National Institute for Health and Care Excellence

Draft

Multiple sclerosis in adults: management (update)

[H1] Appendices for non-pharmacological management of memory and cognitive problems evidence review

NICE guideline <number>

Evidence reviews underpinning recommendations 1.5.37 to 1.5.40 and research recommendations in the NICE guideline

December 2021

Draft for Consultation

These evidence reviews were developed by National Guideline Centre, hosted by the Royal College of Physicians

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

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ISBN:

Contents

Appendices

Appendix A – Review protocols

Review protocol for non-pharmacological management of memory and cognitive problems

ID	Field	Content
0.	PROSPERO registration number	CRD42021244943
1.	Review title	For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of interventions for memory and cognitive problems?
2.	Review question	For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of non-pharmacological interventions for memory and cognitive problems?
3.	Objective	To determine the most clinically effective nonpharmacological intervention for managing memory and cognitive problems in people with multiple sclerosis.
4.	Searches	The following databases will be searched from inception: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • PsycINFO • Epistemonikos Searches will be restricted by: • Date limitations: none • English language studies

		• Human studies • Validated study filters for systematic reviews and RCTs The searches may be re-run 6 weeks before the final committee meeting, and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Multiple sclerosis
6.	Population	Inclusion: Adults (≥18 years) with MS, including people receiving palliative care. Exclusion: Children and young people (≤18 years).
7.	Interventions	**Multi-domain cognitive/neuropsychological rehabilitation** • Brain Training Apps such as luminosity • Neuropsychological intervention for example neuropsychological Compensatory Training (NCT)Computer aided 'Cognifit Personal Coach' for cognition • MS-Rehab computerised tool • Psychoeducation • Insight and awareness (typically termed as 'metacognitve training or metacognitive strategies') **Speed of information processing**

		• Time Pressure Management Training (TPM) **Attention and Working Memory** • CogMed Working Memory Training • Attention Process Training (APT) • Computer aided RehaCom module 'Divided Attention' for attention **Memory** • External compensatory strategies • Errorless Learning Techniques • Personal assistant apps • Computer aided RehaCom module 'memory and Attention' • Computer aided (VILAT-G 1.0) training for memory • Story memory technique (SMT) • Computer aided memory retraining programme (SCRP) **Executive Function** • Goal Management Training (GMT) • Problem Solving Training • Computer aided RehaCom module 'Plan a Day' for organization and planning • Interventions for apathy **Cognition** • Social Cognition Training • Cognitive rehabilitation programmes • Psychotherapy/councelling relating to cognitive impairment **Interventions aimed at improving language** • Retraining type approaches • Compensatory type approaches (for example, use of communication aids) **Interventions aimed improving perception**

		• Psychoeducation • Retraining type approaches (repeated practice on identifying specific objects/patterns) Compensatory type approaches (for example, labelling objects) Combinations may be included as most rehabilitation programmes with a clinician (rather than computerised focus) will be multi-factorial as they will take into account the whole presentation rather than just focus on one part. Report who gave the intervention and whether individual or group
8.	Comparator	• Interventions will be compared to each other, placebo/sham, or usual care. • Waiting list control • Supportive therapy (dedicated time with a supportive clinician)
9.	Types of study to be included	Systematic reviews of RCTs and RCTs will be considered for inclusion. Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Cross over trials will be excluded as many interventions are around learning where it would not be possible to do a cross-over trial as the information cannot be 'unlearned' We consider RCT data to be the best evidence for reviews of interventions. In addition, the surveillance review and GC have highlighted the existence of relevant RCTs in this area. Therefore, if no RCT data is available observational data will not be considered due to the risk of confounding variables influencing the study results, reducing our confidence in the overall results of the review.

		Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question. or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
11.	Context	This review will inform the update of the following recommendations in CG 186: 1.5.31 Be aware that the symptoms of MS can include cognitive problems, including memory problems that the person may not immediately recognise or associate with their MS. 1.5.32 Be aware that anxiety, depression (see the NICE guideline on depression in adults with a chronic physical health problem), difficulty in sleeping and fatigue can impact on cognitive problems. If a person with MS experiences these symptoms and has problems with memory and cognition, offer them an assessment and treatment. 1.5.33 Consider referring people with MS and persisting memory or cognitive problems to both an occupational therapist and a neuropsychologist to assess and manage these symptoms.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical. • Objective Measures o Cognitive functions, such as memory, attention, executive functions, processing speed, for example, symbol digit modality test (SMDT) • Subjective Measures o Health-related Quality of Life, for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale. o Patient-reported outcomes, for example symptoms, activities.(for example Canadian Occupational Performance measure, Cognitive failure questionnaire, perceived deficits questionnaire o Self-efficacy/self-management (MS self-efficacy scale

		• Functional Measures
		  ○ Medication management/ adherence to medication
		  ○ Mood
		  ○ Fatigue (MS fatigue scale includes cognition (perhaps include this- if score reported separately?)
		  ○ Activities of daily living (ADL).
		• Vocational Measures
		  ○ Employment
		  ○ Training
		  ○ Social engagement
		  ○ Relationship satisfaction/ Impact on carers.
		• Engagement Measures
		  ○ Completion/adherence rates
		  ○ Acceptability
		  ○ Satisfaction
		
		Validated measures will be prioritised. If no evidence is available, non-validated may be considered.
		
		Follow up:
		• 3-6 months (minimum of 3 months but can include 1-3 months and downgrade)
		• >6 months – 1 year (data from >1 year follow up may be included but will be downgraded)

14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. The following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences.

		To maximise the amount of data for meta-analysis, where multiple scales have been used for an outcome such as mobility, fatigue or spasticity, the most commonly reported ones across studies will be extracted and meta-analysed with priority given to those included in CG 186. Where available, outcome data from new studies will be meta-analysed with corresponding data included in CG 186. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. If sufficient data is available, meta-regression or NMA-meta-regression will be conducted. WinBUGS will be used for network meta-analysis, if possible, given the data identified.
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS)

<table>
<tr><td></td><td></td><td colspan="3">• According to disability (EDSS <6 and EDSS ≥6)
• Severity of cognitive impairment (mild/moderate/severe)
• Disease modifying treatment status (currently using and not currently using)
• Mood disorders (presence or absence)
• Computerised vs clinician led
• Group vs individual</td></tr>
<tr><td rowspan="8">18.</td><td rowspan="8">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
<tr><td></td><td></td><td colspan="3"></td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3">October 2020</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">July 2022</td></tr>
<tr><td rowspan="3">23.</td><td rowspan="3">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
</table>

		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail MultipleSclerosisUpdate@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Dr Sharon Swain [Guideline lead] Dr Saoussen Ftouh [Senior systematic reviewer] Nicole Downes [Systematic reviewer] Sophia Kemmis Betty [Senior health economist] Lina Gulhane [Information specialist] Emma Clegg [Information specialist] Kate Ashmore [Project Manager]		

26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	

33.	Details of existing review of same topic by same authors		
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

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1 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. For questions being updated, the search will be run from 2014, which was the cut-off date for the searches conducted for NICE guideline CG186.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2005 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[2] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies.

