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das Nair R, Martin KJ, Lincoln NB

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[Intervention Review]

Memory rehabilitation for people with multiple sclerosis

Roshan das Nair[1], Kristy-Jane Martin[1], Nadina B Lincoln[1]

[1]Division of Rehabilitation and Ageing, University of Nottingham, Nottingham, UK

Contact address: Roshan das Nair, Division of Rehabilitation and Ageing, University of Nottingham, B98, B Floor Medical School, Queen's Medical Centre, Nottingham, NG7 2UH, UK. roshan.nair@nottingham.ac.uk.

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ABSTRACT

Background

This is an update of the Cochrane review 'Memory rehabilitation for people with multiple sclerosis' (first published in the Cochrane Library 14 March 2012, Issue 3). Impairments in cognitive function, particularly memory, are common in people with multiple sclerosis (MS) and can potentially affect their ability to complete functional activities. There is evidence from single-case or small group studies that memory rehabilitation can be beneficial for people with MS, but findings from randomised controlled trials (RCTs) and systematic reviews have been inconclusive.

Objectives

To determine whether people with MS who received memory rehabilitation showed: 1. better outcomes in their memory functions compared to those given no treatment or receiving a placebo control; and 2. better functional abilities, in terms of activities of daily living, mood, and quality of life, than those who received no treatment or a placebo.

Search methods

We searched the Trials Specialised Register of the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group (2 June 2015) and the following electronic databases: The NIHR Clinical Research Network Portfolio database (NIHR CRN) (from 2010 to June 2015), The Allied and Complementary Medicine Database (AMED) (2010 to June 2015), British Nursing Index (BNI) (2010 to June 2015), PsycINFO (2011 to June 2015), and CAB Abstracts (2010 to June 2015). Start dates for the electronic databases coincided with the last search for the previous review. We handsearched relevant journals and reference lists.

Selection criteria

We selected RCTs or quasi-randomised trials of memory rehabilitation or cognitive rehabilitation for people with MS in which a memory rehabilitation treatment group was compared to a control group. Selection was conducted independently first and then confirmed through group discussion. We excluded studies that included participants whose memory deficits were the result of conditions other than MS unless we could identify a subgroup of participants with MS with separate results.

Data collection and analysis

Three review authors were involved in this update in terms of study selection, quality assessment, and data extraction. We contacted investigators of primary studies for further information where required. We conducted data analysis and synthesis in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We performed a 'best evidence' synthesis based on the methodological quality of the primary studies included.

Main results

We added seven studies during this update, bringing the total to 15 studies, involving 989 participants. The interventions involved various memory retraining techniques, such as computerised programmes and training on internal and external memory aids. Control groups varied in format from assessment-only groups, discussion and games, non-specific cognitive retraining, and attention or visuospatial training. The risk of bias of the included studies was generally low, but we found eight studies to have high risk of bias related to certain aspects of their methodology.

We found significant effect of intervention on objective assessments of memory in both the immediate and long-term follow-ups: standardised mean difference (SMD) 0.23 (95% confidence interval (CI) 0.05 to 0.41) and SMD 0.26 (95% CI 0.03 to 0.49), respectively. We also found significant effect of intervention for quality of life in the immediate follow-up (SMD 0.23 (95% CI 0.05 to 0.41)). These findings showed that the intervention group performed significantly better than the control group. We also found a significant difference for activities of daily living (ADL) in the long-term follow-up (SMD -0.33 (95% CI -0.63 to -0.03)), showing that the control groups had significantly less difficulty completing ADLs than the intervention groups. We found no significant effects, either immediate or long-term, on subjective reports of memory problems (SMD 0.04 (95% CI -0.19 to 0.27) and SMD 0.04 (95% CI -0.19 to 0.27)); on mood (SMD 0.02 (95% CI -0.16 to 0.20) and SMD -0.01 (95% CI -0.21 to 0.20)); and on immediate follow-up for ADL (SMD -0.13 (95% CI -0.60 to 0.33)) and in the long term for quality of life (SMD 0.16 (95% CI -0.03 to 0.36)). We could not complete a sensitivity analysis of intention-to-treat in comparison with per-protocol analysis, due to insufficient information from the included papers. However, a sensitivity analysis of high- versus low-risk studies suggested that while quality of the trials did not affect most outcomes, differences were seen in the objective memory outcomes (both at immediate and long term) and quality of life (immediate) outcome, with studies with higher risk of bias inflating the overall effect size estimates for these outcomes, and the test of overall effect changing from being statistically significant to not significant when studies at high risk of bias were excluded. This suggests that lower-quality studies may have positively influenced the outcomes.

Authors' conclusions

There is some evidence to support the effectiveness of memory rehabilitation on memory function, as well as on quality of life. However, the evidence is limited and does not extend to subjective reports of memory functioning or mood. Furthermore, the objective measures used are not ecologically valid measures, and thus potentially limit generalisability of these findings into daily life. Further robust RCTs of high methodological quality and better quality of reporting, using ecologically valid outcome assessments, are still needed.

PLAIN LANGUAGE SUMMARY

Memory rehabilitation in multiple sclerosis

Review question

Do people with MS who received memory rehabilitation show: 1. better outcomes in their memory functions compared to those given no treatment or receiving a placebo control; and 2. better functional abilities, in terms of activities of daily living, mood, and quality of life, than those who received no treatment or a placebo.

Background

People with multiple sclerosis (MS) often struggle with memory problems, which can lead to difficulties in everyday life. Memory rehabilitation is offered to help enhance the ability to perform everyday activities and to increase independence by reducing forgetting. Such rehabilitation can involve the use of specific techniques and strategies to change the way a person tries to remember, store, or retrieve memories. However, it is unclear whether memory rehabilitation is effective in reducing forgetting or improving performance of activities of daily living. Currently there are few good-quality studies that have investigated the effectiveness of memory rehabilitation in people with MS.

Study characteristics

This review included 15 studies with 989 participants involving various types of memory retraining techniques, some using computer programs or memory aids such as diaries or calendars.

Key results and quality of the evidence

The results of this review showed some evidence to support the use of memory rehabilitation in people with MS. Those participants who had memory rehabilitation had better memory functioning compared to those who did not receive memory rehabilitation, and this difference between groups was found after the intervention was completed and for some time thereafter. However, this outcome was usually measured on assessments that were abstract and did not reflect people's daily life. Those participants who received memory rehabilitation also showed better quality of life, but this effect was not maintained long term. We also found that those participants who did not receive the memory rehabilitation were better at completing activities of daily living, but these differences between groups were small. The groups who did and did not receive memory rehabilitation did not differ in terms of their subjective reports of memory problems or mood. There are still relatively few large, good-quality studies to base our findings on, so more are needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Memory rehabilitation for people with multiple sclerosis

Patient or population: people with multiple sclerosis
Settings:
Intervention: memory rehabilitation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Memory rehabilitation				
Subjective memory measures - immediate EMQ, MSNQ, MFQ[a] Follow-up: median 1.5 to 5 months	-	The mean subjective memory measures - immediate in the intervention groups was **0.04 standard deviations higher** (0.19 lower to 0.27 higher)	-	314 (5 studies)	⊕⊕⊕◯ **moderate**[b]	SMD 0.04 (-0.19 to 0.27)
Subjective memory measures - long term EMQ, MSNQ, MFQ[a] Follow-up: 3 to 8 months	-	The mean subjective memory measures - long term in the intervention groups was **0.04 standard deviations higher** (0.19 lower to 0.27 higher)	-	305 (5 studies)	⊕⊕⊕◯ **moderate**[b]	SMD 0.04 (-0.19 to 0.27)
Objective memory measures - immediate RBMT,CVLT, AVLT, HVLT, VLT, LNNB, BRBNT, MUSIC[a]	-	The mean objective memory measures - immediate in the intervention groups was **0.23 standard deviations**	-	503 (11 studies)	⊕◯◯◯ **very low**[b,c,d]	SMD 0.23 (0.05 to 0.41)

Follow-up: 1 to 5 months		**higher** (0.05 to 0.41 higher)				
Objective memory measures - long term RBMT, CVLT, AVLT, HVLT, VLT, BRBNT, MUSIC[a] Follow-up: 3 to 8 months	-	The mean objective memory measures - long term in the intervention groups was **0.26 standard deviations higher** (0.03 to 0.49 higher)	-	302 (6 studies)	⊕⊕◯◯ **low**[b,e]	SMD 0.26 (0.03 to 0.49)
Mood - immediate GHQ, BDI, BDI-FS, Chicago Multiscale Depression Inventory[a] Follow-up: 1-5 months	-	The mean mood - immediate in the intervention groups was **0.02 standard deviations higher** (0.16 lower to 0.20 higher)	-	490 (9 studies)	⊕⊕◯◯ **low**[b,f]	SMD 0.02 (-0.16 to 0.20)
Mood - long term GHQ, BDI, BDI-FS, Chicago Multiscale Depression Inventory[a] Follow-up: 3 to 8 months	-	The mean mood - long term in the intervention groups was **0.01 standard deviations lower** (0.21 lower to 0.20 higher)	-	413 (7 studies)	⊕⊕◯◯ **low**[b,g]	SMD -0.01 (-0.21 to 0.20)
Acitivities of daily living - immediate EADL[a] Follow-up: 4 to 5 months	-	The mean activities of daily living - immediate in the intervention groups was **0.13 standard deviations lower** (0.6 lower to 0.33 higher)	-	186 (2 studies)	⊕⊕⊕⊕ **high**	SMD -0.13 (-0.6 to 0.33)

Activities of daily living - long term EADL[a] Follow-up: 7 to 8 months	-	The mean activities of daily living - long term in the intervention groups was **0.33 standard deviations lower** (0.63 to 0.03 lower)	-	186 (2 studies)	⊕⊕⊕⊕ **high**	SMD -0.33 (-0.63 to -0.03)
Quality of life - immediate MSIS, FAMS, MSQOL, SF-36, SF-12[a] Follow-up: 1.5 to 4 months	-	The mean quality of life - immediate in the intervention groups was **0.23 standard deviations higher** (0.05 to 0.41 higher)	-	485 (7 studies)	⊕⊕⊕◯ **moderate**[b]	SMD 0.23 (0.05 to 0.41)
Quality of life - long term MSIS, FAMS, MSQOL SF-36, SF-12[a] Follow-up: 4 to 8 months	-	The mean quality of life - long term in the intervention groups was **0.16 standard deviations higher** (0.03 lower to 0.36 higher)	-	406 (5 studies)	⊕⊕⊕◯ **moderate**[b]	SMD 0.16 (-0.03 to 0.36)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; SMD: standardised mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]EMQ: Everyday Memory Questionnaire, MSNQ: Multiple Sclerosis Neuropsychological Screening Questionnaire, MFQ: Memory Functioning Questionnaire, RBMT: Rivermead Behavioural Memory Test, CVLT: California Verbal Learning Test, AVLT: Auditory Verbal Learning Test, HVLT: Hopkins Verbal Learning Test, VLT: Verbal Learning Test, LNNB: Luria-Nebraska Neuropsychological Battery, BRBNT: Brief Repeatable Battery of Neuropsychological Tests, GHQ: General Health Questionnaire, BDI: Beck Depression Inventory,

BDI-FS: Beck Depression Inventory-Fast Screen, EADL: Extended Activities of Daily Living, MSIS: Multiple Sclerosis Impact Scale, FAMS: Functional Assessment of Multiple Sclerosis, MSQOL: Multiple Sclerosis Quality of Life, SF-36: 36-Item Short Form Health Survey, SF-12: 12-Item Short Form Health Survey

[b] Downgraded by 1 due to 95% confidence intervals including no effect, and the upper or lower confidence intervals limit crosses an effect size of 0.5 in either direction.

[c] 4 of 11 studies had possible risk of bias related to random sequence generation, and in 2 of 11 studies this was unclear. Allocation concealment was potentially biased in 1 study, and unclear in 5 of 11 studies. Blinding was a potential source of bias in 2 studies. Incomplete outcome data may have biased 2 of 11 studies and was unclear in 4 of 11 studies.

[d] 7 of 11 studies used a list-learning task as an objective measure of memory, which has poor ecological validity.

[e] 4 of 6 studies used a list-learning task as an outcome measure for objective memory, which has poor ecological validity.

[f] 2 of the 9 studies showed potential risk of bias relating to random sequence generation, and for 1 study this was unknown. 1 study had potential risk of allocation concealment bias; this was unclear for 2 studies. 1 study had potential risk of bias related to blinding. 2 studies had risk of bias due to incomplete outcome data, and this was unknown for 2 studies.

[g] 1 of 7 studies showed potential risk of bias related to random sequence generation, and for 1 this was unclear. 1 study showed potential risk of bias related to allocation concealment. 1 study showed potential risk of bias related to blinding, and 1 study showed potential risk of bias related to incomplete outcome data; this was unknown for 2 studies.

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system that causes physical or cognitive disturbances, or both. The prevalence of these cognitive problems, which include dysfunctions in memory, attention, speed of information processing, and executive functions, varies from 43% to 72% (Prosiegel 1993). Rao 1993 reported that impaired memory functions were evident in 40% to 60% of people with MS. Impairments in cognitive functions are also related to low mood (Chiaravalloti 2008; Gilchrist 1994), and have the potential to hamper functions related to activities of daily living (ADL) (Kalmar 2008; Langdon 1996).

Description of the intervention

Cognitive rehabilitation is a specialised facet of neuropsychological rehabilitation that assists in the development of functional independence and adjustment of individuals with brain damage through targeted intervention or focused stimulation (Robertson 1993). Robertson 2008 defined cognitive rehabilitation as a "structured, planned experience derived from an understanding of brain function which ameliorates dysfunctional cognitive and brain processes caused by disease or injury and improves everyday life function". Memory rehabilitation is a major component of the management of people with memory problems, and is either implemented as part of a comprehensive cognitive rehabilitation programme or as a stand-alone intervention, depending on the needs and neuropsychological profile of the patient.

How the intervention might work

There is uncertainty about the precise mechanisms by which memory rehabilitation interventions work. However, it is widely believed that they provide people with the knowledge of and information about their memory problems, by teaching them to use internal and external memory aids, different strategies to pay attention, and alternative ways of encoding, storing, and retrieving information. Targeted, repeated stimulation of certain brain areas using drill and practice cognitive exercises are thought to trigger the activation of neural networks. For group-based interventions, the therapeutic effects of being with others with similar problems may also help. Some of these behavioural strategies (referred to as 'restitution' or 'compensation') are believed to map onto the neural networks engaged in performing memory functions.

Why it is important to do this review

Studies have examined the effectiveness of memory rehabilitation using different methodologies. Single-case and small group studies have reported positive results of memory rehabilitation, but the results obtained from randomised controlled trials (RCTs) and some systematic reviews have been less positive and reported inconclusive evidence. Some reviews (for example Cicerone 2005; Cicerone 2011) have concluded that there is compelling evidence for memory strategy training with participants with mild memory problems, that errorless learning may be effective for those with severe memory impairments (albeit with limited generalisability to new tasks or overall memory problems), and that the use of external memory aids may be beneficial for people with moderate to severe memory problems. Cicerone 2011 also suggest that group-based interventions may be considered for remediation of memory deficits. However, these reviews focused mainly on people with traumatic brain injury. Cochrane reviews by Majid 2000 and das Nair 2007a found insufficient evidence to support or refute the effectiveness of memory rehabilitation following stroke. Some reviews have focused on generic psychological interventions for people with MS (Thomas 2006), or neuropsychological interventions for people with MS (Rosti-Otajärvi 2011), however these were not specific to memory rehabilitation. The Thomas 2006 review did not consider grey literature and was unable to draw any "definite conclusions". The Rosti-Otajärvi 2011 review focused on neuropsychological rehabilitation across a number of cognitive domains, as well as associated health-related factors and emotional well-being. This current systematic review is focused solely on the effectiveness of memory rehabilitation for people with MS; databases were searched that were not searched as part of the Rosti-Otajärvi 2011 review, and studies are included that were not in their review. This is an update of the Cochrane review 'Memory rehabilitation for people with multiple sclerosis' (first published in the Cochrane Library 2012, Issue 3).

