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Mitolo, M., Venneri, A., Wilkinson, I.D. et al. (1 more author) (2015) Cognitive rehabilitation in multiple sclerosis: A systematic review. Journal of the Neurological Sciences, 354 (1-2). 1 - 9. ISSN 0022-510X

https://doi.org/10.1016/j.jns.2015.05.004

Cognitive Rehabilitation in Multiple Sclerosis: a systematic review

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Acknowledgment: This work has been supported by an Educational Grant from the Academic Department of Neurology, Royal Hallamshire Hospital, Sheffield

Key Words: Cognitive rehabilitation, Multiple Sclerosis, fMRI, attention, working memory, quality of life

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Abstract

Background: Cognitive impairment is a common clinical feature of Multiple Sclerosis (MS) at both the earlier and later stages of the disease, and has a significant impact on patients' functional status and quality of life. The need to address this deficit should be taken into account in clinical practice and research studies. **Objective:** To conduct an updated systematic review of all published studies of cognitive rehabilitation interventions in people with MS, including studies with methodological shortcomings, to highlight major strengths and weaknesses in the field and provide directions for future research. **Search methods:** We searched electronic databases (PubMed and Web of Science) for articles published in English up until January 2014. The reference lists of all identified articles were also searched to complete the initial list of references. **Data Extraction:** Articles were categorized into outcome measures: cognition, imaging, mood, fatigue, quality of life and self-perceived cognitive deficits. All articles were reviewed independently and assessed according to predetermined criteria. **Results:** A total of 33 studies met the inclusion criteria of which 4 were of level II-1 and none was Level I. Although the majority of these studies reported some improvements in cognitive abilities (N=31), the evidence which has been reported in the literature so far remains inconclusive and no definite conclusions can be drawn about the effect of different types of methodology on cognitive rehabilitation outcomes (recommendation C). **Conclusions:** This review reports conflicting findings about the effectiveness of various heterogeneous forms of cognitive rehabilitation techniques used in patients with MS. Studies with more rigorous methodology are therefore needed to clarify which form of cognitive rehabilitation may lead to greater clinical improvement.

Introduction

Multiple Sclerosis (MS) is a chronic immune mediated disease of the central nervous system (CNS) which is characterised by the presence of widespread lesions affecting the brain, spinal cord and optic nerves. Inflammatory demyelination has traditionally been thought to be the main disease process in MS; however, axonal transection is increasingly being documented to occur early in the disease and to result in permanent disability.[1] Because of the widespread nature of these lesions within the CNS, MS results in a broad range of symptoms, which include visual, bulbar, sensory, motor, sphincter, cognitive, and neuropsychiatric,[2, 3] variable clinical presentations and disease course.[4]

Cognitive impairment is a common clinical feature of MS at both the earlier and later stages of the disease,[5,6] with prevalence rates ranging from 43% to 70%.[7,8] MS has been shown to affect negatively various aspects of cognitive function including those associated with attention, [9,10] efficiency of information processing,[9,11] executive function,[12] processing speed,[13] new learning and memory.[8,13] Cognitive dysfunction is closely associated with functional status in MS. Rao et al[8] found that individuals with MS who were cognitively impaired participated in fewer social and vocational activities, were less likely to be employed, had greater difficulties in doing routine household tasks, and were more vulnerable to psychiatric illness than individuals with a purely physical disability. Functional impairments also include difficulty in shopping independently, completing housework, cooking, driving, and using public transport.[14] Such changes to the patients' personal, occupational, and social lives have a deleterious impact on their quality of life (QoL). For this reason, developing therapeutic measures to alleviate such deficits should take precedence in MS research. So far, few studies have assessed the efficacy of cognitive rehabilitation treatments relating to cognitive deficits in MS, and many authors have highlighted the need for additional effective techniques in this illness.[15] Cognitive rehabilitation has the aim to reduce cognitive deficits and to improve patients' awareness and the ability to take their cognitive impairments into account in daily living activities; it also has the aim to promote neurobiological changes. Although this research is still in its infancy, there have been some well-designed studies of cognitive rehabilitation for patients with MS that can provide a foundation from which to advance the field. Historically, most of the intervention implemented for use with MS patients involved learning and memory-based interventions, [15] but recently the focus has moved to other domains such as executive function and attention [21,23,30,31,32,47,48,49], since these are the cognitive functions that have been shown to be most affected by MS. Interventions based on these functions appear to lead to more consistent results. This element of novelty, however, requires further investigations. In addition, a few recent studies have explored the subtle active processes of neuroplasticity that might be driven by these cognitive treatments. These new aspects have not been analyzed in previous published reviews.[15,16,17] This study aimed to assemble a systematic review of the old and the more recent cognitive rehabilitation interventions in MS, including studies that have looked at neuroimaging as an outcome measure, describing the current status of the field, and providing directions for future research.

