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REVIEW

Treatment of cognitive impairment in multiple sclerosis: position paper

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Abstract Cognitive impairment in multiple sclerosis (MS) is common, debilitating and burdensome. Key evidence from trials was reviewed to enable recommendations to be made to guide clinical practice and research. Behavioural and pharmacological interventions on cognition reported in published studies were reviewed. Most studies evaluating behavioural treatment for impairment in learning and memory, deficits of attention and executive function have demonstrated some improvement. Controlled studies in relapsing remitting MS indicate interferon (IFN) β-1b and IFN β-1a were associated with modest cognitive improvement. The effects of symptomatic therapies such as modafinil and donepezil are inconsistent. Most studies yielding positive findings have significant methodological difficulties limiting the confidence in making any broad treatment recommendations. There are no published reports of glatiramer acetate, natalizumab and fingolimod being effective in improving cognition in controlled trials. The effects of disease modifying therapies in other forms of MS and clinically isolated syndrome have not yielded positive results. Data linking behavioural therapy, symptomatic treatment or disease modifying treatment, to either reducing cognitive decline or improving impaired cognition are limited and inconsistent. The treatment and prevention of cognitive impairment needs to remain a key research focus, identifying new interventions and improving clinical trial methodology.

Keywords Multiple sclerosis · Cognition · Treatment · Cognitive rehabilitation · Disease modifying drugs · Symptomatic treatment

Introduction

Impairment of cognitive function in multiple sclerosis (MS) is estimated to affect 40–60 % of patients [1–4].

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While severe dementia is rare, it has been estimated that up to 20 % of patients develop at least a mild form of dementia [3–5]. Cognitive impairment has been detected in all the disease subtypes [6] although it progresses over time [7] and is most frequent and severe in secondary progressive MS (SPMS) [6, 8] Cognitive deficits are detected in approximately one-third of patients with early relapsing remitting MS (RRMS) [9], 20–30 % of patients with clinically isolated syndromes (CIS) [10, 11] and even and in some patients with radiologically isolated syndrome [12, 13]. The extent of cognitive impairment noted in a subset of patients with so-called benign MS (low EDSS with disease duration of over 15 years) [14] brings into question the appropriateness of the term "benign".

Typically, not all domains of cognitive functioning are impaired in MS. Although the profile of cognitive deficits varies among patients, memory (long-term, explicit, episodic), complex attention, information processing speed and executive functions are most commonly involved; language, semantic memory and attention span are rarely involved [7, 15, 16]. The pathophysiological changes that underpin the development and progression of cognitive impairment in MS patients are complex, highly variable, and incompletely understood [17]. The correlation between magnetic resonance imaging (MRI) findings and cognitive performance in MS is consistently robust, but only one-third to one-half of the variance can be explained by MRI findings [15]. Cognitive reserve, a behavioural adaptation acquired through experience which improves cognitive performance in increase phenotypic expression in the presence of disease, could explain the high interindividual variability in cognitive deficits in MS and the limited correlation with MRI findings [18].

Cognitive dysfunction in MS presents a considerable burden to patients and to society, due to the negative impact on function, including maintaining employment, activities of daily living, social activity, and the capacity to benefit from in-patient rehabilitation [7]. In some individuals with MS the impact of cognitive impairment can be profound, even if physical functioning remains relatively intact. Interventions to ameliorate or reduce cognitive impairment, as part of a comprehensive rehabilitation programme, may benefit patient function and quality of life.

To diagnose and quantify the extent of cognitive impairment, appropriate assessments are essential but often difficult. Patient report is unreliable and highly correlated with depressive symptomatology [19, 20]. Unfortunately, routine neurological examinations for MS are too insensitive to yield valid information on cognitive function. For example, the expanded disability status scale (EDSS), does not include an adequate assessment of cognitive dysfunction. The development of the Multiple Sclerosis Functional Composite (MSFC) which includes the Paced Auditory Serial Addition Test (PASAT) [21] was a step forward towards incorporating a sensitive measure of cognition into a standardized rapid MS assessment tool.

The challenge with more detailed and comprehensive performance-based cognitive evaluations is that while they are the most reliable, they can be time consuming and impractical in many clinical settings. Screening patients to identify those with the highest likelihood of dysfunction would be ideal, but validated screening tools have yet to be developed or applied. One assessment approach is to use test batteries that range from 30 to 90 min in duration. The goal of these batteries is to capture the core features of MS-associated cognitive dysfunction. The Brief Repeatable Neuropsychological Battery (BRNB) [22] assesses those domains most commonly impaired in MS and is most widely used in clinical and research settings [7]. The Minimal Assessment of Cognitive Function in MS (MACFIMS), developed for a similar purpose, is a more recent battery created by expert consensus and published in 2002 [23]. These batteries differ in the specific auditory/verbal memory and visual/spatial memory tests employed, but assess similar domains, and are comparable in their overall sensitivity to disease status [24].

Despite the availability of such batteries, the assessment of cognitive function in research studies of MS is far from optimal. Methodological shortcomings include the variability of the domains assessed and the instruments used, the handling of common confounds such as fatigue and depression, and the inclusion of heterogeneous groups of patients in whom selection criteria for cognitive impairment were either applied inconsistently across studies or not applied at all. Examples of some of these methodological issues are shown in Table 1.

There is little information to guide clinicians on how to interpret the benefit, or lack thereof, of interventions designed to improve cognition in MS. Given the prevalence of cognitive impairment in MS, its adverse effects on daily function, and the fragmented nature of what is known about interventions to treat the condition, we thought it germane to review key evidence from trials with a view to providing interpretation and recommendations to guide practice and further research. Interventions including cognitive rehabilitation, the effects of symptomatic treatments and the effects of disease modifying treatments (DMTs) will be discussed. This is not a systematic review of all available literature that has ever addressed the topic, but rather a review of research that formed the basis of presentations on the topic given at the conference "Cognition Disorders in Multiple Sclerosis" which was held in October 2011.