OBJECTIVES

The aims of this systematic review were to determine whether people with MS who received memory rehabilitation showed:

1. Better outcomes in their memory functions compared to those given no treatment or a placebo control; and

2. Better functional abilities, in terms of activities of daily living, mood, and quality of life, than those who received no treatment or a placebo.

METHODS

Criteria for considering studies for this review

Types of studies

We sought randomised and quasi-randomised controlled trials, as defined by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and the pre-cross-over component of randomised cross-over trials with people with MS, in which a memory treatment was compared to a control, for inclusion in the review. Where papers were based on the same sample, or subset of a larger sample, we included only the study with the full sample so as to avoid double counting. If a study was available through both grey literature (for example conference abstract) and a peer-reviewed publication, we used the peer-reviewed publication in the first instance.

Types of participants

Trials included in this review were limited to those with people with MS (including relapsing remitting, secondary progressive, and primary progressive). We thus excluded trials with participants whose memory deficits were the result of traumatic brain injury, brain tumour, stroke, epilepsy, or any other neurological condition, unless we could define a subgroup of people with MS for which there was separate data. Included studies were to base a diagnosis of MS on well-established diagnostic criteria, for example Paty 1988 and Poser 1983 (and revised versions of the McDonald criteria (Polman 2005; Polman 2011)). We did not define memory deficits in advance as we assumed that those people with MS who were given treatment for impaired memory had memory deficits. We placed no restrictions on the type of memory deficits participants reported.

Types of interventions

We included trials in which there was a comparison between a treatment group that received one of various memory rehabilitation strategies, and a control group that received either a placebo or no memory intervention. We considered rehabilitation to take place over more than a single session; therefore, we did not consider lab-based experiments (such as single-session list-recall or mnemonic strategy training) as rehabilitation. Control groups needed to have people with MS or a subgroup of people with MS amongst those with other diagnoses, for whom separate data were available. We considered memory treatments to be any attempt to modify memory function by means of drill-and-practice, or by the use of internal and/or external memory aids, or by teaching people with MS strategies to cope with their memory problems. We did not include drug studies.

Types of outcome measures

Primary outcomes

Primary outcomes were measures of the extent of memory problems in everyday life. There are several ways in which this is assessed in clinical practice and research, but we only included measures that directly assessed this construct. If there was more than one outcome measure measuring this construct in a study, we used the following hierarchy of commonly used tests:

1. For subjective reports of memory: we considered Everyday Memory Questionnaire (EMQ) (Sunderland 1983), over the Cognitive Failures Questionnaire (Broadbent 1982), over the Subjective Memory Questionnaire (Davis 1995), over the Memory Assessment Clinics Questionnaire (Crook 1992).
2. For objective reports of memory: we considered Rivermead Behavioural Memory Test (RBMT) (Wilson 1985 or newer versions of this test), over Wechsler Memory Scale (WMS) (Wechsler 1997 or newer versions of this test), over Cambridge Test of Prospective Memory (Wilson 2005), over Doors and People Test (Baddeley 1994).

We based these hierarchies on the tests' degree of sensitivity to assess everyday memory problems. For objective assessments where the outcomes were not in the above hierarchy, we used general memory test scores over verbal memory test scores over visual memory test scores. If outcome measures were used that were not in this hierarchy, we arrived at a consensus following discussion regarding which measures to consider as the primary outcome measure, before the statistical analyses were conducted, so as to minimise bias.

Secondary outcomes

1. Mood, such as the General Health Questionnaire (GHQ) (Goldberg 1988), Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983); Beck Depression Inventory-Fast Screen (Beck 2003).
2. Functional abilities, such as the Functional Independence Measure (FIM) (Uniform Data System for Medical Rehab 1993), Functional Assessment Measure (FAM) (Hal 1997), Nottingham Extended Activities of Daily Living (EADL) (Nouri 1987).
3. Quality of life, such as the Multiple Sclerosis Impact Scale (MSIS) (Hobart 2001) World Health Organization Quality of Life assessment (WHO-QoL) (The WHOQOL Group 1993), 36-item Short Form Health Survey (SF-36) (Ware 2001).

We also considered non-standardised measures, such as return to work and goal attainment, if studies had included these as a measure of outcome. If more than one of these scales was reported for each domain, we used the first scale in the list.

We classified all outcomes as immediate or longer-term outcomes, and conducted separate analyses for each of these. We defined immediate outcomes as shortly after the end of intervention, and

longer-term outcomes as the second outcome following the immediate outcome.

We used both total scores and individual domain scores, as appropriate. We included domain scores, as some tests (such as the Doors and People Test, Baddeley 1994) do not provide a total score, but only domain-specific scores. In the event that several types of scores were reported for various outcomes, we used the following hierarchy: total profile scores over index scores (indices) or composite scores over subtest scores.

Search methods for identification of studies

We conducted an electronic search with no restriction, and two review authors (KJM, RdN) identified all potential studies.

Electronic searches

The Trials Search Co-ordinator searched the Trials Specialised Register of the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group (2 June 2015), which contains the following:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2015 Issue 6).
- MEDLINE (PubMed) (1966 to 2 June 2015).
- EMBASE (EMBASE.com) (1974 to 2 June 2015).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO host) (1981 to 2 June 2015).
- Latin American and Caribbean Health Science Information Database (LILACS) (Bireme) (1982 to 2 June 2015).
- ClinicalTrials.gov.
- World Health Organization (WHO) International Clinical Trials Registry Portal (http://apps.who.int/trialsearch/).

Information on the Trial Register of the Review Group and details of search strategies used to identify trials can be found in the 'Specialised Register' section within the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group module.

The keywords used to search for studies for this review are listed in Appendix 1.

We also searched the following databases:

- The NIHR Clinical Research Network database (2010 to June 2015)
- PsycINFO (2011 to June 2015)
- Allied and Complementary Medicine Database (AMED) (2010 to June 2015)
- British Nursing Index (2010 to June 2015)
- CAB Abstracts (2010 to June 2015)

Searching other resources

We citation tracked all primary study articles and scanned reference lists from book chapters and review articles. We also examined studies identified by the Rosti-Otajärvi 2011 and Thomas 2006 MS reviews for inclusion. We did not handsearch scientific journals in this review, as until the early 1990s cognitive impairments were not universally recognised as a common complaint in MS (Rao 1991), and most RCTs have been reported (or updated) on electronic databases or journals. Furthermore, we would have found relevant trials from the search of the Cochrane Central Register of Controlled Trials, for which handsearching is carried out periodically, and we did not wish to duplicate this effort. Where necessary, we contacted authors of relevant trials to enquire whether their registered trials had been published, and to solicit more data where data required for the meta-analysis was not presented in the published paper in a format that could be used. We accessed grey literature by searching GreyNet (http://www.greynet.org/) and the British Library's EThOS database (http://ethos.bl.uk/Home.do). Grey literature is "a field in Library and Information Science that deals with the production, distribution, and access to multiple document types produced on all levels of government, academics, business, and organization in electronic and print formats not controlled by commercial publishing i.e. where publishing is not the primary activity of the producing body" (GreyNet 2011).

Data collection and analysis

Selection of studies

One review author (RdN), developed the search strategy in consultation with a senior librarian and the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group. Two review authors (KJM, RdN) evaluated abstracts of the studies obtained by this search strategy, and identified trials for inclusion in the review using four inclusion criteria (types of trials, participants, interventions, and outcome measures). Another review author (NBL) cross-checked the search strategy, independently appraised the protocol, and confirmed the inclusion and exclusion of studies.

Data extraction and management

Two review authors (RdN, KJM) independently assessed the methodological quality of each of the selected trials and rated them according to the guidelines of The Cochrane Collaboration. In case of disagreement, the third review author (NBL) arbitrated, and a verdict was reached. Our main considerations were whether participant allocation had been random and adequately concealed, and whether outcomes were performed blind to group allocation. We conducted the review using the Cochrane Review Manager software version 5.3 (RevMan 2015). The data extraction tool employed by the das Nair and Lincoln Cochrane review, das Nair 2007a, was used in this study, and is therefore not replicated here.

Assessment of risk of bias in included studies

Two authors (RdN, KJM) independently graded the included trials and completed the 'Risk of bias' table as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The table includes the following domains:

- Random sequence generation
- Allocation concealment
- Blinding (of participants, personnel, and outcome assessors)
- Incomplete outcome data
- Selective outcome reporting
- Other sources of bias

On the basis of the information provided in the studies or by the authors of the primary studies, two review authors (RdN, KJM) independently judged each of these domains as being low or high risk of bias, or unclear if information was insufficient. Any disagreements were arbitrated by another review author (NBL). As review authors working in the field of memory rehabilitation and are familiar with the studies published in this area, we could not be blinded to the names of the authors, institutions, or the publishing journal of the included trials. We made an evaluation of the overall risk of bias, based on the relative importance of the various domains listed. In addition to the 'Risk of bias' table, the review authors used the GRADE approach to assessing quality of studies (GRADE Working Group 2004). This was completed across outcomes and is found in the 'Summary of findings' table. This approach allows for judgements to made about the quality of the studies included in each outcome.

Measures of treatment effect

We used odds ratio with 95% confidence intervals (CI) for the binary outcomes. We used standardised mean difference with 95% CI for the continuous outcomes.

Unit of analysis issues

We included parallel-group, cluster-randomised, cross-over RCTs, and quasi-RCTs, and included the data from all these types of studies for the meta-analysis. For cross-over studies (as mentioned under Types of studies section), we only included the pre-cross-over phase of these trials. We did not combine the first and second phases of the cross-over studies because of uncertainty about the carryover effects in such trials, given that they are psychological interventions, where the wash-out period is difficult to determine. We included trials with more than two intervention groups, and analysed them by pooling together the data on all the treatment groups and compared them with the control group. If there was more than one control group the results from the control groups were pooled together and compared with treatment.

Dealing with missing data

Where data were not available from or unclear in the reports, we contacted the correspondence author of the studies in question for further information. We assessed the rates of attrition and missing data from the included studies (where available) and explored how these may have affected the results of the studies. We rated studies as at high risk of bias if they had a postrandomisation attrition rate of 30% or more (even if the intention-to-treat analysis was used).

Assessment of heterogeneity

We considered heterogeneity by comparing the distribution of important participant factors between trials (age, gender, type of MS), and trial factors (sequence generation, allocation concealment, blinding, losses to follow-up). We employed the I^2 statistic to statistically assess heterogeneity (Higgins 2011; Huedo-Medina 2006). We further scrutinised the studies to explore the reasons for the heterogeneity if the I^2 statistic was significant at >= 50%.

Data synthesis

We consulted the *Cochrane Handbook for Systematic Reviews of Interventions* to plan the data synthesis (Higgins 2011), and followed the procedures outlined therein. As most psychological and neuropsychological outcome measures in memory rehabilitation tend to be ordinal-level measures, we treated these as continuous data (as recommended by Higgins 2011). Standardised mean difference was used as a summary statistic, as it was predicted that multiple trials would employ various outcome measures to assess memory. If low scores represented a better outcome, the valence of the score was changed from positive to negative. In situations where studies combined scores from scales in which high scores are in some instances good outcomes and in some instances poor outcomes, the signs of the discrepant scores were reversed to keep them consistent. We considered only data that we deemed to be similar or comparable enough to meaningfully pool on the basis of the outcome measures employed for the meta-analysis. Depending on the heterogeneity of the data, we considered fixed-effect or random-effects models.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses where at least two trials had separate data available for people with different subtypes of MS.

Sensitivity analysis

We considered sensitivity analyses to assess the impact of study quality (whether there was a difference between studies employing an intention-to-treat analysis and an on-treatment analysis) where data needed to perform such analyses were available from the included papers. We also considered a sensitivity analysis to assess the influence of methodological quality on the intervention

effect for each outcome by comparing the outcomes of those trials with low risk of bias with the outcomes of all the included studies. Following the *Cochrane Handbook* (Higgins 2011), we made only informal comparisons, and did not conduct individual forest plots for each sensitivity analysis, but provided a summary table.

RESULTS

Description of studies

Twelve studies were European (Austria, Denmark, Germany, Italy, Norway, Spain, UK), and three were from the USA. All the European studies were conducted at hospital clinics or rehabilitation centres. One of the USA studies recruited participants from both clinic and community settings; the other two USA studies did not specify the exact location (Chiaravalloti 2005; Chiaravalloti 2013). The study from Italy was the only multicentre study (Solari 2004), with six Italian centres.

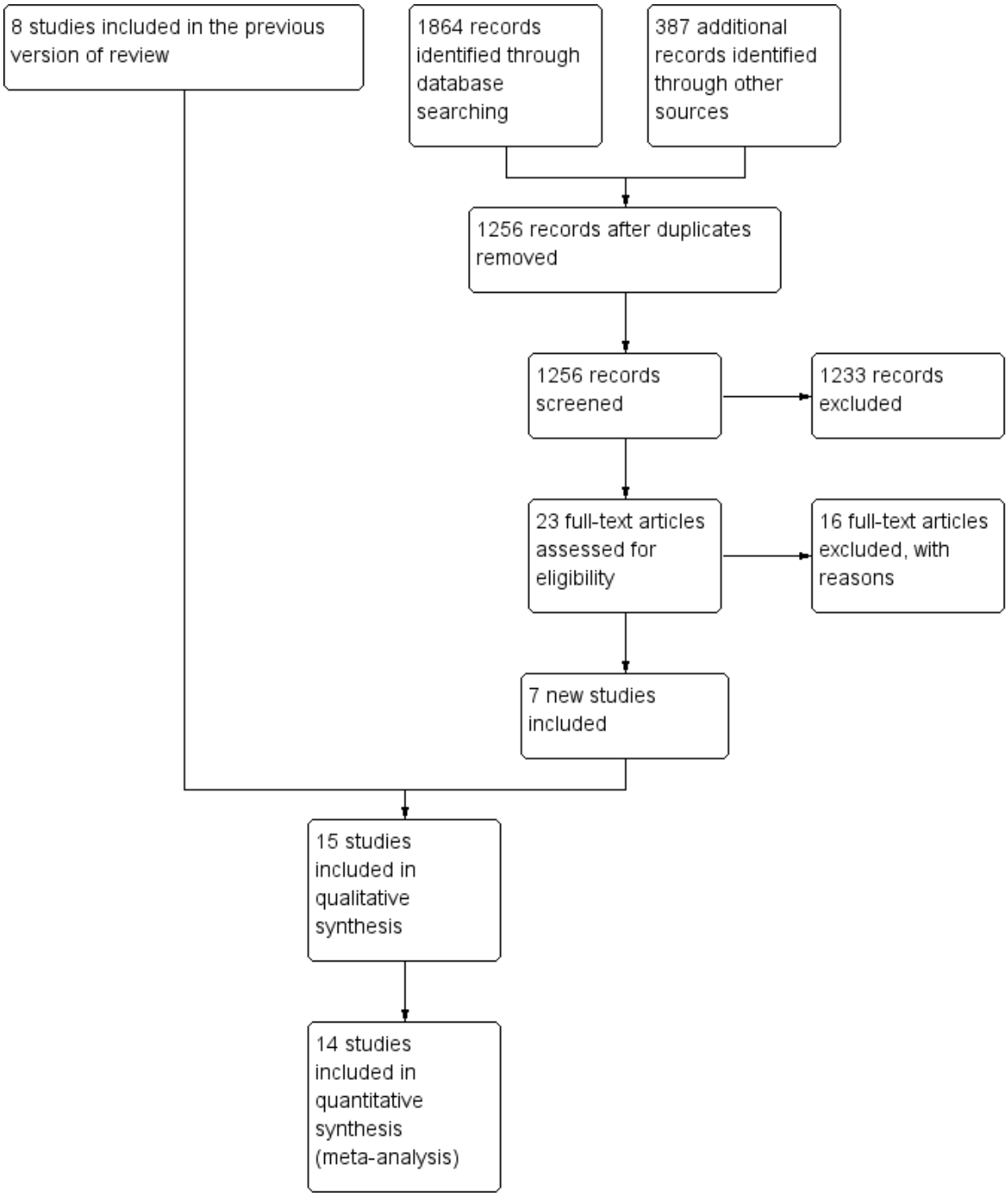
Results of the search

We identified a total of seven studies using the above-mentioned search strategy. We eliminated articles based on the following exclusion criteria:

1. not MS, or a mixed-aetiology group without at least 75% of the sample being people with MS;
2. not a memory study, or did not have a separate memory component if within the context of a larger "cognitive rehabilitation" (or "cognitive retraining" or "neuropsychological rehabilitation") study;
3. not a rehabilitation intervention study; and
4. not an RCT.