Methods

We carried out a systematic review of research studies that have focused on cognitive rehabilitation interventions for people with MS. The aim was to offer an overview of all published cognitive rehabilitation studies, and provide the reader with an objective assessment of the strengths and limitations of the methods and approaches used in the rehabilitation of cognitive symptoms in MS. We elected not to follow the strict inclusion criteria adopted by the Cochrane Collaboration,[16] because we wanted to provide a systematic and comprehensive overview of this research field, with a view of helping clinicians and researchers detect the strengths and weaknesses of different forms of intervention. For this reason we included pilot studies which would not meet the strict inclusion criteria of a Cochrane review, but might provide preliminary findings which could make a valuable contribution to this still evolving field. In addition, unlike previous reviews[15,16,17] we also included studies that have looked at neuroimaging as an outcome measure to assess the neurobiological changes consequent to cognitive intervention.

An online literature search of PubMed and Web of Science using the terms cognitive rehabilitation, cognitive stimulation and cognitive training combined with multiple sclerosis and each of these cognitive domains attention, executive function, memory, learning, working memory, problem solving and language was undertaken for all articles published up until January 2014 (see Appendix). The reference lists from all identified articles were searched to complete the initial list of references. The abstracts or complete reports were reviewed to eliminate articles according to the following exclusion criteria: (1) not cognitive intervention, (2) theoretical article, (3) review articles, (4) studies that included people with other neurological conditions, (5) studies of paediatric participants, (6) non-peer reviewed articles, (7) non-English language articles, (8) case report, and (9) results of cognitive outcomes not reported. A total of 33 articles underwent a full review and classification with the aim of (1) characterizing important elements of each study, (2) identifying the cognitive domain(s) targeted, and (3) describing the intervention, results, outcome measures and the duration and frequency of each study. The quality of the scientific evidence provided by these articles was classified and an overall recommendation for the efficacy of this intervention was provided based on the US Preventive Service Task Force guidelines.[18] (Table 1).

- Please insert Table 1 about here –

Results

The literature search process is described in Figure 1. Overall, we reviewed 904 studies, including overlapping search results from the two different databases. Duplicate publications were excluded and 351 full copies were retrieved and assessed for eligibility. On initial review of the citations, 36 articles were identified as research intervention studies of cognitive rehabilitation in MS. A closer inspection of the full articles showed that 3 of them met the afore-mentioned exclusion criteria and were therefore excluded. Of the 3 eliminated articles, 2 aimed to increase participants' knowledge of cognitive impairments and increase levels of self-efficacy to manage cognitive difficulties without any investigation of specific cognitive outcomes; the other article described the increase of functional independence and QoL after a rehabilitation programme that included physiotherapy, occupational therapy and social work (non cognitive intervention).

- Please insert Figure 1 about here -

The 33 studies included in this review were published between 1993 and 2014. Cognitive tests, imaging techniques, self-perceived cognitive deficits, mood, quality of life and fatigue questionnaires were used as outcome measures. Detailed information are given in Table 1 and described below.

Cognition

All studies focused on cognitive outcomes. Although there was significant diversity in the cognitive domain targeted and the duration of each intervention, the majority of these studies reported some improvements (N=31). Almost half of the studies have been carried out with patients with mixed types of MS (relapsing-remitting, primary progressive, secondary progressive) (N=15); fourteen studies included only relapsing-remitting MS patients (N=14); finally four studies did not specify the typology of MS patients included (N=4).

Cognitive Training Parameters

The length of all cognitive rehabilitation treatments ranged from one day to 6 months, the number of intervention sessions varied from 1 to 36 and the frequency from twice per month to five times per week. One third of the studies (N=11) also tested the persistence of the effects of cognitive rehabilitation at follow-up. In addition to the heterogeneity between the studies, within-study variation was also noted (e.g. Jonsson et al[19] tailored the intervention according to each patient's individual symptoms, therefore making direct comparison of the interventions not possible). Furthermore in other studies cognitive rehabilitation was compared to other active treatments (e.g. specific versus unspecific cognitive rehabilitation), potentially masking beneficial effects, or to similar treatment with different time schedule (high vs. low intensity). For instance, in the study by Vogt et al[20], the authors compared two different cognitive rehabilitation schedules, a high intensity versus distributed rehabilitation. Patients in the high intensity treatment received a 45-minute rehabilitation session 4 times per week for 4 weeks; patients in the distributed treatment underwent a 45-minute rehabilitation session twice a week for 8 weeks. The rehabilitation programme was a specific working memory treatment consisting of three modules: City Map to train spatial orientation; Find Pairs to train the updating function of working memory, and Memorize Numbers to train short-term memory while performing an arithmetic distraction task. The results showed that cognitive rehabilitation significantly improved working memory and mental speed performance. No difference was found between the high intensity and the distributed groups. The authors concluded that cognitive rehabilitation per se led to improvements independently of the time schedule. However, one year later Mattioli et al[21] highlighted the importance of the time schedule (high frequency and long duration of treatment) in facilitating learning strategies during an intensive cognitive rehabilitation programme. No definite conclusions can therefore be drawn about the effect of treatment intensity on cognitive rehabilitation outcomes.

