difficulties in executive function, changes in verbal fluency and reductions in visuospatial analysis, which often occur early in the disease, even before other physical symptoms manifest (2).

Currently, due to the heterogeneity of MS, there is no single pathognomonic feature or diagnostic test that can accurately diagnose MS, so it is essentially based on the integration of various clinical, imaging and laboratory findings (3).

With regard to the assessment of cognitive functions, through neuropsychological tests and Magnetic Resonance Imaging (MRI) evidence, it is very important to perform these assays as early as possible in order to identify possible cognitive impairment, such as to estimate future impairments, progression and limitations. It also became important to consequently mitigate cognitive impairment through pharmacological interventions, as Disease-modifying Therapies (DMTs) and symptomatic treatments, as cognitive rehabilitation and exercise training (4).

In 1996, the International Advisory Committee on Clinical Trials in MS, supported by the US National MS Society (NMSS) and the European Committee for Treatment and Research in MS (ECTRIMS), defined the different clinical courses, also called subtypes or phenotypes, of MS. Subsequently, in 2013, with the increase of knowledge in this field, such as at the level

of imaging and biological markers, the course descriptions were refined. Recently, in 2020, was published an article that clarify some of the concepts underlying the clinical courses descriptors, or also known as modifiers, that were creating confusion. The purpose of having a standardized terminology, in addition to providing temporal information about an individual's disease state, is to have an accurate description of the clinical course descriptors that facilitate communication between the clinicians, people with MS (pwMS), researchers, sponsors, and regulators and that facilitate prognosis, conduct of clinical trials, and decision-making in clinical practice (5).

Currently, the clinical course of MS is characterize as Clinical Isolated Syndrome (CIS), Relapsing Remitting MS (RRMS), Secondary Progressive MS (SPMS), and finally as Primary Progressive MS (PPMS). Inherent, there are two important modifiers to describe an individual's current disease state, that are assessment of activity (showing evidence through clinical relapses or imaging - gadolinium-enhancing lesions and/or new or increasing T2 lesions) and assessment of progression (clinical evidence of disability worsening, independent of relapses, over a given period of time, in patients who are in a progressive phase of the disease). Thus, in order to frame disease activity and progression in time, it is recommended to conduct an evaluation annually (1,5). Additionally, the activity modifier, applies to patients with both relapsing remitting and progressive MS, while the progression modifier applies only to patients in a progressive phase, either SPMS or PPMS. Furthermore, for the purposes of clarity, it is important to highlight the differences between the terms worsening and progression. Thus, the Committee, recommends that the term worsening be used to describe any increase in disability or impairment, regardless of whether this is the result of residual deficits after a relapse or the result of increasing disability during the progressive phase of the disease, and recommends reserving the term progression to describe patients in progressive phases who are cumulating disability, regardless of any relapse activity (5).

Although not considered a subtype of MS, Radiologically Isolated Syndrome (RIS) can be characterized by an incidental MRI finding of brain lesions in the white matter that are highly suggestive of MS, and cannot be explained by another diagnosis in people who have no current historical accounts of typical MS symptoms (6). CIS, on the other hand, is a newly added course of MS, and is often characterized as the first clinical episode with features suggestive of a lesion in the optic nerve, spinal cord, brainstem or cerebellum, which can evolve acutely or sub acutely to MS if eventually additional activity occurs (1,6).

The clinical course of MS is highly unpredictable (Figure 1). Still, in 85% of patients, MS typically starts as the classic form of the disease, in other words, the RRMS form, which is

characterized by recurrent clinical symptoms that are commonly followed by total or partial recovery. After an unpredictable time period of many years, roughly 10 to 15 years, up to 50% of untreated RRMS patients tend to slowly progress to SPMS. In contrast, about 15% of patients actually develop PPMS, which is characterized by the absence of the initial RRMS stage and by a continuous, relentless progression of the disease. Conversion from RRMS to SPMS and the onset of PPMS tends to occur within a well-defined age window, particularly between the ages of 35 and 50, and appears to be related to prolonged chronic inflammation in the CNS and age (7,8).

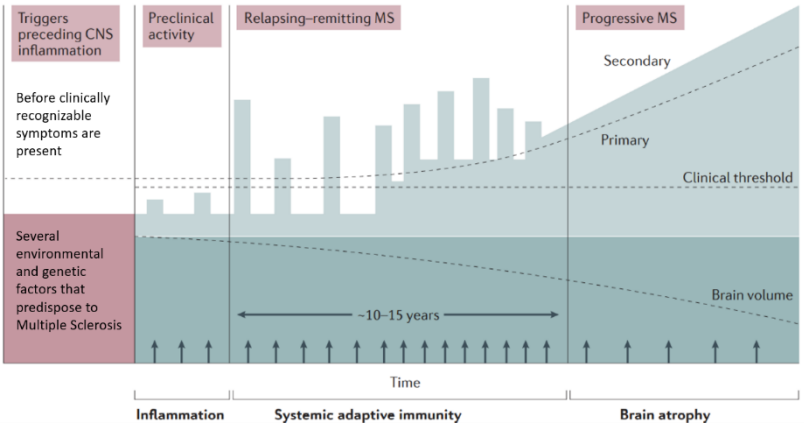

Figure 1. Clinical Course of Multiple Sclerosis

[Figure adapted from (13)]

The terminology and classification used to describe MS is not static, which means that as new developments and information emerge in this field, there is a need to update, reformulate and/or clarify. In this way, it is possible to obtain a terminology and classification as up-to-date and clear as possible at a given time (5). While these terminologies and classifications are useful from a theoretical point of view, in clinical practice they sometimes do not adequately capture the complexity of the different disease subtypes, since there is frequently overlap between them, their transition is not entirely clear, and the classification is based on patients' recollections and descriptions of historical events (9).

Here, information regarding cognitive impairment as an invisible symptom in MS will be discussed, with particular emphasis on the cognitive domains that appear to be most impaired in MS patients, as well as special emphasis on linking these particularly impaired domains with their respective specific impaired areas. Finally, the main current and developing strategies for the diagnosis and treatment of cognitive function in MS patients will also be discussed.

2. Multiple Sclerosis

2.1. Epidemiology, Prevalence and Incidence

The estimated number of people with MS has been increasing worldwide. According to the Atlas of MS, the latest and most extensive epidemiological study of MS, there are currently about 2.8 million people worldwide with MS, which represents a global prevalence of 35.9 per 100.000 people. Although the availability and quality of incidence data have been more poorly reported than prevalence, the incidence rate is 2.1 per 100.000 people/year. The average age of diagnosis is 32 years. Despite this, the study also found that there was a significant increase in pediatric-onset MS (POMS), which refers to MS onset before the age of 18, in some countries. In addition, it was found that women are twice as likely to have MS as men. Intriguingly, this increase in prevalence and incidence of MS can potentially be explained by greater access to services and diagnostic criteria, which results in more cases being detected earlier, and can also be explained by the fact that people in general tend to live longer, even living with MS, due the appearance of new and more effective therapies (10).

The prevalence of MS is not similar around the world. Overall, its prevalence tends to increase with latitude, meaning that it tends to increase as one travels north or south from the equator (Figure 2). Accordingly, Europe and America report having the highest incidence, at 6.8 and 4.8 respectively. Whereas, Southeast Asia and Africa report a much lower incidence of 0.4. Regardless, there are exceptions to this gradient, suggesting that not only geographic but also racial and ethnic differences may be related to risk. In Portugal, according to the Atlas of MS, MS is estimated to affect about 6.000 people (10–12).