Eight studies from the previous review were added to the seven new studies in the final analysis. Please see Figure 1.

Figure 1. Flow diagram showing article screening process



Included studies

Fifteen studies, comprising a total of 989 participants, met the inclusion criteria for this review (Chiaravalloti 2005; Chiaravalloti 2013; Carr 2014; das Nair 2012; Gich 2015; Hancock 2015; Hanssen 2015; Hildebrandt 2007; Lincoln 2002; Mendozzi 1998; Pusswald 2014; Solari 2004; Stuifbergen 2012; Tesar 2005), and the Jønsson 1993 study was included in the review, but excluded from the meta-analysis because the raw data was unattainable.

Solari 2004 was a multicentre trial, and employed a site-stratified schedule. Hancock 2015 utilised a block-stratified randomisation procedure to ensure that equal types of each MS subtype were included in the intervention and control groups, and Gich 2015 stratified by level of cognitive impairment.

All but three studies mentioned the method of generating the random schedule (Hancock 2015; Mendozzi 1998; Tesar 2005). One study reported that randomisation was "performed by a lottery by the director of the rehabilitation centre" (Hanssen 2015). Three studies used quasi-randomisation: Chiaravalloti 2005 used odd-even random allocation, and Hildebrandt 2007 and Pusswald 2014 allocated by alternating between intervention and control. Six trials reported independent randomisation (Carr 2014; Chiaravalloti 2013; das Nair 2012; Lincoln 2002; Solari 2004; Tesar 2005), and Jønsson 1993 and Stuifbergen 2012 used a closed-envelope method. Mendozzi 1998 randomised the first 30 participants, and purposefully assigned the last 30 to balance age, gender, and education between groups; all data were included in our analysis.

Participants were diagnosed with MS using the Poser criteria, Poser 1983, in six studies, using the McDonald criteria, McDonald 2001, in four studies (Chiaravalloti 2013; Hancock 2015; Hildebrandt 2007; Pusswald 2014), and the Schumacher criteria, Schumacher 1965, in one study (Jønsson 1993). Four studies did not report the criteria used to diagnose MS, but merely stated that participants had clinically definite MS (Carr 2014; das Nair 2012; Hanssen 2015; Stuifbergen 2012). Eleven studies included participants with mixed types of MS (relapsing remitting MS (RRMS) and secondary progressive MS (SPMS) in das Nair 2012; Gich 2015; Lincoln 2002; Mendozzi 1998; Tesar 2005; and RRMS, SPMS, and primary progressive MS (PPMS) in Carr 2014; Chiaravalloti 2005; Chiaravalloti 2013; Hancock 2015; Hanssen 2015; Jønsson 1993). One study included participants with RRMS only (Hildebrandt 2007). The type of MS was not reported in three studies (Pusswald 2014; Solari 2004; Stuifbergen 2012). The number of participants in the studies ranged from 19, in Tesar 2005, to 240, in Lincoln 2002, and the number of participants in treatment or control groups ranged from seven, in das Nair 2012, to 82, in Lincoln 2002. Most participants were in their 40s. Varied gender ratios were reported, with percentage of women ranging from 47%, in Jønsson 1993, to 87.5%, in Hancock 2015. The participants had a minimum of elementary education in most studies, with the participants from the USA having the highest number of years of education (15.57 in intervention, 15.61 in control); Chiaravalloti 2013). One study did not report this demographic variable (Tesar 2005). The groups were comparable on assessed baseline characteristics in seven studies (Carr 2014; Chiaravalloti 2013; Gich 2015; Hanssen 2015; Lincoln 2002; Pusswald 2014; Tesar 2005), and in the other studies where differences were observed, they were statistically corrected (Chiaravalloti 2005; das Nair 2012; Hancock 2015; Hildebrandt 2007; Jønsson 1993; Solari 2004), with the exception of Mendozzi 1998 and Stuifbergen 2012.

Twelve studies used two-group comparisons (treatment versus control), and three studies employed three-group comparisons (das Nair 2012; Lincoln 2002; Mendozzi 1998). Lincoln 2002 used assessment versus assessment plus feedback versus assessment plus feedback and treatment; Mendozzi 1998 examined specific cognitive retraining versus non-specific cognitive retraining versus control; and das Nair 2012 investigated restitution versus compensation versus self help control.

Eight studies used individual treatment (Gich 2015; Hancock 2015; Hildebrandt 2007; Jønsson 1993; Lincoln 2002; Mendozzi 1998; Pusswald 2014; Solari 2004), and six had group interventions (Carr 2014; Chiaravalloti 2005; Chiaravalloti 2013; das Nair 2012; Stuifbergen 2012; Tesar 2005). One study used a mix of both group and individual sessions (Hanssen 2015). The structure and content of the treatment programmes varied. Most interventions were of four to eight weeks duration (Chiaravalloti 2005; Chiaravalloti 2013; Hancock 2015; Hanssen 2015; Hildebrandt 2007; Jønsson 1993; Lincoln 2002; Mendozzi 1998; Pusswald 2014; Solari 2004; Stuifbergen 2012; Tesar 2005). Carr 2014 and das Nair 2012 had 10-week programmes, and Gich 2015 used a six-month programme. The Lincoln 2002 study, having had individual treatment sessions, only specified the time frame for the interventions (that is maximum six months' postassessment). Sessions ranged from 30 minutes, in Hildebrandt 2007 and Pusswald 2014, and 2 hours, in Hanssen 2015, and participants met one to three times a week in all studies except Mendozzi 1998, where the treatment was bi-weekly.

In two studies, the contents of the treatment programmes were individualised(Lincoln 2002; Hanssen 2015), depending on the needs of the participants. Six studies used comprehensive memory rehabilitation programmes (including teaching participants to use internal and external memory aids) (Carr 2014; das Nair 2012; Jønsson 1993; Lincoln 2002; Pusswald 2014; Tesar 2005). Seven studies employed computerised memory- and attention-retraining packages (Gich 2015; Hancock 2015; Hildebrandt 2007; Mendozzi 1998; Pusswald 2014; Solari 2004; Stuifbergen 2012),

and Chiaravalloti 2005 and Chiaravalloti 2013 used the Story Memory Technique, which involved the use of imagery and story generation. Studies that had a sham or attention placebo control group reported having ensured that these groups had minimal memory content, thereby reducing contamination (Chiaravalloti 2005; Chiaravalloti 2013; das Nair 2012; Hancock 2015; Jønsson 1993; Solari 2004).

The 15 included studies used a range of outcome measures. All studies included at least one measure of learning or memory, with the exception of Hanssen 2015, where outcomes were related to psychological functioning and impact of disease.

Five studies used subjective measures of memory. Three studies, Carr 2014, das Nair 2012, and Lincoln 2002, used the Everyday Memory Questionnaire (EMQ) (Sunderland 1983), and das Nair 2012 used Internal and External Memory Aids Questionnaires based on the Memory Aids Questionnaire (Wilson 1984); one study, Chiaravalloti 2005, used the Memory Failures Questionnaire (MFQ) (Gilewski 1990); and one study, Stuifbergen 2012, used the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (Benedict 2004).

Seven trials used list-learning tasks: Hopkins Verbal Learning Task-Revised (HVLT-R) (Benedict 1998) (Chiaravalloti 2005); Verbal Learning Test (VLT) (Sturm 1999a) (Tesar 2005); California Verbal Learning Task-II (CVLT) (Delis 2000) (Chiaravalloti 2013; Hildebrandt 2007; Stuifbergen 2012); Auditory Verbal Learning Test (AVLT) (Lezak 2004) (Hancock 2015); Selective Reminding Task (Gich 2015; Rao 1993); and the list-learning task used by one study was not specified (Jønsson 1993). Six studies used neuropsychological test batteries or subtests of these. One study, Mendozzi 1998, used the memory scale of the Luria-Nebraska Neuropsychological Battery (LNNB) consisting of 13 items (Golden 1980). Subtests from other test batteries included Buschke Selective Reminding Test from an Italian version of the Brief Repeatable Battery of Neuropsychological Tests (BRBNT) (Solari 2002), unspecified tests from the Rivermead Behavioural Memory Test (RBMT-E) (Wilson 1999), and the Doors and People Test (Baddeley 1994). Pusswald 2014 used the MUSIC assessment (Calabrese 2004), and Jønsson 1993 used an unspecified battery. Non-verbal memory was assessed using individual tests or part of a battery. Individual tests included the Noverbaler Lerntest (NVLT) (Sturm 1999b) (Tesar 2005), and an unspecified 50-faces recognition test (Jønsson 1993).

The most frequently used mood measure was the Beck Depression Inventory (BDI) (Beck 1987), used in four studies (Chiaravalloti 2005; Hancock 2015; Hildebrandt 2007; Tesar 2005). Three studies, Carr 2014, das Nair 2012, and Lincoln 2002, used the General Health Questionnaire (GHQ-28) (Goldberg 1988); one, Chiaravalloti 2013, used the Chicago Mood Depression Inventory (CMDI) (Nyenhuis 1998); and another, Solari 2004, used the Italian version of the CMDI (Solari 2003).

Three studies (Hancock 2015; Solari 2004; Lincoln 2002) assessed quality of life using the Multiple Sclerosis Quality of Life (MSQOL-54; Vickrey 1995), and two studies, Carr 2014 and Hanssen 2015, used the Multiple Sclerosis Impact Scale (MSIS-29) (Hobart 2001).

Only two studies examined whether their rehabilitation programme had an effect on instrumental ADL (das Nair 2012; Lincoln 2002), by using the Extended Activities of Daily Living scale (EADL) (Nouri 1987). Chiaravalloti 2013 assessed functional independence with the Functional Assessment of Multiple Sclerosis (FAMS) (Cella 1996).

Nine studies were observer-blinded RCTs or quasi-randomised trials (Carr 2014; das Nair 2012; Gich 2015; Hildebrandt 2007; Jønsson 1993; Lincoln 2002; Mendozzi 1998; Stuifbergen 2012; Tesar 2005), and four were observer- and participant-blinded (Chiaravalloti 2005; Chiaravalloti 2013; Hancock 2015; Solari 2004). One study reported that blinding of participants was not possible due to the nature of the intervention, and there was no mention of observer blinding (Hanssen 2015). However, all outcomes were self report questionnaire-based, therefore blinding was not deemed necessary. One study reported that outcome assessors were not blinded (Pusswald 2014). Outcomes were assessed by an individual blind to treatment allocation in all studies, with the exception of four (Hanssen 2015; Jønsson 1993; Pusswald 2014; Tesar 2005).

Excluded studies

We excluded 33 studies on the basis of the exclusion criteria specified for this review. Two were studies of Alzheimer's disease, not MS (Akhtar 2006; Loewenstein 2004); four were not related to memory (comparative study of Barthel Index and Functional Independence Measure in van der Putten 1999, and falls in Aisen 1994, Canellopoulou 1998, and Flavia 2010); and one was a systematic review, not an intervention study (Thomas 2006). Five studies were not specific to memory, but general neuropsychological rehabilitation, attention, or information processing (Amato 2014; Goreover 2011; Mattioli 2012; Mäntynen 2014; Rosti-Otajärvi 2013a; Rosti-Otajärvi 2013b). Three studies used healthy controls instead of an MS control group (Ernst 2013; Vogt 2009; Wilson 2001), and Wilson 2001 also did not distinguish between results for people with MS and others with acquired progressive brain injury. Seven studies were not RCTs or quasi-RCTs (one quasi-experimental waiting-list control: Rodgers 1996; one small group study: Allen 1998; one involving a healthy control group: Aldrich 1995; two without random allocation: Brenk 2008; Brissart 2013; one with no control group: Brissart 2010; and two with healthy controls: Chiaravalloti 2003; Ernst 2013). One study was a brain imaging study and had an active control group (Bonavita 2015). One study used a "music intervention" (Thaut 2014). One study was not considered to be a rehabilitation study according to out inclusion criteria because it only involved one hour-long session of memory retraining (Moore 2008). Three studies used the same sample, or a subgroup of the sample, of Chiaravalloti 2013

(Chiaravalloti 2012; Dobryakova 2014; Leavitt 2012), and another, Martin 2014, was a subgroup analysis of das Nair 2012, and was therefore not included. Finally, one study was a conference poster presentation, and no full text could be found (Nurova 2014).

Risk of bias in included studies

The risk of bias in the 15 included studies was generally low (see Figure 2 and Figure 3), with some high risk of selection bias and detection bias associated with random sequence generation in four studies (Chiaravalloti 2005; Hildebrandt 2007; Mendozzi 1998; Pusswald 2014), allocation concealment in two studies (Chiaravalloti 2005; Hanssen 2015), lack of blinding in two studies (Pusswald 2014; Tesar 2005), incomplete outcome data in two studies (Chiaravalloti 2013; Hancock 2015), and possible selective reporting in one study (Hancock 2015). We judged the risk of bias to be unclear in some instances mainly due to insufficient reporting of the methods used for random sequence generation (Gich 2015; Hanssen 2015; Jønsson 1993; Tesar 2005), allocation concealment (Gich 2015; Hancock 2015; Hildebrandt 2007; Mendozzi 1998; Pusswald 2014), blinding (Hanssen 2015; Jønsson 1993), and handling incomplete outcome data (Chiaravalloti 2005; Hanssen 2015; Jønsson 1993; Mendozzi 1998; Pusswald 2014; Tesar 2005).