Table 1 Methodological problems with many existing rehabilitation studies of cognitive function in multiple sclerosis

Small sample size
Lack of control group, or inadequate control (e.g., "historic controls")
Interventions are multifaceted and difficult to quantify
Inadequate selection of targeted sample, e.g., cognitively intact patients often included
Inclusion criteria for cognitive impairment based on self-report rather than objective assessment
Within sample variability
Selection bias
Treatment is often not impairment specific (e.g., "improve cognition")
Frequency and intensity of treatment often not reported
Specific details of how treatment was delivered often not reported (e.g., non-specific cognitive training)
Unsupervised training sessions (compliance not monitored)
Use of poor outcome measures (e.g., "positive clinical response")
Practise effects not addressed in data analysis
Assessments lack of sensitivity to change
Outcome measurements lack relevance to everyday life
Lack of long-term follow-up

Not all studies suffer from each of these limitations

Cognitive rehabilitation

Effective cognitive rehabilitation programmes in clinical settings do not only employ techniques designed solely to improve specific domains of cognitive function, but also typically include psychotherapy for addressing emotional issues and interventions designed to improve related factors such as behavioural and personality difficulties. While some integrated cognitive rehabilitation programmes exist for individuals with MS in clinical settings, few have been systematically evaluated, although there are exceptions, e.g., Jønsson et al. [25]. As specific cognitive interventions are an important component of a comprehensive rehabilitation programmes an understanding the impact on specific interventions on those domains of function that are of greatest clinical relevance in MS is important. Of particular interest are learning and memory, information processing speed, attention and executive function.

Learning and memory

Learning and memory has received the greatest research attention and may have the greatest impact on everyday life for people with MS. A number of papers have been published over the last two decades, especially more recently, on behavioural rehabilitation of learning and memory in MS patients. However, most studies suffer from significant methodological problems (see Table 1) [26]. A recent evidence-based review yielded only 16 papers, mostly from class II to class IV evidence [27], precluding conclusions about clear treatment benefits. This evidence-based review [27] was a systemic review employing strict inclusion and exclusion criteria for selecting the studies to be included in the review process, and therefore did not include several of the studies we cited in addressing this topic. The recent Cochrane review on the rehabilitation of memory in MS identified only eight studies, involving 521 patients in total, that met their standards for methodological rigour [28]. They concluded that there is no evidence to support the effectiveness of memory rehabilitation on memory function or functional abilities in patients with MS, but noted that this conclusion was made because of the limited quality of some of the primary studies reviewed in this area [28]. Despite methodological problems, there are several published studies that do report significant improvement in neuropsychological performance following behavioural treatment (Table 2).

Targeted interventions

Many of the interventions studied have been targeted on focused behavioural interventions designed to increase learning efficiency, as impaired acquisition of new information has been shown to be the primary problem in the learning and memory problems associated with MS [29–31]. Some of these targeted interventions have shown consistent support for improving learning and memory in MS across several studies and laboratories. For example, the use of self-generated learning (where patients generate the right answer versus being told what to remember) to improve the acquisition of new learning has been shown to improve recall and everyday functional activity, such as financial management and meal preparation [32], as well as the recall of names, appointments and object locations [33, 34].

Other targeted intervention techniques include spaced learning (spreading learning trials over time versus consecutive trials) [35] and spaced retrieval (also known as the 'testing effect') [18]. In the latter study, learning and memory impaired MS patients were required to study three sets of word pairs (in a within–group design); one word pair set was studied twice consecutively (massed trial), another set was studied twice but spaced over time (spaced trial), and the third set was studied only once, but was then tested. During subsequent recall, word pair retention was significantly better when material was tested compared to either the massed trial or the spaced trial, with patients recalling about twice as many word pairings as the massed studied material. A recent study examined whether utilizing two of these behavioural interventions (i.e., self-generation and spaced learning) was better than a single

Table 2 Summary of effects of cognitive rehabilitation in MS

Reference	Interventions	Number of patients treated with intervention	Design	Duration Tx	Key cognitive assessments Attention (A) Executive function (EF) Learning/memory (LM) Processing Speed (PS)	Primary endpoint	Results
Allen et al. [53]	Supervised computerized training of imagery-based strategies for memory training	8	Uncontrolled	15 sessions, scheduled 2–3 times per week	Word recall (RIS method), face-name association (LM)	Effects of training on word recall and face-name association	Non-significant improvements in word recall and face-name association after training. Significant improvement in depression. MS patients learned memory strategies more quickly than an historical control group of head injury patients.
Basso et al. [33]	Comparison of self-generated and didactic learning methods	95	Controlled, unrandomized	Not stated	CVLT-II, paired-associates task, memory for names, appointments and object location tasks (LM)	Comparison of self-generated or didactic learning methods	MS patients remembered more information if it was self-generated rather than didactically presented, even patients with moderate-severe impairment. Self-generated learning yielded near-normal memory function in MS patients
Basso et al. [34]	Comparison of self-generated and didactic learning methods	20	Controlled, unrandomized	Not stated	WMS-III, paired-associates task (LM)	Comparison of self-generated or didactic learning methods	Regardless of participant group, self-generated learning resulted in better recall than didactic learning. The memory-impaired MS group showed the same degree of enhanced recall with self-generated learning as unimpaired patients and normal controls
Brenk et al. [39]	Home-based non-specific cognitive training	27	Matched control	6 weeks	ZNS-V, ZNS-R, VLMT, CFT, TAP, RWT (A, EF, LM, PS)	Training effects on neuropsychological deficits and depression	Cognitive training improved memory and attention in MS patients and controls. MS patients showed improvements in short-term and working memory, complex attention functions and visuoconstructive performances. Improvements generally maintained for at least 6 months. Improvements were also observed in depression and QoL
Brissart et al. [54]	Computer-assisted cognitive rehabilitation	24	Uncontrolled, unrandomized	6 months	BCcog-SEP: SRT, 10/36 test of visuospatial memory, verbal fluency tests, PASAT (A, LM)	Effects of cognitive rehabilitation on cognitive deficits	Sub-tests of the BCcog-SEP showed improvement in verbal memory (SRT), visuospatial memory (10/36), verbal fluency (animal categories) and response to conflicting orders