	Setting: • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2005 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B – Literature search strategies

This literature search strategy was used for the following review:

- The clinical and cost effectiveness of non-pharmacological interventions for memory and cognitive problems for adults with MS, including people receiving palliative care.

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[2]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 1: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 08 September 2021	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, children)
Embase (OVID)	1974 – 08 September 2021	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, conference abstracts, children)
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 9 of 12 CENTRAL to 2021 Issue 9 of 12	None Exclusions (conference abstracts & clinical trials)
PsycINFO (Ovid)	Inception – 08 September 2021	Randomised controlled trials Systematic review studies Exclusions (conference abstracts & clinical trials)
Epistemonikos (The Epistemonikos Foundation)	Inception to 08 September 2021	Systematic Reviews Exclusions (Cochrane Reviews)

Medline (Ovid) search terms

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.

5.	Myelitis, Transverse/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
29.	27 not 28
30.	exp Memory/ or exp Memory Disorders/ or exp Cognition/ or exp Cognition disorders/ or Attention/ or Extinction, Psychological/ or exp Mental processes/ or Neurocognitive disorders/
31.	Neuropsychology/ or Language/ or exp Speech/ or Problem solving/ or Mathematics/ or exp Learning/ or exp Thinking/ or exp Psycholinguistics/
32.	(cogniti* or neuropsychol* or neurocogniti* or memor* or learn* or perceptual or attenti* or information process* or language or visuopat* or visuoconstruct* or problem solving or reason* or execut* or metacognit* or think* or judging or judgement).ti,ab.
33.	or/30-32
34.	Rehabilitation/ or Therapeutics/ or Therapy, computer-assisted/ or exp Neuropsychological Tests/
35.	Remedial teaching/ or "Recovery of function"/ or Exercise/ or exp *Counseling/
36.	(rehabilit* or restitut* or remediat* or restorat* or retrain* or train* or recover* or treat* or guid* or instruct* or teach* or stimulat* or exerci* or counsel* or therap* or intervent* or manag* or computer* tool* or computer* aid* or computer* app* or mobile app* or phone app* or smartphone app*).ti,ab.
37.	or/34-36
38.	33 and 37
39.	Cognitive Behavioral Therapy/ or Reminder systems/
40.	neurorehab*.ti,ab.
41.	((percept* or neurocogniti* or attention* or cogniti* or memory or memories or scanning) adj3 (train* or re-train* or retrain* or rehabilit* or interven* or therap*)).ti,ab.

42.	((metacogniti* or cogniti* or compensat* or memory) adj2 strateg*).ti,ab.
43.	((brain or metacogniti*) adj2 (train* or re-train* or retrain* or rehabilit*)).ti,ab.
44.	(psychoeducat* or psych educat*).ti,ab.
45.	((memory or memories) adj2 (aid* or prompt* or reminder*)).ti,ab.
46.	(apathy adj2 interven*).ti,ab.
47.	or/38-46
48.	(Luminosity or Cognifit or 'time pressure management' or CogMed or 'Attention Process Training' or RehaCom or 'Divided Attention' or 'Story memory technique' or 'story technique* or 'Problem Solving' or 'Goal Management Training' or 'VILAT-G' or 'day plan*' or 'daily plan*').ti,ab.
49.	47 or 48
50.	29 and 49
51.	randomized controlled trial.pt.
52.	controlled clinical trial.pt.
53.	randomi#ed.ti,ab.
54.	placebo.ab.
55.	randomly.ti,ab.
56.	Clinical Trials as topic.sh.
57.	trial.ti.
58.	or/51-57
59.	Meta-Analysis/
60.	exp Meta-Analysis as Topic/
61.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
62.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
63.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
64.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
65.	(search* adj4 literature).ab.
66.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
67.	cochrane.jw.
68.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
69.	or/59-68
70.	50 and (58 or 69)

1 **Embase (Ovid) search terms**

1.	exp *Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	myelitis/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.

11.	(conference abstract or conference paper).pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or rodent* or mouse or mice).ti.
24.	or/16-23
25.	7 not 24
26.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
27.	25 not 26
28.	limit 27 to English language
29.	exp *Memory/ or exp *Memory Disorder/ or exp *Cognition/ or exp *Cognitive defect/ or *Attention/ or *Reinforcement/ or exp *Mental function/ or *Disorders of higher cerebral function/
30.	*Neuropsychology/ or *Language/ or exp *Speech/ or exp *Problem solving/ or *Mathematics/ or exp *Learning/ or exp *Thinking/ or exp *linguistics/
31.	(cogniti* or neuropsychol* or neurocogniti* or memor* or learn* or perceptual or attenti* or information process* or language or visuopat* or visuoconstruct* or problem solving or reason* or execut* or metacognit* or think* or judging or judgement).ti,ab.
32.	or/29-31
33.	*Rehabilitation/ or *Therapy/ or *Computer assisted therapy/ or exp *Neuropsychological test/
34.	exp *Teaching/ or *Convalesence/ or exp *Exercise/ or exp *Counseling/
35.	(rehabilit* or restitut* or remediat* or restorat* or retrain* or train* or recover* or treat* or guid* or instruct* or teach* or stimulat* or exerci* or counsel* or therap* or intervent* or manag* or computer* tool* or computer* aid* or computer* app* or mobile app* or phone app* or smartphone app*).ti,ab.
36.	or/33-35
37.	32 and 36
38.	*Cognitive Therapy/ or exp *Cognitive Behavioral Therapy/ or *Reminder systems/
39.	neurorehab*.ti,ab.
40.	((percept* or neurocogniti* or attention* or cogniti* or memory or memories or scanning) adj3 (train* or re-train* or retrain* or rehabilit* or interven* or therap*)).ti,ab.
41.	((metacogniti* or cogniti* or compensat* or memory) adj2 strateg*).ti,ab.
42.	((brain or metacogniti*) adj2 (train* or re-train* or retrain* or rehabilit*)).ti,ab.
43.	(psychoeducat* or psych educat*).ti,ab.
44.	((memory or memories) adj2 (aid* or prompt* or reminder*)).ti,ab.
45.	(apathy adj2 interven*).ti,ab.
46.	or/37-45
47.	(Luminosity or Cognifit or 'time pressure management' or CogMed or 'Attention Process Training' or RehaCom or 'Divided Attention' or 'Story memory technique' or