Domains of Cognition

Another important aspect to be considered in the analysis of cognitive outcomes, is the typology of cognitive rehabilitation and the cognitive domain targeted. Of the 33 studies analysed in this review, the majority focused on one or two specific cognitive domains (N=23) and the remaining used a non-specific form of cognitive rehabilitation (N=10). The oldest studies focused on improvements of memory and new learning. The most recent publications focused on forms of cognitive rehabilitation targeted to improve other abilities including executive function, attention and processing speed. This change in approach seems to have yielded more beneficial effects, but findings are still preliminary. Brissart et al[22] compared the efficacy of a general cognitive intervention which included "multifunction" exercises with a control intervention based only on general discussion. All patients underwent a neuropsychological assessment before and after treatment. The results showed a small benefit of the cognitive programme mainly in memory and verbal fluency, but some improvements were also found in the control group. The authors concluded that the weak effect of this intervention could relate to the "non-specificity" of the cognitive rehabilitation. More studies were thought to be needed to elaborate the effect of a more specific and focused cognitive programme. Mattioli et al[21] demonstrated the efficacy of an intensive cognitive rehabilitation program, by showing improved performance in tests of information processing, attention and decision making as well as over depression scores. The difference between these results and those from previous studies could be explained by the difference in the methodological approach: the treatment was very specific for divided attention, information processing and executive functions, and the frequency and duration was intense. Furthermore, Fink et al[23] showed that their specific executive function intervention programme was effective in treating some aspects of executive disturbance in MS. This treatment effect was stable over 1 year illustrating that their findings were lasting and not just transitory. However, Solari et al[24] reported that an isolated computer-assisted memory and attention rehabilitation was no better than a non-specific intervention in improving these functions. All of the above evidence suggests that no definite conclusions can be drawn about the effect of these factors on rehabilitation outcomes. Larger studies with bigger samples and longer follow-up periods are needed to generalize these results and to verify whether the effects of these cognitive rehabilitation treatment persist over time.

Imaging

Although a large number of studies (n = 33) have investigated the role of cognitive rehabilitation in the management of cognitive dysfunction in MS patients, only a few recent ones (n = 8) have explored the role of neuroplasticity that might be driven by these cognitive rehabilitation treatments. The majority of these studies (N=5) used active fMRI imaging paradigms even if they are markedly influenced by individual task performance; more recently three studies [31,32,48] have used a resting-state fMRI approach to explore changes in functional connectivity. One of the first task-based studies was carried out by Sastre-Garriga et al[25] to investigate the effect on brain activity of a cognitive rehabilitation programme during the execution of the PASAT test. After rehabilitation, patients showed increased brain fMRI response only in the cerebellum when compared with healthy subjects. Few years later

Chiaravallotti et al[26] explored changes in cerebral activation during the execution of a word learning and a word recognition task after a behavioural memory intervention, the modified Story Memory Technique. Greater activation was evident in the treatment group during performance of a memory task within a widespread cortical network involving frontal and temporal regions; no significant changes were found in the cerebellum. This study was the first to demonstrate a significant change in cerebral activation resulting from a behavioural memory intervention. The main findings of these studies was the induction of a change in brain activation, in frontal and temporal regions, as well as in cerebellum, through cognitive rehabilitation. This increase in brain activation was thought to help compensate for the cognitive deficits seen in these patients[27,28] since failure of such mechanisms as a result of disease damage progressively leads to cognitive deterioration.[29] Furthermore, Cerasa et al[30] focused on attention treatment and assessed its fMRI correlates. The results showed beneficial effects in MS patients both at a phenotypic level (improvement in specific cognitive functions) and at an intermediate phenotypic level (functional reorganization), demonstrating that an intensive computer-based programme specifically tailored for impaired attention abilities yields adaptive neural plasticity of the associated neural network. In particular, the authors suggested that over-activity of the posterior cerebellar lobule and superior parietal cortex might represent a new endophenotype for future cognitive rehabilitative approaches. Overall this study demonstrated that an intensive programme of stimulation, in particular rehabilitation of attention abilities, improved some aspects of cognitive functioning and also affected neural plasticity. This hypothesis has also been recently tested in another fMRI study,[31] where the authors demonstrated that a cognitive rehabilitation programme focused on attention and information processing yielded enhanced neural activity in the parieto-prefrontal regions during the execution of a Stroop Test. Because active fMRI imaging paradigms are markedly influenced by individual task performance, they also performed resting-state functional MR imaging to control for this issue. The results demonstrated a significant treatment effect in several cognitive-related resting-state networks (e.g. anterior cingulate cortex, prefrontal cortex and posterior cingulate cortex), which showed an increase (or stability) of activity over time in the treatment group but a decrease in the control group. Recently the same research group[32] investigated whether the benefits of this cognitive rehabilitation persisted six months after the end of treatment. Results showed that changes in resting-state functional connectivity of cognitive-related networks help to explain the persistence of the effects of cognitive rehabilitation at follow-up. These preliminary studies highlight the important role of neuroimaging techniques in the assessment of cognitive rehabilitation; however further investigations with bigger sample size are needed to confirm the present findings and to improve rehabilitation programmes.