Table 2 continued

Reference	Interventions	Number of patients treated with intervention	Design	Duration Tx	Key cognitive assessments Attention (A) Executive function (EF) Learning/memory (LM) Processing Speed (PS)	Primary endpoint	Results
Chiaravalloti et al. [55]	Comparison of self-generated and provided learning methods	31	Controlled, unrandomized	Single test day with recall at 30 min and 1 week	DST, PASAT, Stroop Color-Word Test, oral TMTA and TMTB, WCST, WMS-R (A, LM, EF, PS)	Comparison of self-generated or provided learning methods	Recall and recognition of generated stimuli were significantly higher than provided stimuli across testing sessions. This effect was similar in MS patients and controls. Recall performance for generated stimuli correlated with indices of episodic memory, information processing and language but not executive function
Chiaravalloti et al. [37]	Story memory technique for memory retraining	15	SB, RCT	4 weeks	SRT, DST, WAIS-R, oral TMTA & TMTB, WAIS-III, PASAT, SDMT, MFQ (A, LM, PS)	Effect of memory retraining on learning and memory performance	MS patients with moderate to severe learning deficits showed significant improvements in learning abilities compared to controls after SMT training. Little improvement noted in those with mild deficits at baseline
Fink et al. [52]	Executive function training (various techniques used)	11	RCT, PC, DB	6 weeks	Executive function computer tasks (preference shifting, response shifting, 2-back), CVLT (EF, LM)	Neuropsychological performance after training	At 6 weeks, verbal learning and changes in response shift time had improved in the cognitive intervention group (CIG) relative to the placebo intervention group (PG) and untreated group (UG). The treatment effect on verbal learning was still present at 1 year
Goverover et al. [32]	Comparison of self-generated and provided learning methods	20	Controlled, unrandomized	Single test day with recall at 30 min and 1 week	DST, SDMT oral version, D-KEFS, CVLT (A, LM, EF, PS)	Effect of learning method on learning and performance of everyday tasks (meal preparation and managing finances)	Recall similar in MS and healthy groups. Self-generated learning significantly improved recall of information and performance of everyday tasks across groups
Goverover et al. [35]	Comparison of spaced or massed learning trials	20	Controlled, unrandomized	Single test day with immediate recall	DST, SDMT oral version, D-KEFS, CVLT (A, LM, EF, PS)	Effect of learning method on memory performance	Spaced learning (5-minute break between trial) improved recall of a verbal learning task relative to massed learning (consecutive trials) but not of a visual learning task

Table 2 continued

Reference	Interventions	Number of patients treated with intervention	Design	Duration Tx	Key cognitive assessments Attention (A) Executive function (EF) Learning/memory (LM) Processing Speed (PS)	Primary endpoint	Results
Goverover et al. [36]	Comparison of self-generated and spaced learning with spaced and massed learning methods	20	Controlled unrandomized	Single test day with immediate and 30-min recall	CVLT-II, BVMT-R (LM)	Effect of learning method on memory performance	The combination of self-generated and spaced learning improved recall of everyday functional tasks compared with spaced or massed learning alone in MS patients. Spaced learning improved recall relative to massed learning
Hildebrandt et al. [41]	Home-based computer-assisted training	17	SB, RCT	6 weeks	CVLT, PASAT, alertness test of the TAP (A, LM, PS)	Training effects on memory and working memory	Treatment group showed better verbal learning, long-delay verbal memory performance and working memory performance after training. Impact of treatment on long delay verbal memory independent of extent of brain atrophy; for other findings, brain atrophy played a significant role. No effect on fatigue or QoL
Jønsson et al. [25]	Specific cognitive treatment or non-specific mental stimulation	20	RCT	46 days (mean)	Tests of verbal intelligence, memory span, verbal learning, visuospatial memory, recognition memory, abstract reasoning, visuomotor speed, visual perception, concentration, verbal fluency (A, LM, EF, PS)	Broad treatment effects evaluated	Significant short-term treatment effect only on visual perception. At 6 months, only visuospatial memory differed between groups. Treatment produced significant improvements in BDI scores immediately after treatment and at 6 months
Mattioli et al. [48]	Supervised computer-assisted training	10	DB, controlled study, with 'casual assignment'	3 months	PASAT, WCST (A, LM, EF, PS)	Effects of training on attention and executive function	After rehabilitation, the study group had significantly improved tests of attention, information processing and decision making as well as depression scores compared to the control group
Mendozzi et al. [42]	Supervised computer-assisted specific memory retraining	20	Part-randomized, controlled	8 weeks	WMS, Corsi's test, memory scale of the LNNB, signal detection task (A, LM, PS)	Effects of specific vs. non-specific memory re-training	Specific memory retraining resulted in improvements in 7 out of 11 memory and attention tests compared to only 1 in the non-specific training group and none in the control group

Table 2 continued

Reference	Interventions	Number of patients treated with intervention	Design	Duration Tx	Key cognitive assessments Attention (A) Executive function (EF) Learning/memory (LM) Processing Speed (PS)	Primary endpoint	Results
O'Brien et al. [49]	Comparison of self-generated or didactic learning methods	31	Uncontrolled, unrandomized	Not stated	DST, PASAT, Stroop Color-Word test, oral TMTB, WMS-R (A, LM, EF, PS)	Comparison of self-generated or didactic learning methods	Self-generation significantly increased recall vs didactic learning in MS patients; differences were apparent at 30-mins but not at 1-week recall. Individuals with multiple cognitive impairments benefitted more than those with no or one impaired domain
Plohmann et al. [46]	Supervised computer-assisted training targeted at individual attentional domains	22	Consecutively enrolled patients. No control group	2 × 3 weeks	TAP (A, PS)	Training effects on attentional impairments	Significant improvement of performance for the domains of alertness, divided attention, and all subsets of selective attention could only be achieved by the respective training programmes, not by the others. Treatment effects were stable for 9 weeks. Daily functioning improved. No effect on behaviour
Sastre-Garriga et al. [50]	Computer-assisted and non-computer assisted training	15	Controlled, open-label pilot	5 weeks	TMTA, TMTB, SDMT, RAVLT, DST, PASAT (A, LM, PS)	Changes in brain activity as measured by fMRI after a cognitive rehabilitation programme	After rehabilitation, patients significantly improved their performance on the backward version of the DST and on a composite score of the TMTA, TMTB, SDMT and DST. Patients showed an increase in their brain fMRI activity in two mostly cerebellar regions compared with controls. No correlations were observed between cognitive improvement and regional increases in brain activation
Shatil et al. [56]	Home-based computer-assisted training	59	Controlled, unrandomized	12 weeks	N-CPCC (A, LM)	Adherence to, and impact on cognitive performance of, training programme	Training group improved over control group in 3 memory-based cognitive abilities: general memory, visual working memory, verbal working memory. Cognitive training was also associated with increased naming speed, speed of information recall, focussed attention and visuomotor vigilance

