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Cognitive impairment in multiple sclerosis: "classic" knowledge and recent acquisitions

Deficiência cognitiva na esclerose múltipla: conhecimentos "clássicos" e aquisições recentes

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Abstract

Multiple sclerosis (MS) is a central nervous system (CNS) disease characterized by inflammation, axonal demyelination, and neurodegeneration, which can have a strong impact on all aspects of the life of the patient. Multiple sclerosis causes motor, sensory, cerebellar, and autonomic dysfunctions, as well as cognitive and psychoemotional impairment. The most frequently compromised cognitive domains are complex attention/information processing, memory, executive and visuospatial functions. Recently, alterations have also been evidenced in complex cognitive functions, such as social cognition, moral judgment, and decision-making. Cognitive impairment is characterized by high variability and can affect work skills, social interactions, coping strategies and more generally the quality of life of patients and their families. With the use of sensitive and easy-to-administer test batteries, an increasingly accurate and early diagnosis is feasible: this allows to determine the effectiveness of possible preventive measures, to predict the future progression of the disease and to improve the quality of life of patients. There is currently limited evidence regarding the efficacy, on cognitive impairment, of disease-modifying therapies. The most promising approach, which has received strong empirical support, is cognitive rehabilitation.

Keywords
- Multiple Sclerosis
- Cognitive Dysfunction
- Social Cognition
- Decision Making
- Neuropsychological Tests
- Morale

Resumo

A esclerose múltipla (EM) é uma doença do sistema nervoso central (SNC) caracterizada por inflamação, desmielinização axonal e neurodegeneração, que pode ter um forte impacto em todos os aspectos da vida dos pacientes. A EM causa disfunções motoras, sensoriais, cerebelares, autonômicas, comprometimento cognitivo e déficits psicoemocionais. Os domínios cognitivos mais frequentemente comprometidos são a atenção complexa/processamento da informação, memória, funções executivas e habilidades visuais-espaciais. Recentemente, também foram evidenciadas alterações em funções cognitivas complexas, como cognição social, julgamento moral e tomada de decisão. O comprometimento cognitivo é caracterizado por alta variabilidade e

Palavras-chave
- Esclerose Múltipla
- Disfunção Cognitiva
- Cognição Social
- Tomada de Decisões
- Testes Neuropsicológicos
- Moral

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pode afetar as habilidades laborais, as interações sociais, as estratégias de enfrentamento e, de forma mais geral, a qualidade de vida dos pacientes e de seus familiares. Com o uso de baterias de testes sensíveis e fáceis de administrar, é viável um diagnóstico cada vez mais preciso e precoce: isso permite determinar a eficácia de possíveis medidas preventivas, prever a progressão futura da doença e melhorar a qualidade de vida dos pacientes. Atualmente, há evidências limitadas sobre a eficácia, no comprometimento cognitivo, de terapias modificadoras da doença. A abordagem mais promissora, que tem recebido forte apoio empírico, é a reabilitação cognitiva.

INTRODUCTION

Multiple Sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by inflammation, axonal demyelination, and neurodegeneration.[1] Due to its early onset, it is the most common cause of nontraumatic neurological disability in young adults worldwide.[2] Its chronic course is characterized by relapses, remissions, and progression of disabilities that can interfere with all neurological functions. Patients with MS (pMS) present a rather heterogeneous clinical condition, characterized by motor, sensory, cerebellar, autonomic dysfunctions, cognitive impairment (CI),[3] and mood disorders.[4] For a complete review of the frequencies of various MS related disorders refer to DeLuca et al.[5]

Despite being first described by Charcot and other early authors in the mid-1800s,[6] MS-related CI has been neglected for many years, and only starting from the last quarter of the 20th century, interest in it grew: with the use of specific and sensitive test batteries, the qualitative and quantitative characteristics of cognitive disorders have been identified and, thanks to neuroimaging techniques, correlations with the neuropathological picture have emerged.

Cognitive impairment can affect pMS at any stage of the disease,[4] with prevalence rates ranging from 42 to 70%.[7] Cognitive symptoms are usually hidden as opposed to more visible deficits, such as sensorimotor symptoms. Patients with MS may not be fully aware of or underestimate them with respect to emotional complaints, fatigue or pain.[8] For this reason, physicians should not rely on self-reported CI, but on the performance on objective cognitive tests.[9]

According to the most common literature in the field of MS,[7,10,11] the most frequently compromised cognitive domains are complex attention/information processing (IP), memory, executive functions (EF), and visuospatial functions. Other cognitive domains that may be altered, and which have recently been arousing great interest, are social cognition (SC), decision-making (DM) and moral judgment (MJ).

