Chapter 16
Cognitive Impairment in Multiple Sclerosis

Aurélie Ruet

Abstract Cognitive impairment (CI) is important to be detected in patients living with MS due to several following reasons. First, even if CI is often underestimated by patients and physicians, patients with MS are frequently cognitively impaired, and cognitive deficits could be observed in different stages and phenotypes of MS. Information processing speed has been proposed to be the main cognitive domain impaired in patients with MS. It appears crucial to take cognition into account in the clinical practice and to perform neuropsychological assessment with dedicated tools. Concretely, CI could affect daily, familial, social, and vocational activities and alter the health-related quality of life of patients with MS. The pathophysiology of CI is still not completely elucidated, and this research field gains interest. Both focal and diffuse white and gray matter damage participate in explaining CI in MS. At the early stage of the disease, CI could be used as a prognostic marker and could contribute in defining the severity of the pathology. Consequently, detecting CI could influence the therapeutic strategy in MS and studies investigating specific treatment are in progress.

Keywords Cognition • Neuropsychological battery • Information processing speed • Episodic memory • Executive function • Prognostic • Cognitive compensation • Cognitive reserve • Cognitive remediation

Introduction

The nature, frequency, severity, and evolution of cognitive impairment (CI) seen in patients with multiple sclerosis (MS) will be explained in the first part of this chapter. Then, the neuropsychological (NP) batteries used in MS will be described and each NP test will be detailed. In the third part, the consequences of CI will be

A. Ruet, MD, PhD (✉)
Centre Hospitalier Universitaire Pellegrin, Bordeaux, France

Department of Neurology, Université de Bordeaux, Bordeaux 33076, France
e-mail: aurelie.ruet@chu-bordeaux.fr

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addressed. Concerning the pathophysiology of CI, imaging and histopathological data will be reported in order to illustrate anatomical substrates underlying CI in MS. Cognitive compensation and cognitive reserve will be approached in order to explain the clinico-radiological paradox and heterogeneity seen in patients with MS. Based on these correlates, the prognostic value of CI in MS will be demonstrated in the fifth part. Finally, therapeutic options will be discussed for managing CI in patients with MS.

Nature, Frequency, Severity, and Evolution of Cognitive Deficits

Cognitive dysfunction in patients with MS has long been underestimated both by patients and physicians in part due to the fact that cognitive deficits are invisible compared to motor or cerebellar symptoms, for instance. This topic has progressively gained interest in research and in clinical practice, and there is now increasing evidence that CI is common in MS [1, 2].

Nature of Cognitive Deficits

Information processing speed (IPS) is commonly reduced in patients with MS. There are some controversial data concerning the respective contribution of IPS and working memory on cognitive functioning. One approach is to consider that impairment in IPS could affect primarily the functioning of the other cognitive domains. Thus, patients with MS could perform normally if they have enough time at least in the beginning of the disease. Some studies have supported this theory suggesting that IPS impairment is a central and key cognitive defect in this disease [3, 4]. Another approach is to consider the mediating role of working memory that has been recently proposed in a study performed in patients with early relapsing-remitting MS (RRMS) [5]. Besides this important deficit in IPS, episodic memory is frequently impaired in MS [6, 7]. In a mixed sample of patients with MS, impairment in verbal and visuospatial episodic memories has been reported [7]. Poor performances were found at both the immediate and delayed recall suggesting impairment in the coding of the information. Impairment of executive functions is also an important cognitive deficit occurring during the disease with a negative impact [7].

Frequency of Cognitive Deficits

It has been recognized that CI is frequent in MS and could be identified in all types and stages of MS [1, 2, 8]. The frequency rates of CI in patients with MS could vary from 35 to 70 % at both early and late stages of clinically definite MS (CDMS) [6, 8].