Table 2 continued

Reference	Interventions	Number of patients treated with intervention	Design	Duration Tx	Key cognitive assessments Attention (A) Executive function (EF) Learning/memory (LM) Processing Speed (PS)	Primary endpoint	Results
Solari et al. [47]	Outpatient-based computer-assisted training	82	RCT	8 weeks	BRBNT(A, LM)	Increase of 20 % or more in at least 2 BRBNT test scores at 8 weeks	An improvement occurred in 45 % of study patients and 43 % of control patients at 8 weeks. The study treatment was better than control only on the word list generation test of the BRBNT
Sumowski et al. [57]	Comparison of 3 learning conditions: massed restudy, spaced restudy & spaced testing	32	Controlled, within-subject design	Not stated	VPA (LM)	Comparison of learning conditions	MS patients and healthy controls produced significantly better delayed recall for VPAs learned through spaced testing relative to massed or spaced restudy. The same pattern was observed for MS patients with objective memory impairment
Tesar et al. [40]	Outpatient-based computer-assisted training	19	Controlled, unrandomized	4 weeks	VLT, NVLT, DAUF, CKV, mosaic test from HAWIE-R (A, LM, EF, PS)	Neuropsychological performance after training	Improvements in executive function (CKV) and spatial-constructional abilities (HAWIE-R) most apparent in treatment group. No improvements in memory with training, however, verbal (VLT) and non-verbal (NVLT) improved significantly with treatment
Vogt et al. [58]	Home-based computer-assisted training	45	Controlled, unrandomized	4 weeks and 8 weeks	WMS-R, TAP, PASAT, BRBNT, FST, SDMT (A, LM, PS)	Improvement in working memory	Intense and distributed training equally effective. Significant improvements in fatigue, working memory and mental speed performances. No effects on short-term memory, quality of life or depression

A attention, *BCcogSEP* a French adaptation of the BRBNT (A, LM), *BRBNT* Brief Repeatable Battery of Neuropsychological Tests (A, LM), *BVMT-R* Brief Visual Spatial Memory Test—Revised (BVMT-R) (LM), *CFT* Delayed condition of the Rey-Osterrieth Complex Figure Test (LM), *CKV* computer-aided card sorting procedure (EF), *CVLT-II* California Verbal Learning Test-II (LM), *DAUF* Daueraufmerksamkeit (sustained attention) (A), *DB* double blind, *D-KEFS* Delis–Kaplan executive function system (EF), *DST* Digit Span Test (A, LM), *EF* executive function, *FST* Faces Symbol Test (PS), *HAWIE-R* Hamburg Wechsler Intelligence Test—revised version (PS), *HVLT-R* Hopkins Verbal Learning Test Revised (LM), *LM* learning/memory, *LNNB* Luria-Nebraska neuropsychological battery (LM), *MFQ* Memory Functioning Questionnaire (LM), *N-CPC* Neuropsychological Examination—CogniFit Personal Coach® (A, LM), *NVLT* Non-Verbal Learning Test (LM), *PASAT* paced auditory serial addition task (A, LM, PS), *PC* placebo controlled, *PS* processing speed, *RAVLT* Rey Auditory Visual Learning Test (LM), *RCT* randomized controlled trial, *RIS* ridiculously imaged story (LM), *RWT* Regensburger test of Word Fluency (EF), *SB* single blind, *SDMT* Symbol Digit Modalities Test (LM, PS), *SMT* story memory technique (LM), *SRT* Selective Reminding Test (LM), *TAP* Test Battery of Attention (A), *TAP* Test for Attentional Performance (A, PS), *TMTA* Trail Making Test A (A, PS), *TMTB* Trail Making Test B (A, PS), *VLMT* Verbal Learning and Memory Test (LM), *VLT* Verbal Learning Test (LM), *VPA* verbal paired associates (LM), *WAIS-R* Wechsler Adult Intelligence Scale—revised (A, PS), *WAIS-III* Wechsler Adult Intelligence Scale-III (A, PS), *WCST* Wisconsin Card Sorting Test (EF), *WMS-III* Wechsler Memory Scale-III (LM), *WMS-R* Wechsler Memory Scale—revised (LM), *ZNS-R* verbal repeating of numbers backwards (LM), *ZNS-V* verbal repeating of numbers forward (LM)

intervention alone (i.e., spaced learning). It demonstrated that the combined intervention achieved almost 50 % greater recall than the single technique alone [36]. A double-blind, placebo-controlled randomized clinical trial (RCT) designed to improve new learning by training use of context and imagery, to improve the strength of encoding, resulted in significantly improved recall on neuropsychological testing as well as self-report of everyday activities [37]. A recent study using this intervention showed increased activation in a variety of brain regions using functional MRI only in MS subjects who received training in context and imagery compared to placebo controls [38]. Taken together, these behavioural techniques, designed to improve information acquisition, have consistently resulted in significant improvement in learning and memory performance in persons with MS.

Non-specific interventions

In contrast to targeted interventions, several studies have employed "non-specific cognitive training" to improve learning and memory in MS patients. For example, Brenk et al. [39] claim that short-term, home-based, computer-delivered, non-specific training improved performance in several cognitive areas, including learning and memory. However, a non-treatment MS control group was not included, and having cognitive impairment was not an inclusion criterion in this study. In contrast, Tesar et al. [40] also utilized a computer-based non-specific training intervention and did not show improvement in memory performance.