	'story technique* or 'Problem Solving' or 'Goal Management Training' or 'VILAT-G' or 'day plan*' or 'daily plan*').ti,ab.
48.	46 or 47
49.	28 and 48
50.	random*.ti,ab.
51.	factorial*.ti,ab.
52.	(crossover* or cross over*).ti,ab.
53.	((doubl* or singl*) adj blind*).ti,ab.
54.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
55.	crossover procedure/
56.	single blind procedure/
57.	randomized controlled trial/
58.	double blind procedure/
59.	or/50-58
60.	systematic review/
61.	meta-analysis/
62.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
63.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
64.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
65.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
66.	(search* adj4 literature).ab.
67.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
68.	cochrane.jw.
69.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
70.	or/60-69
71.	49 and (59 or 70)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Multiple Sclerosis] explode all trees
#2.	((multiple or disseminated) NEAR/2 scleros*):ti,ab
#3.	encephalomyelitis disseminata:ti,ab
#4.	MS:ti
#5.	MeSH descriptor: [Myelitis, Transverse] this term only
#6.	transverse myelitis:ti,ab
#7.	(or #1-#6)
#8.	MeSH descriptor: [Memory] explode all trees
#9.	MeSH descriptor: [Memory Disorders] explode all trees
#10.	MeSH descriptor: [Cognition] explode all trees
#11.	MeSH descriptor: [Cognition Disorders] explode all trees
#12.	MeSH descriptor: [Attention] this term only
#13.	MeSH descriptor: [Extinction, Psychological] this term only
#14.	MeSH descriptor: [Mental Processes] explode all trees
#15.	MeSH descriptor: [Neurocognitive Disorders] this term only
#16.	MeSH descriptor: [Neuropsychology] this term only

#17.	MeSH descriptor: [Language] this term only
#18.	MeSH descriptor: [Speech] explode all trees
#19.	MeSH descriptor: [Problem Solving] this term only
#20.	MeSH descriptor: [Mathematics] this term only
#21.	MeSH descriptor: [Learning] explode all trees
#22.	MeSH descriptor: [Thinking] explode all trees
#23.	MeSH descriptor: [Psycholinguistics] this term only
#24.	(cogniti* or neuropsychol* or neurocogniti* or memor* or learn* or perceptual or attenti* or information process* or language or visuopat* or visuoconstruct* or problem solving or reason* or execut* or metacognit* or think* or judging or judgement):ti,ab
#25.	(or #8-#24)
#26.	MeSH descriptor: [Rehabilitation] this term only
#27.	MeSH descriptor: [Therapeutics] this term only
#28.	MeSH descriptor: [Therapy, Computer-Assisted] this term only
#29.	MeSH descriptor: [Neuropsychological Tests] this term only
#30.	MeSH descriptor: [Remedial Teaching] this term only
#31.	MeSH descriptor: [Recovery of Function] this term only
#32.	MeSH descriptor: [Exercise] this term only
#33.	MeSH descriptor: [Counseling] this term only
#34.	(rehabilit* or restitut* or remediat* or restorat* or retrain* or train* or recover* or treat* or guid* or instruct* or teach* or stimulat* or exerci* or counsel* or therap* or intervent* or manag* or computer* tool* or computer* aid* or computer* app* or mobile app* or phone app* or smartphone app*):ti,ab
#35.	(or #26-#34)
#36.	#25 and #35
#37.	MeSH descriptor: [Cognitive Behavioral Therapy] this term only
#38.	MeSH descriptor: [Reminder Systems] this term only
#39.	neurorehab*:ti,ab
#40.	((percept* or neurocogniti* or attention* or cogniti* or memory or memories or scanning) near/3 (train* or re-train* or retrain* or rehabilit* or interven* or therap*)):ti,ab
#41.	((metacogniti* or cogniti* or compensat* or memory) near/2 strateg*):ti,ab
#42.	((brain or metacogniti*) near/2 (train* or re-train* or retrain* or rehabilit*)):ti,ab
#43.	(psychoeducat* or psych educat*):ti,ab
#44.	((memory or memories) near/2 (aid* or prompt* or reminder*)):ti,ab
#45.	(apathy near/2 interven*):ti,ab
#46.	(or #36-#45)
#47.	(Luminosity or Cognifit or 'time pressure management' or CogMed or 'Attention Process Training' or RehaCom or 'Divided Attention' or 'Story memory technique' or 'story technique* or 'Problem Solving' or 'Goal Management Training' or 'VILAT-G' or 'day plan*' or 'daily plan*'):ti,ab
#48.	#46 or #47
#49.	#7 and #48
#50.	conference:pt or (clinicaltrials or trialsearch):so
#51.	#49 not #50

1 **PsycINFO (Ovid) search terms**

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.