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

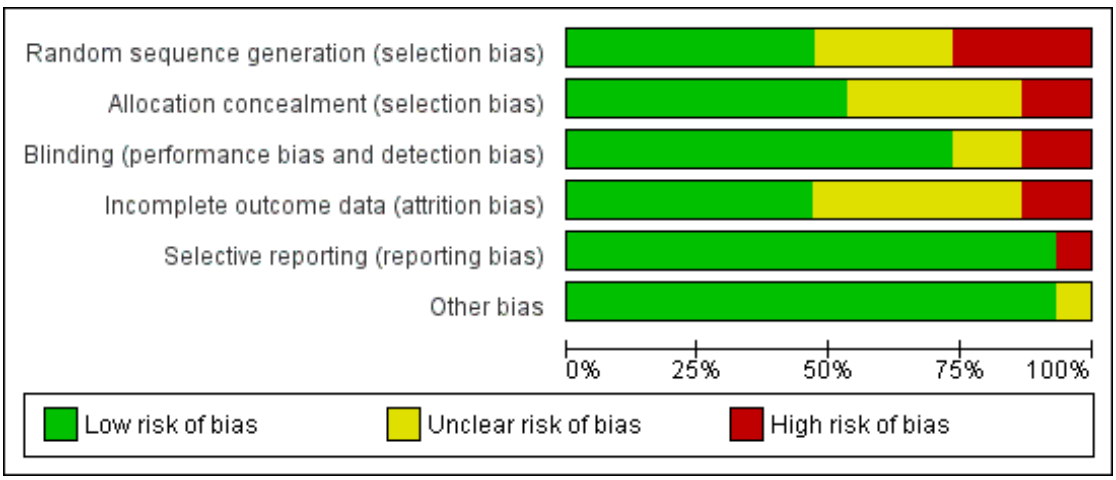
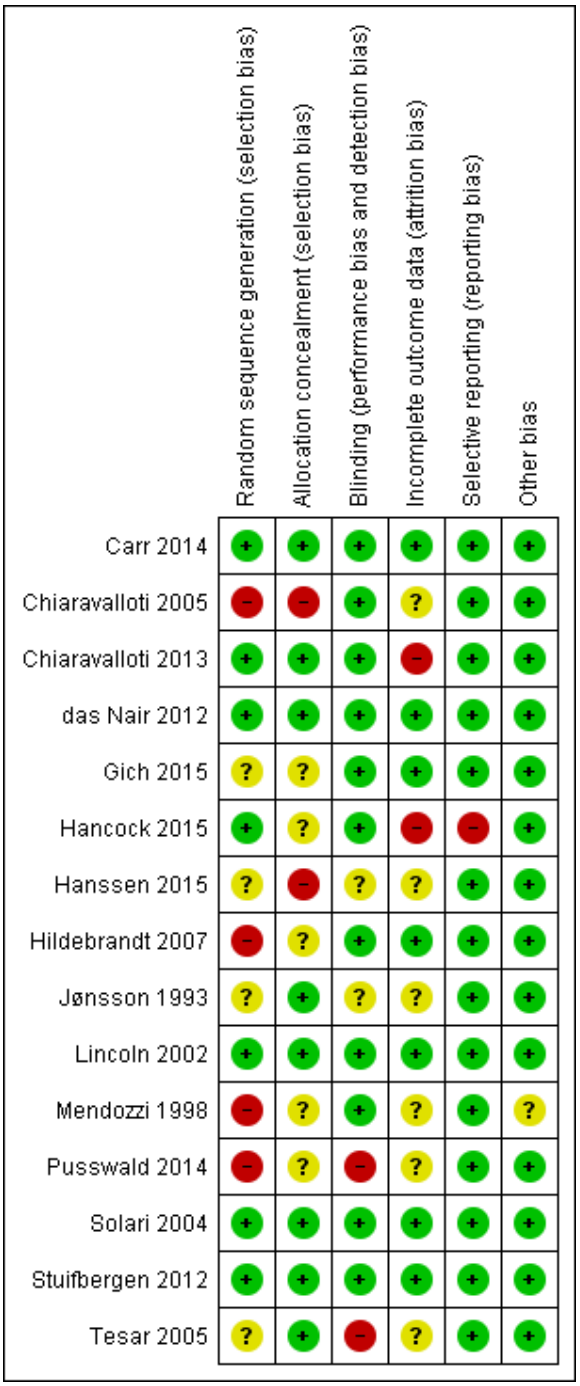


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Random sequence generation

Four studies were judged to have a low risk of selection bias due to having adequate random sequence generation, having used a computerised random number generator by an independent unit (Carr 2014; Chiaravalloti 2013; das Nair 2012; Lincoln 2002; Solari 2004) and one used a random number generator from the study data analyst that was created prior to recruitment and kept in sealed envelopes (Stuifbergen 2012). Four studies were judged not to have adequate sequence generation and therefore a high risk of bias as the methods involved were quasi-random 'odd-even' or alternating allocation (Chiaravalloti 2005; Hildebrandt 2007; Pusswald 2014), and one study only randomised half the sample with no generation method stated (Mendozzi 1998). The method used for random sequence generation and the risk of bias in four other studies was unclear (Gich 2015; Hanssen 2015; Jønsson 1993; Tesar 2005).

Allocation

We judged eight studies to have a low risk of selection bias due to effectively concealing allocation into groups using a computerised random number generator by an independent unit (Carr 2014; Chiaravalloti 2013; das Nair 2012; Lincoln 2002; Solari 2004), a closed envelope system (Jønsson 1993; Stuifbergen 2012), or having a separate staff member who was not otherwise involved in the study complete allocation (Tesar 2005). We judged two studies as not having concealed allocation to groups, suggesting a high risk of bias: one having used "odd-even" allocation completed by the principal investigator (Chiaravalloti 2005), and one stating that allocation concealment was not possible (Hanssen 2015). Five studies were unclear in their explanation of allocation concealment: one informing participants whether they were to receive the intervention or assessment only (Hildebrandt 2007); one in which the principal investigator allocated groups and what other involvement he or she had in the study was not clearly explained (Mendozzi 1998); and three studies not mentioning allocation concealment (Gich 2015; Hancock 2015; Pusswald 2014).

Blinding

Seven studies were observer blinded (Carr 2014; das Nair 2012; Gich 2015; Hildebrandt 2007; Lincoln 2002; Mendozzi 1998; Stuifbergen 2012), and four were double blind (Chiaravalloti 2005; Chiaravalloti 2013; Hancock 2015; Solari 2004), therefore suggesting a low risk of performance and detection bias. One study reported that blinding of participants was not possible due to the nature of the intervention (Hanssen 2015), and there was no mention of observer blinding, but because the outcomes were self report questionnaire based, we deemed this study to have an unclear risk of bias. Two studies did not use any blinding procedures, suggesting a high risk of bias (Pusswald 2014; Tesar 2005), and another was unclear in its description of the methodology used (Jønsson 1993).

Incomplete outcome data

We deemed two studies to be at high risk of attrition bias: in one study (Chiaravalloti 2013), there were multiple dropouts but no discussion of how missing data were dealt with, and the study did not employ intention-to-treat analysis; in the other study, the postrandomisation attrition level was 44% (Hancock 2015). Five studies did not address incomplete outcome data, which we deemed to be at unclear risk of bias: two studies did not use intention-to-treat analysis and reported one dropout, in Chiaravalloti 2005, and two dropouts, in Hanssen 2015; in another, participant outcome data were replaced with mid-trial data if a participant dropped out (Mendozzi 1998); and two studies did not explain how drop-out data were handled (Jønsson 1993; Tesar 2005). One study conducted analyses on data for those participants who completed the outcome assessments (Lincoln 2002), one used listwise deletion and baseline data imputed for any missing follow-up data (das Nair 2012), and in two studies (Solari 2004; Stuifbergen 2012), missing values were imputed according to the last observation carried forward method. In one study, where less than 10% of items were missed on a questionnaire, these were replaced with the mean for the questionnaire (Carr 2014).

Selective reporting

We deemed one study to have a high risk of reporting bias (Hancock 2015), as the paper only reported on the memory outcomes, despite other outcomes having been assessed at follow-up, and data were only reported for "good adherers" to the intervention.

Other potential sources of bias

We judged 14 studies to have a low risk of other potential sources of bias (Carr 2014; Chiaravalloti 2005; Chiaravalloti 2013; das Nair 2012; Gich 2015; Hancock 2015; Hanssen 2015; Hildebrandt 2007; Jønsson 1993; Lincoln 2002; Pusswald 2014; Solari 2004; Stuifbergen 2012; Tesar 2005). One study had a potential source of bias, as one participant in the treatment group discontinued cognitive retraining and was replaced by a new entry without further explanation (Mendozzi 1998).

Effects of interventions

See: **Summary of findings for the main comparison** Memory rehabilitation for people with multiple sclerosis

In this section, we first present study-specific information regarding intervention effect on memory outcomes, and then present the meta-analysis, synthesising results on various domains.

Seven studies concluded that there were no significant differences between the treatment and control groups on measures of memory, particularly after adjustments were made for multiple testing (Carr 2014; Chiaravalloti 2005; das Nair 2012; Hancock 2015; Jønsson 1993; Lincoln 2002; Solari 2004). Seven studies reported significant differences on memory measures favouring the treatment groups (Chiaravalloti 2013; Gich 2015; Hildebrandt 2007; Mendozzi 1998; Pusswald 2014; Stuifbergen 2012; Tesar 2005). One study did not use memory outcomes (Hanssen 2015). Gich 2015 reported significant differences favouring treatment on some subtests of the BRBN (Rao 1993), although no significant differences were reported on the list-learning task of the BRBN used in this meta-analysis. Hildebrandt 2007 reported improvements for the treatment group in the Learning Trials and Long Delay Free Recall subtests of the CVLT (Niemann 2003). Stuifbergen 2012 reported improvements in the CVLT total both over time and by group, and showed significantly more use of memory strategies in the intervention compared with control. Chiaravalloti 2013 showed a greater learning slope for the treatment group compared to the control on the CVLT-II (Delis 2000). Tesar 2005 reported improvements on the computer-aided card-sorting test (CKV), Drühe-Wienholt 1998, and the Mosaic Test of the Hamburg Wechsler Intelligence Test (HAWIE-R), Tewes 1991, for the treatment group. Chiaravalloti 2005 observed no significant difference between the treatment and control groups on their list-learning task (HVLT-R) (Benedict 1998), but on subgroup analysis, we observed significant improvement on this task for the moderate-to-severe memory-impaired subgroup, but not for other groups. However, this subgroup analysis was carried out only on the treatment group, which had 14 participants. Mendozzi 1998 reported improvement in the specific cognitive-retraining group on seven measures of memory (Spatial Span from the Corsi, Digit Span Forward and Backward, Visual Reproduction, and Paired Associates-Hard from the Italian Weschler Memory Scale (WMS), Wechsler 1945, and the LNNB, Golden 1980. There was an improvement in Digit Span Forward only in the non-specific cognitive rehabilitation group.

Outcome 1: Subjective memory measures

Five studies included subjective measures of participants' immediate and long-term memory functioning (Carr 2014; Chiaravalloti 2005; das Nair 2012; Lincoln 2002; Stuifbergen 2012). Three of these studies, Carr 2014, das Nair 2012, and Lincoln 2002, used the EMQ (Sunderland 1983); one, Stuifbergen 2012, used the MSNQ (Benedict 2004); and one, Chiaravalloti 2005, used the MFQ (Gilewski 1990). However, we found no significant effect of treatment on subjective reports of memory either immediately (standardised mean difference (SMD) of 0.04 (95% CI -0.19 to 0.27) P = 0.73) Analysis 1.1 or long term (SMD of 0.04 (95% CI -0.19 to 0.27) P = 0.71) Analysis 1.2.

Outcome 2: Objective memory measures

Eleven studies included objective measures of memory immediately after treatment (Chiaravalloti 2005; Chiaravalloti 2013; das Nair 2012; Gich 2015; Hancock 2015; Hildebrandt 2007; Mendozzi 1998; Pusswald 2014; Solari 2004; Stuifbergen 2012; Tesar 2005), and six of these studies examined long-term effects of treatment (Chiaravalloti 2005; Chiaravalloti 2013; das Nair 2012; Solari 2004; Stuifbergen 2012; Tesar 2005). The outcome measures used were idiosyncratic to each study. We found significant differences between intervention and control in objective memory measures at both immediate and long-term follow-ups, with a SMD of 0.23 (95% CI 0.05 to 0.41) P = 0.01 Analysis 2.1 and SMD of 0.26 (95% CI 0.03 to 0.49) P = 0.03 Analysis 2.2, respectively. The intervention group performed significantly better than the control on both immediate and long-term follow-ups.

Outcome 3: Mood

Nine studies included measures of participants' mood immediately after treatment (Carr 2014; Chiaravalloti 2005; Chiaravalloti 2013; das Nair 2012; Hancock 2015; Hildebrandt 2007; Lincoln 2002; Solari 2004; Tesar 2005), and seven of these studies examined long-term effects on mood (Carr 2014; Chiaravalloti 2005; Chiaravalloti 2013; das Nair 2012; Lincoln 2002; Solari 2004; Tesar 2005). Four studies, Chiaravalloti 2005, Hancock 2015, Hildebrandt 2007, and Tesar 2005, used the BDI (Beck 1987), three, Carr 2014, das Nair 2012, and Lincoln 2002, used the GHQ (Goldberg 1988), and two, Chiaravalloti 2013 and Solari 2004, used the CMDI (Nyenhuis 1998). However, we found no significant effect of treatment on mood either immediately (SMD of 0.02 (95% CI -0.16 to 0.20) P = 0.81) Analysis 3.1 or long term (SMD of -0.01 (95% CI -0.21 to 0.20) P = 0.96) Analysis 3.2.

Outcome 4: Functional abilities / Activities of daily living (ADL)

Two studies included measures of participants' ADL immediately after treatment and long term (das Nair 2012; Lincoln 2002). Both studies used the EADL (Nouri 1987). However, we found no effect of treatment on ADL immediately (SMD of -0.13 (95% CI -0.60 to 0.33) P = 0.57) Analysis 4.1, and at the long-term follow up it appeared that the intervention group performed worse than the control group (SMD of -0.33 (95% CI -0.63 to -0.03) P = 0.03) Analysis 4.2.

Outcome 5: Quality of life (QoL)

Seven studies included measures of participants' QoL immediately after treatment (Carr 2014; Chiaravalloti 2013; Hancock 2015; Hanssen 2015; Hildebrandt 2007; Lincoln 2002; Solari 2004), and five of these studies examined the long-term effects on QoL (Carr 2014; Chiaravalloti 2013; Hanssen 2015; Lincoln 2002; Solari 2004). Two studies used the 36-Item Short Form Health Survey (SF-36) (Ware 2001), one used the Mental Health composite score from the SF-36 (Lincoln 2002) and one, Hildebrandt 2007, calculated a mental score using the 12-Item Short Form Health Survey (SF-12) (Bullinger 1998). Two studies, Carr 2014 and Hanssen 2015, used the MSIS-29(Hobart 2001), one, Chiaravalloti 2013, used the FAMS(Cella 1996), and two studies, Hancock 2015 and Solari 2004, used the MSQOL-54(The WHOQOL Group 1993). We found a significant effect on the immediate follow-up (SMD 0.23 (95% CI 0.05 to 0.41) P = 0.01), showing the intervention group to have significantly higher scores for QoL compared with the control group Analysis 5.1. We found no significant effect of treatment at the long-term follow-up (SMD 0.16 (95% CI -0.03 to 0.36) P = 0.11) Analysis 5.2.

DISCUSSION

Summary of main results

In the last two decades research groups from Europe and North America have begun to address memory problems associated with MS. However, the literature base examining the effectiveness of memory rehabilitation for MS is weak. While single-case and uncontrolled studies have found memory rehabilitation to be effective in reducing memory or psychological problems, these results have not been consistently replicated in RCTs.

We included 15 RCTs or quasi-randomised trials in this review. These studies were either memory rehabilitation studies or cognitive rehabilitation trials with a specific memory component that included a memory intervention. These trials were mostly of relatively poor quality, with many still not adhering to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Moher 2001). Descriptions of the randomisation protocol, blinding, and content of treatment and control groups were poor in most studies.