On one hand, a comprehensive NP battery was administered to 100 community-based heterogeneous patients with MS, and 43 % of CI was detected in this pivotal study reported by Rao et al. [6]. One the other hand, previous university-based medical centers have reported that cognitive deficits were present in 54–65 % in patients with MS [9–11]. Recent studies have focused on more homogeneous sample of patients with MS. Thus, in a cohort of 44 early relapsing-remitting MS (RRMS), CI was detected in 45 % of patients within six months after MS diagnosis (defined by at least two abnormal NP tests below the fifth percentile compared to matched healthy controls (HCs)) [12]. In the same stage and using the same definition, an Italian multicentric study has reported 34.9 % of CI in a large cohort of more than 500 early RRMS patients [13]. In the same sample using a more stringent definition for CI (at least three abnormal NP tests below the fifth percentile compared to matched HCs), only 19.5 % of patients were classified as having CI. In contrast, at later stages of the disease but with mild disability assessed by the Expanded Disability Status Scale (EDSS), CI was observed in 45 % of a group of 163 patients who have been so-called benign MS (BMS) defined by a score of EDSS less or equal to 3.0 after at least 15 years of disease duration [14]. In fact, the real proportion of BMS patients could be overestimated through the lack of systematic cognitive assessment in MS in practice.

It is noteworthy that the frequency of CI reported in studies including patients with MS is basically heterogeneous. This is mainly due to methodological aspects. Indeed, the estimation of CI could vary in relation to the sample composition and could depend on the norms used for the interpretation of the results (published normative data or own sample of HCs matched to the studied patients for age, sex, and educational level). Moreover, the determination of CI depends on the method and the chosen definition used for classifying patients with or without CI. In fact, this comes from a lack of consensus on how to define CI in MS. Thus, the questions remain concerning the minimal numbers of abnormal NP tests or cognitive domains before classifying a patient as cognitively impaired. Another approach is to use Z-scores with the following formula for each NP score: “MS patient’s score - mean value of their own matched HCs group)/SD of the matched HCs.” Then, a chosen cut-off could be applied to Z-score per NP test in order to define a cognitively impaired patient for a given NP test. Besides, there is no strong consensus on the cut-off for defining an abnormal performance. The data are not homogeneous across the studies and could vary between 1 standard deviation (SD) to 2 SD when comparing the scores or Z-scores of patients to matched HCs. Considering a threshold of 1.64 SD (equivalent to the fifth percentile) could be a good compromise. This important question has been addressed in an interesting paper comparing the criteria of CI in MS studies according to inclusion criteria of patients (early versus late stages of MS) [15]. Three classification strategies have been individualized among 20 approaches used for classifying CI in MS and were applied differently depending on the stage of MS. One strategy is based on the number of abnormal NP tests, another on the determination of a composite score, and the last is a combination of the first two. Even if most of the researchers applied the first strategy, they used different cut-off for defining an abnormal score for each NP test. Nevertheless, it appears that the cut-off on about 20 % of abnormal tests with a score below the fifth

percentile is used in most of the cases. One of the conclusions is that the choice of the classification appears to be driven by the sample of patients (early versus late stage of MS). In studies done at the early stage of the disease, a more liberal definition is mainly chosen, whereas a more stringent and conservative definition is applied at later stage of the pathology.

The relationship between the frequency of CI and disease duration has been questioned. After the first clinical event suggestive of MS called clinically isolated syndrome (CIS), there is increasing evidence that cognitive deficits could be present even if they could be detected in a lower frequency than those observed in RRMS (from 25 to 30 %). Additionally, the deficits are more focused in CIS than in later stage of MS [10, 16–21], and the most impaired cognitive domains are IPS, working memory, attention, and verbal fluency. Moreover, at a preclinical stage suggestive of MS called radiologically isolated syndrome (RIS), the same pattern of cognitive deficits has been observed as previously described in one third of the sample (from 27.6 [22] to 30.8 % [23].

In contrast to RRMS, little information is available concerning cognitive dysfunction in progressive MS patients [24–30]. In one study comparing CIS, RRMS, and progressive MS divided by primary and secondary progressive MS (PPMS and SPMS, respectively), a continuum has been demonstrated in terms of frequency of cognitively impaired patients taking into account the scores of each NP test included in the battery [29]. These data suggest that there is an increase of CI from CIS to RRMS to SPMS.