3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	*myelitis/
6.	*demyelination/
7.	transverse myelitis.ti,ab.
8.	or/1-7
9.	Case report/
10.	letter/
11.	exp Mice/
12.	exp Rodents/
13.	exp Animals/ not (exp Human Males/ or Human Females/)
14.	(rat or rats or mouse or mice or rodent*).ti,ab.
15.	or/9-14
16.	8 not 15
17.	limit 16 to English language
18.	First posting.ps.
19.	16 and 18
20.	17 or 19
21.	exp cognition/ or exp cognitive development/ or exp cognitive impairment/ or exp cognitive processes/ or information processing model/ or metacognition/ or need for cognition/ or exp comprehension/ or concentration/ or exp concept formation/ or exp decision making/ or naming/ or exp problem solving/ or exp thinking/
22.	neuropsychology/ or exp memory/ or exp memory disorders/ or exp learning/ or exp attention/ or exp visual perception/ or exp language/ or exp mathematical ability/ or exp awareness/
23.	(cogniti* or neuropsychol* or neurocogniti* or memor* or learn* or perceptual or attenti* or information process* or language or visuopat* or visuoconstruct* or problem solving or reason* or execut* or metacognit* or think* or judging or judgement).ti,ab.
24.	or/21-23
25.	exp rehabilitation/ or exp training/ or exp "recovery (disorders)"/ or exp treatment/ or exp cognitive techniques/ or exp intervention/ or exp counseling/ or rehabilitation counseling/ or exp Computer assisted therapy/
26.	exp teaching/ or exp exercise/ or exp neuropsychological rehabilitation/
27.	(rehabilit* or restitut* or remediat* or restorat* or retrain* or train* or recover* or treat* or guid* or instruct* or teach* or stimulat* or exerci* or counsel* or therap* or intervent* or manag* or computer* tool* or computer* aid* or computer* app* or mobile app* or phone app* or smartphone app*).ti,ab.
28.	or/25-27
29.	24 and 28
30.	*Cognitive Therapy/ or exp *Cognitive Behavioral Therapy/ or *Reminder systems/
31.	neurorehab*.ti,ab.
32.	((percept* or neurocogniti* or attention* or cogniti* or memory or memories or scanning) adj3 (train* or re-train* or retrain* or rehabilit* or interven* or therap*)).ti,ab.
33.	((metacogniti* or cogniti* or compensat* or memory) adj2 strateg*).ti,ab.
34.	((brain or metacogniti*) adj2 (train* or re-train* or retrain* or rehabilit*)).ti,ab.
35.	(psychoeducat* or psych educat*).ti,ab.
36.	((memory or memories) adj2 (aid* or prompt* or reminder*)).ti,ab.
37.	(apathy adj2 interven*).ti,ab.

38.	(Luminosity or Cognifit or 'time pressure management' or CogMed or 'Attention Process Training' or RehaCom or 'Divided Attention' or 'Story memory technique' or 'story technique* or 'Problem Solving' or 'Goal Management Training' or 'VILAT-G' or 'day plan*' or 'daily plan*').ti,ab.
39.	or/30-38
40.	29 or 39
41.	20 and 40
42.	exp Clinical Trial/
43.	randomi*.ti,ab.
44.	((clinical* or control*) adj3 trial*).ti,ab.
45.	((singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)).ti,ab.
46.	Placebos/ or placebo*.ti,ab.
47.	((crossover or cross-over or cross over) adj2 (design* or stud* or procedure* or trial*)).ti,ab.
48.	or/42-47
49.	"review"/ or review.pt. or review.ti.
50.	(systematic or evidence* or methodol* or quantitativ*).ti,ab.
51.	49 and 50
52.	Meta-Analysis/
53.	(meta-analy* or metanaly* or metaanaly* or meta analy*).ti,ab.
54.	((systematic* or evidence* or methodol* or quantitativ*) adj3 (review* or overview*)).ti,ab.
55.	((pool* or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
56.	(systematic* or meta*).pt. or (literature review or meta-analysis or systematic review).md.
57.	or/52-56
58.	41 and (48 or 51 or 57)

Epistemonikos search terms

1.	(advanced_title_en:(multiple sclerosis) OR advanced_abstract_en:(multiple sclerosis)) AND (advanced_title_en:((memory OR cognition OR cognitive neurocognitive OR neurocognition)) OR advanced_abstract_en:((memory OR cognition OR cognitive neurocognitive OR neurocognition)))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search with the Multiple Sclerosis population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics. Searches for quality-of-life studies were run for general information.

Table 2: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 07 September 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, children)

Database	Dates searched	Search filter used
Embase	01 January 2014 – 07 September 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, conference abstracts, children)
Centre for Research and Dissemination (CRD)	HTA – 01 January 2014 – 31 March 2018 NHSEED – 01 January 2014 – March 2015	None
The International Network of Agencies for Health Technology Assessment (INAHTA)	01 January 2018 – 07 September 2021	None

1 **Medline (Ovid) search terms**

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	Myelitis, Transverse/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	*Demyelinating Diseases/
9.	*Demyelinating Autoimmune Diseases, CNS/
10.	(Demyelinat* adj2 (syndrome* or disease* or autoimmun*)).ti,ab.
11.	(Chronic Cerebrospinal Venous Insufficiency or CCSVI).ti,ab.
12.	Venous Insufficiency/cf, co, di, dg, et [Cerebrospinal Fluid, Complications, Diagnosis, Diagnostic Imaging, Etiology]
13.	(Devic* adj (disease or syndrome)).ti,ab.
14.	((clinical* isolat* or radiological* isolat*) adj2 syndrome*).ti,ab.
15.	exp Optic Neuritis/
16.	((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*)).ti,ab.
17.	(NMO or NMOSD).ti,ab.
18.	or/1-17
19.	letter/
20.	editorial/
21.	news/
22.	exp historical article/
23.	Anecdotes as Topic/
24.	comment/
25.	case report/
26.	(letter or comment*).ti.
27.	or/19-26

28.	randomized controlled trial/ or random*.ti,ab.
29.	27 not 28
30.	animals/ not humans/
31.	exp Animals, Laboratory/
32.	exp Animal Experimentation/
33.	exp Models, Animal/
34.	exp Rodentia/
35.	(rat or rats or rodent* or mouse or mice).ti.
36.	or/29-35
37.	18 not 36
38.	limit 37 to English language
39.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
40.	38 not 39
41.	Economics/
42.	Value of life/
43.	exp "Costs and Cost Analysis"/
44.	exp Economics, Hospital/
45.	exp Economics, Medical/
46.	Economics, Nursing/
47.	Economics, Pharmaceutical/
48.	exp "Fees and Charges"/
49.	exp Budgets/
50.	budget*.ti,ab.
51.	cost*.ti.
52.	(economic* or pharmaco?economic*).ti.
53.	(price* or pricing*).ti,ab.
54.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
55.	(financ* or fee or fees).ti,ab.
56.	(value adj2 (money or monetary)).ti,ab.
57.	or/41-56
58.	quality-adjusted life years/
59.	sickness impact profile/
60.	(quality adj2 (wellbeing or well being)).ti,ab.
61.	sickness impact profile.ti,ab.
62.	disability adjusted life.ti,ab.
63.	(qal* or qtime* or qwb* or daly*).ti,ab.
64.	(euroqol* or eq5d* or eq 5*).ti,ab.
65.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
66.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.