Studies generally had modest sample sizes, and used impairment-level outcome assessments to determine the effectiveness of the intervention. One limitation was we could only obtain information on whether the studies used intention-to-treat or per-protocol analyses for six studies (Carr 2014; das Nair 2012; Hildebrandt 2007; Lincoln 2002; Solari 2004; Stuifbergen 2012), therefore we could not complete a sensitivity analysis of intention-to-treat in comparison with per-protocol analysis. However, we were able to conduct a sensitivity analysis comparing studies judged to be at low risk of bias to all included studies (see Table 1). Our interpretation of the sensitivity analysis suggests that while the quality of the trials did not affect most outcomes, some differences were observed in the objective memory outcomes (both at immediate and long term) and quality of life (immediate) outcome, with studies with higher risk of bias inflating the overall effect size estimates for these outcomes, and the test of overall effect changing from being statistically significant to not significant when studies at high risk of bias were excluded. This suggests that lower-quality studies may have positively influenced the outcomes. Only one study had a large sample size and sufficient data available to complete a subgroup analysis (Lincoln 2002). A subgroup meta-analysis on the basis of type of MS will therefore need to be completed in a future review update when more studies become available.

Seven individual studies reported positive results on memory outcomes from their memory rehabilitation groups (Chiaravalloti 2005; Gich 2015; Hildebrandt 2007; Mendozzi 1998; Pusswald 2014; Stuifbergen 2012; Tesar 2005). However, these results need to be interpreted in the context of the methodological limitations and the measures used to assess effectiveness, which may have influenced the outcome. In fact, most of the studies that reported a positive memory outcome for the intervention groups were also rated as having a high or unclear risk of bias. Two well-designed studies with larger sample sizes did not find evidence of effectiveness of cognitive or memory rehabilitation for people with MS (Lincoln 2002; Solari 2004). Indeed, one study, Lincoln 2002, found that the intervention group performed worse than the control group on the EADL (Nouri 1987) scale assessed at long-term follow up, which contributed to an overall SMD of -0.33, suggesting control performed significantly (P = 0.03) better than intervention on ADL. However, this difference, the authors state, could have been caused by chance occurrences resulting from uneven randomisation. We could not control for this variable (EADL) as a covariant, because baseline scores on this measure were not available. Other individual studies found significant effects favouring the treatment relating to mood, in Chiaravalloti 2013, das Nair 2012, and Jønsson 1993, and QoL, Chiaravalloti 2013 and Solari 2004.

The results of this review suggest there is some evidence to support the effectiveness of memory rehabilitation on objective memory tests or observer-rated measures of memory. However, this needs to be viewed in relation to the quality of the evidence for this outcome, with the GRADE rating showing as very low for immediate follow-up, and low for long-term follow-up. Furthermore, improvements seen for the intervention groups were on outcome measures that assessed function at an impairment level, that is mainly list-learning tasks. The degree to which this has the potential to generalise to everyday life, given the lack of ecological validity of these tests, is questionable. Results also suggest that treatment groups had better QoL scores immediately after the in-

tervention, but this was not maintained at long-term follow-up. Other results of this review suggest there is insufficient evidence to support or refute the effectiveness of memory rehabilitation on subjective memory tests. However, again, it is important to note the methodological quality on the GRADE rating was shown to be moderate for these outcomes.

Quality of the evidence

The literature-base examining the effectiveness of memory rehabilitation for people with MS is poor. We identified only 15 RCTs of memory rehabilitation for people with MS, and all but two had small sample sizes (Hanssen 2015; Lincoln 2002). However, studies included in this review were more methodologically sound than the memory rehabilitation RCTs included in systematic reviews of stroke or traumatic brain injury literature (das Nair 2007a; das Nair 2007b). This may be because most of these studies were conducted after the publication of the CONSORT statement and guidelines (Moher 2001). However, the guidelines were not always followed in these trials. The randomisation protocol was inadequate and was poorly reported for four studies (Chiaravalloti 2005; Hildebrandt 2007; Mendozzi 1998; Pusswald 2014). Gich 2015, Hanssen 2015, and Tesar 2005 did not clearly mention how the randomisation list was created or what procedures were undertaken; Jønsson 1993 used closed envelopes, but did not mention who created the random lists; Chiaravalloti 2005 employed odd-even random allocation; and Hildebrandt 2007 and Pusswald 2014 used alternating allocation. These two latter forms of allocation are not technically considered acceptable to qualify as an RCT (Glanville 2006), but are classed by Cochrane as a quasi-randomised trial (Higgins 2011), and were therefore included in this review. Mendozzi 1998 randomised only half the sample, with no stated random generation method. Seven studies reported their randomisation protocols adequately (Carr 2014; Chiaravalloti 2013; das Nair 2012; Hancock 2015; Lincoln 2002; Solari 2004; Stuifbergen 2012). Issues related to the success of blinding were not appropriately reported in the included studies, with the notable exception of Solari 2004, who stated how this was assessed. Jønsson 1993 acknowledged that adequate blinding was not possible in their trial. The studies we have added in this update have only marginally improved in terms of quality of reporting of trials (Carr 2014; Chiaravalloti 2013; Gich 2015; Hancock 2015; Hanssen 2015; Pusswald 2014; Stuifbergen 2012). This suggests that more work is needed to ensure that trialists follow the CONSORT statement (Moher 2001).

Furthermore, given that memory rehabilitation is a complex intervention (Craig 2008), much more detail is required about what participants experience in both the intervention and the control arms of the trial. Indeed, the description of the interventions was inadequate in most studies, and control groups were even less well described. Recently published guidelines such as the Template for Intervention Description and Replication (TIDieR) and the Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: revised guideline (Hoffman 2014; Möhler 2015), alongside more specific guidance for memory rehabilitation (Martin 2015), may help improve the quality of reporting of trials of complex interventions.

Inclusion and exclusion criteria were relatively well-defined, with all studies except three, Carr 2014, Hanssen 2015 and Stuifbergen 2012, employing the McDonald 2001, Poser 1983, Schumacher 1965 (or later) criteria to establish a diagnosis of MS. The three studies that did not use the above criteria did not mention how the diagnosis of MS was confirmed (Carr 2014; Hanssen 2015; Stuifbergen 2012). While most studies described the flow of participants through the trial, one did not (Tesar 2005), and only 11 of the 15 studies had flowcharts (Carr 2014; Chiaravalloti 2005; Chiaravalloti 2013; das Nair 2012; Gich 2015; Hancock 2015; Hanssen 2015; Lincoln 2002; Pusswald 2014; Solari 2004; Stuifbergen 2012).

The selection of outcome measures was poor, with most trials having opted for impairment-level measures or tests with modest ecological validity and minimal chance of generalisation of treatment effects to ADL. Only five studies employed subjective measures of memory (Carr 2014; Chiaravalloti 2005; das Nair 2012; Lincoln 2002; Stuifbergen 2012), which had some degree of ecological validity and were activity-level measures. However, these are prone to subjective reporting biases common to most Patient-Reported Outcome Measures (PROMs). Furthermore, another aspect of validity that should be considered relates to the cultural appropriateness of outcomes, which takes into account not only translation and adaptation of assessment tools, but also their validation.

Both parametric and nonparametric statistical tests were used to compare groups. Change scores were compared in five studies (Chiaravalloti 2005; Chiaravalloti 2013; Gich 2015; Hanssen 2015; Stuifbergen 2012), and all studies were concerned with significance testing. However, exact P values were only mentioned in seven trials (Carr 2014; das Nair 2012; Gich 2015; Hancock 2015; Lincoln 2002; Pusswald 2014; Solari 2004), with one trial providing all P values in tables that were readily accessible online as supplementary information (Chiaravalloti 2013). Three studies mentioned confidence intervals (Chiaravalloti 2005; Lincoln 2002; Solari 2004), and Lincoln 2002 and Solari 2004 also reported the post-hoc tests or statistical corrections or adjustments performed on their data. Six studies used intention-to-treat analysis (Carr 2014; das Nair 2012; Hildebrandt 2007; Lincoln 2002; Solari 2004; Stuifbergen 2012).

Only two studies reported feedback from the participants (Carr 2014; Tesar 2005), both of which used a feedback questionnaire. The feedback obtained was positive.

Potential biases in the review process

Two of the review authors were lead investigators for two of the included studies (das Nair 2012, Lincoln 2002), and named au-

thors on another included study (Carr 2014).

Other limitations of the review were that we only searched for papers in English, and we could only include mixed-diagnosis studies where separate data for those participants with MS were provided. Therefore, there may be more data available that we did not have access to. There were also potential overlaps between attention and memory retraining, where an intervention could be described as attention when it actually addressed memory, but to mitigate this we checked papers at full-text review to ensure that they were not excluded if a memory component was presented as part of the treatment. Finally, we searched GreyNet and the EThOS databases; however, we are not sure of the comprehensiveness of these, thus creating the possibility of further relevant grey literature that was not obtained via the searches.

Agreements and disagreements with other studies or reviews

This review complements the 'Psychological interventions for multiple sclerosis' intervention review (Thomas 2006). In one of their mini-reviews, Thomas 2006 found "some evidence of effectiveness of cognitive rehabilitation on cognitive outcomes, although this was difficult to interpret because of the large number of outcome measures used". Their interpretations have therefore been based on a narrative review of results from individual studies. The Thomas 2006 review covered interventions that were not specific to 'memory rehabilitation', however, their findings related to effectiveness of interventions to help people with cognitive impairments were inconclusive.

Similarly, the Rosti-Otajärvi 2011 review found evidence that memory span, working memory, and delayed memory were significantly improved for the treatment compared with the control group. However, their review found no significant differences between intervention and control for emotional functions, whereas this review has found some significant differences, notably QoL and ADL. Any discrepancies are likely due to the differences in inclusion criteria, as this review was specific to memory rehabilitation, or a cognitive rehabilitation with a memory component, whereas the Rosti-Otajärvi 2011 review evaluated a much larger breadth of neuropsychological interventions and outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

In the last two decades increasing attention has been given to memory problems as a frequent complaint for people with MS. Memory rehabilitation programmes are offered to some people with MS, but their effectiveness has been questionable. Small studies employing a mixture of internal and external memory aids, errorless learning, and environmental manipulation have yielded positive results. This review examined the evidence from RCTs and quasi-RCTs and found some evidence to suggest that memory rehabilitation is effective in improving memory performance on objective assessments across immediate and long-term follow-ups, but found no difference between intervention and control in subjective memory measures. Some improvement was also shown in quality of life for the intervention group at immediate follow-up. However, given the methodological limitations, and the low GRADE scores for significant outcomes, more research is required. There appeared to be no indication of harm caused by the interventions, but it must be noted that studies did not routinely report adverse effects.

Implications for research

The research base from which to draw inferences for clinical practice regarding the effectiveness of memory rehabilitation for MS is both quantitatively and qualitatively poor, but it has marginally improved since the previous review (das Nair 2012). RCTs, when conducted, tend to be of modest sample size, and mostly utilise impairment-level outcome measures, which have limited value in assessing the effectiveness of neurorehabilitation. These trials do not always adhere to the CONSORT guidelines (Moher 2001), which makes it difficult to get a full and true picture of the studies, and therefore limits the reader from making an informed decision regarding the fidelity of their conclusions. Missing information from such reports also make collating information for a meta-analysis difficult. Furthermore, results from positive trials may be difficult to implement in clinical practice if sufficient details about the actual intervention are not clearly spelt out. The TiDieR checklist and other more specific guidance for reporting of memory rehabilitation trials may help improve the quality of reporting trials of complex interventions (Hoffman 2014; Martin 2015). The results of this review indicate that more research is required to arrive at a definitive answer as to whether or not memory rehabilitation for MS is effective in reducing disability. It also highlights the need for more well-conceptualised, executed, and reported RCTs of memory rehabilitation that take into consideration the issues raised in this review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Carr 2014

Methods	Single-blind RCT, randomisation by off-site independent randomisation centre, computer generated random number sequence
Participants	n = 48 (E: 24, C: 24) Mean age E: 55.8, C: 52.9 Mean years of education E: 15.7, C: 13.5
Interventions	Group format, 10 sessions, each 1.5 hours long. Sessions included both compensation and restitution, including memory education, strategies to help focus attention, internal memory strategies, use of external aids
Outcomes	Intention-to-treat analysis used No significant differences between groups at 4 or 8 months on EMQ, MSIS-29. Experimental group scored better than control on GHQ-28 at 8 months' follow-up, no difference at 4 months
Notes	RCT: Randomised controlled trial, E: Experimental, C: Control, EMQ: Everyday Memory Questionnaire, MSIS-29: Multiple Sclerosis Impact Scale, GHQ-28: General Health Questionnaire

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "computer generated list prepared in advance of the study and held by an independent researcher at the University of Nottingham"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	Postal outcomes that were "scored by a researcher blind to group allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention to treat used. If less than 10% of items missed, these were replaced with mean for questionnaire
Selective reporting (reporting bias)	Low risk	All outcomes analysed and reported
Other bias	Low risk	None identified

Chiaravalloti 2005

Methods	Odd-even random allocation Participants kept blind to treatment
Participants	n = 29 Randomised (E: 15, C: 14) Completed: (E: 14, C: 14) Age: 45 to 46 years Education: 14 to 15 years Groups comparable on all but duration of illness variable (E: group longer disease duration)
Interventions	Group format 8 sessions (45-min sessions, 2/week) E: SMT (imagery and story) C: reading story and recall without SMT
Outcomes	Intention-to-treat analysis not used Non-significant results of group or time on HVLT-R, STAI, BDI Significant difference on MFQ (E > C); but subgroup analysis: significant difference in learning ability (HVLT-R) at follow-up 1 and 2 for moderate-severe group (E > C)
Notes	E: Experimental; C: Control; SMT: Story Memory Technique; HVLT-R: Hopkins Verbal Learning Test-Revised; STAI: State Trait Anxiety Inventory; BDI: Beck Depression Inventory; MFQ: Memory Functioning Questionnaire

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-random "odd-even" allocation
Allocation concealment (selection bias)	High risk	Odd/even allocation by primary investigator
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and assessors had no knowledge of group allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention to treat not used. 1 dropout
Selective reporting (reporting bias)	Low risk	No selective reporting apparent
Other bias	Low risk	None identified

Chiaravalloti 2013

Methods	Double-blind, placebo-controlled, randomised controlled trial
Participants	n = 86 (E: 41, C: 45) Groups similar in demographic and disease characteristics, disease-modifying therapy, pretreatment cognition, and emotional symptomatology
Interventions	mSMT, 10 sessions over 5 weeks (2 per week) Session length 45 minutes to 1 hour, focused on imagery and context 2 sessions on applying mSMT to real-life scenarios
Outcomes	Intention-to-treat analysis not used. Immediate follow-up: E group showed greater learning slope on CVLT (P = 0.007), E also showed significant improvement from baseline to follow-up on CVLT slope (P = 0.009). Significant differences (E > C) on RBMT story, FAMS general contentment, FrSBe Long-term follow-up: Decline in CVLT slope from immediate to 6 months' follow-up. Significant difference (E > C) on FAMS general contentment
Notes	E: Experimental; C: Control; mSMT: modified Story Memory Technique; CVLT: California Verbal Learning Task; RBMT: Rivermead Behavioural Memory Test; FAMS: Functional Assessment of Multiple Sclerosis; FrSBe: Frontal Systems Behaviour Scale

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computerised random number generator ... the individual responsible for group assignment was not otherwise involved in data collection and group assignment was verified by a second individual via duplicate copy of the randomization table generated before initiation of data collection"
Allocation concealment (selection bias)	Low risk	"treatment allocation was concealed"
Blinding (performance bias and detection bias) All outcomes	Low risk	"All RAs conducting assessments were blinded to group membership". Masking details given. Participants also blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	88 were randomised (E = 46, C = 42), but immediate outcomes were for E = 45, C = 41, and long term outcomes were for E = 40 and C = 38. No intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Tables given as supplement to all outcomes and statistical analyses

Chiaravalloti 2013 (*Continued*)