In contrast, the actual frequency and the nature of CI in patients with PPMS are not fully established due to some methodological limitations of studies including heterogeneous samples of patients with MS. Indeed, patients with RRMS and those with PPMS are frequently different in terms of demographics findings such as age and gender, so appropriate control groups are needed for correct matching a priori. One study has specifically taken these differences into account by including more than 400 HCs in order to match adequately patients and controls for age, sex, and educational level [30]. It has been demonstrated that patients with PPMS had more diffuse CI than those with RRMS form. IPS was the most frequently impaired cognitive domain in both PPMS and RRMS patients, and the two cognitive domains, which differed between these two types of MS, were verbal episodic memory and executive function with respect to the frequency.

Severity of Cognitive Impairment

Few studies have directly compared the severity of CI in different types of MS [24–30]. In the study comparing 415 HCs, 60 RRMS patients, and 41 PPMS patients, one important finding was the difference of CI in terms of severity between these two types of MS [30]. Patients with PPMS had not only more diffuse CI but also more severe cognitive deficits than patients with RRMS especially in verbal episodic memory and working memory. Notably, patients with PPMS had more

pronounced CI than patients with RRMS, even after controlling for physical disability, as assessed using the EDSS score, with the same mean disease duration.

Evolution of Cognition in MS

Whereas there are a lot of cross-sectional studies on cognition in MS, few studies had a longitudinal design that could investigate the progression of cognitive deficits in patients with MS. One should be cautious in the interpretation of the results in that type of studies due to inter-patient variability. The follow-up period varies in range from 1 to 18 years [31–38]. The course of cognitive performance in patients with MS is partly contradictory, as some studies have reported the preservation of cognitive functioning, whereas others have observed a mild to moderate cognitive decline over time in MS [39]. In fact, methodological factors often limit the direct comparison of the results, such as the difference in the composition of studied sample, the length of the follow-up period, and the definition chosen for cognitive decline over time. In one 3-year follow-up study, patients with MS were divided into two groups – a group of cognitively preserved (CP) and a group of cognitively impaired patients at baseline – with the same level of physical disability [32]. The patients from the first group remained cognitively stable in the majority of cases, except for one third of patients who exhibited slight deterioration. In contrast, more than two thirds of the patients considered impaired at baseline presented a cognitive decline in many NP tests. These findings suggest that early cognitive decline could predict further widespread and progressive deterioration, whereas patients with intact cognitive performances might remain stable. The relative short-term of follow-up could explain the absence of cognitive decline in the first group of patients. In a 10-year longitudinal study of 45 MS patients, cognitive deterioration was reported in all patients, even in patients without initial CI [33]. During the first 7 years after MS diagnosis, 40.9 % of cognitively impaired patients and 59.1 % of CP patients showed deterioration in memory domains, whereas almost one third of patients (22.7 %) – including both patients with and without CI – presented IPS deterioration [40]. One recent study has reported the cognitive performances of patients included in one phase III clinical trial of intramuscular interferon beta 1a [38]. One advantage of this study is the long period of follow-up since the last assessment was performed 18 years after the inclusion. A cognitive deterioration has been observed and it concerns mainly IPS domain. Interestingly, the decline over time of IPS was found more frequently in the unimpaired patients than the impaired group of patients at baseline. Looking at the early stage of the disease, it has been reported that the proportion of cognitively impaired patients could almost double in the years following the CIS (from 29 % at the CIS stage to 54 % 5 years later) [41]. In one-year follow-up study, the occurrence of isolated cognitive relapses (ICRs) was associated with poor cognitive performance suggesting ICRs as a factor for cognitive decline in MS [42]. The ICRs were defined as a transient reduction of the Symbol Digit Modalities Test (SDMT) [43] score of at least four points during

the relapse in comparison to pre- and post-relapse assessment. Notably, ICRs were not reported by patients who did not feel any change either in cognition, mood, or fatigue and were detected only by objective evaluation.