67.	(hui or hui1 or hui2 or hui3).ti,ab.
68.	(health* year* equivalent* or hye or hyes).ti,ab.
69.	discrete choice*.ti,ab.
70.	rosser.ti,ab.
71.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
72.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
73.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
74.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
75.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
76.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
77.	or/58-76
78.	40 and 57
79.	40 and 77
80.	78 or 79

1 **Embase (Ovid) search terms**

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	myelitis/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	demyelinating disease/
9.	(Demyelinat* adj2 (syndrome* or disease* or autoimmun*)).ti,ab.
10.	(Chronic Cerebrospinal Venous Insufficiency or CCSVI).ti,ab.
11.	vein insufficiency/co, di, et [Complication, Diagnosis, Etiology]
12.	(Devic* adj (disease or syndrome)).ti,ab.
13.	((clinical* isolat* or radiological* isolat*) adj2 syndrome*).ti,ab.
14.	exp optic neuritis/
15.	((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*)).ti,ab.
16.	(NMO or NMOSD).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	(conference abstract or conference paper).pt.
22.	case report/ or case study/
23.	(letter or comment*).ti.
24.	or/18-23
25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25

27.	animal/ not human/
28.	nonhuman/
29.	exp Animal Experiment/
30.	exp Experimental Animal/
31.	animal model/
32.	exp Rodent/
33.	(rat or rats or rodent* or mouse or mice).ti.
34.	or/26-33
35.	17 not 34
36.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
37.	35 not 36
38.	limit 37 to English language
39.	health economics/
40.	exp economic evaluation/
41.	exp health care cost/
42.	exp fee/
43.	budget/
44.	funding/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/39-51
53.	quality adjusted life year/
54.	"quality of life index"/
55.	short form 12/ or short form 20/ or short form 36/ or short form 8/
56.	sickness impact profile/
57.	(quality adj2 (wellbeing or well being)).ti,ab.
58.	sickness impact profile.ti,ab.
59.	disability adjusted life.ti,ab.
60.	(qal* or qtime* or qwb* or daly*).ti,ab.
61.	(euroqol* or eq5d* or eq 5*).ti,ab.
62.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
63.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
64.	(hui or hui1 or hui2 or hui3).ti,ab.
65.	(health* year* equivalent* or hye or hyes).ti,ab.
66.	discrete choice*.ti,ab.
67.	rosser.ti,ab.
68.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
69.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
70.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.

71.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
72.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
73.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
74.	or/53-73
75.	38 and 52
76.	38 and 74
77.	75 or 76

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Multiple Sclerosis EXPLODE ALL TREES
#2.	(((multiple or disseminated) adj2 scleros*))
#3.	(encephalomyelitis disseminata)
#4.	(MS)
#5.	MeSH DESCRIPTOR Myelitis, Transverse EXPLODE ALL TREES
#6.	(transverse myelitis)
#7.	MeSH DESCRIPTOR Demyelinating Diseases EXPLODE ALL TREES
#8.	((Demyelinat* adj2 (syndrome or disease)))
#9.	(Chronic Cerebrospinal Venous Insufficiency)
#10.	MeSH DESCRIPTOR Venous Insufficiency
#11.	(((Devic or "devic's") adj (disease or syndrome)))
#12.	(((clinically isolated or radiologically isolated) adj syndrome))
#13.	MeSH DESCRIPTOR Optic Neuritis EXPLODE ALL TREES
#14.	(Neuromyelitis Optica)
#15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