Like all symptoms of MS, cognitive deficits are characterized by high variability[12] and strongly impact on work skills, social interactions, and quality of life of patients.[4] An accurate and early assessment of CI is of great importance as it would allow to determine the effectiveness of possible preventive measures, predict, and monitor disease progression,[13] prevent and/or reduce the high unemployment rate associated with the disease[14] and more generally improve the quality of life of pMS.[15]

Being aware that pediatric cases often show a different profile of impairment, it was decided to focus the review work on adult-onset cases. Therefore, the following topics will be covered:

- cognitive impairment in MS
- cognitive reserve and brain reserve;
- neuropsychological assessment;
- management of CI.

Considering the aim of the present work, for a complete review on the neuropathological basis of cognitive deficits related to MS as detected by neuroimaging, refer to Filippi et al.[16]

COGNITIVE IMPAIRMENT IN MS

Complex attention/information processing

Attention
Attention is a sophisticated cognitive function made up of several sub-components. A widespread clinical model divides attention into five main sub-components: focused attention; sustained attention; selective attention, alternating attention, and divided attention.[17] Attentional deficits affect ∼ 12 to 25% of pMS.[18] The attentional processes most affected in MS are the more complex ones, that is selective attention, sustained attention, and divided attention, while focused attention is often preserved.[19] Independent evaluation of this cognitive domain can be difficult. First, attention is strongly associated with IP speed (IPS) and working memory (WM): to distinguish the tasks for these different domains is complex. Second, fatigue can affect performance on attentional tasks.[20]

Information Processing
Information processing represents the efficiency with which neural networks transmit and integrate information.[21] The first studies on IP functioning showed that pMS needed more time than healthy controls (HCs) to determine whether a specific number was included in a series of to be remembered numbers.[22] A subsequent study, aimed at measuring

both IPS and performance accuracy, suggested that when pMS were given necessary time to encode information, their performance was as that of HCs in terms of accuracy.[23] The results of these two studies show that the IP of pMS is adequate if they are given more time, so it is not the accuracy with which the information is processed, but it is IPS that is impaired.

Information processing speed, in addition to being the most commonly compromised cognitive function in pMS, with a percentage ranging from 40 to 70%,[7] is frequently the first to be impaired. Furthermore, IPS is important for the functionality of higher-order cognitive processes such as memory and EF.[24]

Information processing speed efficiency depends on both WM and processing speed.[19] Although both are compromised, according to some authors, IPS is the primary deficit in MS, which primarily affects information encoding, while WM impairment seems to depend on reduced IPS.[25] The study by Kouvatsou et al. evaluated the relationship between IPS and WM and found a strong correlation between IPS, central executive and episodic buffer. However, after the chronological age of the patients was entered into the statistical analyzes, IPS and central executive relationship disappeared, suggesting that this subcomponent of WM may not be directly affected by IPS, but that other factors such as age could mediate their relationship.[25]

Information processing speed is strongly related to some clinical aspects of pMS. In fact, several studies have observed that a reduced IPS correlates with an increase of motor disability, fatigue, depression, and a reduced social support quality.[24]

Memory

Memory impairment is among the most observed cognitive deficits in MS,[4] with prevalence rates ranging from 22 to 65%.[7,20]

In most cases, long-term memory (LTM) and WM are compromised.[7,18] Recently, it has been highlighted that in MS the visual subcomponent of the visuospatial sketchpad is preserved, while the episodic buffer is the most impaired component.[26]

Regarding LTM deficits, they mainly concern explicit (declarative) memory, while implicit (nondeclarative) memory appears to be mostly preserved.[27] According to the traditional classification by Tulving et al.,[28] explicit memory is divided into episodic memory and semantic memory. Of these, the first is the most compromised[29] in pMS. Episodic memory can be divided into retrospective memory (RM) and prospective memory (PM). Until now, most of the research in pMS has focused on RM. The first studies suggested that RM deficit may lie in the inability of pMS to retrieve information stored in LTM. Subsequent studies have traced the origin of problem to the initial learning difficulty:[4] pMS simply need a greater number of repetitions to acquire memory traces. Difficulty in new information acquisition could be linked to the concomitant presence of EF deficits, sensory deficits, of a slowdown in IP and of a greater susceptibility to interference.[30] Recently, it has been reported that pMS, in addition to having RM deficiencies, have some gaps in PM defined as difficulties in remembering what they intended to do. In everyday life, failure to execute a planned action (or intention) at the right time can have relevant consequences with a negative impact on the functional autonomy of patients.[31]