Mood, Fatigue, Quality of Life (QoL) and self-perceived cognitive deficits

It is well established that the cognitive deficits in MS patients have a negative effect on their personal, occupational and social lives.[33] In the majority of the cognitive rehabilitation studies, outcomes were also evaluated with self rating mood questionnaires (n = 19), questionnaires on fatigue (n = 10), QoL (n = 10) and subjectively experienced effects of cognitive problems (n = 4). The studies provided evidence about the positive effect of cognitive rehabilitation on mood (N=4), fatigue (N=2), QoL (N=4) and self-report outcomes (N=2). Vogt et al[20] suggested that the most important finding in their study with regard to treatment effects was a significant decrease in self-reported fatigue in both groups. However, no improvements in depression were found in the treatment groups and self-reported quality of life revealed no significant treatment effect. Rosti-Otajarvi et al[34] reported that their intervention resulted in fewer fatigue symptoms and less depressive mood in the intervention group. Different findings have been reported by other authors: Tesar et al[35] showed no significant difference in the level of fatigue between the treatment group and controls; Shatil et al[36] reported no significant correlations between change in subjective fatigue and change in cognitive performance in the treatment group; Lincoln et al[37] showed no effect of the intervention on mood, quality of life, subjective cognitive impairment or independence; Hildebrandt et al[38] showed no effect on quality of life or fatigue after cognitive rehabilitation and Plohmann et al[39] reported less attention related problems in everyday situations. These contradictory results could be related to a number of factors including the difference in the typology of the cognitive rehabilitation treatment (less or more related to daily living situations); the different inclusion and exclusion criteria used to select the sample (some studies included patients with a perceived moderate level of cognitive difficulty rather than an objective performance measure of cognitive impairment on neuropsychological tests); the choice of outcome measures, including measures of quality of life, that may take longer to change. Future research should compare different types of methodology, taking all these aspects into account.

Conclusions and future directions

This review aimed to evaluate the effects of neuropsychological rehabilitation in MS including old and new studies, describe the current status of the field, and provide direction for ongoing MS research. Our investigation showed that the oldest studies focused on rehabilitation of memory and new learning, but most recently the focus of interventions has moved to cognitive rehabilitation treatment targeted to improve other abilities such as executive function, attention and processing speed and these latter studies have led to more consistent findings and better treatment effects.

The potential for individuals to improve their own cognitive brain health by habitually exercising high-order mental strategies is intriguing and is just beginning to be more fully exploited. It has been demonstrated that complex mental activity induces improvements in cognition and brain function, but it is not clear to what extent the brain is capable of such plasticity.[40] Overall, our review identified conflicting findings about the effectiveness of the various cognitive rehabilitation techniques and therefore no definite conclusions can be drawn about their effect on cognition, mood, quality of life, fatigue and self-efficacy. The lack of conclusive evidence in these studies may be due to the heterogeneous rehabilitative approaches, methodological weaknesses and the small sample size which characterise the majority of the studies identified by the search. Another important aspect is also the selection of outcome measures which might have not been sufficiently sensitive to detect all possible effects. Possible positive effects might have occurred, but if outcome measures are not appropriate to detect those changes then these remain undocumented leading to incorrect conclusions.

In a detailed theoretical framework, Lövdén et al[41] refined the notion of adult cognitive plasticity. The authors suggested that cognitive plasticity is driven by a prolonged mismatch between functional organismic supplies and environmental demands and denotes the brain's capacity for anatomically implementing reactive changes in behavioural flexibility.