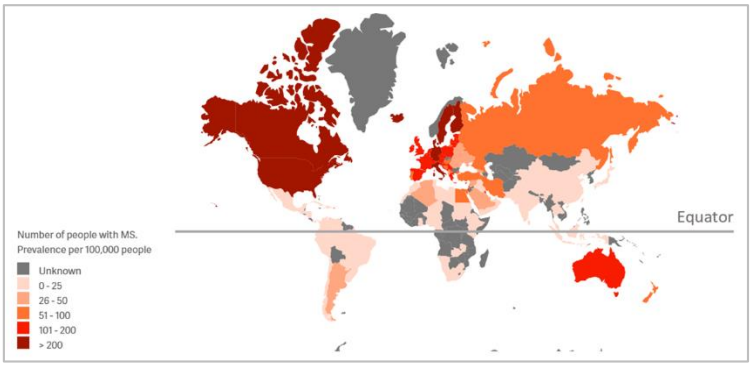

Figure 2. Worldwide prevalence of Multiple Sclerosis, in 2020

[Figure adapted from (11)]

Although the underlying cause of MS is still unknown, several risk factors have already been adequately established as contributors to MS. These can include environmental factors as Epstein-Barr virus (EBV) infection, low Vitamin D and lack of sun exposure, tobacco exposure through active or passive smoking, and, more recently established, childhood and adolescent obesity. Others, less-established, environmental risk factors may include night work, excessive alcohol or caffeine consumption. In addition, it is also known that genetic risk factors, with a particular highlighting on Human Leukocyte Antigen (HLA) variants, may be associated with an individual's susceptibility to trigger and/or exacerbate MS (13,14). Although the underlying mechanistic understanding it is still premature, the influence of lifestyle, environmental factors and genetic predisposing factors that have been already established can be traced back to their effects on the immune system in MS (13).

2.2. Pathophysiology

In spite of the intense research, the pathology of MS remains incompletely understood. However, the most commonly accepted theory of its pathophysiology starts with the activation of autoreactive T-lymphocytes, activated by a yet unknown factor, which once activated cross the blood-brain-barrier (BBB) and migrate into the CNS, interacting with myelin autoantigens (14), which ultimately leads to further inflammation and demyelination, which is followed by oligodendrocyte loss, reactive gliosis and neuro-axonal degeneration (15).

The pathological hallmarks of all MS subtypes are focal plaques, or also called lesions, representing areas of demyelination that are predominantly found around post capillary venules. They occur in both white and gray matter (cortical and deep) and are found throughout the CNS, including in the brain, optic nerve and spinal cord (15). Interestingly, MS was initially thought to be a white matter disease only, however, gray matter lesions have currently been associated in the course of MS, particularly in the pathogenesis of MS-related cognitive impairment (16). Thus, anatomical location of lesions are related to specific and different clinical manifestations of MS (15), as are quantitative differences of these in the different subtypes of the disease (8).

Following on from the above, MS is considered a primarily inflammatory disease of the brain and spinal cord, where myelin and axon damage can be observed. Inflammation is initially transient, as it is normally followed by remyelination, so that the course of disease is early and mainly characterised by neurological dysfunction that usually recover, so-called relapses. Then,

widespread microglial activation is associated with extensive and chronic neurodegeneration, which leads to progressive accumulation of disability over time (17).

2.3. Cognitive Impairment

MS is a complex condition that is mainly diagnosed in young adults, between the ages of 20 and 40, although it can also be found and/or affect younger children and older adults. The symptoms that people with MS experience are variable and ultimately unpredictable, as these depend on which areas of the CNS are affected. Accordingly, no two people have the same exact symptoms, they can change between people and even fluctuate over time within the same individual (18).

MS is a complex condition that is mainly diagnosed in young adults between the ages of 20 and 40, however it can also be found and affect younger children and older adults.

Among the most common symptoms mentioned, cognitive impairment, specifically, can be reported in all stages and subtypes of MS, which is characterised by an alteration in one of the six key domains of cognitive function, which, according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), are perceptual-motor function, language, learning and memory, social cognition, complex attention and executive functions, where each of them has several subdomains (19) (Figure 3).

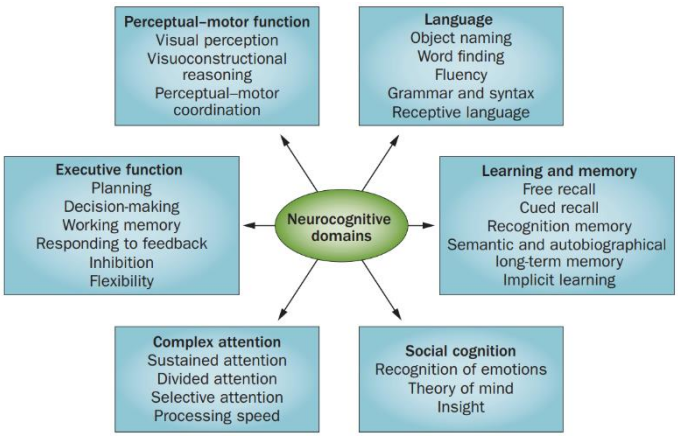

Figure 3. Neurocognitive domains and subdomains, according with DSM-5

[Figure adapted from (19)]

Cognitive impairment in MS patients has been neglected for several years, possibly due to the fact that it is an invisible symptom, that means, a symptom that is not exactly observable or easily understood by those around them. Regardless, cognitive impairment is a very common symptom, since it is present in the majority of MS patients, in approximately 40 to 70%, with no significant gender differences observed. Thus, it is important to note that if these symptoms are not addressed, they end up having a negative impact on their quality of life (20).

It is interesting that only half of the MS patients exhibit cognitive impairment. So there appears to be a dynamic balance here between brain destruction and brain reorganization or, in other words, neuroplasticity. Hence, naturally, this balance works to keep all the brain systems functioning properly, but not only does this not happen in all cases, it does not last forever, that is, there comes a point when the systems sooner or later collapse, the reorganization of the brain is no longer effective, and subsequently cognitive impairment becomes evident. However, it is hoped that brain reorganization can be managed through neurorehabilitation interventions (21).

As previously stated, cognitive impairment can be reported in all stages and subtypes of MS, and its prevalence tends to increase over time. In other terms, in more advanced stages and in progressive forms of the disease, as SPMS and PPMS, cognitive impairment tends to be even more pronounced than in earlier stages, as RIS, CIS and RRMS (6). Furthermore, although not yet completely well defined, the presence of cognitive impairment, more prevalently processing speed and memory, is thought to be related to a higher risk of conversion or disease progression in subsequent years, therefore showing that its presence may be an early predictor of this and further highlight the importance of cognitive assessment in newly diagnosed patients (22).

Unfortunately, in spite of its highly prevalent and considerable impact, the mechanisms underlying the onset and progression of cognitive impairment are still largely unknown, and its origin seems to be even more complex and multifactorial than previously thought. It then seems to arise from a combination of pathological changes in normal-appearing white matter, as in the CNS gray matter, through the presence of focal gray matter lesions and gray matter atrophy. In addition, what is verified is that in the earliest stages of the disease axonal damage occurs which, over time, along with diffuse microglial activation, begins to dominate the pathological changes of MS. These, are accompanied by a progressive accumulation of neurological disability that is typically irreversible, thus affecting many functional domains, from mobility to cognition. It is also important to reinforce that linking a damaged cognitive domain with the respective specific impaired area and/or neuronal network can be a complicated task, however, it is always possible to infer some causal associations (6).