Visuospatial functions

Although visuospatial functions have received less consideration, it has been reported that 25% of pMS have visual-perceptual deficits independent of the presence of primary visual deficits.[32] Visuospatial abilities impairments result in deficits in the representation and integration of images and in the spatial localization and tracking of an object.[33] A recent paper found that there is a relationship between visual IPS deficits and visual system abnormalities, defined by a reduced pMS ability to detect visual stimuli.[34]

Executive functions

The studies conducted on EF in pMS are not easily comparable due to the high conceptual and methodological variability; in general, it is established that, in pMS, EF are altered with different degrees and frequency (20 to 80%).[35] While some authors believe that, in MS, EF deficits have a lower prevalence than memory deficits,[7,36] others declare a higher prevalence of the former.[37]

Drew et al.[37] noted that 17% of pMS have difficulty with a range of executive skills (for example, displacement, inhibition, and fluency). Using a similar approach, Cerezo Garcia et al.[35] observed a predominant influence of MS on three components of EF: cognitive flexibility, inhibition, and abstraction. This suggests that there may be a specific EF deterioration profile in MS, with better preserved planning and reasoning skills than cognitive flexibility, inhibition, and abstraction. Furthermore, pMS would seem to repeatedly propose concepts and solutions that are no longer adequate with respect to a modified situation.[38]

A relationship between EF and PM has been observed.[39] Several studies have shown that PM requires both RM and EF. Dagenais et al.,[39] examining the influence of EF on pMS PM, revealed that good performance is modulated by the efficiency of EF, while RM appears to have a minimal impact on PM performance.

Recently, it has been found that EF deficits can be largely explained by a loss of general intelligence.[40] In fact, both cognitive functions are supported by the prefrontal cortex (PFC) and the EF deficits have been found to be related to lesions of the frontosubcortical tracts.

Leavitt and colleagues believe that EF deficits may be partly explained by IPS deficits: evaluating and comparing pMS with HC, they found that the former had worse scores than HCs in EF and IPS, but that the differences diminished when more time is provided.[41]

In a 2017 study, a relationship between EF and coping[42] was demonstrated: active coping strategies (such as problem solving) require prediction and perspective taking. The alteration of these abilities would lead pMS to use maladaptive and less cognitively demanding coping strategies (for example, acceptance or avoidance), with negative consequences on quality of life.

Language

In MS, language has been poorly studied, and while some researches have shown largely preserved linguistic functionality,[7] more recent studies have reported speech disturbances in 20% of relapsing-remitting pMS (RRMS) and in 58% of secondary-progressive pMS (SPMS).[43] Some researchers argue that pMS experience subtle language deficits not easily detectable,[44] such as the difficulty in finding words.[45] Indeed, several papers suggest that individuals with MS show deficits in pragmatics[46] and in morphosyntactic production.[47,48] Typically, verbal fluency (VF) is the only language-related measure included in the batteries used to assess cognitive deficits in pMS. A standard VF test is aimed at evaluating phonemic and/or semantic fluency. Often, difficulties in VF are attributed to EF deficits rather than language skills.[4] In general, as phonemic characteristics are cognitively more demanding, pMS have better performance in the semantic than in the phonemic fluency task. Indeed, phonemic fluency is more based on cognitive control and EF, while semantic fluency is dependent on semantic knowledge[49] and episodic memory.[50] This dissociation is supported by the fact that phonemic fluency is associated with white matter dorsal (occipito-parietal) tract integrity, while semantic fluency is associated with ventral (occipito-temporal) tract integrity.[51] Despite this, research conducted with healthy individuals indicates that both EF, IPS, and language-specific abilities contribute to VF. Furthermore, a recent study has shown that both vocabulary and IPS can predict phonemic fluency; otherwise, semantic fluency is uniquely related to vocabulary. These results suggest that VF deficits in pMS are the consequence of a reduction in both language skills and IPS.[44]

In MS, aphasia is a very rare clinical manifestation, with a percentage ranging from 0.7 to 3%.[52] Among the various forms of aphasia, Broca's aphasia appears to be the most frequent in pMS, followed by mixed transcortical aphasia.[53] Although most cases of aphasia are induced by cortical lesions, unusually extensive subcortical white matter lesions have been reported in MS. In this regard, extensive plaques ($>$ 5-cm) have been identified in language subcortical areas of pMS. As an explanation for subcortical injury-induced aphasia, the concept of diaschisis has been proposed. According to this, lesions of white matter tracts, anatomically related to cortical language centers, could produce aphasias that are sometimes difficult to distinguish from aphasias associated with cortical lesions.[54]