On this basis, it was suggested that cognitive interventions attempting to improve processing efficiency should administer practice tasks that tap one central cognitive process.[41] Targeting a specific cognitive process, rather than tasks that involve several processes, should maximize the duration and magnitude of a supply demand mismatch (given limited amount of time and effort to spend). Rehabilitation of cognitive processes that play central roles in the cognitive architecture and in brain areas that are active across a wide range of tasks[42] will maximize the applicability of the intervention effect (i.e. generality). Cognitive (executive) control processes and working memory are perhaps the most prominent abilities in this regard.[43]

In this review, the most recent studies that focused their intervention on a limited number of domains, specifically executive functions, attention and processing speed, seem to provide convincing evidence of a beneficial effect, however this growing pattern of results is still preliminary. It also remains open to debate whether the use of specific vs non-specific forms of intervention in which a plethora of cognitive functions are rehabilitated is more effective. Most of the studies which reported successful results of cognitive rehabilitation in MS prior to 2008 involved learning and memory-based interventions. Recently there has been this change of focus to other abilities (e.g. executive functions) and this seems to have led to more positive results, but the evidence is insufficient and further investigations are required.

In the review process we attempted to reduce bias by performing a systematic search of all available study in the field. However we cannot rule out the possibility that some studies have been missed. The possibility of a possible publication bias cannot be ruled out since positive effects are more likely to be published while relevant studies with unclear or negative results may have remained unpublished. Furthermore this review present other limitations, such as the exclusion of studies with mixed aetiology samples, the exclusion of any other internet source (e.g. dissertation databases) during the articles selection and the restriction to studies written in English,

The study of cognitive rehabilitation has recently moved towards the use of models describing changes in brain structure and function that result from neuroplastic effects.[44] Study designs incorporating neuroimaging measurements and experimental hypotheses linking cognitive exercises with specific mechanisms of neural modifications should be taken into account. So far, only a few studies based on neuroimaging measures have been published.

These were explorative and have described remarkable changes in brain structure and/or function. However, they have not detailed the exact mechanism by which the repeated administration of exercises would influence the neural substrate by inducing specific expected changes.

Some preliminary studies have reported findings suggesting that it is possible to induce an increase in brain activation through cognitive rehabilitation; however, the role of fMRI in the assessment of cognitive rehabilitation schemes warrants further investigation. Well-designed studies with MS patients, rehabilitated with different techniques are needed to elucidate the nature of the functional correlates of cognitive improvement. Future studies should also include the appropriate measurement of benefits triggered by the cognitive rehabilitation treatment, using the most appropriate neuroimaging techniques, in association with classical testing of cognitive function and, possibly, daily-life functionality. Finally, on the basis of several studies we can conclude that there is controversial evidence related to the impact of cognitive rehabilitation intervention on patients' mood, quality of life and self-perceived cognitive deficits. Appropriate outcome measures should be used to explore short-term changes (e.g. the use of new cognitive strategies, changes in level of productivity, or measures of subjective well-being) and not only measures such as quality of life that may take longer periods of intervention to result in measurable change.

To make further progress in the field of cognitive rehabilitation in MS, future studies should take into account the above mentioned observations as well as the need to focus on methods which are potentially of paramount importance from the patients' perspective: being able to detect possible effects of interventions on their everyday life.

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Figure 1 Flow chart of the study selection process