Other bias	Low risk	None identified

das Nair 2012

Methods	Single-blind RCT, randomisation by off-site independent randomisation centre, computer generated random number sequence
Participants	n = 39 with MS Randomised (A: 17, B: 12, C: 10) Mean age: 47.2 years Education years: 14.1 years
Interventions	Groups: A: Restitution - encoding and retrieval strategies, attention retraining B: Compensation - external memory aids C: Attention placebo - relaxation techniques 10 weekly sessions, 90 mins each
Outcomes	Intention-to-treat analysis used Non-significant differences between groups on RBMT-E, EMQ, EMAQ, GHQ, MATBD, and EADL; significant differences in IMAQ between groups; significant main-effect on RBMT-E and MATBD over time but across all 3 groups
Notes	Analysis used in this review: A + B vs C RCT: Randomised controlled trial; RBMT-E: Rivermead Behavioural Memory Test-Extended; EMQ: Everyday Memory Questionnaire; EMAQ: External Memory Aids Questionnaire; GHQ: General Health Questionnaire; MATBD: Mental Adjustment to Brain Damage; EADL: Extended Activities of Daily Living; IMAQ: Internal Memory Aids Questionnaire

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised random number generation by independent agency
Allocation concealment (selection bias)	Low risk	Allocation was not known by intervention provider until all 4 participants were allocated to a group
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessors were blind to the random allocation and the intervention participants received. Participants were requested not to disclose any information about intervention at follow-up

das Nair 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	List-wise deletion utilised and baseline data were imputed for missing follow-up data
Selective reporting (reporting bias)	Low risk	All data were analysed and results disclosed
Other bias	Low risk	None identified

Gich 2015

Methods	Randomised, controlled, single-blind pilot study
Participants	n = 43 (only 41 analysed), RRMS and SPMS E: 22 (21 analysed), C: 21 (20 analysed)
Interventions	Experimental group received 2x 75-minute sessions per week for 6 months, included written (crosswords, word searches), manipulative (origami, spatial games) and computerised tasks (working memory games, log and reasoning games), additionally participants completed 5-minute daily cognitive activities at home Control group received no treatment.
Outcomes	BRBNT: significant differences favouring experimental on 10/36 spatial task and word list generation. No significant differences on list-learning task (selective reminding task) - used in the meta-analysis
Notes	BRBNT: Brief Repeatable Battery of Neuropsychological Tests; RRMS: Relapsing remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Participants were randomly assigned to one of the two arms in a 1:1 ratio. The randomization was stratified to avoid possible confounding variables, using the level of cognitive impairment as strata". No mention of how the random sequence was generated
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessors blind to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysed only those who completed outcomes, only 1 withdrew from each group

Gich 2015 (*Continued*)

Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Hancock 2015

Methods	Blinded, placebo-controlled design, block-stratified randomisation method
Participants	n = 40 (n = 30 analysed) Mean age: 48.8y Mean education: 15.45y
Interventions	Active training group: completed a computerised cognitive training programme that specifically aimed to improve information-processing speed and working memory. Completed 30-minute intervals, 6 days per week for 6 weeks Control group: completed a computerised cognitive training programme that is almost identical to the active training group, but this programme is not intended to improve information-processing speed or working memory. This programme employed the same tasks as the former, but it did not increase in difficulty in order to challenge participants to improve. Same time intervals and length as active training group
Outcomes	Completed immediately after the 6-week training programme. No significant differences between groups on AVLT, BDI-FS, MSIS, MSQOL
Notes	AVLT: Auditory Verbal Learning Test; BDI-FS: Beck Depression Inventory-Fast Screen; MSIS: Multiple Sclerosis Impact Scale; MSQOL: Multiple Sclerosis Quality of Life

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A block stratified randomization method was employed"
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Invesigator who conducted assessment was blind to allocation, as were participants
Incomplete outcome data (attrition bias) All outcomes	High risk	71 were randomised and 31 "either withdrew from the study or were lost to follow up", however, no statistical differences were observed for those who completed compared to those who withdrew/lost to follow-up. Analysis on only those who completed the trial, and were "good adherers"

Hancock 2015 (*Continued*)

		to intervention (at least 80% sessions attended)
Selective reporting (reporting bias)	High risk	Analysis only on those who were "good adherers" and completed trial. Not all outcomes reported in published article (BDI and MSQOL not reported), unpublished data (received from author) used in this meta-analysis
Other bias	Low risk	None identified

Hanssen 2015

Methods	Prospective, randomised controlled design
Participants	n = 120, E: 60, C: 60 Inpatients at multidisciplinary rehabilitation centre
Interventions	Inpatient cognitive rehabilitation. All participants given baseline neuropsychological testing, control offered no feedback. Experimental group offered feedback, used to develop individualised plan Mix of individual and group sessions, focused around goal attainment. Sessions included psychoeducation, learning strategies for "keeping track of appointments and belongings". After discharge, those in experimental group had 6 bi-weekly telephone sessions focused on the goals they had set during the intervention
Outcomes	No memory outcomes. MSIS-29. Significant effect of group at 7 months' follow-up (experimental less distressed than control)
Notes	MSIS-29: Multiple Sclerosis Impact Scale; Analysis only on those completing outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomization was performed by a lottery controlled by the director of the rehabilitation center"
Allocation concealment (selection bias)	High risk	"Concealment of treatment allocation was not possible due to the nature of the intervention"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of blinding, however self reported questionnaires used as follow-ups

Hanssen 2015 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analysis only on those who completed follow-up assessments
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Hildebrandt 2007

Methods	Alternating allocation. Participants informed of intervention or assessment. Outcome assessor blind
Participants	n = 42; RRMS only Randomised: E: 17, C: 25 Mean age: E: 42 years; C: 36.5 years
Interventions	E: Memory and working memory rehab tasks. 30 mins/day, 5 days/week, for 6 weeks C: Assessments only
Outcomes	Intention-to-treat analysis used Non-significant results of CVLT - Short Delay Free/Cued Recall or CVLT - Long Delay Cued Recall Significant differences on CVLT long delay free recall Non-significant results of BDI, SF-12, EDSS
Notes	E: Experimental; C: Control; RRMS: Relapsing remitting multiple sclerosis; CVLT: California Verbal Learning Test; BDI: Beck Depression Inventory; SF-12: 12-Item Short Form Health Survey; EDSS: Expanded Disability Status Scale

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"Before the patients' assessment, randomisation was done by alternating between intervention and control group"
Allocation concealment (selection bias)	Unclear risk	"Assignment and enrolment was done by randomisation according to groups before the patients were contacted". Participants were informed of whether they would receive intervention, or assessment only
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants not blinded, healthcare providers not blinded. Outcome assessors reportedly blinded: "done by colleagues, who were not involved

Hildebrandt 2007 (*Continued*)

		in the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data
Selective reporting (reporting bias)	Low risk	No selective reporting apparent
Other bias	Low risk	None identified

Jønsson 1993

Methods	Closed-envelope randomisation
Participants	n = 40 (E: 20; C: 20) hospital inpatients; (16 + 16 completed) Mean age: 44.5 years (SD: 8.3) Education: 11.5 years (SD: 2.5) Gender: 19F, 21M Groups comparable on all variables, except visuospatial memory and visual perception (more impaired in E group) Mild-moderate cognitive impairments
Interventions	Individual treatment 1-1.5h, 3 times/week; mean total hrs: 17.2 (5.1) E: compensation (internal and external memory aids), substitution, direct training (puzzles, etc.) + neuropsychotherapy C: attention placebo: discussion and games
Outcomes	Intention-to-treat analysis not used Follow-up 1: E > C on visual perception (but could be due to regression towards the mean and ceiling effects) and BDI Follow-up 2: E > C on visuospatial memory and BDI (C group became more depressed)
Notes	E: Experimental; C: Control; SD: Standard deviation; BDI: Beck Depression Inventory

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly recruited"
Allocation concealment (selection bias)	Low risk	Closed-envelope system
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Patients were told there were 2 treatments, but not which was better"... and .. "Healthcare providers were not told of patients' allocation, but a few words would have given it away" ... and ..

Jønsson 1993 (*Continued*)

		"At follow up we were in principle blinded to what kind of treatment patients had been given", but patient report/talk could have broken blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	No selective reporting apparent
Other bias	Low risk	None identified

Lincoln 2002

Methods	Single-blind RCT; independent phone randomisation Computer generated numbers
Participants	n = 240 Randomised (A: 82; B: 79; C: 79) Completed (A: 77; B: 71; C: 73) Median age: 40 to 43 years Age left education: 16 years Groups comparable on baseline variables
Interventions	Individual treatment A: only baseline assessment with no feedback B: detailed cognitive assessment with feedback C: detailed cognitive assessment + feedback + internal and external memory aids
Outcomes	Intention-to-treat analysis used No significant differences between 3 groups on any measures at follow-up 1 or 2 for patient and relative data, except QoL (Questions 53 and 54 of the MSQOL-54) at follow-up 2
Notes	For this review A vs C compared; RCT: Randomised controlled trial; QoL: Quality of life

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"telephoning an independent department who had a computer generated allocation list"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias)	Low risk	"An independent assessor, who was unaware of the group allocation, assessed the

Lincoln 2002 (*Continued*)

All outcomes		outcome at 4 and 8 months after randomisation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis was just on those who completed the outcome assessments, however it included those who did not get the intervention as planned
Selective reporting (reporting bias)	Low risk	No selective reporting apparent
Other bias	Low risk	None identified

Mendozzi 1998

Methods	Single-blind, quasi-RCT
Participants	n = 30 randomly allocated to groups, n = 30 matched on age, gender, and education
Interventions	Computerised treatment A: Specific cognitive retraining B: Non-specific cognitive retraining C: Control group 15 bi-weekly sessions, 45 mins
Outcomes	Intention-to-treat analysis not used Specific group improved on 7 outcome measures, non-specific on 1 measure
Notes	For this review A vs C compared, because B was not considered cognitive rehabilitation; RCT: Randomised controlled trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Only half the sample randomised, with no stated generation method
Allocation concealment (selection bias)	Unclear risk	"Assignment by principal investigator, who was not involved in the CR or cognitive testing and scoring"
Blinding (performance bias and detection bias) All outcomes	Low risk	Single blinding: "the tests were always administered and scored by the same investigator who was not involved in the clinical work and was unaware of the treatment assignments"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participant data replaced mid-trial if dropped out
Selective reporting (reporting bias)	Low risk	No selective reporting apparent

Mendozzi 1998 (*Continued*)

Other bias	Unclear risk	1 participant in the specific cognitive retraining group discontinued retraining and was replaced by a new entry

Pusswald 2014

Methods	Alternating allocation
Participants	n = 40 (Intervention: 20, Control: 20) Both groups comparable on clinical and sociodemographic baseline characteristics
Interventions	Cognitive functional training, computer-based home training of divided attention, carried out 3/week for 30 minutes for 5 weeks alongside weekly 90-minute sessions in groups focusing on cognitive rehabilitation techniques and approaches, and included memory retraining Control group received no specific training.
Outcomes	Significant within-group effect on objective memory for intervention group when comparing before training to after training
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Alternating allocation
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Outcome assessor not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of incomplete data
Selective reporting (reporting bias)	Low risk	No selective reporting apparent
Other bias	Low risk	None identified

Solari 2004

Methods	Independent randomisation; computer-generated, site-stratified schedule; double-blind
Participants	n = 82 Randomised: E: 42; C: 40 Analysed: E: 40; C: 37 Age: E: 46.2 years (SD: 9.2); C: 41.2 years (SD: 10.6) Education: E: 21 C: 20 high school+
Interventions	Individual treatment 45 min, 2 per week, 8 weeks Computerised programmes E: memory and attention retraining C: visuoconstruction and visuomotor co-ordination
Outcomes	Intention-to-treat analysis used No significant differences between groups on any measures at follow-up 1 or 2, when Bonferroni adjustments made
Notes	E: Experimental; C: Control; SD: Standard deviation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"were assigned to one of the two interventions by an independent randomisation unit, using a computer-generated, site-stratified, randomisation schedule."
Allocation concealment (selection bias)	Low risk	"were assigned to one of the two interventions by an independent randomisation unit, using a computer-generated, site-stratified, randomisation schedule."
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, healthcare providers, and outcome assessors all blinded Outcome assessor asked to guess participant group
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Missing values were imputed according to the 'last observation carried forward' method"
Selective reporting (reporting bias)	Low risk	No selective reporting apparent
Other bias	Low risk	None identified

Stuifbergen 2012

Methods	Single-blind randomised controlled trial
Participants	n = 61 (Intervention: 34, Control: 27) Age range 24 to 60 years, mean: 47.95 Length of time since diagnosis range 1 to 29 years, mean: 12.2
Interventions	Group based; MAPSS-MS (Memory, Attention, and Problem Solving Skills for People with Multiple Sclerosis) 8 weekly, 2-hour group sessions focused on building efficacy for use of compensatory strategies, and use of a computer-assisted training programme. Home-based practice using the computer program
Outcomes	Significant difference between groups on CVLT-total (medium effect size) and Strategy subscale of the Multifactorial Memory Questionnaire (large effect size), E > C Both groups improved over time on neuropsychological testing, ADLs, and use of compensatory strategies
Notes	CVLT-total: California Verbal Learning Test; ADL: Activities of daily living; E: Experimental, C: Control

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Prior to the initiation of data collection, the data analysts for the project generated a random number sequence for randomization to intervention and control"
Allocation concealment (selection bias)	Low risk	Each allocation placed in sealed envelope prior to study start and opened by project director when participant randomised, to let them know their allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	"The staff members conducting neuropsychological assessments were blinded to participants' group assignment". States that those involved in intervention were not involved in collecting, entering, or analysing data
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention to treat; participant analysed if completed baseline and attended at least 1 class. Missing values replaced using last observation carried forward. If participant missed time point 2, but completed 1 and 3, then 2 was an average of 1 and 3

Stuifbergen 2012 (*Continued*)

Selective reporting (reporting bias)	Low risk	No selective reporting apparent, full analyses available
Other bias	Low risk	None identified

Tesar 2005

Methods	Simple random sampling with independent allocation
Participants	n = 19 (E: 10; C: 9) Mild-moderate cognitive deficits Groups comparable on baseline variables
Interventions	Group treatment E: 12 1-hour sessions in 4 weeks; neuropsychological training programme; computer-based direct functional training internal and external memory C: rehabilitation only
Outcomes	Intention-to-treat analysis not used Significant differences between groups seen only on CKV and HAWIE-R (but practice effects as no parallel forms used?) No other significant differences on other measures Based on feedback interview, authors conclude treatment effectiveness
Notes	E: Experimental; C: Control; CKV: Computer-aided card-sorting procedure; HAWIE-R: Hamburg Wechsler Intelligence Test-Revised

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"simple random sampling"
Allocation concealment (selection bias)	Low risk	"Allocation to the two study groups (treated and control group) was done by a person who worked in an out-patient MS facility and who was not involved in the study"
Blinding (performance bias and detection bias) All outcomes	High risk	"The participants were aware of each intervention" but no indication of assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of how drop-out data handled
Selective reporting (reporting bias)	Low risk	No selective reporting apparent

Other bias	Low risk	None identified

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aisen 1994	Non-RCT with a mixed aetiology group, non-memory
Akhtar 2006	Not MS
Aldrich 1995	Not just MS, non-RCT
Allen 1998	Non-RCT, no control
Amato 2014	Focus on attention, not memory
Bonavita 2015	No memory focus, active control
Brenk 2008	Non-RCT, allocated participants by demographics
Brissart 2010	Non-RCT, no control group
Brissart 2013	Non-RCT
Cabrera-Gomez 2010	No memory focus, non-RCT
Canellopoulou 1998	Not memory rehabilitation, not MS control group
Chiaravalloti 2003	Non-RCT, healthy controls
Chiaravalloti 2012	Same sample as Chiaravalloti 2013
Dobryakova 2014	Same sample as Chiaravalloti 2013
Ernst 2013	Non-RCT, healthy controls
Flavia 2010	Not memory rehabilitation
Goreover 2011	Not memory rehabilitation
Leavitt 2012	Subgroup analysis of Chiaravalloti 2013
Loewenstein 2004	Not MS: Alzheimer's disease