The cognitive domains that seem to be most impaired in MS are information processing efficiency, memory, attention, executive functions, and visual perceptual functions (Table 1). Usually, the domains occur in combination with one or two of the other domains. It is estimated that information processing efficiency affects around 20 to 50% of MS patients, and numerous authors consider this to be the first and most impaired domain. This involves working memory, responsible for maintaining and manipulating information in the brain in a short period of time, and processing speed, responsible for the top speed at which that information can be processed. Memory, the other domain that appears to be most impaired in MS patients, with a prevalence of 33 to 65%, is predominantly related to long-term memory, which is reflected in the patient's difficulty in acquiring, retaining and retrieving new information. In addition, within long-term memory, changes in MS occur mainly at the level of explicit memory (declarative), and more precisely, in episodic memory, responsible for the conscious retrieval of personal experiences. Regarding attention, it appears to affect 12 to 25% of MS patients, and it is believed that, among the various components of attention, divided attention is the most impaired. Executive functions can affect, approximately, 17 to 19% of MS patients, and in which some difficulties in planning and problem solving can be observed. Finally, visual perceptual functions refer to the patient's inability to recognize and evaluate a visual stimulus, and they are thought to affect more than 25% of MS patients (23).

Cognitive Domain Impaired	Prevalence in MS patients (%)
Information Processing Speed	20-50
Memory	33-65
Attention	12-25
Executive Functions	17-19
Visual Perceptual Functions	> 25

Table 1. Prevalence of the most impaired cognitive domains in Multiple Sclerosis.

[Table adapted from (23)]

When considering the two cognitive domains most frequently impaired in earlier RRMS patients, that is, where mechanisms may be more simply disentangled, information processing speed and memory may be associated with different mechanisms. Some studies have suggested that information processing speed appears to be the first and most impaired domain, however it progresses more slowly throughout the disease, while memory, as well as executive functions,

appear to be more impaired in a more advance stage of the disease (24). In summary, thalamic atrophy is involved in the pathogenesis of information processing speed, and the involvement of other cortical areas may account for failure in specific cognitive domains, such as lesions in the limbic system, particularly, the hippocampus for learning and memory, and frontal lobe for executive functions (6).

Pediatric MS represents only 2 to 5% of the MS patient population, and about one-third of these patients ultimately experience cognitive impairment. When compared to patients with an adult onset of the disease, in addition to processing speed and memory, other domains such as language and intelligence appears to affect pediatric MS patients, reproducing a major long-term impact on their academic and social quality of life. CNS demyelination and neural network negatively affects cognitive functions, however, compared to adults, children have better neural plasticity and compensatory capacity, which have a positive effect on cognitive functions. On the other hand, their cognitive performance may deteriorate over time compared to their initial performance, and this worsening can be explained by deteriorating maturation and development of an immature CNS, resulting from demyelinating and neurodegenerative processes (20,25).

Social cognition, one of the domains of cognitive function as defined by DSM-5, reflects how people process, store and apply information in social interactions with others, and in some MS patients it could also be impaired. This comprises subdomains such as emotion recognition, theory of mind (ToM), and insight, which, when are impaired, can be associated with significant psychosocial impairment including difficulties in employment and inter-personal domains, that are more exacerbate in a more progressive phase of the disease. With special attention to ToM, this refers to the ability to attribute mental states to others, and to use these attributions to better understand and predict behavior. In addition, ToM can be divided into affective ToM that refers to the ability to understand others emotional states, and cognitive ToM that refers to the ability to infer others thoughts, intentions and beliefs (26). Moreover, the subdomains have been linked to different social cognition networks and, recently, overall impairment in ToM has been linked to amygdala atrophy, widespread normal-appearing white matter damage and to disconnection, reduced parietal and temporal white matter volume and atrophy in the cingulate cortex (6).

A recent study suggests that clinical predictors for cognitive impairment in people with MS may include low educational level, longer duration of disease, type of first attacks, frequent relapses, progressive form, higher disability, and immunosuppressive treatments. Interestingly, higher levels of intelligence and education have the ability to reduce the likelihood of patients developing cognitive impairment, and this can be explained by the fact that they form a certain

level of cognitive reserve that can affect the resilience of the brain in the presence of insult (27). Cognitive reserve is strongly related to individual features, as variation in cell number, dendritic density and other neuronal genetic or environmental factors, as maximal lifetime brain growth (MLBG) and intellectual enrichment, respectively, which mediate increased activation of usual or alternative neural works and are crucial for cognitive adaptation in conditions as MS (23).

It is sometimes difficult to tell whether the symptoms that the MS patient is experiencing are really due to the disease itself or, on the other hand, if they are due to a possible confounding factor such as depression, anxiety, fatigue, or even side effects resulting from the treatment of the disease. The most prevalent confounding factor is depression, affecting approximately 50% of MS patients. Some studies show that its presence is more common when the MS patient has cognitive impairment present. The association of both seems to lead to worse results in different neuropsychological tests, suggesting that the most affected cognitive functions are processing speed, working memory, learning and executive functions. MS patients who have brain lesions, compared to those who have them in the spinal cord, are more probable to develop depression, mainly if the lesions are located in the temporal lobe, as this is where the main brain structures, responsible for the aforementioned cognitive functions, are located. Accordingly, the need for a diagnostic evaluation of depression is stressed, since if it is present in the patient, appropriate pharmacological and psychological intervention is crucial to reverse the symptoms experienced by MS patients and improve their quality of life. Even though anxiety is not as well studied as depression, it can also be a confounding factor. It has a prevalence of 12 to 40% of MS patients and mainly affects newly diagnosed patients. Fatigue, physical or emotional, is one of the most common symptoms of MS and is characterized by an overwhelming feeling of exhaustion and that can make it difficult to carry out any activity. MS fatigue is frequently associated with sleep disorders. Overall, all the confounders are very challenging to quantify due to their subjectivity. Does physical disability and/or cognitive impairment make the patient more depressed, anxious, fatigued and sleep deprived or is it the other way around (28)?

2.4. Impact of MS-associated Cognitive Impairment on Quality of Life

World Health Organization (WHO) defines quality of life as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns (29). This is a comprehensive term

that comprises physical, psychological and social factors, and is focused on whether the disease and/or impairments affects a person's ability to play a normal role (28).

MS disease, and specifically cognitive impairment, can negatively affect various aspects of a patient's life, including daily functioning, employment, leisure activities, and relationships, which can obviously affect quality of life (15). Even though some of the MS patients continue to live independently to some extent, others require more ongoing care and support from their informal caregivers, including family members and friends. In general, this can also negatively affect the health and well-being of caregivers, such as their physical and mental health, as well as their financial situation and employment status. In spite of the fact that caregivers' challenges go through are still frequently overlooked, their role is critical in helping to meet the gaps left by deficits in formal caregivers/healthcare supports (30).