How to Assess Cognitive Function

One challenging question is how to assess cognitive function in patients with MS in clinical practice and in research activities. The gold standard consists of the administration of a comprehensive NP battery performed by a qualified practitioner (neuropsychologist, neurologist). Thus, the most commonly used NP battery in MS is the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) proposed by Rao et al. [44], which includes tests of attention, IPS, episodic verbal and visuospatial memory, and verbal fluency (Tables 16.1 and 16.2). A French NP battery has been proposed after modifying some NP tests and adding others in order to explore executive functions in particular [45] (Table 16.1). In 2002, a group of experts proposed a new battery called the Minimal Assessment of Cognitive Function in MS (MACFIMS) based on a consensus approach [46] (Table 16.1). The aim of that battery is to cover five cognitive domains commonly impaired in MS such as IPS/working memory, learning and memory, executive function, visual-spatial processing, and language. In

Table 16.1 Neuropsychological tests included in neuropsychological batteries used in multiple sclerosis [44–46]

	BRB-N [44]	BCcogSEP [45]	MACFIMS [46]
Information processing speed	SDMT	WAIS	SDMT
Working memory	PASAT 3 s	PASAT	PASAT 3 s
		Numeral backward span test	PASAT 2 s
Verbal episodic memory	SRT	Modified SRT	CVLT-II
Visuospatial episodic memory	SPART (10/36)	SPART	BVMT-R
		Numeral forward span test	
Executive functions	WLG	WLG	COWAT
Language, verbal fluency		Opposite orders, Go/No-Go, letter/numbers sequences	D-KEFS sorting test
Others			
Visual perception/spatial processing			JLOT

BRB-N Brief Repeatable Battery of Neuropsychological Tests [44], BCcogSEP [45], *MACFIMS* Minimal Assessment of Cognitive Function in Multiple Sclerosis [46], *SDMT* Symbol Digit Modalities Test, *WAIS* Wechsler Adult Intelligence Scale, *PASAT 3 s* Paced Auditory Serial Addition Test 3.0 s, *PASAT 2 s* Paced Auditory Serial Addition Test 2.0 s, *SRT* Selective Reminding Test, *CVLT-II* California Verbal Learning Test-Second Edition, *SPART (10/36)* Spatial Recall Test, *BVMT-R* Brief Visuospatial Memory Test-Revised, *WLG 90* Word List Generation Test, *COWAT* Controlled Oral Word Association Test, *D-KEFS sorting test* Delis-Kaplan Executive Function System Sorting Test, *JLOT* Judgment of Line Orientation Test

parallel, it is worth to mention that confounding factors like fatigue, depression, and anxiety must be assessed as they could influence cognitive performance.

Another option to assess cognition is the administration of self-questionnaires. Thus, one auto-questionnaire called the MS Neuropsychological Screening Questionnaire (MSNQ) has been proposed for patients and informants [47]. Unluckily, the cognitive self-report complaints do not reflect cognitive test performance in MS, but are more likely associated with depressive symptoms [47–49]. Nevertheless, fulfilling this type of questionnaires by informants could be helpful as it has been considered more reliable than self-reports fulfilled directly by patients with MS [47, 49].

One limitation of the use of comprehensive NP is that its administration is not feasible everywhere in clinical practice and it is time consuming. So, the issue has been to determine which relevant NP tests could be used minimally for detecting cognitive dysfunction in MS and for selecting patients who require additional evaluation from an expert. The SDMT [43] has been proposed as a good candidate for detecting CI in comparison to other NP tests in early RRMS patients [48] and in a mixed sample of patients with MS (both RRMS and SPMS patients) [50]. This test described in Table 16.2 is part of both the BRB-N and MACFIMS batteries. Notably, it is associated with a good reliability in several assessments [51, 52]. Thus, this IPS test has been chosen to be part of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) which consists of the minimal cognitive evaluation required for patients with MS [53] (Table 16.3). Nevertheless, one weakness of the SDMT is its practice effect, and a computerized screening cognitive test (CSCT) [54], detailed in Table 16.2, has been proposed for limiting this. The CSCT was associated with a good accuracy for assessing IPS in patients with MS in comparison to other IPS tests included in the test of attentional performance (TAP) [57]. In addition to the SDMT, it has been recommended by this group of experts to include the California Verbal Learning Test-Second Edition [58] to assess episodic verbal memory and the Brief Visuospatial Memory Test-Revised [59] to explore episodic visuospatial memory as memory dysfunction occurs frequently in MS too (Tables 16.2 and 16.3). The application of this brief cognitive assessment is ongoing in international research studies in MS.