Cognitive impairment according to clinical phenotype

Cognitive impairment occurs in all MS phenotypes, affecting between 20 and 25% of patients with clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS); 30 to 45% of RRMS and 75% of patients with SPMS. The prevalence of CI in primary-progressive MS (PPMS) is very variable. Clinically isolated syndrome and RRMS show similar cognitive profiles with significant involvement of IPS, EF, and verbal and visuospatial memory. However, a higher overall CI index was observed in RRMS patients than in those with CIS. A CI profile like that of RRMS was observed in RIS patients, with involvement of IPS and memory.[55] Progressive forms have a relatively similar cognitive profile, with a prevalent involvement of EF and memory.[12] In a study conducted by Dackovic et al.,[56] patients with PPMS and SPMS were found to be more frequently compromised than those with CIS and RRMS in all cognitive tests evaluated by the Brief Repeatable Battery of Neuropsychological Tests (BRBNT).[10] Until now, pMS have always been classified as cognitively preserved or cognitively impaired. With the aim of eliminating this too reductive dichotomous classification, a group of researchers[57] managed to identify 5 cognitive phenotypes: preserved cognition; mild involvement of verbal memory and semantic fluency; mild multidomain involvement; severe executive/attentional involvement; and severe multidomain involvement. Furthermore, in support of Dackovic's work,[56] they found that progressive phenotypes are those with more prevalent CI.

Cognitive impairment and mood disorders

Patients with MS are often diagnosed with mood disorders such as: major depressive disorder, bipolar disorder, anxiety disorders, euphoria, and pseudobulbar syndrome. Among these, depressive and anxiety disorders were found to be correlated with CI. The most common depressive symptoms in MS include irritability, discouragement, concentration problems, fatigue, insomnia, and poor appetite; while guilt, low self-esteem, and social withdrawal are less frequent than in the general population.[58] These symptoms affect 50% of pMS. Prevalence estimates are generally 2-3 times higher than those of the general population.[59] Several studies have suggested that depression, in pMS, is associated with WM, EF and IPS deficits. In contrast to the extensive literature on depression, in pMS, anxiety disorders have been the subject of fewer studies. The prevalence of anxiety disorders in MS is estimated to be between 13 and 31.7%,[60] and it is 3 times higher in the latter than in the general population.[61] Generalized anxiety disorder appears to be the most common form, with 18.6% of patients meeting the criteria. This is followed by panic disorder (10%) and obsessive-compulsive disorder (8.6%).[62] Several studies have shown the existence of an association between anxiety and attention, WM, IPS, immediate and delayed visual memory, VF, and verbal memory deficits.[63–66]

Cognitive impairment and other factors

Recently, factors directly associated with the pathophysiological mechanisms of MS have been identified, which can contribute to the development of CI. Noteworthy are sleep disturbances and fatigue. About 50% of pMS suffer from sleep disorders.[67] Studies examining the relationships between sleep disorders and CI have produced discrepant association patterns derived from the use of different sleep measurement tools: using objective measures (polysomnography and actigraphy), sleep was found to correlate with attention and

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IPS. Subjective measures (of self-reported insomnia through the Pittsburgh Sleep Quality Index, Insomnia Severity Index) were found to be predictive of self-reported cognitive deficits; however, these associations were mediated by depression and fatigue, suggesting that these symptoms may contribute to the CI perceived by pMS. Unlike objective measures, self-reported sleep was a poor indicator of CI detected by standardized batteries.[68] One of the most commonly complained and most disabling symptoms is fatigue, which affects up to 75 to 90% of pMS.[69] Unlike some research,[70,71] recent studies have highlighted the existence of a strong association between fatigue, attention[72] and IPS.[73] Another variable that can influence CI is hypothyroidism: a syndrome caused by insufficient secretion of thyroid hormone. Thyroid hormones have a vital impact on normal brain development and function, as well as cognition. Clinical psychology studies have shown that the attention, memory and spatial capacity of patients with hypothyroidism are significantly reduced, while the index of depression and anxiety is increased.[74] Also, hyperhomocysteinemia, vitamin B12 and folate deficiency have been linked to CI in MS.[75]