MS is usually diagnosed between the ages of 20 and 40, thus precisely during the years of employment. The manifestation of certain specific symptoms, such as mobility impairment, cognitive impairment, weakness and fatigue in MS patients can strongly influence the patient’s employment status. In this way, it is estimated that about 40% to 80% of patients at any point in their illness report being unemployed. In addition to these specific symptoms, some personal demographic factors and positions may influence the employment status of the patient, namely a diagnosis at an earlier age, shorter duration of disease, higher education, and being male seem to be associated with positive work outcomes. Moreover, in a work and socio-structural context, positive support from colleagues, managers and/or supervisors appear to be strongly associated with organizational embeddedness and continuity of patient work status. In brief, a continued and long-term employment in MS patients is allied with higher quality of life, less dependence, and a more and better disease management. Hence, for this to happen and for patients to achieve the best employment outcomes as possible, it is necessary to equip them with early assessment, advices, and resources that will allow them to best manage their employment in the future (31).

To corroborate the aforesaid, a significant difference in the performance of unemployed and employed MS patients in different neuropsychological tests has been observed in numerous studies, in other words, unemployed patients performed worse in these tests compared to those who were employed, revealing that information processing speed, and both verbal learning and visuo-spatial memory are related to employment status. In addition, differences were observed in certain executive functions, specifically in tasks requiring idea generation, and set shifting, but they were not significant. In summary, MS patients who were unemployed or had reduced

working hours had a higher level of cognitive impairment than MS patients who, conversely, remained employed or had maintained their working hours (32).

Accordingly, studies have showed that quality of life of MS patients depends to a large extent on how they adapt and cope with the disease, that is, how they respond to the combined psychological, social and structural influences to manage their lives, work and the disease itself. In the literature, there are coping strategies, namely problem-focused and emotion-focused, that can help the patients to do something active to alleviate stressful circumstances, and to regulate the emotional consequences of stressful or potentially stressful events. However, it is pertinent to point out that both have their consequences, which means that a strategy could be positive or negative, depending on its context. In this way, the effectiveness of a coping strategy depends on continuous assessment in relation to the dynamics of the disease course (31).

All in all, the impact of cognitive impairment on MS patient's lives tends to change over time, along with changing priorities and coping. According to this, several studies showed that newly diagnosed patients have greater difficulty accepting the disease and therefore the impact on quality of life is greater. While patients who have been living with the disease for some time, although cognitive impairment tends to increase, the impact that cognitive impairment has on their quality of life is less, because, according to their limitations, they have already developed their own coping strategies (33,34).

Several specific scales have been developed to assess the quality of life of MS patients, even though their use in clinical practice is somewhat limited. These include, the documentation of patient-reported outcomes (PROs), MS Quality of Life 54 (MSQoL-54), MS Quality of Life Inventory (MSQLI), and MS International Quality of Life (MusiQoL), among many others (15).

3. Multiple Sclerosis Characterization

3.1. Clinical and Neuropsychological Assessment

The diagnosis of MS is complex as no single test can positively diagnose it. Moreover, most symptoms presented by MS patients may resemble other neurological conditions, so there are currently several strategies to diagnose MS. These may include a meticulous patient history, neurological testing, MRI, evoked potentials, cerebrospinal fluid analysis, and blood tests (35). The aim is to make a rapid and accurate diagnosis of MS to allow proper management, taking

full account of the potential dangers that may arise from misdiagnosis a time when there are an increasing number of MS treatment options, all with varying degrees of risk (3).

More particularly, a meticulous analysis of the patient's history allows for the collection of information about both patient's and family's clinical histories, the identification of present or past symptoms that may be associated with MS, and identification of environmental and/or genetic MS risk factors, among others. Neurological testing collects information by performing tests covering cranial nerves, sensations, reflexes, coordination, gait and balance (15). Evoked potentials tests, both sensory and motor, assess functionally relevant pathways and can identify clinically silent CNS lesions, that might be missed during standard routine clinical examination (35). Blood tests, even though none are specific for MS, can exclude other conditions that cause MS-like symptoms, as other inflammatory CNS diseases, some infections, vitamin and mineral deficiencies, and rare inherited diseases (15).

In previous years, many findings have been published about potential biomarkers of the disease, which include antibodies, cytokine and chemokine molecules involved in damage and repair processes, proteins of the complement system, and nucleic acids, which may help in the diagnosis of MS, differential diagnosis, prognosis, and monitoring of MS and its therapies (36). The ideal biomarker is then characterized by high sensitivity and specificity, in addition to being a simple, cost-effective, reproducible, and non-invasive detection method. Hence, cerebrospinal fluid findings have allowed the identification of features that support the diagnosis of MS, such as the presence of cerebrospinal fluid-specific IgG oligoclonal bands (OCBs), which are found in the vast majority of MS patients. Although not specific for MS, they can be a very predictive biomarker if the others inflammatory CNS diseases have been excluded from the diagnosis. In addition, they can play an important role in providing information about the course of disease activity and indicating conversion to another subtype of MS (15,37). In addition, there are also other diagnostic biomarkers that can help differentiate MS patients from healthy people or from other diseases, including anti-AQP-4 antibodies, anti-MOG antibodies or antinuclear antibodies (ANA), as well as new biomarkers that are currently being investigated, such as neurofilaments (NfL)(37).

With regard to McDonald Criteria, the most updated revision, The Revised McDonald Criteria, published in 2017 by the International Panel on the Diagnosis of MS, it presents several recommendations regarding the diagnosis of MS, allowing it to be as accurate and early in the patient's clinical course as possible, and also allowing the patient to access the most appropriate treatment quicker (A1). As the fundamental requirement for a diagnosis of MS is evidence of

CNS damage that is disseminated in time (DIT), which refers to the development or appearance of new CNS lesions over time, and in space (DIS), which refers to the development of lesions at distinct anatomical locations within the CNS, that are essential and necessary to exclude other neurological conditions. In particular, MRI can provide this evidence with high sensitivity and specificity, and can be applied to diagnose patients who present with typical MS symptoms and in whom the diagnosis of MS is suspected. Therefore, given that the lesions can be found even in someone with few or no clinical symptoms, these can be an evidence for DIS. Furthermore, it has recently been added to the criteria that the presence of cerebrospinal fluid-specific OCBs is a good marker for MS, as mentioned previously, and that these allow confirmation of whether or not disease activity has occurred in the past and can therefore be evidence for DIT (3,38).

The most widely used method to quantify and monitor disability over time in MS is the Expanded Disability Status Scale (EDSS), and is mainly used in clinical practice, observational studies and clinical trials. Particularly, EDSS scale ranges from 0 (normal neurological exam, no disability in any functional system) to 10 (death due to MS) with an increase of 0.5 units for each higher level of disability. The EDSS scale of 1.0 to 4.5 refers to people with MS who are able to walk without any aid and it is based on other impaired functional systems as pyramidal, cerebellar, brainstem, sensory, bowel, bladder, visual, cerebral functions, among others, while the scale of 5.0 to 9.5 refers to people with MS who are not able to walk without any aid. Even though this scale includes more severe stages of the disease, the majority of MS patients do not reach these scores. In spite of being widely used, this method has its own limitations, including complex scoring rules, subjective nature, changes between steps in the scale are uneven, focuses almost fully on walking ability as the main physical measure of disability among MS patients, and does not sufficiently emphasize other symptoms and the impact these can have (39)(A2).