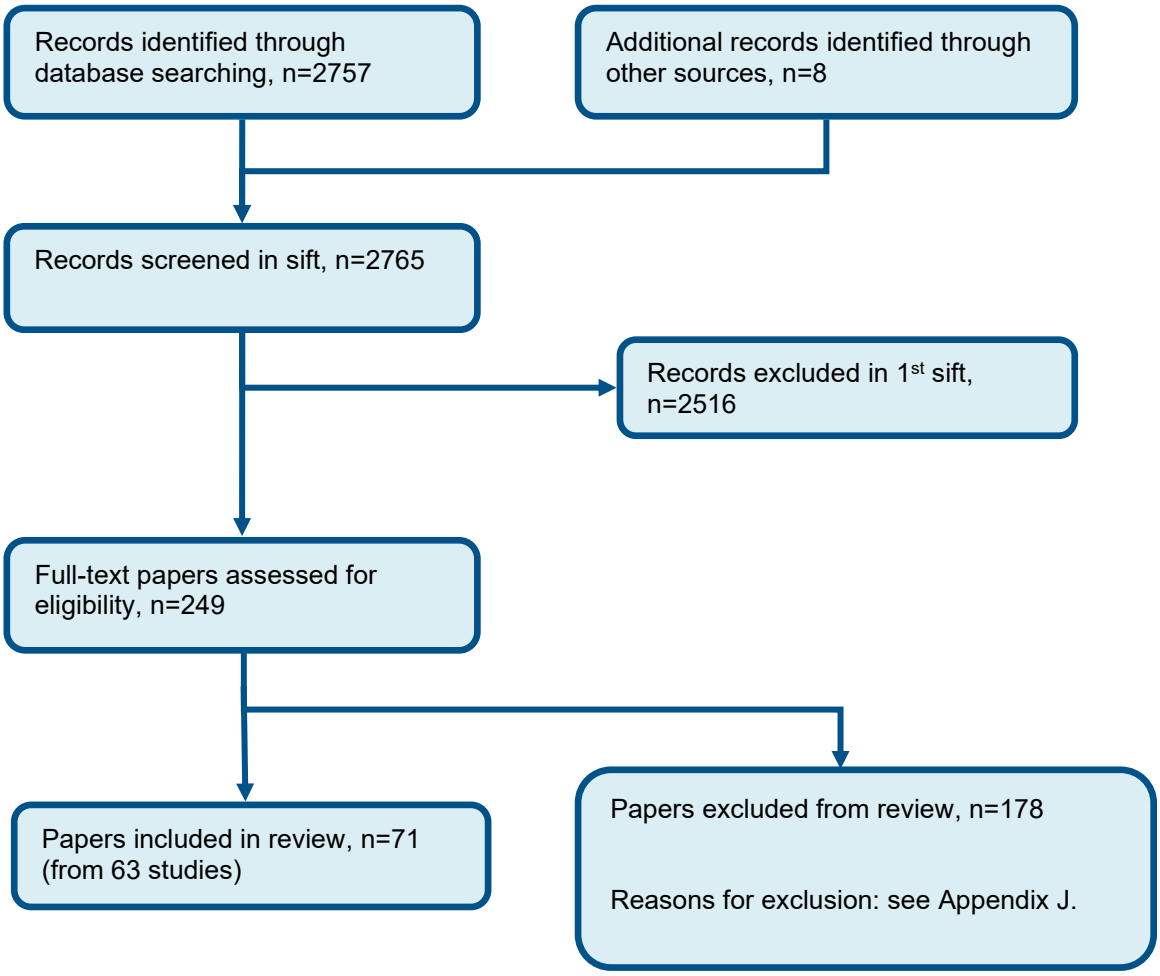
2 **INAHTA search terms**

1.	(multiple sclerosis)[mh] OR (((multiple or disseminated) adj2 scleros*)) OR (encephalomyelitis disseminata) OR (MS)[Title] OR (Myelitis, Transverse)[mh] OR (transverse myelitis) OR (Demyelinating Diseases)[mh] OR (Demyelinating Autoimmune Diseases, CNS)[mh] OR ((Demyelinat* adj2 (syndrome* or disease* or autoimmun*))) OR ((Chronic Cerebrospinal Venous Insufficiency or CCSVI)) OR (venous insufficiency)[mh] OR ((Devic* adj (disease or syndrome))) OR (((clinical* isolat* or radiological* isolat*) adj2 syndrome*)) OR (optic neuritis)[mh] OR (((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*))) OR ((NMO or NMOSD))

3
4

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of non-pharmacological management of memory and cognitive problems



Appendix D – Effectiveness evidence

D.1 Studies extracted using EPPI reviewer (new studies identified in current update)

Arian Darestani, 2020

Bibliographic Reference	Arian Darestani, A.; Naeeni Davarani, M.; Hassani-Abharian, P.; Zarrindast, M. R.; Nasehi, M.; The therapeutic effect of treatment with RehaCom software on verbal performance in patients with multiple sclerosis; Journal of Clinical Neuroscience; 2020; vol. 72; 93-97

Study details

Trial name / registration number	Not reported
Study location	Iran
Study setting	Outpatient - those referred to a brain and cognition clinic
Study dates	Not reported
Sources of funding	No financial support provided.
Inclusion criteria	People with MS referred to Brain and Cognition clinic; and aged 18-65 years.
Exclusion criteria	Sensory aphasia; impaired speech comprehension; hemianopia; visual disturbances; and hand-related mechanical or neuromuscular disorders.
Recruitment / selection of participants	Recruited from those referred to Brain and Cognition Clinic.

Intervention(s)	Verbal fluency intervention - RehaCom cognitive rehabilitation software: comprehensive software to rehabilitate cognitive dysfunctions. Involves 20 modules in English and is auto-adaptive with difficulty increasing and reducing depending on performance of the patient. Therapist can take into account information obtained from assessment of sessions and provide modules to strengthen brain cognitive functions. 10 sessions over 5 weeks (2 per week with each session 1 h duration).
Population subgroups	None
Comparator	Control - description not given but likely no intervention.
Number of participants	60 randomised, 53 analysed at week 10
Duration of follow-up	Up to 10 weeks following start of treatment (5 weeks after the end of treatment).
Indirectness	Outcomes - follow-up <3 months minimum in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - unclear • According to disability (EDSS <6 and EDSS ≥6) - unclear • Severity of cognitive impairment (mild/moderate/severe) - unclear (referred to cognition clinic but severity unclear) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear • Computerised vs clinician led - mixed/unclear (computerised software but performed in clinic) • Group vs individual - individual Analysis - those with data (available case analysis) appear to have been reported in paper

Study arms

Verbal fluency - RehaCom cognitive rehabilitation software (N = 30)

Control - no intervention? (N = 30)

Characteristics

Arm-level characteristics

Characteristic	Verbal fluency - RehaCom cognitive rehabilitation software (N = 30)	Control - no intervention? (N = 30)
% Female Sample size	n = 21 ; % = 78	n = 22 ; % = 85
Mean age (SD) Mean (SD)	37.11 (8.12)	39.23 (7.81)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR

Note data available and analysed for n=27 and n=26 in intervention and control groups, respectively. Baseline values given for those analysed not randomised.

Outcomes

Study timepoints

- Baseline
- 10 week (10 weeks post-baseline (5 weeks after the end of intervention sessions). 5-week time-point not extracted as 10 weeks better fits protocol.)

Results - final values raw data

Outcome	Verbal fluency - RehaCom cognitive rehabilitation software, Baseline, N = 27	Verbal fluency - RehaCom cognitive rehabilitation software, 10-week, N = 27	Control - no intervention?, Baseline, N = 26	Control - no intervention?, 10-week, N = 26
CVLT-II California Verbal Learning Test - Second Edition. Measures episodic verbal learning and memory. Mean (SD)	50.11 (13.43)	54 (14.17)	48.08 (11.22)	46.62 (10.1)
COWAT Controlled Oral Word Association Test. Verbal fluency test. Mean (SD)	25.22 (8.47)	28.62 (8.62)	24.04 (7.39)	23.73 (7.07)
Optional dropout of treatment Note that this was measured at end of treatment (5 weeks) not 10 weeks as intervention only lasted 5 weeks. No of events	n = NA ; % = NA	n = 3 ; % = 10	n = NA ; % = NA	n = 4 ; % = 13.3
Optional dropout of treatment Note that this was measured at end of treatment (5 weeks) not 10	NA	30	NA	30

Outcome	Verbal fluency - RehaCom cognitive rehabilitation software, Baseline, N = 27	Verbal fluency - RehaCom cognitive rehabilitation software, 10-week, N = 27	Control - no intervention?, Baseline, N = 26	Control - no intervention?, 10-week, N = 26
weeks as intervention only lasted 5 weeks. Number analysed				

CVLT-II - Polarity - Higher values are better
COWAT - Polarity - Higher values are better
Baseline and follow-up results given for those analysed (n=27 and n=27), not those randomised (n=30 per group)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_CVLT II episodic verbal learning and memory_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up <3 months minimum)*