Social cognition

Social cognition is a multidimensional construct including a wide range of neurocognitive processes that allow humans to perceive and make inferences about mental states, understand the behavior of others, interact adequately with other people, and adaptively orient their behaviors towards appropriate goals.[76,77] Social perception, social understanding and social DM are the basilar processes of SC. The first refers to the perception of emotions through prosody or facial expressions, the second refers to affective empathy, that is, the ability to experience and interpret others' feelings, while the third process concerns the theory of mind (ToM) or mentalization, defined as the ability to decode and interpret the mental states of others and use them to make inferences and predict their behaviors.[76,78] These skills are vital for the development of complex social interactions and can impact employment, relationships with family, friends, and healthcare professionals.[79]

A total of 20 to 40% of pMS have a SC deterioration, sometimes evident from the early stages of the disease.[80] In pMS, SC disorders generally do not correlate with disease course and duration, degree of disability, or relapse rate.[80] Otherwise, a correlation between SC and fatigue was found, probably due to common underlying neural networks.[81]

Recently, numerous studies investigated the relationship between SC and CI in pMS leading to inconsistent results. While, on the one hand, significant correlations were found between SC and IPS, WM, reasoning, and problem-solving deficits, on the other hand, no association was found among these variables.[77]

Deficits in facial emotional recognition (FER) and ToM are the most frequent in pMS and, therefore, also the most investigated.[76] Theory of mind is a multifaceted construct that can be further divided into cognitive and affective components.[82] A recent meta-analysis[77] conducted on 1,708 pMS and 1,518 HCs showed that compared to the latter, pMS (RRMS, PPMS, SPMS) showed alterations in the overall ToM, of its two subcomponents, and FER. Usually, no differences in impairment levels were observed between MS phenotypes. In contrast, Argento et al.[83] demonstrated the presence of specific patterns of impairment of SC skills by phenotype: both RRMS and SPMS performed poorly on the Reading the Mind in the Eyes test compared with HCs, but only SPMS patients reached a statistically significant difference.[83] Individuals with MS are not only less accurate in recognizing basic emotions than healthy individuals, but they have longer reaction times.[84]

Regarding empathy, while some studies have highlighted subtle difficulties in pMS,[84] recent research found no difference in empathy between pMS and the healthy population.[79] In pMS, a correlation was observed between higher empathy levels and a higher education level, better verbal learning, fewer depressive symptoms, greater extroversion, higher levels of agreeableness and conscientiousness, and better occupational functioning.[79]

Currently, great importance for the empathy's modulation has been given to alexithymia.[85] Indeed, a higher incidence of alexithymia in pMS was associated with lower levels of empathy and potentially impaired moral cognition, even in the early stages of the disease.[86] Although it can affect $\sim$ 10% of the general population, the prevalence of alexithymia in pMS can reach 53%,[87] becoming a variable of great interest when evaluating SC.

Moral judgment

The set of habits and values that guide social conduct in a given cultural group is called MJ, and is measured through tasks that involve moral dilemmas, that is, situations in which an agent cannot meet all applicable moral requirements.[88] Moral judgement deficits can be deleterious to both pMS and their social circle; despite the emerging literature on socioemotional skills, moral cognition is still poorly studied in MS.[89,90] Three important aspects of MJ are moral acceptability/admissibility related to an acted-out behavior (that is, morally acceptable, or unacceptable), emotional valence (evaluation of the experience as pleasant or unpleasant) and emotional arousal (state of arousal or calm).[91]

Preliminary evidence[89,90] demonstrated a reduced valuation capacity of moral acceptability, higher levels of emotional reactivity and an egocentric projection of the moral problem. These results led to the hypothesis that, in MS, there is a shift from a MJ "utilitarian model", based on a careful cost-benefit analysis of the specific moral situation, towards a "nonutilitarian moral model"[89] driven by an instinctive emotional aversion to harm other people. These data were partly supported by a recent study[92]: the authors observed a reduced sensitivity to moral admissibility in RRMS patients compared with HCs; on the other hand, they found reduced emotional reactivity levels suggesting an alteration in the emotional reaction rather than in the evaluation of moral dilemmas per se. Emotional detachment can be explained according to two different hypotheses: the presence of high levels of alexithymia impairing emotional reactivity (reduced emotional arousal) during DM in moral dilemmas;[89] the fact that pMS implement coping strategies based on emotional detachment to maintain a good quality of life and obtain a better adaptation to their social context.[93]