3.2. Detection of Cognitive Impairment

Cognitive impairment is not the core symptom of MS and, per se, is not a sufficient and necessary criterion for the diagnosis of MS. However, as previously stated, patients may present cognitive impairment in the early stages of the disease, even before the appearance of the first physical symptoms characteristic of MS (40), then it is important to assess and, if appropriate, monitor the activity and effects of treatment using a variety of neuropsychological batteries that assess the different domains of cognitive function (20).

In the last decades, different neuropsychological batteries have been proposed. The first and most frequent neuropsychological batteries for MS were the Brief Repeatable Battery of Neuropsychological tests (BRB-N) and the Minimal Assessment of Cognitive Function in MS (MACFIMS). Even though both have a high sensitivity and specificity, their implementation in everyday clinical practice is limited, since they require considerable time to perform, to be more precise 45 and 95 minutes respectively, and require a professional neuropsychologist to perform and interpret them. In order to overcome these last limitations, the Brief International Cognitive Assessment for MS (BICAMS) has recently been developed, which is an easier test to perform, requires only about 15 minutes to run, and does not require a professional. This is composed by the Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test-II (CVLT-II) and the Brief Visuo-spatial Memory Test Revised (BVMT-R), which have been shown to have good psychometric properties (41,42). Besides, current studies have shown that, in addition to adults, these tests could equally be used effectively in screening cognitive functions in pediatric MS (25)(Table 2).

Battery	Time	Test	Targeted cognitive domains
BRB-N	45’	Selective Reminding Test **(SRT)**	Verbal learning and memory
		10/36 Spatial Recall Test **(10/36 SPART)**	Visuo-spatial learning and memory
		Paced Auditory Serial Addition Test **(PASAT)**	Working memory/processing speed
		Symbol Digit Modalities Test **(SDMT)**	Processing speed
		Word List Generation Test (**WLG)**	Verbal fluency/word retrieval
MACFIMS	95’	Paced Auditory Serial Addition Test **(PASAT)**	Working memory/processing speed
		Symbol Digit Modalities Test (**SDMT)**	Processing speed
		California Verbal Learning Test-II (**CVLT-II)**	Verbal learning and memory
		Brief Visuo-spatial Memory Test-Revised (**BVMT-R)**	Visuo-spatial learning and memory
		Delis-Kaplan Executive Function System Sorting Test (**D-KEFS)**	Executive functions and problem solving
		Judgement of Line Orientation Test **(JLO)**	Visuo-spatial processing
		Controlled Oral Word Association Test **(COWAT)**	Verbal fluency/word retrieval
BICAMS	15’	Symbol Digit Modalities Test **(SDMT)**	Processing speed
		California Verbal Learning Test-II **(CVLT-II)**	Verbal learning and memory
		Brief Visuo-spatial Memory Test-Revised **(BVMT-R)**	Visuo-spatial learning and memory

Table 2. Neuropsychological test batteries for Multiple Sclerosis

[Table adapted from (52)]

To formally quantify information processing speed, one of the main domains involved in MS patients, there are essentially two neuropsychological tests, the Paced Auditory Serial Addition Test (PASAT) and the SDMT. Both of these tests are included in the BRB-N and the MACFIMS batteries, however, the BICAMS battery, on the other hand, ultimately sees the SDMT test as a preferable alternative to the PASAT. This is mainly due to the fact that the SDMT is an easier test to administer in everyday practice, has greater acceptance by patients and has greater long-term reliability, validity and sensitivity compared to the PASAT (43).

Therefore, the PASAT test quantifies auditory information processing speed, flexibility, and calculation ability. In this test, participants are presented with single digits every 3 seconds, or an even shorter interval between stimuli, which is also associated with a more difficult test. Then, the participant have to add the new digit to the digit that appeared immediately before it, and so on (44). With reference to the SMDT test, it quantifies information processing speed, however, the patient's performance on this test eventually depends on other cognitive functions as working memory, paired-associate learning, and visual scanning. In the oral version of this test, participants are presented with a set of symbols numbered 1 to 9. Then, they only have 90 seconds to match the number to its symbol, as rapidly as possible (20,45)(A3).

Some studies have shown that MS patients perform worse on the SDMT test in a relapse phase when compared to a stable/remission one, and then an improvement in their performance can be observed in the time period after relapse, which may be associated with a recovery phase (16). In other words, contrast-enhancing lesions on brain MRI can be associated with transient cognitive impairment or worse performance on the SDMT neuropsychological test, due to the detrimental effect of focal demyelination on circuit dynamics, which may be partially mitigated by the cognitive reserve effects (6,20). In conclusion, loss in deep grey matter volume (thalamic atrophy) is involved in the pathogenesis of information processing speed during MS (6).

Interestingly, a recent study exhibited some results regarding the attitude of patients of different subtypes, to be exact RRMS and SPMS, towards the administration of tests that assess cognitive function in MS, such as the SDMT. In this study, in general, all patients support the introduction of routine SDMT testing due to its simplicity of administration and to the fact that they consider cognitive symptoms to be an integrant part of MS as well as physical symptoms, but support it for different reasons. The underlying reasons why patients with RRMS, patients who are at an early stage of the disease, support these tests are more related to the support they can provide in choosing their treatment, to any information their results may provide in future research, and also to aspects related to their psychological well-being. Patients with SPMS, who

are in a more advanced stage of the disease, however, support these due to the lack of treatments observed at their stage, and also support them as a means of personal awareness of their disease and "proof" of the cognitive difficulties they experience. Furthermore, this study highlights the limitation that neuropsychological tests have in that they can only partially explain how patients function in the real world, which remains a challenge to assess (33).

Memory, one of the other major domains involving MS patients, can be quantified using the CVLT-II and BVMT-R tests, which, in addition to memory, quantify verbal learning and visuospatial learning, respectively. In the CVLT-II test, participants are read a list of 16 words and then have to remember as many words as possible across a series of 5 trials. In the BVMT-R test, participants are presented with 6 figures for 10 seconds and then have to draw as many figures as they can in the correct location (42). It should be noted that these types of tests are as effective as the SDMT in the process of distinguishing cognitive impairment in MS patients from healthy people (20,45)(A3).

Written and oral versions of neuropsychological tests have existed for a long time, only more recently have their versions been adapted to digital, for computers, tablets or smartphones. These were adapted in order to complement traditional tests, and also to have a more positive impact on the quality of life of MS patients and their caregiver. In this way, when compared to traditional tests, some benefits can be evidenced, such as an automated assessment, easy access of patient records, more complete monitoring of the patient over time, minimization of time, costs, and geographic barriers, among others (20). Moreover, this became even more important with the pandemic of COVID-19, recognized by the WHO on 11 March 2020, considering that access to healthcare was compromised. Consequently, to ensure that MS patients were not be left unattended, some battery tests were proposed and adapted to digital platforms and existing digital battery tests and telemedicine practices were improved.

3.3. Neuroimaging

In recent years, the development of new MRI sequences and modelling approaches have made it possible to determine structural and functional correlates of cognitive impairments, thus providing new tools for disease monitoring and identifying potential novel therapeutic targets. Although this is a field where several questions still remain unanswered, its value as a tool for

investigating pathological changes *in vivo* is indisputable, and future developments in this field will contribute to a more effective understanding regarding cognitive impairments (46).

3.3.1. Magnetic Resonance Imaging

MRI is currently the most frequently used technique as a primary assessor of MS (16). MRI can essentially be separated into two categories, conventional and advanced, or also called un-conventional (47). Even though conventional imaging can only give a small insight into the complex underlying mechanisms, the un-conventional neuroimaging techniques allows a more comprehensive picture of the different correlates of cognitive impairment (46).