Results_COWAT verbal fluency test_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up <3 months minimum)*

Results_optional dropout from intervention_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Azimian, 2021

Bibliographic Reference	Azimian, M.; Yaghoubi, Z.; Ahmadi Kahjoogh, M.; Akbarfahimi, N.; Haghgoo, H. A.; Vahedi, M.; The Effect of Cognitive Rehabilitation on Balance Skills of Individuals with Multiple Sclerosis; Occupational Therapy in Health Care; 2021; vol. 35 (no. 1); 93-104

Study details

Trial name / registration number	Not reported
Study location	Iran
Study setting	Outpatient - those receiving occupational therapy services in a public rehabilitation hospital recruited
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	Aged between 20 and 50 years; diagnosis of MS; score <5.0 on EDSS; no history of other psychological disorders (e.g., depression or substance abuse); ability to use the computer; and not receiving corticosteroid medications within last 28 days.
Exclusion criteria	Disease was relapsed; or had not completed the intervention.
Recruitment / selection of participants	People with MS receiving occupational therapy services in a public rehabilitation hospital recruited by phone call as well as people with MS referred to hospital were screened to participate in the study.
Intervention(s)	Cognitive-based rehabilitation focused on processing speed + usual occupational therapy: usual occupational therapy involved several exercises for 30 min in 12 sessions across 4 weeks (bending to sides in standing position, forward bending, toe standing, heel standing, heel cord stretch with bent knee, one leg standing, one leg standing with eyes closed, rotating the head in standing position or while walking, maintaining quadruped position, kneel standing and walking).

	Cognitive-based rehab involved processing speed tasks for 4 weeks (3 sessions per week, each session 30 min). At least two tasks performed in each session.
Population subgroups	None
Comparator	Usual occupational therapy only: usual occupational therapy involved several exercises for 1 h in 12 sessions across 4 weeks (bending to sides in standing position, forward bending, toe standing, heel standing, heel cord stretch with bent knee, one leg standing, one leg standing with eyes closed, rotating the head in standing position or while walking, maintaining quadruped position, kneel standing and walking).
Number of participants	71 randomised, 64 analysed at follow-up (n=4 and n=3 in intervention and control groups, respectively, excluded either because of relapsing symptoms in n=4, falling in n=1 and family problems in n=2).
Duration of follow-up	Up to 2 months following completion of training (3 months following start of intervention)
Indirectness	Population - unclear if they had a cognitive deficit at baseline
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority primary progressive (51%) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 • Severity of cognitive impairment (mild/moderate/severe) - unclear whether any cognitive deficit was present at baseline • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - absent (history of psychological disorders an exclusion criterion) • Computerised vs clinician led - clinician-led • Group vs individual - individual Unclear if results are given for those randomised or those randomised minus those with missing data/excluded

Study arms

Cognitive rehabilitation focused on processing speed + occupational therapy (N = 35)

Control - occupational therapy only (N = 36)

Characteristics

Arm-level characteristics

Characteristic	Cognitive rehabilitation focused on processing speed + occupational therapy (N = 35)	Control - occupational therapy only (N = 36)
% Female Sample size	n = 25 ; % = 71.4	n = 26 ; % = 72.2
Mean age (SD) Mean (SD)	43.62 (9.26)	43.27 (10.53)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Duration (years) Mean (SD)	12.31 (6.3)	13.03 (7.2)

Characteristic	Cognitive rehabilitation focused on processing speed + occupational therapy (N = 35)	Control - occupational therapy only (N = 36)
Relapsing-remitting Sample size	n = 9 ; % = 25.7	n = 8 ; % = 22.2
Primary-progressive Sample size	n = 17 ; % = 48.6	n = 19 ; % = 52.8
Secondary-progressive Sample size	n = 9 ; % = 25.7	n = 7 ; % = 19.4
Progressive-relapsing Sample size	n = 0 ; % = 0	n = 2 ; % = 5.6
EDSS score Median	5.0	5.0

Outcomes

Study timepoints

- Baseline
- 3 month (3 months post-randomisation (2 months after last session). 4-week time-point not extracted as this time-point better fits protocol.)

Results - final values raw data

Outcome	Cognitive rehabilitation focused on processing speed + occupational therapy, Baseline, N = 35	Cognitive rehabilitation focused on processing speed + occupational therapy, 3-month, N = 31	Control - occupational therapy only, Baseline, N = 36	Control - occupational therapy only, 3-month, N = 33
PASAT Paced Auditory Serial Addition Test. Measures working memory and auditory information processing speed. Mean (SD)	34.77 (14.02)	37.9 (13)	33.52 (13.22)	31.97 (13.41)
SDMT Symbol Digit Modalities Test. Assesses processing speed presented in the visual modality. Mean (SD)	32.16 (10.4)	36.19 (10.36)	34.15 (11.74)	32.75 (11.43)

PASAT - Polarity - Higher values are better

SDMT - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_PASAT_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Blair, 2021**

Bibliographic Reference	Blair, M.; Goveas, D.; Safi, A.; Marshall, C.; Rosehart, H.; Orenczuk, S.; Morrow, S. A.; Does cognitive training improve attention/working memory in persons with MS? A pilot study using the Cogmed Working Memory Training program; Multiple Sclerosis and Related Disorders; 2021; vol. 49; 102770

3

4 ## Study details

Trial name / registration number	Not reported
Study location	Canada
Study setting	Outpatient - recruited from those that had been referred to a tertiary care centre