Comparative studies

Several studies directly compared interventions targeting the treatment of learning and memory to non-specific interventions. In a single-blind RCT, Hildebrandt et al. [41] compared computer-based memory rehabilitation (home-based programme) with a non-intervention control group. The treatment group performed significantly better than the control group on verbal learning and delayed verbal recall as well as working memory performance. Mendozzi et al. [42] compared the efficacy and specificity of direct computer-assisted memory retraining with non-specific retraining and a no-training control group. Of the 11 tests administered before and after training, improvements were observed in seven tests for the specific memory retraining group, one for the non-specific retraining group, and none for the no-treatment control group. In contrast to these two RCTs, Jønsson et al. [25] compared a "specific cognitive treatment" and psychotherapy with "non-specific mental stimulation". The overall results showed no group differences in verbal and visual memory following treatment, but the treatment group did show improvements in visual memory at 6 months' follow-up, an overall less-than-impressive effect. Taken together, targeted interventions can result in significant improvement in learning and memory, but the nature of the "targeted" programme may be important. For instance, the results of specific memory training of Hildebrandt et al. [41] and Mendozzi et al. [42] were much more impressive than those of Jønsson et al. [25] whose programme involved training not only for memory, but concentration, visuospatial and orientation training.

Overall, despite the lack of well-designed studies and the multiple methodological limitations of those studies that have been performed, there appears to be moderate support for behavioural interventions for the treatment of impaired learning and memory in individuals with MS. Targeted interventions designed to specifically address problems in learning and memory are most beneficial compared with generalized cognitive interventions that have little support overall.

Processing speed

In contrast to work in learning and memory, there are no behavioural studies specifically designed to improve processing speed in persons with MS, despite the fact that it is the most prevalent problem in people with MS [43] and its putative importance in underlying the observed deficits in other domains of cognition. In contrast to MS, studies of the effects of nonpharmacological interventions on processing speed have been undertaken in other cognitive disorders such as Alzheimer's disease [44] and aging [45]. While the reason for the lack of behavioural intervention studies for processing speed in MS is unclear, there are a series of well-designed studies in aging populations which clearly show significant improvement in processing speed and everyday functional activity [45]. Such studies provide a framework from which studies in persons with MS can be investigated. The need for studies designed to improve processing speed in MS is clear and a fruitful area for future research.

Attention

Attention encompasses a variety of cognitive processes involved with the processing of information. Several studies have evaluated the effects of computerized attention training packages, which have the advantages of a being a reliably administered and reproducible intervention. One of the earliest studies [46] used a computerized assessment of the MS patients' attention skills at baseline. Only those with attention deficits on computer assessment were recruited to the study. A computerized training package was then selected for each patient to target one of their two weakest attention domains. The results showed

that specific training of individual impaired domains of attention (alertness, divided attention, vigilance, or selective attention) uniquely improved the target domain and not other aspects of attention [46]. A small randomized, controlled trial (RCT) [40] allocated half the MS patients to computer-based treatment targeting their two most impaired cognitive areas, being taught everyday compensation strategies, and self-control techniques. Patients also received out-patient multidisciplinary rehabilitation that did not address cognition, structured according to individual needs. The MS control group only received the multidisciplinary rehabilitation. The authors do not report results separately for those patients who received training in attention; however, overall the treated group did no better than the control group on tests of attention [40].

One of the largest and best designed studies of attention training in MS was a RCT in which MS patients were selected if they had both self-reported impairments in attention and impairments on neuropsychological tests [47]. Participants were randomized to either memory and attention computer retraining (treatment group) or to visual construction and visual-motor coordination computer training (control group). Both groups received 16 training sessions across 8 weeks. Approximately 45 % of patients improved in both groups, with no treatment effect on tests of attention [47].

More recently, Mattioli et al. [48] investigated the use of intensive computer-assisted training of attention, information processing and executive function in 20 MS patients with objectively confirmed deficits compared with 10 control patients and reported significant improvements in all three cognitive domains after 3 months of training carried out three times a week. Another small study [39] utilized non-specific cognitive training tasks on paper that were distributed weekly for 6 weeks for participants to complete at home several times a day, and compared MS patients with healthy control subjects. At baseline, the patients were significantly worse than the control group on some computer assessments of attentional skills (but not on memory or executive tests), and both groups showed significant improvements on some parts of the computerized assessment of attention. However, there was no group effect of treatment, with both groups improving to a similar extent.

Sastre-Garriga et al. [50] used functional magnetic resonance imaging (fMRI) in a cognitive rehabilitation study of 15 MS patients with impaired attention and/or memory compared with five healthy controls. After 5 weeks of computer-aided and non–computer-aided exercises designed to target attention and other frequently affected cognitive domains, significant improvements were observed on the backward version of the digit span test and on a composite score of neuropsychological outcomes. Patients also showed an increase in their brain fMRI activity compared with controls during rehabilitation, primarily in cerebellar brain regions. There was, however, no correlation observed between cognitive improvements and regional increases in brain activation.

Overall, the studies of moderately intensive attention training yielded contradictory results. In addition, access to and individual suitability of retraining programmes restricts their usefulness. It seems safe to conclude that they are unlikely to cause harm and, if sufficiently precisely targeted, may bring improvement.

Executive function

Executive function processes are involved in planning, problem solving, judgement, reasoning, and organisation. When asked to choose and complete several simple cognitive tasks from an array, to maximize points scored within a given time, MS patients do significantly worse than healthy controls [51]. Because of their superordinate, supervisory role, executive function processes are involved in many aspects of everyday life, especially those that are not routine. Executive function processes could in principle be improved by direct training and, because of their involvement in all novel and challenging tasks, could also be improved by cognitive training of other skills.

There are few retraining programmes that have specifically targeted executive function. Fink et al. [52] evaluated the efficacy of an executive function intervention programme in a double-blind, placebo-controlled, "pseudo-randomized" study involving 40 MS patients. Patients in the intervention group completed textbook exercises for executive functioning for 25–30 min per day, four times per week, with weekly feedback from a psychologist for 6 weeks. Executive function (and verbal learning) improved significantly in the intervention group compared with the placebo and untreated groups after 6 weeks.