Consequences of Cognitive Impairment

Cognitive impairment could affect different aspects in the lives of persons with MS. There are some direct and indirect consequences in terms of daily activities, social function, leisure activities, and interpersonal relationships with family, partners, and friends [1, 2, 60]. Moreover, cognitively impaired patients were more unemployed than cognitively unimpaired patients in several studies [60–62]. Importantly, early cognitive status, independently to physical disability, contributed to the vocational status change in a cohort of patients included after the diagnosis of

Table 16.2 Neuropsychological tests used for assessing the different cognitive domains impaired in multiple sclerosis [44, 46, 54–57]

Cognitive domains and functions	Neuropsychological tests	Description	Score	Advantage	Weakness
Information processing speed (visual)	Oral SDMT	Nine digits/symbols, oral substitution test during 90 s	Number of accurate answers	Very sensitive test, short test	Practice effect
		A unique key showing the association of symbols with digits is provided, and it is similar for each test session			
	CSCT	Nine digits/symbols, oral substitution computerized test during 90 s	Number of accurate answers	Very sensitive test	Need to be validated in multicentric study
		The sequences of symbols and digits of the key are automatically generated for each session of training and testing and are different from one session to another		Short test	
				Weak practice effect	
	WAIS-R	Nonverbal digits/symbols, substitution tasks	Number of accurate answers		Written test
	Digit symbol				Less sensitive than the SDMT
					Could be affected by hand deficiencies
Information processing speed (auditory) and working memory	PASAT	Oral and auditory test	Number of correct sums	Two alternative forms	Important practice effect
	Version 2 or 3 s	61 numbers are given orally every 2 or 3 s and the subjects should add the number they just heard with the number they heard before			Stressful
					Exploration of different functions (working memory, IPS, inhibition, mental arithmetic)

	Numeral backward span test	Oral test The subject should repeat a sequence of numbers in reverse	Number of correct sequences of numbers	Working memory could be analyzed independently of IPS	
Verbal episodic memory	SRT	Oral test A list of 12 unrelated words is read aloud to the subject who is asked to repeat as many words as possible in any sequence. The examiner then provides any words not recalled, after which the subject could try to recall the entire list. This test is repeated five times, followed by a 20- to 25-min interval, after which the subject should recall and replicate the list again	Immediate and delayed recall scores: number of corrected words	Two alternative forms	Important practice effect Only short- and long-term memory are investigated No exploration of indexing
	Modified SRT	Oral test	Immediate and delayed recall scores: number of corrected words	16 words of the BcCog	
	CVLT	Oral test Learning test of 16 words with five learning trials and interference learning task before the delayed recall after 20- to 25-min interval	Immediate and delayed recall scores: number of corrected words	Learning task More comprehensive test of memory: interference could be investigated	
	Numeral forward span test	Oral test The subject should repeat a sequence of numbers in the correct order	Number of correct sequences of numbers		Low sensibility of this test

(continued)

Table 16.2 (continued)

Cognitive domains and functions	Neuropsychological tests	Description	Score	Advantage	Weakness
Visual/spatial episodic memory	10/36 SPART	Memory test using a 6 X 6 checkerboard with 10 pieces placed in specific locations. After 10 s, the subject should replicate the pattern on a blank checkerboard. The test is repeated 3 times, followed by a 20- to 25-min interval, and then the subject should recall and replicate the pattern again	Immediate and delayed recall scores: number of correct location of the pieces		Low sensibility of this test
	BVMT-R	A piece of paper with six visual designs is presented	Immediate and delayed recall scores: number of correct drawn design	Sensitive test	Could be affected by hand deficiencies
		After 10 s, the subject is given a blank sheet of paper and should draw each of the designs in the correct location		Six alternative forms	
		After a 20- to 25-min interval, the subject should recall and draw as many designs as possible			
Executive functions					
Verbal fluency	WLG/COWAT	Oral test	Number of adequate nouns		Could be affected by reduced IPS
		Verbal fluency is tested (a maximum of nouns of animals starting with letter "P" should be given) in 90 s			
Sorting test	WCST	Executive test	Number of correct series		Long test
		Card sorting test with different rules			
Sorting test	D-KEF Sorting Test	Executive test	Number of correct series		Long test
		Card sorting test with different rules			