Decision-making

Decision-making is commonly perceived as a highly rational and conscious process that allows to comparing arguments for or against a specific behavioral choice.[94] Decisione-making is organized according to a well-defined basic structure. input-process-output-feedback. Input refers to the presentation of individual stimuli, each of which is capable of providing a rewarding or punishing response; the process allows you to evaluate the stimuli in order to choose one according to your preferences; the output refers to the action implemented in response to the chosen stimulus; feedback refers to the assessment and experience made by the subject following the action taken. It is evident that DM is guided by both cognitive and emotional components associated with a vast cortico-subcortical network.[95] A theory supporting the significant influence of emotions on DM performance is that of the somatic marker, developed by Damasio.[96] This theory states that, when faced with a decision, a first selection of the choices is made by balancing the positive and negative somatic markers. Accordingly, the choice would be conditioned by the somatic and emotional responses experienced by the subject, sometimes unconsciously.[96] In this regard, two studies that measured emotional reactivity using the reactivity of skin conductance (RSC) have given conflicting results. In one study, it was found that pMS, compared with HCs, had a reduced RSC in DM performance under ambiguity (when neither the outcome nor the probability of specific results is known), which, however, was preserved in the DM under risk (when the probabilities for possible outcome scenarios are given but the outcome is not).[97] In the second study, however, the pMS showed reduced expression of only negative emotions (disappointment and regret) in the face of negative outcomes of their choices.[98]

In the healthy population, good memory capacity predicts adaptive DM in a wide range of cognitive tasks[99] and real-life contexts.[100] In pMS, the worst decisions were found to correlate with IPS, EF, and memory deficits.[101] Regarding memory, several studies have highlighted how WM deficits are able to predict resistance to framing (influence on DM of the way information is presented) and the ability to follow decision rules,[101] suggesting an involvement of WM in supporting the most cognitively demanding decisions. Semantic memory turned out to predict an over and/or underestimation of risk perception and consistency in the application of decision rules: this suggests that DM tasks (ranging from understanding complex instructions to judging the probability of events) require the recovery of knowledge previously learned and stored in LTM.[101] A recent review[95] that analyzed 12 studies found that 64.7% of pMS exhibit a DM performance reduction: 67% of patients have an alteration in under risk DM performance and 64% in under ambiguity DM. Furthermore, all the included studies indicated a tendency for pMS to seek risk: this could be explained by reward hypersensitivity or a reduced ability to assess immediate gain versus long-term outcome, a so-called "myopia for the future."[95] Recently, it has been shown that although RRMS patients are able to collect as much information as HCs before deciding, they are twice as likely to make irrational decisions, that is, against gathered evidence. Furthermore, in line with previous studies, it has been confirmed that RRMS patients are more influenced by the way information is presented (framing effect) than HC. Overall, these results push towards greater caution in communicating with pMS, especially regarding medical information.[102]

COGNITIVE RESERVE AND BRAIN RESERVE

The theory of cognitive reserve postulates that life experiences (education, work, hobbies) interacting with hereditary/genetic and environmental factors can influence the efficiency and flexibility of brain networks, allowing individuals to better cope with neurodegenerative processes at the basis of aging and brain diseases.[103] Specifically, increased intellectual enrichment mitigates the negative effect of the disease burden of MS on cognitive status.[104] Differently, the concept of brain reserve refers to the structural characteristics of the brain at any given moment. It can protect individuals from age-related or disease-related brain changes by influencing the critical threshold after which cognitive decline emerges.[103] For example, people with bigger maximal lifetime brain growth (MLBG; estimated based on head size or intracranial volume) can bear a more severe disease burden without developing CI. These subjects, compared with those with reduced MLBG, may lose more brain volume before exceeding the critical threshold assigned to CI. These considerations can help to identify patients at greater risk of CI and therefore to intervene early with specific rehabilitation interventions.[104]

NEUROPSYCHOLOGICAL ASSESSMENT

Tests commonly used to screen for cognitive deficits in dementia, such as the Mini-Mental State Examination or the Montreal Cognitive Assessment, which primarily assess cortical functions, are not sufficiently sensitive and specific to assess the domains typically affected in MS. Neuropsychological Screening Battery for MS (NSBMS)[10] is one of the first neuropsychological test batteries used for the assessment of cognitive deficits in MS, developed by neuroscientists of the Cognitive Function Study Group. This battery included the Selective Reminding Test (SRT), the 7/24 Spatial Recall Test (SPART), the Paced Auditory Serial Addition Test (PASAT) and the Word List Generation Test (WGLT). Subsequently, the same group proposed the applicability of the BRBNT, integrating the Symbol Digit Modality Test (SDMT) and using the SPART 10/36 instead of 7/24 version.[15] Although the BRBNT is considered one of the most valid neuropsychological test batteries for CI evaluation in pMS, some uncertainties have been raised: the first concerns the absence of sufficient data regarding psychometric properties for test-retest evaluations and for the use of parallel forms;

the second is that it does not cover all the cognitive domains deficient in MS.[105]