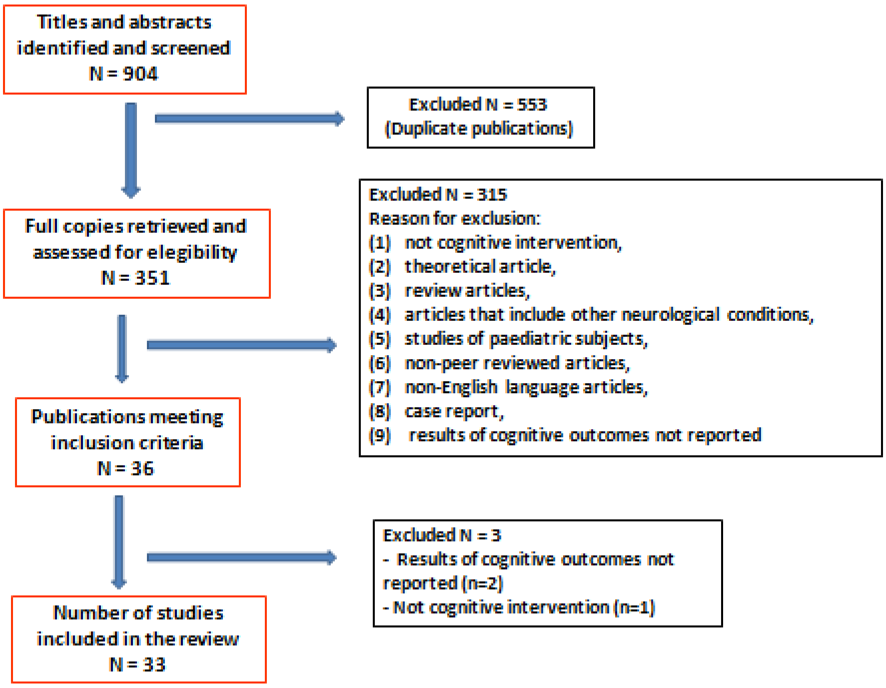

Table 1 Summary Table of Reviewed Articles

Authors	Cognitive Domain Targeted	Type of MS	Number of Participants	Technique/ Design / Evidence***	Outcome measure	Duration/ Frequency/ P value	Results
Brenk et al[45]	Non-specific/ multiple skills	Relapsing remitting	Experimental group: 27 Control group: 14	Short-term non-specific (Pre-Post) Level II-3	Cognition, mood and QoL	6 weeks/ Five times per week No follow up P range 0.05-0.001	Treatment group significantly improved in several skills (e.g. visuo-constructive and figural long-term memory).Improvements were also observed in mood and quality of life
Vogt et al[20]	Working memory	Relapsing remitting Secondary progressive Primary progressive	Experimental group 1: 15 Experimental group 2: 15 Control group: 15	Computer-assisted program (Pre-Post) Level II-3	Cognition, mood, fatigue and QoL	Group 1: 4 weeks/ 4 times per week Group 2: 8 weeks/ 2 times. No follow up P range 0.05-0.001	Intense and distributed training equally improved fatigue symptoms, working memory and mental speed performance
Shatil et al[36]	Non-specific/ multiple skills	Relapsing remitting Relapsing progressive	Experimental group: 22 Control group: 24	Computer-assisted program (Pre-Post) Level II-3	Cognition, mood and fatigue	12 week/ Three days per week No follow up P range 0.05-0.001	Training group improved in 3 memory-based cognitive abilities, in speed of information recall, focused attention and visuo-motor vigilance
Mattioli et al[21]	Attention and Executive function	Relapsing remitting	Experimental group: 10 Control group: 10	Computer-assisted program (Double-blind controlled study) Level II-2	Cognition, mood, QoL	12 weeks/Three days per week Follow-up: 3 months P range 0.05-0.001	Only the treated group improved in tests of attention, information processing, executive functions, and also in depression scores

Sastre-Garriga et al[25]	Non-specific/ multiple skills	Non specified	Experimental group: 15 Control group: 5	Computer and non-computer exercises (Controlled pilot study) Level II-2	Cognition and imaging	5 weeks/Three days per week No follow up P range 0.05-0.001	After rehabilitation patients improved their performance on the backward version of the Digit Span and on a composite score of cognitive outcomes. They also increased brain fMRI activity in several cerebellar areas
Fink et al[23]	Executive functions	Relapsing remitting	Experimental group 1: 14 Placebo group: 17 Untreated group: 19	Textbook exercises (Placebo-controlled and pseudo-randomized trial) Level II-2	Cognition and imaging	6 weeks/Four days per week Follow-up: 1 year P range 0.05-0.001	Verbal learning and executive functioning improved significantly more in the cognitive intervention group than the placebo and the untreated group
Brissart et al[22]	Non-specific/ multiple skills	Relapsing remitting	Experimental group: 10 Control group: 10	Computer-assisted programme (Pre-Post) Level II-3	Cognition	6 months/ Twice a month No follow up P range 0.05-0.001	A benefit of the cognitive programme was observed mainly in verbal and visual memory, and in verbal fluency
Chiaravallotti et al[26]	Memory and new learning	Non specified	Experimental group: 8 Control group: 8	Story Memory Tecnique (SMT) (Double-blind, placebo-controlled, randomized clinical trial) Level II-2	Cognition and imaging	5 weeks/ Twice a week No follow up P < 0.05	Training group showed greater improvement on a memory sub-test than controls. They also showed increased activation during a memory task in frontal and temporal regions

Ernst et al[46]	Autobiographical Memory (AbM)	Relapsing remitting	Experimental group: 8 Control group: 15	Computer-assisted program (Pre-Post) Level II-3	Cognition, fatigue and imaging	6 weeks/ Once a week No follow up P range 0.05-0.001	Significant improvements of autobiographical memory performance were observed after the facilitation programme. This was accompanied by an increased cerebral activity in posterior cerebral regions
Stuifbergen et al[47]	Memory, Attention and problem solving	Non specified	Experimental group: 34 Control group: 27	Computer-assisted programme combined with 8 group meetings (Randomized controlled trial) Level I	Cognition and self-efficacy	8 weeks/ Three days per week Follow-up: 5 months P range 0.05-0.001	Both groups improved significantly on most measures in the cognitive assessment, as well as the measures of strategy use and neuropsychological competence in activities of daily living
Cerasa et al[30]	Attention	Relapsing remitting	Experimental group: 12 Control group: 11	Computer-assisted program (Randomized trial) Level II-2	Cognition, mood, fatigue and imaging	6 weeks/ Twice a week No follow up P range 0.05-0.001	The experimental group showed an improvement in attention abilities, which was associated with increased activity in the posterior cerebellar lobule and in the superior parietal lobule
*Parisi et al[48]	Attention and Executive function	Relapsing remitting	Experimental group: 10 Control group: 10	Computer-assisted program (Pre-Post) Level II-3	Imaging (RS fMRI)	12 weeks/ Three days per week No follow up P range 0.05-0.001	Training group showed an increased functional connectivity of the anterior cingulate cortex, while the controls showed a decrease