In a pathological setting of MS, focal lesions can be observed in most MS patients (47). Gadolinium contrast-enhanced T1-weighted images allow visualisation of the damaged BBB and consequent continuous inflammation, allowing distinguish active and inactive lesions (16). Lesions that appear persistently hypointense on post-contrast T1-weighted images, also known as black holes (BHs), are associated with more severe tissue damage, which is highly suggestive of a combination of demyelination and axonal loss (47). Instead, T2-weighted lesions generate a hyperintense appearance, allowing the visualisation of demyelination lesions, and subsequent understanding of possible functional disconnections between cortical and deep gray and white matter. In addition, T1- and T2-weighted lesions in specific brain regions contribute to define cognitive impairment and provide prognostic information about its development (16).

The un-conventional MRI techniques may include proton MR spectroscopy (^{1}H-MRS), magnetization transfer MRI (MT-MRI) or diffusion tensor imaging (DTI), among others. These MRI techniques although very useful in linking MRI results to pathological processes, such as demyelination, axonal loss and gliosis, remain of limited use in clinical practice (16).

Regarding ^{1}H-MRS, it complements conventional techniques by performing an *in vivo* quantification of metabolic concentrations that reflect pathological processes. N-acetylaspartate acetylaspartate (NAA) is an amino acid derivative synthesised in neurons and transported down over axons, therefore considered a specific marker of neuron, axon and dendrite integrity. Thus, a progressive reduction in NAA concentration can be considered a marker of axonal loss and/or metabolic dysfunction and can be clinically associated with attention functioning in MS (46). On the other hand, glutamate/glutamine, excitatory neurotransmitters, are considered specific

markers of inflammation. Thus, increased concentration of these can be considered a marker of neurotoxicity and can been clinically associated with memory loss in RRMS patients (16,46).

The un-conventional MT-MRI technique is based on interactions and exchange between mobile protons in a “free” water pool with those bound to macromolecules, which are typically measured semiquantitatively as a ratio (47). This technique extant considerable advantages over conventional MRI in the study of MS, namely it can access macroscopic abnormalities in brain, tissue, including demyelination, gliosis, and inflammation that cannot be seen on conventional MRI, and that are relevant in diagnosing cognitive impairment in patients with MS (16).

Additionally, in the DTI technique, water shows random molecular motion that is forced by various cellular structures in biological tissue. DTI-based tractography provides insight into the specific mechanisms underlying the development of both physical and cognitive impairment (16).

Novel methods for detecting neuroinflammation include superparamagnetic iron oxide particles (USPIO) and positron emission tomography (PET). More particularly, PET associated with radioactive ligands to the 18-kD translocator protein (TSPO) permits *in vivo* quantification of microglial activation in the different brain regions. Despite its promising results and potential applications it is very challenging and is still hindered by high costs (16,46,47).

3.3.2. Functional Magnetic Resonance Imaging

Functional MRI (fMRI) is also an un-conventional imaging technique that relies on the detection of blood oxygen level-dependent (BOLD) changes during neuronal activity. Briefly, fMRI studies can be divided into task and rest-related experiments. While task fMRI quantifies BOLD changes after an active execution of any performance, such as a motor task or a verbal fluency test, the latter experiment assesses the interactions that occur between the different brain areas without the execution of any task, what explains its name, resting-state fMRI (RS-fMRI). This allows the demonstration of the presence of functional connectivity (FC) between cerebral structures, which results in organized and stable and reliable networks. Although in recent years studies have investigated possible changes in brain function by performing tasks in MS patients, the greatest contribution to the understanding of functional brain damage, especially at the level of cognition, comes from the RS-fMRI studies. Among the networks studied, modifications of

default-mode networks (DMN) appear to show a major role in MS, as a matter of fact, changes in FC affecting this network have been reported, both in terms of an increase and a decrease, as in local regional FC homogeneity and variability (46). Regard, this technique has revealed great potential in providing main insights into the role of brain reorganization following structural damage to the CNS and in improving our understanding of the factors that are associated with cognitive impairment (48).

4. Current Disease-modifying Therapies, Cognitive Enhancers and Cognitive Rehabilitation

Although pharmacological interventions, explicitly DMTs and symptomatic treatments, have been shown to be effective in reducing relapse rates in MS and, in some cases, in reducing disability progression and improving MRI parameters, the impact that these treatments have on cognitive impairment is still very limited. On the other hand, other approaches such as cognitive rehabilitation and exercise training alone are not sufficiently able to restore cognitive function, however, along with DMTs, they have already been shown to have a positive effect on cognitive impairment, which is of great value given that their management is still very poor in MS patients (49,50).

Several treatments are currently available for RRMS, whereas treatments for SPMS and PPMS are still very limited. Briefly, for the treatment of RRMS two different strategies can be highlighted, escalation therapy and induction therapy. The basis of escalation therapy is to start with a DMT with a better safety profile but moderate efficacy, namely IFN-β, glatiramer acetate (the only DMT considered to be safe during pregnancy), teriflunomide, or dimethylfumare, and switch to another first-line DMT in patients with intolerable adverse effects, or to a second- or third-line DMT in patients with new relapses or MRI lesions. Regarding induction therapy, this refers to a strong immune intervention starting with a DMT with a lower safety profile (due to the higher risk of serious adverse effects that are associated) but high efficacy, as alemtuzumab or ocrelizumab, practically after a confirmed diagnosis of a MS patient associated with a poor prognosis, to prevent the accumulation of irreversible CNS damage and clinical impairment. Hence, for the treatment of progressive phases, for SPMS in specific, Mitoxatrone, a cytostatic drug is available, however, with certain limitations of use due to its cardiotoxic and mutagenic

adverse effects. Further, for PPMS, some drugs have shown positive results in reducing the risk of disability progression comparing to placebo, such as anti-CD20 DMTs, like Rituximab and Ocrelizumab, mainly in patients with shorter disease duration and signs of active inflammation on MRI. In addition, one of the most established treatments for managing MS relapses is high-dose corticosteroids, as methylprednisolone (15). It is also important to note that this should be a tailored treatment, with shared decision-making and high agreement between the MS patient and the physician, in order to improve patient adherence and medication persistence (51)(A4).

Despite the widespread use of different DMTs in MS, there is no consensus as to which therapy effectively improves cognitive impairment. However, despite these difficulties, a study applied meta-analysis on longitudinal cognitive changes in tests of processing speed revealed a robust, small-to-moderate positive effect of DMTs, underlining the current recommendation to start treating RRMS patients with DMTs shortly after their diagnosis. Other curious finding is that no main differences were found between the use of the different therapies abovementioned, which is curious precisely because these therapies have significant differences in efficacy. This may be explained by the fact that the superior impact of therapies that act on the inflammatory component of the disease may simply not lead to superior effects on cognitive test performance, as the latter may be primarily driven by neurodegeneration. Additional explanation for this may be the influence of cognitive reserve, which as previously stated, refers to the extent to which the brain can be damaged without affecting intellectual capacity on standard performance tests. All in all, this field urgently needs large-scale randomized controlled trials (RCTs) that analyse the cognitive outcomes of new or established therapies, taking into account the heterogeneity of the disease (50).