Inhibition	Stroop	Oral test The subject should read color nouns written with an ink in a different color	Number of correct denominations	Interference task	
	Go-No-Go	Executive test The subject should perform an action given certain stimuli (e.g., press a button – Go) and inhibit that action under a different set of stimuli (e.g., not press that same button – No-Go)	Reaction times		Low sensitivity of this test
Flexibility	TMT-A/TMT-B	Executive test The subject should link letters and numbers according to a predefined rule Two versions: TMT-A and TMT-B	Number of correct series	TMT-B investigates mental flexibility	
Attention	TAP	Computerized battery of different aspect of attention such as visual and auditory divided attention, alertness without and with warning, visual scanning with and without target	Number of accurate answers	Reaction times and number of accurate answers could be analyzed separately	Long

*SDMT** Symbol Digit Modalities Test, *CSCT* Computerized Screening Cognitive Test [54], *WAIS-R Digit Symbol* Wechsler Adult Intelligence Scale-Revised Digit Symbol, *PASAT** Paced Auditory Serial Addition Test, *SRT** Selective Reminding Test, *CVLT** California Verbal Learning Test, *10/36 SPART** Spatial Recall Test, *BVMT-R** Brief Visuospatial Memory Test-Revised, *WLG** Word List Generation Test, *COWAT** Controlled Oral Word Association Test, *WCST* Wisconsin Card Sorting Test [55], *D-KEFS** Delis-Kaplan Executive Function System Sorting Test, *TMT* Trail Making Test [56], *TAP* Test of Attentional Performance [57]. * Neuropsychological tests included in the BRB-N, BCcogSEP, and/or MACFIMS batteries [44, 46]

Table 16.3 Proposition for minimal cognitive assessment for multiple sclerosis (BICAMS) [53]

Cognitive domain	Neuropsychological test
Information processing speed	SDMT
Verbal episodic memory	CVLT-II: first five recalls
Visuospatial episodic memory	BVMT-R: first three recalls

BICAMS Brief International Cognitive Assessment for Multiple Sclerosis [53], *SDMT* Symbol Digit Modalities Test, *CVLT-II* California Verbal Learning Test-Second Edition, *BVMT-R* Brief Visuospatial Memory Test-Revised

MS and followed during seven years [62]. In particular, IPS impairment could predict this change, and cognitive deterioration was associated with both the vocational status at the end of the follow-up and its change over the first seven years after the diagnosis.

There is a negative impact on mood too and CI could interfere in self-esteem feeling and copying strategy. In general, CI could alter life satisfaction and the health-related quality of life [60, 62–67]. Driving capacities could be compromised depending on the extent and the severity of CI. In terms of the general treatment of the disease, the presence of CI does modify medical decisions and medication adherence. The management of CI and rehabilitation programs are further detailed in part VI of this chapter.

Pathophysiology of Cognitive Impairment

The pathological substrate of CI in patients with MS is not completely understood. Structural and functional imaging and histopathological studies have provided data suggesting the role of both focal and diffuse brain damage within and outside MS lesions in white and gray matter (WM and GM, respectively) [Review in 68–70].

The first approach is to consider simple imaging parameters such as the distribution, amount, and the extent of focal WM lesions. White matter lesion volume has been found greater in cognitively impaired than in CP patients with MS in many studies [68, 70], but there are only mild to moderate correlation with CI. These modest associations between WM lesions and CI in MS could be explained by the fact that T2 hyperintensities reflect heterogeneous pathologic substrates, including edema, inflammation, demyelination, remyelination, gliosis, axonal loss, and there is a lack of pathological specificity. More importantly, specific locations have been highlighted, and lesions in corpus callosum have been associated with CI in patients with MS [71]. Moreover, some clinical and imaging studies have suggested the role of the cerebellum in CI and in particular in IPS impairment in MS [72–75]. Secondly, it appears interesting to focus on diffuse brain damage and in particular to study the so-called normal-appearing white matter or brain tissue (NAWM and NABT, respectively). In a cross-sectional study, diffuse brain damage assessed by magnetization transfer imaging (MTI) was associated with early CI in patients