*Filippi et al[31]	Attention and Executive function	Relapsing remitting	Experimental group: 10 Control group: 10	Computer-assisted program (Pre-Post) Level II-3	Imaging (structural and functional MRI)	12 weeks/ Three days per week No follow up P range 0.05-0.001	In the treatment group modifications of the activity of the posterior cingulate cortex (PCC) and dorsolater prefrontal cortex during the Stroop task, as well as modifications of the activity of the anterior cingulum and PCC at rest. No structural modifications
*Parisi et al[32]	Attention and Executive function	Relapsing remitting	Experimental group: 10 Control group: 10	Computer-assisted program (Pre-Post-Followup) Level II-3	Cognition, mood , QoL and RS fMRI	12 weeks/ Three days per week Follow-up: 6 months P range 0.05-0.001	Treated group improved in test of attention, executive function, depression and quality of life. These scores correlated with functional connectivity of the anterior cingulum and cognitive-related networks
Amato et al[49]	Attention	Relapsing remitting	Experimental group: 55 Control group: 33	Computer-assisted program: specific vs non-specific training (Randomized double-blind trial) Level I	Cognition, mood and fatigue	12 weeks/ Twice a week Follow-up: 6 months P range 0.05-0.001	A benefit of the specific training was observed on the PASAT, however patient self-report did not reveal differences between specific and non-specific
**Rosti-Otajarvi et al[34]	Non-specific/ multiple skills	Relapsing remitting	Experimental group: 50 Control group: 28	Computer-assisted program: strategy-oriented neuropsychological rehabilitation (Pre-Post-Followup) Level II-3	Cognition, mood, fatigue and QoL	13 weeks/ Once a week Follow-up: 6 months and 1 year P range 0.05-0.001	Treated group showed positive effects on perceived cognitive deficits, maintained also after 1 year. Patients with moderate/severe deficit showed even more evident positive results

**Rosti-Otajarvi et al[50]	Non-specific/ multiple skills	Relapsing remitting	Experimental group: 58 Control group: 40	Computer-assisted program: multimodal neuropsychological intervention (Pre-Post) Level II-3	Cognition, mood and fatigue	13 weeks/ Once a week No follow up P range 0.05-0.001	Patient-related factors affected rehabilitation outcome. Patients with male gender and more severe attentional deficits benefited more from the intervention
**Mantynen et al[51]	Non-specific/ multiple skills	Relapsing remitting	Experimental group: 58 Control group: 40	Computer-assisted program: strategy-oriented neuropsychological rehabilitation (Randomized, controlled trial) Level I	Cognition, mood, fatigue, QoL and self-efficacy	13 weeks/ Once a week Follow-up: 3 months and 6 months P range 0.05-0.001	Treated group did not improve cognitive performance but had a positive effect on perceived cognitive deficits, immediately and at 6 months follow-up
Goverover et al[52]	Learning and memory of functional activities	Relapsing remitting Primary progressive Secondary progressive	Experimental group: 20 Control group: 18	Comparison of self-generated and provided learning methods (Mixed-design) Level II-3	Cognition, mood, specific recall tests	Single test day No follow up P range 0.05-0.001	Self-generated learning significantly improve subsequent recall of information and performance of everyday activities
Goverover et al[53]	Learning and memory	Relapsing remitting Primary progressive Secondary progressive	Experimental group: 20 Control group: 18	Comparison of spaced and massed learning trials (Within subjects) Level II-3	Cognition, mood, verbal and visual learning tasks	Single test day No follow up P range 0.05-0.001	Spaced learning improve recall of a verbal learning task relative to massed learning, but not of a visual learning task
Goverover et al[54]	Learning and memory	Relapsing remitting Primary progressive Secondary progressive	Experimental group: 20 Control group: 18	Comparison of self-generated and spaced learning with spaced and assed learning (Within) Level II-3	Cognition, mood, functional learning tasks	Single test day No follow up $P < 0.05$	The combination of self-generated and spaced learning yielded better recall than did spaced learning alone