In addition to DMTs, MS patients are often prescribed treatments for specific symptoms such as mobility, spasticity, fatigue, pain, loss of bowel and bladder control, sexual dysfunction, cognitive symptoms, among others. Thus, the most extensively studied symptomatic treatments in MS include dalfampridine, a potassium channel blocker, used to improve walking difficulties and nabiximols, a cannabis extract that contains Tetrahydrocannabinol (THC) and Cannabidiol (CBD) to improve spasticity (15). For the treatment of cognitive function some drugs have been studied such as donepezil, rivastigmine, memantine, fampridine, among others, however, these demonstrate mixed results that are not sufficient to support benefits in cognitive impairment. Hence, higher-quality RCTs are needed to establish the cognitive efficacy of pharmacological treatments for MS-related cognitive dysfunction, where cognition is the primary endpoint (50).

Other MS treatment options may also rely heavily on prevention. Based on evidence of the impact EBV has on MS, research is currently underway to develop specific treatments, as antiviral therapies, prophylactic and therapeutic EBV vaccines, viral neutralization antibodies, which may help prevent MS. Vitamin D supplementation may reduce the incidence of MS and, at the same time, promote benefits for the prevention of other diseases, such as osteoporosis. Smoking cessation may be associated with a lower risk and better prognosis of MS, as well as a lower risk of developing other comorbidities. Educational interventions are also important, particularly for overweight and obese children and adolescents, in order to promote healthier lifestyles, such as adopting a balanced diet and regular exercise, thus decreasing MS risk (15).

Cognitive rehabilitation refers to a set of systematically applied medical and therapeutic services that are designed to improve the cognitive functions of MS patients and increase their participation in daily activities, which might be affected by difficulties in one or more cognitive domains (52). Currently, these programs are usually computer-assisted and can focus on one or various aspects of cognition either simultaneously or consecutively, which can include learning and memory, attention, and executive functions. Because these programs are usually tailored to the individual patient's needs, there is inevitably a great deal of heterogeneity regarding to their content, duration, and frequency of administration (50). Fortunately, there has recently been an increase in cognitive rehabilitation research studies to address the need for effective treatments for cognitive impairment in MS (Table 3).

Regarding learning and memory, several double-blind, placebo-controlled RCTs in the literature support the efficacy of modified Story Memory Technique (mSMT). More precisely, these studies demonstrated improvements in objective memory over neuropsychological tests as the CVLT-II, Hopkins Verbal Learning Test-Revised (HVLT-R), and Memory Assessment Scales, as well as over subjective tests regarding the patient's daily living abilities. In addition, these studies also demonstrated the efficacy of mSMT using neuroimaging data, fMRI revealed increased brain activation and functional connectivity in areas linked with learning and memory after treatment. Although most studies to date focused more on RRMS patients, some studies demonstrate that MS patients in progressive stages also demonstrated improvements in learning abilities and self-reported memory functioning, whereas more studies are needed to corroborate this (20,52). Furthermore, the application of visual imagery also demonstrated improvements in autobiographical memory and future episodic memory in MS patients. Last but not least, the use of learning strategies such as self-generation, spaced learning and self-testing demonstrated to significantly improve learning and memory, that are the basis of a new treatment paradigm

aimed at teaching patients how to apply these strategies in their daily life, called Strategy-Based Techniques to Enhance Memory (STEM)(52).

Attention Process Training (APT) and RehaCom have demonstrated promising effects in improving attention and general cognitive abilities, respectively, in both adult and pediatric populations. ATP-3, the most recent version, has been moved to a computer-based interface, in order to facilitate its administration, scoring, and data collection, and includes several attention exercises that can be used in individuals with a wide range of attention deficits, however, the effectiveness of this approach is mostly based on literature from other neurological populations. RehaCom, a computerized home-based cognitive rehabilitation program, it has demonstrate to have a significant long-term effect on attention, processing speed, and verbal memory in MS patients. Impaired processing speed is directly correlated with attention, and since both are often needed in patients' daily lives, many programs have focused on correcting both simultaneously. Then, as mentioned, computerized home-based programs have proven to be a good medium for training, since it is able to present stimuli more faster and repeatedly, and since there is abundant patients compliance. Among these programs are BrainHQ, COGNI-TRAcK, or BrainStim, this, even though encouraging, additional high-quality studies are required (20,52).

To finish, with regard to executive functions, treatments consisting of textbook exercises for executive functioning and goal attainment scales (GAS) have been demonstrated to improve patients' executive functions, psychological well-being, and QoL. GAS, is an important part of rehabilitation, as it consists of the prior identification of goals that the patient desires to achieve with the intervention, and subsequent evaluation of the degree to which these goals have been achieved, and is a good tool to evaluate their responsiveness compared with standard measures used to evaluate progress in rehabilitation (20,52).

Cognitive Rehabilitation	**Improved Cognitive Domain**
modified Story Memory Technique **(mSMT)** Visual Imagery Strategy-Based Techniques to Enhance Memory **(STEM)**	Learning and Memory
Attention Process Training **(APT)** RehaCom BrainHQ, COGNI-TRAcK, BrainStim	Attention Processing Speed and Working Memory
Goal Attainment Scales **(GAS)**	Executive Functions

Table 3. Cognitive Rehabilitation approaches in Multiple Sclerosis

Exercise training refers to a planned structured and repetitive physical activity, such as aerobic training, resistance training, and balance training, among other training modalities, that are performed to improve or maintain one or more aspects of physical fitness, and are performed to manage MS-related cognitive impairment, which should preferably be introduced at an early stage of the disease. Even though very promising, the effects of exercise training are still very premature and more work is needed to establish its clear role in clinical practice (52).

5. Conclusion and Future Perspectives

MS is estimated to affect, approximately, 2.8 million people worldwide, and appears to be diagnosed mainly in young adult women aged between 20 and 40. To date, several disease triggers have been associated with the development of MS, and although their exact underlying mechanisms are not yet understood, it is useful to have knowledge about these factors in order to incorporate them into practical health and perhaps prevention, especially for those who have a family history of MS and therefore have a higher risk of developing the disease.

In recent years, cognitive impairment as an invisible symptom in MS has become a focal point of disease research. It is now considered one of the most common and disabling symptoms among MS patients. Regarding this, the cognitive functions that appear to be most impaired are processing speed and memory, which tend to be more pronounced in further progressive stages of MS. Moreover, cognitive impairment has been strongly associated with neurodegeneration, concomitant brain atrophy, and functional network disruption, which are more linked to cortical gray matter rather than white matter lesions.

Only by setting high standards for the assessment and treatment of cognitive impairment is it possible to MS patients receive the most adequate care in this critical domain. Over the past years, remarkable improvements have been made in neuropsychological tests and neuroimaging techniques. Particularly, SDMT neuropsychological test to assess processing speed has been an important instrument to better understand the respectably affected areas; MRI with gadolinium contrast is the most reliable technique for identifying demyelinating and inflamed lesions; fMRI has brought knowledge to this field by allowing visualization of the neuronal networks function. The improvements have contributed to the development of new information and, subsequently,

to the development of further therapeutic options that are more effective and better tolerated by MS patients, aiming to alleviate cognitive symptoms and improve their quality of life.