To overcome these limitations, a conference was held with 16 clinical psychologists and neuropsychologists to recommend a minimum set of neuropsychological tests to be included in a routine evaluation. A new battery of tests called Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS)[11] emerged, in which the 10/36 SPART was replaced with the Brief Visuospatial Memory Test Revised (BVMT-R) and the SRT has been replaced with the California Verbal Learning Test-Second Edition (CVLT-II). In addition, two new tests have been added: Judgment of Line Orientation (BJLO) and Delis-Kaplan Executive Function System Sorting Test (D-KEFS ST). Although this battery has considerable validity as a tool for the neuropsychological assessment of pMS, unfortunately the long time required for its administration and interpretation, and the high costs due to the need for adequately trained personnel, make it difficult to use outside specialized centers. To overcome the aforementioned problems, in 2010 an expert panel recommended the use of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS).[106] This battery includes the SDMT, the first five trials of the CVLT-II and the first three trials of the BVMT-R.[105] A reliable and sensitive endpoint to be used to determine the efficacy of disease-modifying drugs in improving cognitive functioning in pMS is the Multiple Sclerosis Cognition Assessment Battery (MS-COG).[107] This battery of tests is composed of SDMT, PASAT 3 'and 2', SRT and BVMT-R.[105] ►**Table 1** shows the main neuropsychological batteries used for the evaluation of pMS, with the respective tests and cognitive domains investigated.

In case of limited available time, long test batteries can be substituted by more targeted tests. The single most sensitive and specific test to identify CI in pMS is the SDMT.[15] Furthermore, the SDMT is a significant marker of active disease, as it is the only test that provides results consistently associated with isolated cognitive relapses (ICR).[12] While transient cognitive disturbances are described in association with other symptomatic neurological deficits during disease activity, ICR is characterized by a significant transient cognitive decline in objective neuropsychological performance, with no clinical or subjective evidence of other associated new neurological signs and symptoms to the activity of brain disease defined by the increase of gadolinium on magnetic resonance.[108]

Due to the physical disabilities of pMS, the oral versions are preferred. SDMT is relatively free from practice effects, so it is suitable for serial assessments. Furthermore, it is highly predictive of the future cognitive decline and unemployment status of pMS.[15]

Recently, van Oirschot et al.[109] validated a variant of SDMT (sSDMT; Orikami Digital Health Products) that can be used on smartphones via the MS sherpa application. Obviously, interest in cognitive tests with a digital interface is increasing. These, in fact, would not only allow an automated assessment of cognitive functions, but would reduce the need for qualified professionals.[12] For a review of computerized tests, refer to the work of Wojcik et al.[110] Other tests believed to be effective in distinguishing pMS from HCs are the memory test: CVLT, the BVMT and the Rey Auditory Verbal Learning Test (RAVLT).[12]

In standard clinical practice, usually, the neuropsychological assessment conducted using objective measures is

Table 1 Table showing the main neuropsychological batteries used for evaluation in MS, the tests that compose them, and the cognitive domains under investigation

Battery	Test	Cognitive Domain
	SRT	Verbal learning and memory
NSBMS	7/24 SPART	Visuospatial learning and memory
	WGLT	Verbal fluency and word retrieval
	PASAT	Working memory and processing speed
BRBNT	SRT 10/36 SPART SDMT WGLT PASAT	Verbal learning and memory Visuospatial learning and memory Processing speed Verbal fluency and word retrieval Working memory and processing speed
MACFIMS	PASAT	Working memory and/or processing speed
	CVLT-II	Verbal learning and memory
	BVMT-R	Visuospatial learning and memory
	SDMT	Processing speed
	BJLO	Visuospatial processing
	COWAT D-KEFS ST	Verbal fluency or word retrieval Executive functioning and problem solving
BICAMS	SDMT BVMT-R CVLT-II	Processing speed Visuospatial learning and memory Verbal learning and memory
MS-COG	PASAT	Working memory and processing speed
	SRT	Verbal learning and memory
	BVMT-R	Visuospatial learning and memory

Abbreviations: 10/36 SPART, 10/36 Spatial Recall Test; 7/24 SPART, 7/24 Spatial Recall Test; BICAMS, The Brief International Cognitive Assessment for Multiple Sclerosis; BJLO, Judgment of Line Orientation; BRBNT, The Brief Repeatable Battery of Neuropsychological Tests; BVMT-R, Brief Visuospatial Memory Test Revised; CVLT-II, California Verbal Learning Test-Second Edition; D-KEFS ST, Delis-Kaplan Executive Function System Sorting Test; MACFIMS, The Minimal Assessment of Cognitive Functioning in Multiple Sclerosis; MS-COG, Multiple Sclerosis Cognition Assessment Battery; NSBMS, The Neuropsychological Screening Battery for MS; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modality Test; SRT, Selective Reminding Test; WGLT, Word List Generation Test.

completed by the use of self-assessment questionnaires and semi-structured interviews that allow to have a more complete view of the impact of CI on the daily functioning of patients.