Tesar et al. [40] did not separately report the outcomes of patients who received computer-based executive skills training, but overall the MS treated group showed improvement on a test of executive functioning, compared to the MS control group receiving non-specific rehabilitation, and the advantage was maintained at a 3-month follow up. It is worth noting that the general compensatory strategy package that all the treatment groups received included building up routines of behaviour and 'problem-solving and planning', which could explain the improvement in executive test scores [40]. Solari et al. [47] utilized a computer programme designed to train attention and memory skills. However, the one test that showed superior performance after training was a test of executive function. The authors suggest that this may be explicable by regression to the mean since the control arm was significantly better at

baseline than the intervention group [47]. Mattioli et al. [48] also investigated the use of intensive computer-assisted training on executive function and reported significant improvements in this domain after 3 months of training for three times a week.

Although there is no body of convincing evidence that training executive processes results in specific improvements in executive functions, the evidence hints at general cognitive training, inevitably involving executive processes, may improve them.

Symptomatic drug treatments

The two strategies for assessing the effects of medication to ameliorate MS-associated cognitive impairment have been either to add cognitive measures to the pivotal trials of DMTs for RRMS (based on the assumption that improving the disease course will help cognition) or to focus on symptomatic therapies that may enhance specific domains of cognitive functioning.

In contrast to the DMT clinical trials, studies applying the strategy of using cognitive enhancing medications in MS have specified inclusion criteria relative to cognitive performance and have focused on improving performance in specific cognitive domains. Given that the core neuropsychological deficits in MS are a slowing of information processing speed [43, 59], and defective anterograde episodic memory [30, 60], it is not surprising that efforts to treat MS-associated cognitive impairment with medication have targeted these domains. As shown in Table 3, treatment studies that have addressed cognition using neuropsychological tests as either primary or secondary outcomes show wide variability in the medications tested, research designs, and patient sample sizes.

Stimulants

Slowed mental processing often coexists with impairments in various aspects of complex information processing, such as divided attention, working memory, or in lay terms "multi-tasking". Multiple sclerosis patients seldom have problems allocating attention resources, but many suffer from marked limitations in attention capacity. It is therefore reasonable to consider central nervous system (CNS) stimulant medication for patients with this constellation of impairments. Negative results were reported by Geisler et al. [61] on the effects of amantadine, although there was a trend for benefit on the Symbol Digit Modalities Test (SDMT) [62], which may be the most sensitive [4] and reliable [63] of the tests available for MS research. Two studies reported positive effects following single-doses of the stimulants, methylphenidate [64] and L-amphetamine [65] when outcomes were administered shortly after administration. However, the L-amphetamine effects were not replicated in a continuous dosing, larger-sample study [66]. A re-examination of the effects of L-amphetamine on patients selected for memory impairment compared with those with normal memory performance showed more promising findings [67]. It was noted that some memory effects were seen in both previous studies [65, 66], especially on visual memory outcomes. Although the retrospective analysis proved positive, it is difficult to draw any firm conclusions from a subgroup analysis such as this. The effects of other stimulants such as lisdexamfetamine are currently under investigation.

Modafinil, an agent designed to improve excessive sleepiness, has been examined for its effects on aspects of cognitive dysfunction in MS. A recent double-blind, placebo-controlled RCT involving 121 patients with MS and fatigue found that modafinil had no convincing effects on fatigue or cognitive dysfunction [68]. In this study, there was a significant improvement the SDMT with modafinil but not in the PASAT, which actually improved significantly in the placebo group. In a double-blind, placebo-controlled RCT of 21 patients with MS by Lange et al. [69], a total of 18 patients (eight in the treatment arm) were tested using the D2 Alertness Test [70], which measures focusing of attention. While modafinil-treated patients showed relative improvement on the D2 test and subjectively reported fatigue, another larger study involving 115 patients did not replicate the benefit on fatigue [71], and the small sample size and potential for regression to the mean in the original study limit the interpretation of the findings. Another study with modafinil suggested a positive treatment effect on other neuropsychological tests, but this study was not placebo controlled [72]. Hence, the cognitive enhancing effects of modafinil on attention in MS patients remain uncertain.

Potassium channel blockers

In demyelinated axons, abnormal potassium currents contribute to impaired action potential duration and amplitude [73]. Potassium channel blockers could conceivably facilitate neuronal function in regions important for attention or processing efficiency. Pilot work with 3,4 diaminopyridine [74] and 4 aminopyridine [75, 76], which included some cognitive testing, showed largely negative results. However, the study methodologies were weak, and there is now renewed interest in this class of medications. Research with dalfampridine to improve cognitive function is also underway.

Acetylcholinesterase inhibitors

The neuropharmacology of episodic memory involves cholinergic transmission, and there is a vast literature on

Table 3 Summary of pharmacological treatments on cognitive function in MS

Reference	Drug	Number treated	Design	Duration	Primary outcome	Result
Smits et al. [80]	4 aminopyridine	20	DB, PC, RCT, CO	4 weeks	Cognitive function	−
Bever et al. [74]	3,4 diaminopyridine	28	DB, PC, RCT, CO	2 × 30 days	Leg strength	−
Rossini et al. [76]	4 aminopyridine	49	DB, PC, RCT, CO	6 months	Fatigue (NP Tests secondary)	−
Geisler et al. [61]	Amantadine or pemoline	16	DB, PC, RCT	6 weeks	Multiple NPTests	−
Wilken et al. [72]	Modafinil	23	Randomized, evaluator blind	4 months	Multiple NP Tests	+
Lange et al. [69]	Modafinil	8	DB, PC, RCT	8 weeks	D2 Alertness Test	+
Stankoff et al. [71]	Modafinil	59	DB, PC, RCT	5 weeks	MFIS cognitive dimension Trail making A & B	−
Möller et al. [68]	Modafinil	62	DB, PC, RCT	8 weeks	Symbol Digit Modalities Test Paced Auditory Serial Addition Test	−
Harel et al. [64]	Methylphenidate	14	DB, PC, RCT	Single dose	Paced Auditory Serial Addition Test	+
Benedict et al. [65]	*l*-amphetamine	19	Counterbalanced, within-subject	4× single doses	Multiple NP Tests	+
Morrow et al. [66]	*l*-amphetamine	108	DB, PC, RCT	4 weeks	Symbol Digit Modalities Test	−
Sumowki et al. [67] (re-analysis of 66)	*l*-amphetamine	108	DB, PC, RCT	4 weeks	California Verbal Learning Test 2; Brief Visuospatial Memory Test Revised	+
Krupp et al. [77]	Donepezil	35	DB, PC, RCT	24 weeks	Selective Reminding Test; Self Report	+
Krupp et al. [78]	Donepezil	61	DB, PC, RCT	24 weeks	Selective Reminding Test; Self Report	−
Shaygannejad et al. [79]	Rivastigmine	30	DB, PC, RCT	12 weeks	Wechsler Memory Scale	−
Lovera et al. [81]	Memantine	58	DB, PC, RCT	16 weeks	Paced Auditory Serial Addition Test and Selective Reminding Test	−