Following, the use of DMTs are the gold standard in MS therapy, though some therapies show promising results for cognitive impairment, unfortunately data in this regard are still very scarce. However, exciting approaches to maximise the DMTs success involve the combination of cognitive rehabilitation and exercise training approaches that appear to result in a synergistic improvement in cognitive outcomes. Even though some of the effects of the latter approaches are indeed very promising, they not yet sufficient to establish a clear role in clinical practice. It is important to also reinforce that these therapies focus mainly on the RRMS phase of MS, and, consequently, a very restricted understanding can be observed in the more progressive phases, including SPMS and PPMS. Therefore, future studies focusing on this field are necessary and fundamental to acquire new information and improve the quality of life of patients.

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Appendices

A.1 Summary of 2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis

✓ *Requires elimination of more likely diagnoses* ✓ *Requires demonstration of dissemination of lesions in the central nervous system in space and time*		
DIT = dissemination in time **DIS** = dissemination in space	**CNS** = central nervous system **CSF** = cerebrospinal fluid	**T2 lesion** = hyperintense lesion on T2-weighted MRI

CLINICAL PRESENTATION	ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS
...in a person who has experienced a typical attack/CIS at onset	
• 2 or more attacks and clinical evidence of 2 or more lesions; OR • 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in different location	None, DIS and DIT have been met
• 2 or more attacks and clinical evidence of 1 lesion	DIS shown by <u>one</u> of these criteria: - additional clinical attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial, or spinal cord
• 1 attack and clinical evidence of 2 or more lesions	DIT shown by <u>one</u> of these criteria: - Additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
• 1 attack and clinical evidence of 1 lesion	DIS shown by <u>one</u> of these criteria: - Additional attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial, or spinal cord **AND** DIT shown by <u>one</u> of these criteria: - additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
...in a person who has steady progression of disease since onset	
1 year of disease progression (retrospective or prospective)	DIS shown by at least <u>two</u> of these criteria: - 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical, or infratentorial) - 2 or more T2 spinal cord lesions - CSF oligoclonal bands

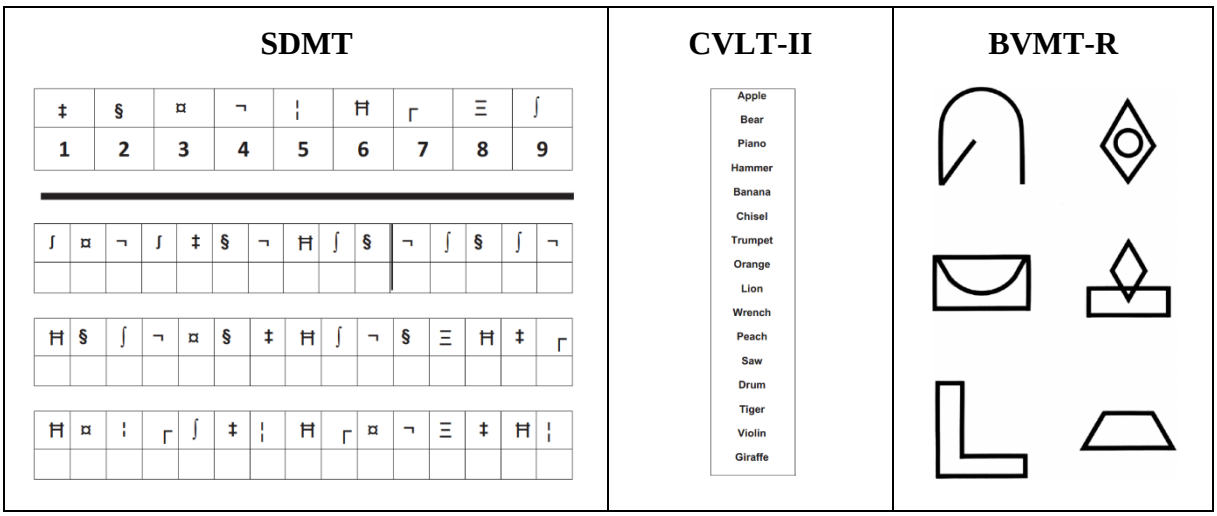
[Adapted from National Multiple Sclerosis Society]

A2. EDSS scale for assessing the level of disability in Multiple Sclerosis

Score	Description
0.0	No disability
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid - cane, crutch, etc. - to walk about 100m with or without resting
6.5	Requires two walking aids - pair of canes, crutches, etc. - to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

[Adapted from (39)]

A3. Example of SDMT, CVLT-II, and BVMT-R tests in Multiple Sclerosis



[Adapted from (45)]

A4. Relapse rates and adverse effects of DMTs in RRMS patients

DMT	Type	Reduction of annualized relapse rate[a]	Adverse effects
First line			
Glatiramer acetate	s.c. mixture of synthetic polypeptides	30%	• Injection site reactions (erythema, inflammation, induration or pain at injection site) • Flushing • Chest tightness or pain • Palpitations • Anxiety • Trouble breathing
IFNβ1a	s.c. recombinant protein	32%	• Injection site reactions (erythema, inflammation, induration or pain at injection site) • Flu-like symptoms • Leukopenia (neutropenia or lymphopenia) • Thrombocytopenia • Anaemia • Infections • Thyroid dysfunction (hypothyroidism or hyperthyroidism) • Liver damage (transaminase increase) • Fatigue • Mood disturbances (depressive symptoms)
IFNβ1a	i.m. recombinant protein	32%	
IFNβ1b	s.c. recombinant protein	34%	
Pegylated IFNβ1a	s.c. pegylated recombinant protein	35%	
Teriflunomide	Oral pyrimidine synthesis inhibitor	34%	• Headache • Diarrhoea • Hair thinning or loss • Liver damage (transaminase increase) • Increased blood pressure • Paresthesia • Leukopenia (neutropenia or lymphopenia) • Infections
Dimethyl fumarate	Oral NRF2 agonist	49%	• Flushing • Liver damage (transaminase increase) • Gastrointestinal disturbances (abdominal pain, nausea and vomiting) • Leukopenia (mainly lymphopenia) • Infections • PML • Allergic reactions
Second line			
Fingolimod	Oral S1P inhibitor	54%	• Reduced heart rate • Increased blood pressure • Leukopenia (mainly lymphopenia) • Infections • Liver damage (transaminase increase) • Macular oedema • PML • Skin cancer (basal and Merkel cell carcinoma) and melanoma
Daclizumab (withdrawn)	i.v. monoclonal anti-CD25 antibody	44%[b]	• Liver damage (transaminase increase) • Gastrointestinal disturbances (abdominal pain, nausea and vomiting) • Allergic reactions • Infections • Immune-mediated encephalitis
Alemtuzumab	i.v. monoclonal anti-CD52 antibody	52%	• Infusion-related reactions • Leukopenia (mainly lymphopenia) • Infections • Autoimmune reactions (immune thrombocytopenia, immune thyroiditis and immune glomerulonephritis) • Cancers (thyroid cancer, melanoma and lymphoproliferative disorders)
Cladribine	Oral purine analogue	58%	• Leukopenia (neutropenia or lymphopenia) • Infections • Rash • Alopecia • Cancers
Ocrelizumab	i.v. monoclonal anti-CD20 antibody	45%[b]	• Infusion-related reactions • Leukopenia (mainly lymphopenia) • Decreased blood immunoglobulin • Infections • Cancers
Natalizumab	i.v. monoclonal anti-VLA4 antibody	69%	• Infusion-related reactions • Allergic reactions • Infections • Progressive multifocal leukoencephalopathy

[Adapted from (15)]