recently diagnosed with RRMS [12]. These results were replicated in other studies and especially in sample including patients after the first clinical demyelinating event suggestive of MS [76]. Cognitive impairment could be the consequence of brain disconnection due to these abnormalities located in WM tracts. Diffusion tensor imaging (DTI) protocols have allowed to study different metrics including fractional anisotropy in the whole WM skeleton using a tract-based spatial statistic analysis [77, 78] or in specific WM tracts [79] showing the relative contribution of lesional and non-lesional WM in cognitive performance in patients with MS. Several functional MRI (fMRI) studies have also provided interesting findings in patients with MS without CI and with CI and illustrated cortical reorganization that is different according to the stage of MS [68–70]. Brain compensatory mechanisms have been found at early stage of the disease [74, 80, 81], and functional disconnection may affect these mechanisms needed to overcome focal and diffuse structural damage occurring during the disease. There are only few longitudinal studies that included early RRMS patients with several cognitive and MRI evaluations with a long-term follow-up. In one 7-year follow-up study, MRI parameters reflecting the extent and the severity of the diffuse damage in NABT and the net consequence of the diffuse brain damage assessed by atrophy measurements (whole brain and central atrophy) more strongly predicted CI in RRMS patients than visible lesions in the WM [40].

Besides WM, there is increasing interest concerning the damage within the GM for explaining CI in MS [82]. Cortical lesion volume has been found to be higher in cognitively impaired than CP patients with MS [83]. Once again, lesions in specific locations have been considered clinically relevant and were associated with CI in patients with MS. In particular, the regions of interest are deep GM structures such as the thalamus and other basal ganglia and the hippocampus [68–70]. Moreover, brain atrophy appears as a better predictor of cognitive deterioration in patients with MS than WM lesion load [68]. In particular, GM atrophy might play a significant role in the physiopathology of CI in MS, and both cortical and subcortical atrophy have been significantly correlated to CI in patients with MS [68, 82]. Some studies have investigated the role of thalamic atrophy in CI in patients with MS and this topic gains interest [70, 82]. Moreover, a few studies have focused on the hippocampus showing the role of its atrophy mainly in memory impairment in patients with MS [70, 84].

Finally, structural and functional approaches could be combined in order to better explore cognitive functions in patients with MS. A functional disconnection between GM structures at least, partially secondary to damage located in specific WM areas, has been suggested as one of the most important mechanisms leading to CI in MS. A promising method could be to investigate resting-state connectivity. In early MS patients, both structural damage and resting-state functional connectivity changes in brain networks have been investigated [85]. Interestingly, when comparing the different effect sizes of MRI metrics, the highest value was found among the functional connectivity measurements. Moreover, atrophy in one specific area, namely, the posterior cingulate cortex (PCC), was the only predictor of the functional

correlation between the medial prefrontal cortex and the PCC. Moreover, the presence of brain and cognitive reserve could attenuate the negative effect of the cumulative brain damage on cognitive performance in patients with MS [86–88]. An interesting longitudinal study including patients after the first clinical demyelinating event (CIS) was performed to investigate the correlates of the evolution of cognitive scores with the change of MRI parameters within 2-years of follow-up [89]. Surprisingly, no significant differences were observed between baseline cognitive status and both baseline and change of MRI metrics in this CIS cohort. One of the explanations could be the presence of cognitive reserve present at this very early stage of the disease.

Few studies have focused only on patients with PPMS. Focal and diffuse WM damage and GM pathology have been reported as significant predictors of cognitive performance in IPS, attention, and executive function in a 5-year follow-up study including 31 patients with PPMS [90]. Additionally, in an immunohistochemical study of postmortem brains of 26 patients with PPMS, a generalized diffuse meningeal inflammation was reported [91]. This confined inflammation might play a significant role in the pathogenesis of cortical GM lesions and contribute to the clinical disability in these patients.