(*Continued*)

Martin 2014	Subgroup analysis of das Nair 2012
Mattioli 2012	Not memory specific
Moore 2008	No rehabilitation, as intervention only involved 1 session of 1 hour
Mäntynen 2014	Not memory specific
Nurova 2014	Conference poster presentation, no full text available
Rodgers 1996	Non-RCT
Rosti-Otajärvi 2013a	Not memory specific
Rosti-Otajärvi 2013b	Not memory specific
Shatil 2010	Non-RCT
Thaut 2014	No cognitive rehabilitation
Thomas 2006	Non-RCT: systematic review
van der Putten 1999	Stroke and MS patients, non-RCT, non-memory
Vogt 2009	No MS control group, only healthy controls
Wilson 2001	They do not distinguish results for participants with MS from those for participants with acquired progressive brain injury; no MS control group

MS: multiple sclerosis
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

ISRCTN09697576

Trial name or title	Cognitive Rehabilitation for Attention and Memory for people with Multiple Sclerosis (CRAMMS): a pragmatic randomised controlled trial
Methods	Single-blind, randomised controlled trial Cluster randomisation where participants will be individually randomised (6:5) to allow for clustering in the intervention arm, stratified by recruitment site and minimised by MS type (relapsing remitting or progressive) and gender. The randomisation will take place once 9 to 11 individuals have consented who are able to attend the same therapy group (location, day of the week and time of day) should they be randomised to receive it

Participants	Planned sample size: 400 Age: 18 to 70 Inclusion criteria: 1. Are 18 or over and under 70 years of age. The lower age limit is because MS is usually diagnosed in adulthood, and treatment strategies tend to be different for children. People aged 70 and over may start to encounter age-related cognitive problems, which may confound the effects of cognitive problem due to MS. Also, most tests are standardised on this adult age group. 2. Have relapsing or progressive MS, diagnosed at least 3 months prior to the baseline assessment contact with the study team, to allow for adjustment to diagnosis. Report having cognitive problems as determined by a cut-off score of > 27 on the patient version of the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ). This cut-off is based on previous research and is 2 standard deviations below the mean for healthy participant. 3. Have cognitive deficits, defined as performance below the 25th percentile on the Brief Repeatable Battery of Neuropsychological Tests (BRBN). 4. Are able to travel to one of the centres and attend group sessions. 5. Are able to speak English sufficiently to complete the cognitive assessments and take part in group sessions. 6. Give informed consent. Exclusion criteria: 1. Vision or hearing problems, such that they are unable to complete the cognitive assessments, judged by assessor. 2. Have concurrent severe medical or psychiatric conditions that would prevent person from engaging in treatment, if allocated. 3. Are involved in other psychological intervention trial.
Interventions	The intervention is cognitive rehabilitation, offered in addition to usual clinical care. The rehabilitation is delivered to groups of 4 to 6 participants for 10 weekly sessions. The programme will be tailored to each person's cognitive status, while maintaining a systematic approach to attention and memory by following a treatment manual. The control group participants will receive their usual clinical care, which may include information on cognitive problems but not cognitive rehabilitation
Outcomes	**Primary outcome measures** Psychological impact of MS; time point(s): 12 months **Secondary outcome measures** 1. Memory problems in everyday life; time point(s): 6 and 12 months 2. Mood; time point(s): 6 and 12 months 3. Fatigue; time point(s): 6 and 12 months 4. Carer strain; time point(s): 6 and 12 months 5. Quality of life; time point(s): 6 and 12 months 6. Attention and memory abilities; time point(s): 6 and 12 months 7. Physical impact of MS; time point(s): 6 and 12 months 8. Cost-effectiveness; time point(s): 6 and 12 months 9. Employment status; time point(s): 6 and 12 months 10. Number of reported relapses in the previous 6 months; time point(s): 6 and 12 months 11. Disability; time point(s): 6 and 12 months
Starting date	September 2014

ISRCTN09697576 (*Continued*)

Contact information	cramms@nottingham.ac.uk
Notes	

ISRCTN54901925

Trial name or title	A randomised study of cognitive rehabilitation in multiple sclerosis
Methods	Randomised controlled trial
Participants	Planned sample size: 50 Adult Participant inclusion criteria: 1. Diagnosis of MS by consultant neurologist to best current criteria. 2. Able and willing to give informed consent. 3. Cognitive impairment defined by scoring below 5th percentile on 1 or more of BICAMS scales (Langdon 2012) as identified at the clinic. 4. Willing to commit to 3x 45-minute computer training sessions for 6 weeks. 5. Home PC fulfilling experimental spec. 6. Willing to attend total of 3 MRI scans at the University of Sussex MRI scanner. 7. Age between 18 and 70. Participant exclusion criteria: 1. Significant change in medications in last 4 weeks. 2. Relapse recovery within last 4 weeks. 3. Sensorimotor dysfunction likely to interfere with PC interface. 4. Significant psychiatric history/condition. 5. Significant medical condition (other than MS), personal or social circumstances likely to influence cognition or study participation. 6. Women who are pregnant.
Interventions	Participants will be randomised to undergo either cognitive rehabilitation with RehaCom Software (3x 45-minute training sessions per week for 6 weeks) or be placed in the placebo arm to spend the same amount of time in the control condition (natural history DVDs). During this period, they will be expected to undertake 3x 45-minute computer training sessions per week for the 6-week period. There will also be an MRI brain scan at baseline prior to undertaking the training. Following completion of the 6-week training period, both the full cognitive assessments and MRI scanning will be repeated immediately following the training period and again at approximately 3 to 6 months
Outcomes	**Primary outcome measures** 1. Objective cognitive performance: BICAMS (a 15-minute screening tool). 2. Quality of life: i) EQ-5D, a generic health-related quality of life scale (EuroQoL Group 1990) ii) Functional Assessment of MS (FAMS), an MS-specific quality-of-life scale (Cella 1996) **Secondary outcome measures** MRI: The data will be acquired on the 1.5T Siemens machine. The following analyses will be completed: 1. Voxel-based morphometry 2. Tensor-based morphometry 3. Cortical thickness

ISRCTN54901925 (*Continued*)

	4. Lesion load 5. Resting state analysis (default mode network) 6. Diffusion tensor imaging analysis
Starting date	November 2013
Contact information	Dr Waqar Rashid Department of Neurology Royal Sussex County Hospital Eastern Road Brighton BN25BE
Notes	

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis, MRI: Magnetic resonance imaging

DATA AND ANALYSES

Comparison 1. Subjective memory measures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Immediate	5	314	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.19, 0.27]
2 Long term	5	305	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.19, 0.27]

Comparison 2. Objective memory measures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Immediate	11	503	Std. Mean Difference (IV, Random, 95% CI)	0.23 [0.05, 0.41]
2 Long term	6	302	Std. Mean Difference (IV, Random, 95% CI)	0.26 [0.03, 0.49]

Comparison 3. Mood

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Immediate	9	490	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.16, 0.20]
2 Long term	7	413	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.21, 0.20]

Comparison 4. ADL

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Immediate	2	186	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.60, 0.33]
2 Long term	2	186	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.63, -0.03]

Comparison 5. Quality of life

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Immediate	7	485	Std. Mean Difference (IV, Random, 95% CI)	0.23 [0.05, 0.41]
2 Long term	5	406	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.03, 0.36]

Analysis 1.1. Comparison 1 Subjective memory measures, Outcome 1 Immediate.

Review: Memory rehabilitation for people with multiple sclerosis

Comparison: 1 Subjective memory measures

Outcome: 1 Immediate

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Carr 2014	17	-21.7 (13.1)	21	-25.8 (19.9)		12.3 %	0.23 [-0.41, 0.88]
Chiaravalloti 2005	13	77.67 (26.69)	13	81.38 (22.19)		8.6 %	-0.15 [-0.92, 0.62]
das Nair 2012	29	-42.48 (22.44)	10	-41.1 (18.95)		9.8 %	-0.06 [-0.78, 0.66]
Lincoln 2002	74	-23.32 (20.28)	76	-26.11 (24.02)		49.5 %	0.12 [-0.20, 0.45]
Stuifbergen 2012	34	-29.68 (10.74)	27	-27.92 (11.11)		19.8 %	-0.16 [-0.67, 0.35]
Total (95% CI)	**167**		**147**			**100.0 %**	**0.04 [-0.19, 0.27]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.52$, df = 4 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 0.35 (P = 0.73)

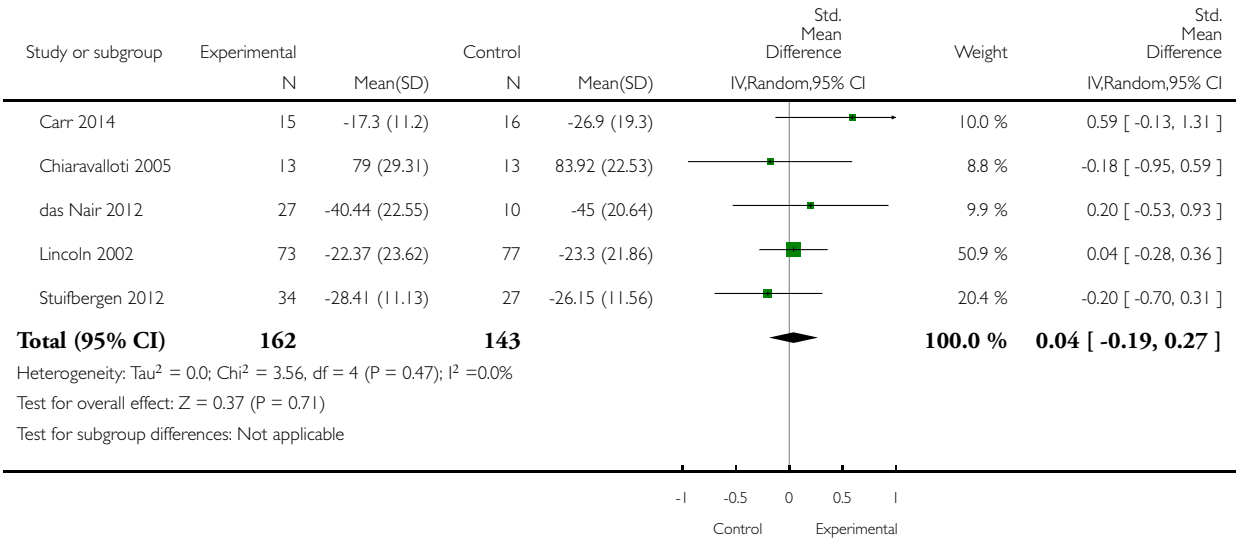
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Subjective memory measures, Outcome 2 Long term.

Review: Memory rehabilitation for people with multiple sclerosis

Comparison: 1 Subjective memory measures

Outcome: 2 Long term

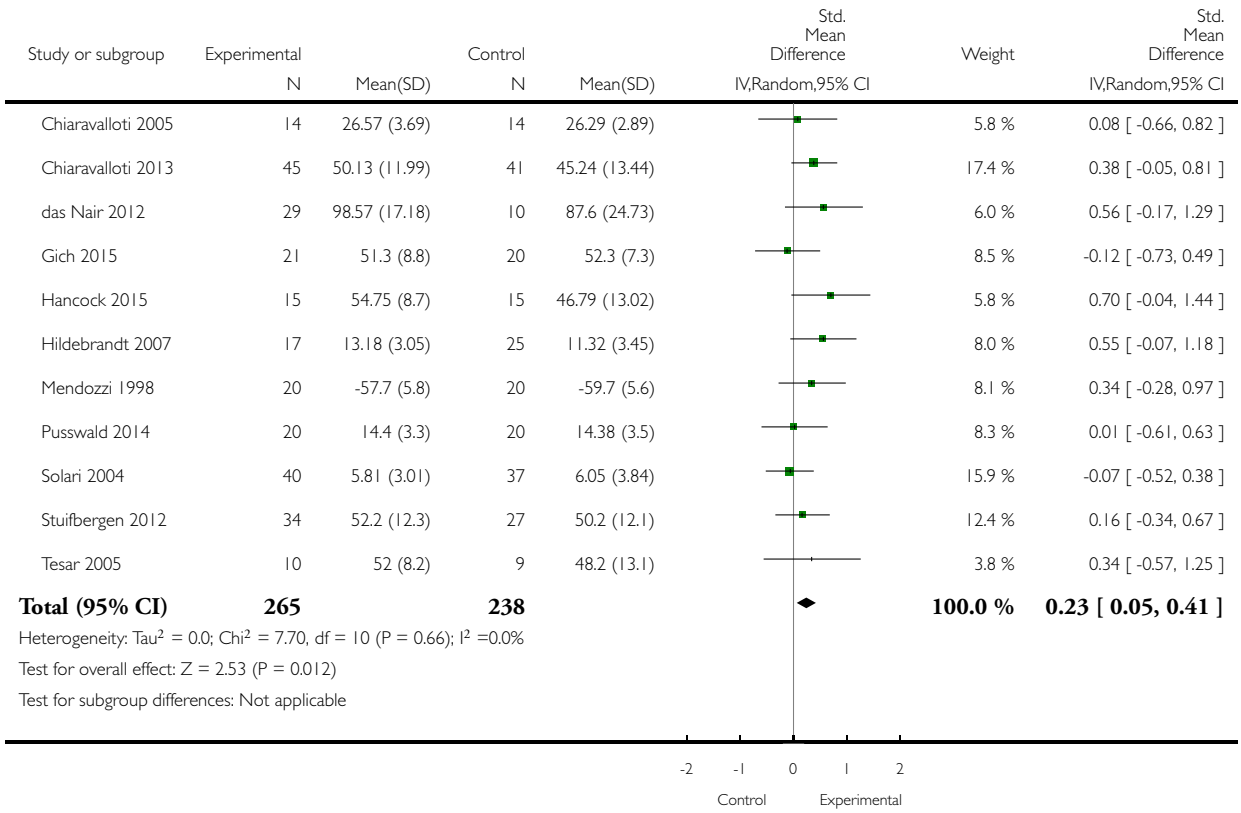


Analysis 2.1. Comparison 2 Objective memory measures, Outcome 1 Immediate.