Number treated is the number who received the active drug

−, Negative; +, positive

CO crossover, *DB* double blind, *MFIS* Modified Fatigue Impact Scale, *NP* neuropsychological, *PC* placebo controlled, *RCT* randomized controlled trial

acetylcholinesterase inhibitors and improved memory in Alzheimers' disease. Krupp and colleagues [77] reported that donepezil improves cognitive performance and subjective ratings of memory over 24 weeks. However, the sample was small and there were a few noteworthy methodological shortcomings in the study (e.g., treatment groups not matched on disease course, lack of independent clinician rates) leading the investigators to conduct a larger, better controlled, multicentre, replication study [78]. Unfortunately, the results of this study were negative. The positive donepezil findings were not replicated in another study examining the effects of a similar acetylcholinesterase inhibitor, rivastigmine [79].

Overall, these studies suggest only possible benefits of symptomatic drug treatments on cognitive impairment in MS. Some positive results have been reported, but these have often been followed by replication failure. There are many challenges associated with clinical trial design. Methodological issues relevant to all symptomatic therapy trials include variability in the degree of impairment required for inclusion, optimizing primary and secondary outcomes, determining realistic effect sizes and hence sample size, and standardizing treatment duration. Requiring too cognitively impaired patients could adversely affect recruitment. However, enrolling patients without sufficient impairment might obscure an otherwise positive treatment effect [67]. Several studies with improved clinical designs and potentially more effective treatments are underway and could lead to more promising therapeutic option.

Disease modifying treatments

The DMTs have the potential to positively influence the cognitive outcome of the patients by acting on some key pathogenic mechanisms of MS-related cognitive impairment. In particular, all the approved DMTs reduce the accumulation of irreversible nervous damage, as shown by the positive effects on T2 and T1 lesion load, and some of them have also effects on the brain atrophy [82]. The

decrease of the ongoing inflammatory activity may also contribute to better cognitive performances. Moreover, moreover, it has been speculated that some of the DMTs may also exert a direct neuroprotective/neurotrophic effect [82].

However, evidence in the field is limited. Interpretation of available data is complicated by issues largely related to methodological problems of study design and execution (Table 1). In DMT clinical trials, cognitive assessment is often limited to just the PASAT, administered in the context of the MSFC. In most of the published studies, the cognitive outcome represents a secondary endpoint and therefore patient inclusion criteria and sample size calculations may not be appropriate to assess cognitive outcomes.

Relapsing-remitting MS

Interferon (IFN) β can have an indirect effect on cognition since it reduces immune mediated inflammation and demyelinization thus preserving function. One of the earliest RCTs [83] evaluated the effects on cognition of low-dose IFN β-1b (50 mg, $n = 8$), high dose IFN β-1b (250 mg, $n = 9$) and placebo ($n = 13$) in a small group of 30 relapsing–remitting MS (RRMS) patients from one centre. A focused neuropsychological assessment was conducted between the second and fourth years, and therefore baseline neuropsychological status was not known. High-dose IFN β-1b therapy was associated with better performance on only one test of 13 examined, a measure of delayed visual recall, although group differences in visual memory were also observed at baseline. This finding was related to a reduced MRI lesion burden ($r = 0.43$, $p = 0.03$), although the main effect on the test remained after controlling for MRI changes. In another, small, open-label study [84] of IFN β-1b 250 mg in RRMS patients ($n = 46$), a benefit was suggested in the treated group ($n = 23$, EDSS <5.5) on measures of attention, visuospatial learning and recall after 1 year of treatment.

The effects of intramuscular (IM) IFN β-1a on cognition were evaluated as part of a multicentre, phase III RCT conducted in the USA [85]. A comprehensive (at baseline and week 104) and also a brief neuropsychological battery (every 6 months) were administered to a large subgroup of 166 patients with RRMS. After adjusting for baseline performance, IFN β-1a had a significant beneficial effect on tests of information processing, learning/memory, as well as a positive trend on tests of visuospatial abilities and problem solving. Interestingly, the brief battery revealed a clear practise effect in both arms, with a significant difference favouring patients on active treatment. Moreover, IFN β-1a significantly increased the time to sustained deterioration in the PASAT processing rate. In interpreting the study's findings, a few issues should be considered. Data from only the 60 % of the baseline group were included in the analysis of change over 2 years, a few outcome measures were determined post hoc, and it is not specified how statistically significant effects were taken into account in the analysis. It is also difficult to extrapolate the study findings to everyday life due to the extremely extensive and lengthy neuropsychological assessment, which took approximately 3 h.

The effects IFN β-1a on cognitive function in early, mildly disabled RRMS patients were also addressed in a large, multicentre, post-marketing study [86]. The COGIMUS study [86] was a prospective cohort study including 459 early RRMS patients treated with IFN β-1a s.c. 22 or 44 mcg. The patients were assessed through the BRNB and the Stroop test at baseline and at 12 monthly intervals for 3 years. At baseline there were no differences between the two dose groups in demographic and clinical characteristics or in the proportions of patients impaired on more than three tests. Data on cognitive function at 3 years were available for 318 patients of the original cohort (72.1 %; 22 mcg, $n = 153$; 44 mcg, $n = 165$) and showed a 32 % risk reduction of developing impairment in three or more tests for patients on high dose compared with those on the lower dose.