Hildebrandt et al[38]	Memory and working memory	Relapsing remitting	Experimental group: 17 Control group: 25	Computer-assisted programme (home-based) (Single-blinded controlled study design) Level II-3	Cognition, mood, fatigue, QoL	Six weeks No follow up P range 0.05-0.001	Treatment group showed better verbal learning, verbal memory performance and working memory performance after training. No effect on fatigue or QoL
Jonsson et al[19]	Non-specific/ multiple skills	Relapsing remitting Primary progressive Secondary progressive	Experimental group: 20 Control group: 20	Specific cognitive treatment or non-specific mental stimulation (Pre-Post) Level II-3	Cognition, mood	46 days No follow up P range 0.05-0.001	The specific cognitive treatment group reported immediately and after 6 months significant less depression. This group showed also an improvement in visuo-spatial memory
Mendozzi et al[55]	Memory	Relapsing remitting Secondary progressive	Experimental group 1: 20 Experimental group 2: 20 Control group: 20	Computer-assisted memory retraining (specific vs. non-specific retraining) Pre-Post-Followup Level II-3	Cognition	8 weeks/ Twice a week Follow-up: 6 months P range 0.05-0.001	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
Basso et al[56]	Learning and memory	Relapsing remitting Primary progressive Secondary progressive	Experimental group: 95 Control group: 22	Comparison of self-generated and didactic learning Level II-3	Cognition	Not stated No follow up P range 0.05-0.001	MS patients remembered more information if it was self-generated rather than didactically presented
Chiaravallotti et al[57]	Learning and memory	Non specified	Experimental group: 31 Control group: 17	Comparison of self-generated and didactic learning methods (Between) Level II-3	Cognition	Single test day No follow up P range 0.05-0.001	Recall and recognition of generated stimuli were significantly higher than provided stimuli across testing sessions.

Chiaravallotti et al[58]	Memory and new learning	Relapsing remitting Primary progressive Secondary progressive	Experimental group: 15 Control group: 14	Story Memory Tecnique (SMT) (Randomized clinical trial) Level I	Cognition, mood and self-report	4 weeks/ Twice a week Follow-up: 3 months P range 0.05-0.001	MS patients with moderate-severe impairment showed a significant improvement than controls. Little improvement noted in those with mild impairments
Plohmann et al[39]	Attention	Relapsing remitting Secondary progressive	Experimental group: 22	Computer-assisted retraining of specific attentional domains Level II-3	Cognition and quality of life	2 X 3 weeks No follow up $P < 0.05$	Significant improvements of performance could almost exclusively be achieved by the specific training programmes. Daily functioning improved
Solari et al[24]	Memory and attention	Relapsing remitting Relapsing progressive Chronic progressive	Experimental group: 42 Control group: 40	Computer-aided retraining of memory and attention (Randomized, double-blind controlled trial) Level I	Cognition, mood and quality of life	8 weeks/ Twice a week No follow up P range 0.05-0.001	An improvement occurred in 45% of study patients and 43% of control patients. The study treatment was better than control only on the word list generation test
Tesar et al[35]	Non-specific/ multiple skills	Relapsing remitting Secondary progressive	Experimental group: 10 Control group: 9	Computer-based neuropsychological training (Randomized controlled trial) Level I	Cognition, mood, fatigue	4 weeks/ Once a week Follow-up: 3 months $P < 0.05$	Treatment group showed significant improvement in executive function and spatial-constructional abilities. No significant differences in memory and fatigue values

Sumowski et al[59]	Learning and memory	Relapsing remitting Secondary progressive Primary progressive Relapsing progressive	Experimental group: 32 Control group: 16	Comparison of 3 learning methods: Massed Restudy (MR), Spaced Restudy (SR), and Spaced Testing (ST) (Within subjects) Level II-3	Cognition	Not stated No follow up P range 0.05-0.001	MS patients and healthy controls produced significantly better delayed recall for Verbal Paired Associates learned through ST relative to MR or SR
Lincoln et al[37]	Non-specific/ multiple skills (based on impaired domain)	Relapsing remitting Secondary progressive Primary progressive	Experimental group: 79 Assessment group: 79 Control group: 82	Use of diaries, calendars, notebooks and lists (Single blind randomized controlled trial) Level I	Mood, quality of life, subjective reports	Not stated Follow-up: 4 months and 8 months P < 0.05	Overall, the results showed no effect of the interventions on mood, quality of life, subjective cognitive impairment or independence
Chiaravallotti et al[60]	Verbal learning and memory	Relapsing remitting Secondary progressive Primary progressive	Experimental group: 64 Control group: 20	Repetition effect (a list of words to remember) (Prospective between-group design) Level II-3	Cognition	Single test day No follow up P range 0.05-0.001	Individuals with MS may not benefit from repetition in isolation, but rather require the use of more intensive cognitive rehabilitation strategies

* Authors shared the same sample
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***(18) Level I: Evidence obtained from properly designed randomized controlled trial
Level II-1: Evidence obtained from well-designed controlled trials without randomization
Level II-2: Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one center or research group
Level II-3: Evidence obtained from multiple time series studies with or without the intervention
Level III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

Appendix: Search Strategy