Review: Memory rehabilitation for people with multiple sclerosis

Comparison: 2 Objective memory measures

Outcome: 1 Immediate

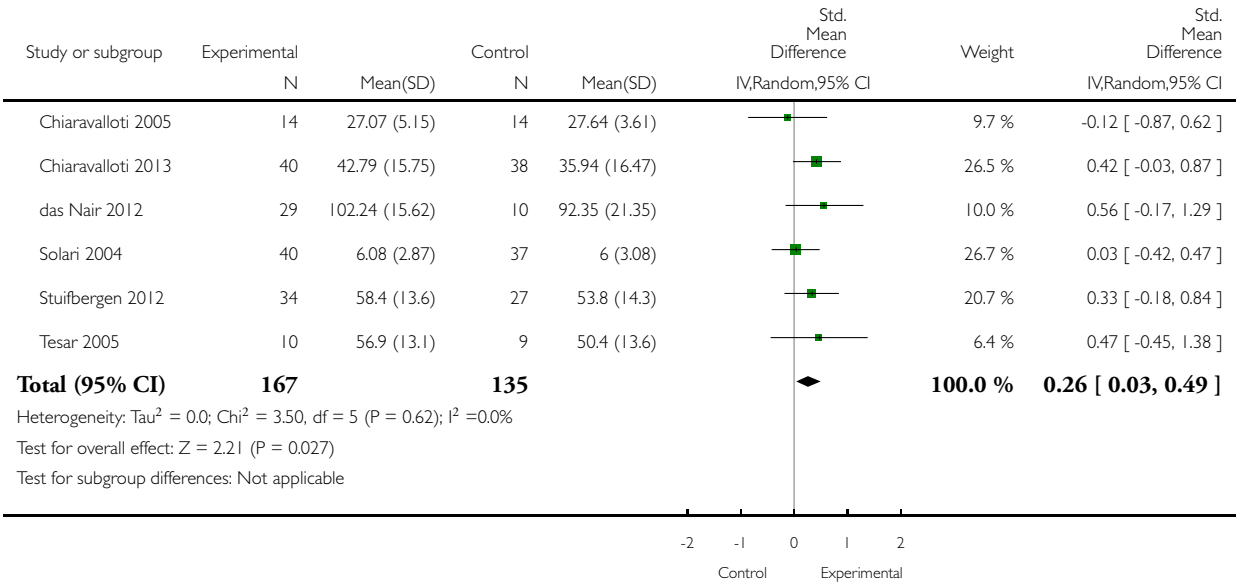


Analysis 2.2. Comparison 2 Objective memory measures, Outcome 2 Long term.

Review: Memory rehabilitation for people with multiple sclerosis

Comparison: 2 Objective memory measures

Outcome: 2 Long term

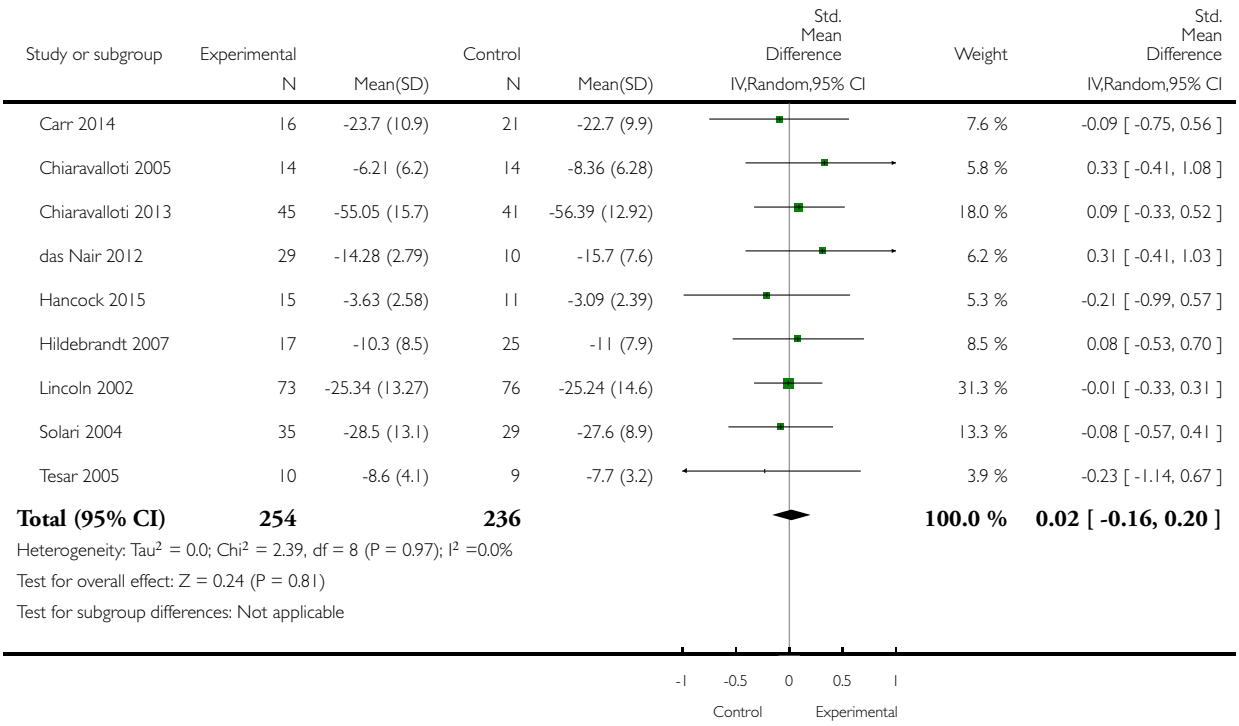


Analysis 3.1. Comparison 3 Mood, Outcome 1 Immediate.

Review: Memory rehabilitation for people with multiple sclerosis

Comparison: 3 Mood

Outcome: 1 Immediate



Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.39$, df = 8 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 0.24 (P = 0.81)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Mood, Outcome 2 Long term.

Review: Memory rehabilitation for people with multiple sclerosis

Comparison: 3 Mood

Outcome: 2 Long term

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Carr 2014	17	-18.4 (7)	16	-25.3 (10.9)		8.1 %	0.74 [0.03, 1.45]
Chiaravalloti 2005	14	-6.79 (8.15)	14	-7.29 (6.8)		7.4 %	0.06 [-0.68, 0.81]
Chiaravalloti 2013	40	-54.44 (15.62)	38	-56.48 (11.46)		19.6 %	0.15 [-0.30, 0.59]
das Nair 2012	29	-15.93 (8.61)	10	-14.1 (6.14)		7.8 %	-0.22 [-0.94, 0.50]
Lincoln 2002	73	-27 (15.7)	77	-24.9 (14.7)		35.2 %	-0.14 [-0.46, 0.18]
Solari 2004	34	-28.03 (12.87)	32	-25.84 (8.45)		16.7 %	-0.20 [-0.68, 0.29]
Tesar 2005	10	-8.3 (5.8)	9	-8.3 (3.4)		5.1 %	0.0 [-0.90, 0.90]
Total (95% CI)	**217**		**196**			**100.0 %**	**-0.01 [-0.21, 0.20]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.34$, df = 6 (P = 0.39); $I^2 = 5\%$

Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 ADL, Outcome 1 Immediate.

Review: Memory rehabilitation for people with multiple sclerosis

Comparison: 4 ADL

Outcome: 1 Immediate

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
das Nair 2012	26	48.54 (10.87)	9	45.56 (14.14)		28.0 %	0.25 [-0.51, 1.01]
Lincoln 2002	74	40.87 (18.39)	77	45.82 (16.49)		72.0 %	-0.28 [-0.60, 0.04]
Total (95% CI)	**100**		**86**			**100.0 %**	**-0.13 [-0.60, 0.33]**

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 1.59$, df = 1 (P = 0.21); $I^2 = 37\%$

Test for overall effect: Z = 0.56 (P = 0.57)

Test for subgroup differences: Not applicable

Analysis 4.2. Comparison 4 ADL, Outcome 2 Long term.

Review: Memory rehabilitation for people with multiple sclerosis

Comparison: 4 ADL

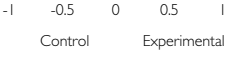
Outcome: 2 Long term

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
das Nair 2012	27	48.52 (11.28)	9	50.89 (12.41)		15.4 %	-0.20 [-0.96, 0.56]
Lincoln 2002	73	39.96 (18.18)	77	46.2 (16.93)		84.6 %	-0.35 [-0.68, -0.03]
Total (95% CI)	**100**		**86**			**100.0 %**	**-0.33 [-0.63, -0.03]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.13$, df = 1 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 2.18 (P = 0.029)

Test for subgroup differences: Not applicable

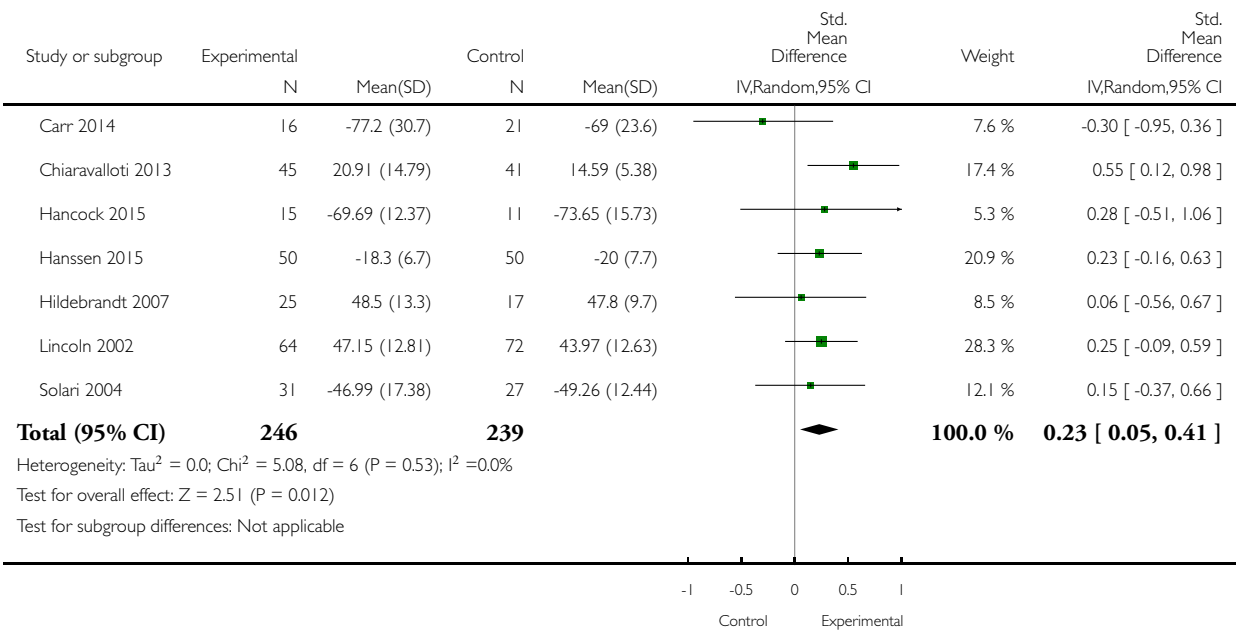


Analysis 5.1. Comparison 5 Quality of life, Outcome 1 Immediate.

Review: Memory rehabilitation for people with multiple sclerosis

Comparison: 5 Quality of life

Outcome: 1 Immediate

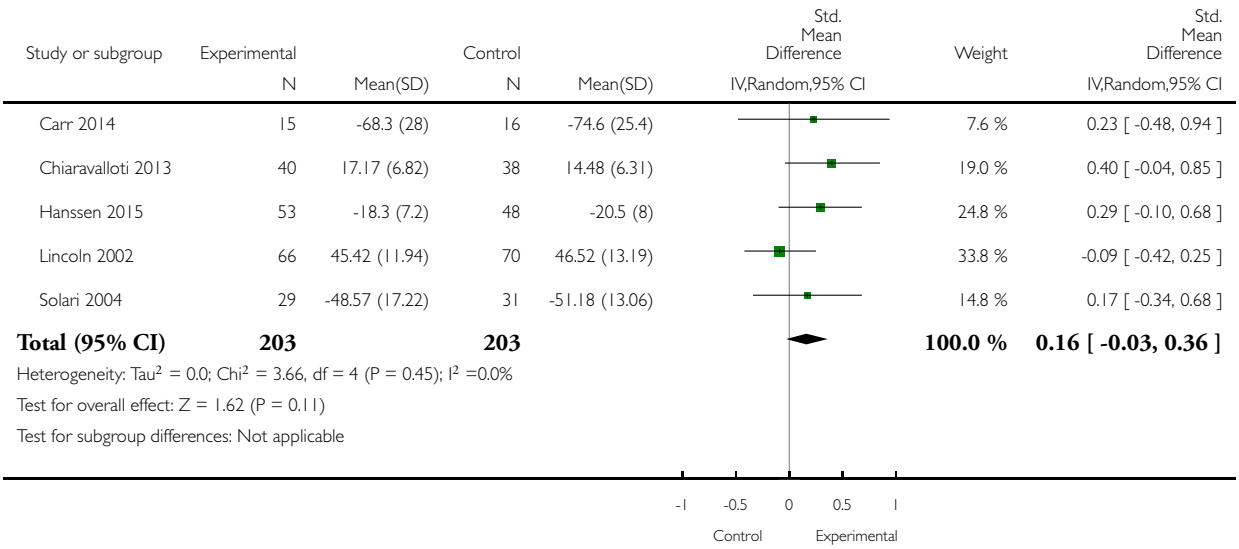


Analysis 5.2. Comparison 5 Quality of life, Outcome 2 Long term.

Review: Memory rehabilitation for people with multiple sclerosis

Comparison: 5 Quality of life

Outcome: 2 Long term



ADDITIONAL TABLES

Table 1. Sensitivity analysis

Outcome	No. of studies	No. of participants	Effect size SMD (95% CI)	Heterogeneity (I^2)	Test for overall effect
Subjective memory - immediate	4	E = 154 C = 134	0.06 [-0.18, 0.29]	0%	Z = 0.48 (P = 0.63)
Subjective memory - long term	4	E = 149 C = 130	0.07 [-0.18, 0.32]	6%	Z = 0.54 (P = 0.59)
Objective memory - immediate	3	E = 103 C = 74	0.13 [-0.19, 0.44]	4%	Z = 0.79 (P = 0.43)
Objective memory - long term	3	E = 103 C = 74	0.23 [-0.08, 0.53]	0%	Z = 1.47 (P = 0.14)
Mood - immediate	4	E = 153 C = 136	-0.00 [-0.24, 0.23]	0%	Z = 0.01 (P = 0.99)

Table 1. Sensitivity analysis (*Continued*)

Mood - delayed	4	E = 153 C = 135	-0.02 [-0.37, 0.34]	47%	Z = 0.08 (P = 0.93)
Quality of life - immediate	3	E = 111 C = 120	0.13 [-0.14, 0.40]	6%	Z = 0.94 (P = 0.34)
Quality of life - long term	3	E = 110 C = 117	0.02 [-0.24, 0.28]	0%	Z = 0.18 (P = 0.86)

E: Experimental, C: Control, SMD: Standardised mean difference

APPENDICES

Appendix 1. Keywords

{attention*} OR {cognition} OR {cognition disorder*} OR {cognitive} OR {concentration} OR {distract*} OR {alert*} AND {training} OR {retraining} OR {therap*} OR {rehabilitation} OR {treatment*} OR {therapeutic*} OR {computer assisted therap*} OR {computer*} OR {neuropsychological test*} OR {neurorehabilitation} OR {neuropsychological rehabilitation} OR {rehabilitation} OR {cognition} OR {neurological system and disorders} OR {memory} OR {cognitive retraining}

WHAT'S NEW

Last assessed as up-to-date: 2 June 2015.

Date	Event	Description
7 November 2015	New search has been performed	Update search completed 2 June 2015. The review now includes 15 trials
7 November 2015	Amended	The review team has been amended
7 November 2015	New citation required and conclusions have changed	7 studies have been added. Conclusion changed. In this version of the review, the quality of the evidence from the included studies was assessed using GRADE approach and a 'Summary of findings' table was added

CONTRIBUTIONS OF AUTHORS

RdN and NBL conceptualised the protocol for the review. KJM ran the searches and collected the studies. KJM and RdN reviewed the studies, which were verified by NBL. RdN and KJM wrote the review with input from NBL.

DECLARATIONS OF INTEREST

RdN and NBL have conducted memory rehabilitation studies in MS that have been included in this review. KJM has nothing to declare.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not perform subgroup analyses because data were not available.

INDEX TERMS

Medical Subject Headings (MeSH)

Audiovisual Aids; Memory Disorders [etiology; *rehabilitation]; Multiple Sclerosis [*complications]; Randomized Controlled Trials as Topic; Therapy, Computer-Assisted [methods]

MeSH check words

Humans