Prognostic Factor

Physical disability and CI could occur independently from each other during the course of the disease, and patients could present CI even before the manifestation of physical symptoms. Aforementioned, patients who are so-called BMS could have CI despite of a low EDSS supporting the need to detect cognitive deficits for evaluating the severity of the disease. Notably, it has been proposed a modification of the definition of BMS in order to include cognitive assessment [92]. The relationship between physical disability and cognition has been questioned in MS. Significant correlations between the EDSS score and cognitive test performances have been reported [93, 94]. Even if modest relationships are typically observed between CI and physical disability in MS, the majority of these results primarily concern the measurement of IPS [94–97]. These data highlight the prognostic value of IPS impairment that is considered as a central defect in MS. In a 7-year longitudinal study, the cognitive deterioration was correlated with MRI parameters reflecting mainly the initial brain diffuse axonal injury and its early change within the first two years [40]. These results support the role of early central atrophy in CI in patients with RRMS and in particular its correlation with IPS decline in early MS. The early identification of IPS impairment could be a relevant marker of early central atrophy that has been used for predicting the progression of the disability assessed through changes in EDSS [98].

Management of Cognitive Impairment

Medications: Disease-Modifying Drugs and Symptomatic Treatment

Aforementioned, cognitive status should be included in treatment decisions independently of physical disability as it represents a marker for disease severity and progression. Nevertheless, the historical clinical trials did not take into account these data in defining the efficacy of treatments in MS. Cognitive functions have been evaluated mainly in post hoc analysis of the first clinical trials of disease-modifying drugs in MS. Few studies have chosen cognitive outcome as a primary endpoint. Cognitive secondary outcome measures of randomized controlled trials or their extension have been reported [99]. For instance, a positive effect of interferon beta 1b subcutaneous has been demonstrated in patients included after a CIS [100]. Another randomized clinical trial was performed for evaluating the effect on cognitive function of different types of interferon beta (Avonex, Rebif, and Betaferon) in newly diagnosed RRMS with one-year of follow-up [101]. In accordance with some previous studies focusing on the effect on interferon beta in MS [102, 103], the results suggest a positive effect on these disease-modifying drugs in preventing cognitive deterioration in MS. Encouragingly, cognitive performances have been also improved during an observational open-label study testing one monoclonal antibody in RRMS patients [104]. Moreover, fingolimod was tested in lipopolysaccharide (LPS) model in rats in order to explore the link between immune activation and cognition [105]. Indeed, the LPS was used as an agent inducing microglial cell activation and brain inflammation. Interestingly, a protective effect of fingolimod was demonstrated at different experimental levels (functional, histological, and transcriptional steps) suggesting its application in treating memory impairment in neuroinflammatory conditions.

Moreover, several symptomatic drugs have been tested to improve cognition in patients with MS, such as anticholinesterasics (donepezil, rivastigmine) and channel blockers [99]. However, no drug has shown positive results in large randomized controlled trials. Some positive results have been reported on short-term follow-up with L-amphétamine [99]. In conclusion, these studies provide insufficient data for prescribing symptomatic treatment for preventing and treating CI in patients with MS.

Cognitive Rehabilitation and Remediation

There is a lack of well-designed research studies investigating the effectiveness of cognitive rehabilitation programs in patients with MS [106, 107]. As the impairment of IPS is a key deficit in MS and has a prognostic value in this disease, its early

detection and management seem to be clinically relevant and justify putting some efforts to investigate the impact of specific cognitive rehabilitation and remediation programs. Moreover, managing episodic memory is also a challenge of this type of programs and some specific studies are in progress. Besides, it is clinically relevant to focus on ecological validity of this type of rehabilitation.

Conclusion

Cognitive impairment is common in MS and could be seen in each type and stage of the disease. It affects primarily information processing speed, and episodic memory is frequently impaired too. CI has a negative impact on daily activities and in particular on vocational status of patients living with MS. Even if there is a high variability, cognitive functions tend to deteriorate over time as cumulative brain damage occurs. There is increasing evidence that CI could be due to a disconnection syndrome relative to the accumulated focal and diffuse brain damage within the white and gray matter structures. Educational level, leisure activities, and intelligence quotient contribute to cognitive reserve and have the potential to attenuate the consequences of cognitive deficits at least at the beginning of the pathology. The presence of brain compensatory mechanisms supported the development of rehabilitation and cognitive remediation programs. Longitudinal studies with long follow-up including clinical, neuropsychological, and imaging assessments are still needed to better understand the pathophysiology of cognitive impairment in both active and non-active patients with MS. One of the remaining challenge is the treatment of cognitive impairment in patients with MS, and works are in progress.

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