The effect of glatiramer acetate (GA) on cognition was also evaluated as part of a phase III US RCT [87]. Two hundred and forty-eight patients were tested at baseline and after 1–2 years using the BRNB. At baseline, neuropsychological test performance was similar in both arms, with mean scores falling within the range of normal performance with the exception of the word list generation test. Both arms showed a significant improvement in cognitive performance because of the practise effect. No differences were detected between the treatment groups for any of the neuropsychological tests. No significant interactions were observed between the effects of treatment and either time or baseline level of impairment. Both the low level of baseline cognitive abnormalities and the strong practise effects may explain the absence of an effect of GA on cognitive function despite the fact that the trial showed a significant effect on disease activity. A subgroup of 153 patients (65 %) was re-examined 10 years after inclusion into the clinical trial [88]. Attention tests and the PASAT showed a significant decline in patients who originally received either GA or placebo. However, other tests had not deteriorated significantly, despite the long-term follow-up. The Z score of the BRNB revealed a decline of more than 0.5 of a standard deviation of the mean in only 19 % of participants. There were no differences between patients originally in the placebo arm or the GA arm.

In the assessment of the effects of natalizumab on cognitive functioning in the AFFIRM and SENTINEL phase III three clinical trials of RRMS patients [89, 90] the

PASAT was the only instrument used. Thus far, no results from this assessment have been published. The impact of natalizumab on cognitive functioning was also investigated in a small post-marketing study of RRMS patients ($n = 17$) [91] and the results suggested natalizumab had a positive effect on neuropsychological performance.

In a 24 month, RCT of oral fingolimod compared with placebo in patients with RMRS a significant effect on the MSFC was observed in both active groups compared with placebo [92] although no data for the PASAT component have been published yet.

Secondary progressive MS

Published evidence dealing with secondary progressive MS (SPMS) are limited to one study. The IMPACT trial [93], which was performed to determine whether IM IFN β-1a reduced disability progression in 217 secondary progressive MS (SPMS) patients (EDSS between 3.5 and 6.5), demonstrated an overall MSFC benefit driven predominantly by the 9HPT and, to a lesser extent, the PASAT3 ($p = 0.061$). No results have been published on cognitive function form the other three large trials of IFN β-1b [93, 94] or subcutaneous IFN β-1a [95].

Primary progressive MS

Trials in primary progressive MS have failed to demonstrate any benefit on cognitive performance. No cognitive assessments were performed in the pilot trial of IM IFN β-1a. [96]. In one study of IFN β-1b, 73 patients were assessed with the BRNB at baseline, at 12 months and at 24 months [97]. No significant differences between IFN β-1b and placebo groups were observed at any time point in any of the cognitive domains tested. A total of 943 patients with primary progressive multiple sclerosis were randomized to GA or placebo in a 3-year, double-blind RCT [98]. The trial was stopped after an interim analysis by an independent data safety monitoring board indicated no discernible treatment effect on the primary outcome. Although the MSFC was performed no results from the PASAT are reported.

Clinically isolated syndromes

The effect of IFN β-1b on cognition in patients with clinically isolated syndromes (CIS) has been assessed in the phase III, BENEFIT RCT [99] and its extension at 3 [100] and 5 years [101]. The mean MSFC score improved over the 5 years in most patients, and there was no significant difference between those who had received IFN β-1b during the initial 2-year trial and those who received it only during the extension trial (delayed treatment) ($p = 0.608$). Improvement of the overall MSFC score was largely due to improvement in the PASAT, and this was more pronounced in the early treatment group compared with the delayed treatment group; the difference between these groups increased during the course of the study until year 5 (year 3, $p = 0.064$; year 5, $p = 0.005$).

In summary, the effect of DMTs on cognition has not been adequately studied and methodological limitations render it difficult to draw any firm conclusions. Nevertheless, most of the studies with DMTs have shown weak positive effects on cognition. On the basis of studies focusing on CIS and early RRMS patients, it is hypothesized that early treatment will help preserve intact cognitive functioning and delay the development of cognitive impairment. Studies to test this hypothesis are needed.

Table 4 Challenges and recommendations

Cognitive impairment is common in MS but under-recognized, reliable screeningtools are needed; cognitive dysfunction should be incorporated intocomprehensive management
Cognitive impairment is not addressed in defining current MS subtypes, futureclassifications schemes e.g. benign MS, should consider cognitive status
Cognitive rehabilitation is incompletely studied, correlations of changes on neuroimaging with successful cognitive rehabilitation should spur future research
Cognitive rehabilitative research has methodologic limitations, targeted interventions to improve acquisition in verbal memory and learning show promise but require further study
Treatment effects for acetylcholinesterase inhibitors and central nervous system stimulants are inconsistent, improved trial design, e.g., enrolling subjects with greater impairments, using realistic estimates of effect sizes, and optimizing outcomes
While promising, DMT effects on cognition have been inconsistent, improved trial design is needed, e.g., "enriching" enrolment with cognitively impaired participants, conducting subgroup analyses, or conducting separate, appropriately powered and designed trials with cognition as a primary outcome
Interpretation of cognitive outcomes based on current evidence is difficult, cognitive outcomes must be sensitive and reliable but also correlate with clinically meaningful change

Summary

Cognitive impairment in MS is important and is associated with meaningful functional impairment and adverse effects on quality of life. The fact that cognitive impairment and associated disability can predate the onset of physical disability amplifies the importance of managing this aspect of the disease and maximizing clinical outcomes. Management of cognitive impairment may encompass slowing of further deterioration of impairment or improvement in already impaired cognition. Currently, data linking interventions to either slow cognitive decline or improve

already impaired cognitive function are limited and at times, have yield inconsistent results. Further, linking any changes as a result of specific interventions with actual functional outcomes, or even surrogate proxy outcome measures, is currently a theoretical construct and requires validation using appropriate research studies and endpoints. Brief assessment of cognitive impairment should be incorporated in future clinical trials. Recently, based on literature review and expert opinion, a Brief International Cognitive Assessment for MS has been proposed (BICAMS) which focuses on measures of processing speed, visual-spatial and verbal memory; validation studies of this instrument are currently ongoing in different countries [102]. Based on the findings described above we have proposed a summary of current challenges and recommendations that we hope can inform and guide the clinical and research communities (Table 4).

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