Among the subjective measures, stands out the Neuropsychological Questionnaire on Multiple Sclerosis,[111] which provides useful information on the patient's perception of cognitive difficulties.[105]

MANAGEMENT OF COGNITIVE IMPAIRMENT

Pharmacological treatment

Evidence supporting a positive influence of disease-modifying therapies (DMTs) on MS-related CI is limited, and to date no drugs have been approved.[112,113] No class I evidence was detected for these types of drugs, and class II investigations showed small, non-significant or negligible effects.[112] On the other hand, class III and IV observational studies have produced positive results. Despite this, due to a multitude of methodological limitations, their results cannot be generalized.[112] In contrast to DMTs studies, those conducted on symptomatic therapies produced stronger treatment effect sizes. However, considering the data emerged so far, it is not yet possible to draw conclusions regarding their effectiveness on CI.[112,114]

Rehabilitation

Cognitive rehabilitation (CR) consists of a series of behavioral treatments aimed at helping patients improve their cognitive functions and daily living activities. Generally, there are two different approaches to CR: restorative and compensatory. Restorative CR (rCR) aims to strengthen and restore cognitive abilities using repetitive cognitive exercises based on computer-assisted paradigms. Differently, compensatory CR (cCR) aims to compensate cognitive difficulties of patients through the use of various internal (for example, visualization) and external (for example, reminder)[115] strategies. A rehabilitation program supported by a randomized controlled trial (RCT) is the BrainHQ, composed of 15 specific exercises for EF, IPS, attention, and WM. Attention Processing Training (APT) was found to be effective in the treatment of attention deficits, while the Cognitive Training Kit (COGNITRAcK) was found to be optimal in the rehabilitation of WM.[116]

One of the most widely used computer programs for pMS CR is RehaCom, a software consisting of several specific modules for different cognitive domains (attention, concentration, memory, perception), activities of daily living and much more. It can be used both on single domains and on multiple cognitive processes simultaneously. Its effectiveness has been supported by several RTCs.[115] Excellent results have been observed from the use of REHACOP, an integrative neuropsychological rehabilitation program that trains various cognitive functions including attention, IPS, learning, memory, language, EF, and SC.[117]

Regarding cCR, two programs that have been shown to significantly improve learning and memory of pMS are the Story Memory Technique (KF-mSMT) and the Kessler Foundation Strategy Based Techniques to Enhance Memory (KF-STEM).[115]

Currently, several studies have documented the benefits induced by exercise on the cognitive functions of healthy and elderly adults with CI and in patients with various neuropsychiatric diseases. Despite this, due to conflicting results, a recent 3-level meta-analysis underline the lack of sufficient evidence in favor of motor rehabilitation as a treatment for pMS cognitive deficits.[118]

In conclusion, although starting only in the last quarter of the last century, interest and knowledge about CI in MS grew, research and clinical experience have revealed a strong influence of cognitive deficits on many aspects of the daily life of patients and their families. For these reasons, the assessment of cognitive functioning should be standard clinical practice aimed at ensuring early diagnosis, preventing and/or predicting future disease progression and implementing adequate treatment supported by scientific evidence. If time and resources were available, it would be desirable to prioritize the use of test batteries, rather than single screening tools, accompanied by self-assessment questionnaires and semi-structured interviews that allow a more complete view of the impact of CI on the daily functioning of patients. This type of neuropsychological assessment would allow the clinician not only to investigate all cognitive domains and identify those specifically compromised, but also to develop targeted and specific rehabilitation treatments that take into account the challenges and daily needs of each patient. Furthermore, the strong associations between CI, mood disorders and factors directly related to the pathophysiology of MS should be considered. Thus, specific treatments could be developed for these variables that indirectly affect cognition.

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CP, OA: selection and examination of articles – writing – original draft preparation; UN: review & editing. All authors have approved the submitted version of the present manuscript and agree to be personally accountable for the author's own contributions.

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Conflict of Interest
The authors have no conflict of interest to declare.

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