Study dates	Not reported
Sources of funding	Not reported - Cogmed services/training programmes provided at no cost to the study.
Inclusion criteria	Attending London MS or MS Cognitive Clinic in Canada; reporting cognitive difficulties; relapsing-remitting, primary progressive or secondary progressive MS; aged 18-64 years; EDSS score ≤7.0; visual acuity of at least 20/70; and z-score <-1.5 on at least 2 of 3 measures (PASAT, SDMT and DKFES Color-Word Interference Test) and therefore characterised as having attention/working memory deficits.
Exclusion criteria	Clinical relapse/corticosteroid treatment for at least 1 month prior to study entry; daily marijuana use; loss of visual acuity; history of bipolar disorder; and other psychiatric illness.
Recruitment / selection of participants	Consecutive people with MS attending London MS or affiliative MS Cognitive Clinic in Canada (tertiary care MS clinic).
Intervention(s)	Computer-assisted working memory training - CogMed: 25 training sessions conducted online. Completed 8 exercises per day taking 30-45 min per session. Lasts 5 weeks with 5 sessions per week. Uses adaptive training approach where difficulty level is adjusted in real time based on performance. Each session involves various tasks targeting different aspects of working memory including visuospatial working memory and verbal working memory tasks. Reinforcement built into program in form of small weekly rewards. Each person had a qualified coach responsible for providing structure, motivation and feedback on training progress to Maximise training gains. Cogmed coaches were trained and certified and overseen by a healthcare professional. Initial in-home visit by coach for first training session followed by tracking of performance online and once weekly phone meetings throughout the 5 weeks. At end of training, coach summarised training with participant and feedback data provided.
Population subgroups	None
Comparator	Treatment as usual - standard medical care group.
Number of participants	30 randomised, 22 analysed at 6-month follow-up
Duration of follow-up	Up to 6 months follow-up (~4-5 months after end of training)

Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (>55%) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (median 4.0 or 4.5) • Severity of cognitive impairment (mild/moderate/severe) - unclear (those with z-score <-1.5 on at least 2 of 3 cognitive measures included) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (psychiatric conditions excluded) • Computerised vs clinician led - computerised with involvement of coach • Group vs individual - individual Appears to be intention to treat analysis with those dropping out/withdrawing consent removed from analysis. n=4 in training group withdrew before starting training, n=2 in control group withdrew consent prior to completion and n=2 in the control group withdrew consent prior to completing 6-month follow-up.

Study arms

CogMed working memory training for working memory and attention (N = 15)

Treatment as usual - standard medical care (N = 15)

Characteristics

Arm-level characteristics

Characteristic	CogMed working memory training for working memory and attention (N = 15)	Treatment as usual - standard medical care (N = 15)
% Female Sample size	n = 12 ; % = 80	n = 9 ; % = 60
Mean age (SD) Mean (SD)	51.07 (7.29)	52.13 (8.71)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Relapsing-remitting Sample size	n = 9 ; % = 60	n = 8 ; % = 53.3
Secondary progressive Sample size	n = 6 ; % = 40	n = 6 ; % = 40
Primary progressive Sample size	n = 0 ; % = 0	n = 1 ; % = 6.7

Characteristic	CogMed working memory training for working memory and attention (N = 15)	Treatment as usual - standard medical care (N = 15)
Duration of MS (years) Mean (SD)	14.87 (8.47)	16.25 (10.94)
EDSS score Median (range)	4.5 (1.5-7.0)	4.0 (2.0-6.5)

Outcomes

Study timepoints

- Baseline
- 6 month (6-month follow-up - ~4-5 months following last intervention session (5-week period). 5-week time-point not extracted as 6 months better fits protocol.)

Results - raw data final values

Outcome	CogMed working memory training for working memory and attention, Baseline, N = 15	CogMed working memory training for working memory and attention, 6-month, N = 11	Treatment as usual - standard medical care, Baseline, N = 15	Treatment as usual - standard medical care, 6-month, N = 11
PASAT Paced Auditory Serial Addition Test.	27.73 (14.43)	35.18 (10.69)	28.07 (12.66)	33.91 (12.2)

Outcome	CogMed working memory training for working memory and attention, Baseline, N = 15	CogMed working memory training for working memory and attention, 6-month, N = 11	Treatment as usual - standard medical care, Baseline, N = 15	Treatment as usual - standard medical care, 6-month, N = 11
Mean (SD)				
SDMT Symbol Digit Modality Test. Mean (SD)	39.2 (9.58)	39.73 (7.51)	39.6 (7.94)	40.64 (9.79)
DKEFS Color-Word Interference Delis-Kaplan Executive Function System. Mean (SD)	25.07 (10.26)	28.27 (10.87)	26.13 (5.17)	29.73 (4.32)
CVLT2 Total Immediate Recall California Verbal Learning Test Second Edition. Mean (SD)	40.67 (10.08)	46.55 (13.53)	42.47 (10.23)	45 (13.09)
BVMT-R Total Immediate Recall Brief Visuospatial Memory Test – Revised Mean (SD)	17.2 (7.06)	19.27 (10.43)	19.4 (8.77)	17.64 (8.38)
WMS-III Spatial Span - forward Wechsler Memory Scale Third Edition.	6.67 (1.8)	6.09 (1.22)	6.67 (1.59)	6.82 (1.47)

Outcome	CogMed working memory training for working memory and attention, Baseline, N = 15	CogMed working memory training for working memory and attention, 6-month, N = 11	Treatment as usual - standard medical care, Baseline, N = 15	Treatment as usual - standard medical care, 6-month, N = 11
Mean (SD)				
WMS-III Spatial Span - backward Wechsler Memory Scale Third Edition. Mean (SD)	5.87 (2)	6.18 (1.66)	6.27 (2.02)	6.45 (1.51)
WAIS-III Arithmetic Wechsler Adult Intelligence Scale Mean (SD)	10.8 (2.96)	12 (3)	10.87 (3.66)	11 (2.61)
WAIS-III Letter-Number Sequencing Wechsler Adult Intelligence Scale Mean (SD)	7.07 (2.99)	8.45 (2.58)	7.33 (2.8)	7.82 (3.28)
WAIS-III Digit Span - forward Wechsler Adult Intelligence Scale Mean (SD)	9.2 (2.04)	9.18 (2.32)	9.67 (1.63)	8.82 (1.66)
WAIS-III Digit Span - backward Wechsler Adult Intelligence Scale Mean (SD)	5.07 (1.28)	6.09 (1.3)	4.73 (1.28)	5.36 (1.86)

Outcome	CogMed working memory training for working memory and attention, Baseline, N = 15	CogMed working memory training for working memory and attention, 6-month, N = 11	Treatment as usual - standard medical care, Baseline, N = 15	Treatment as usual - standard medical care, 6-month, N = 11
MSNQ Multiple Sclerosis Neuropsychological Screening Questionnaire - self-report version. Scale not reported but is usually 0-60. Mean (SD)	34.07 (12.47)	28.55 (15.16)	27.27 (9.07)	29.91 (10.83)
BDI-FS Beck Depression Inventory Fast Screen. Scale not reported but is usually 0-21. Mean (SD)	4.67 (2.85)	2.64 (3.26)	3.73 (2.84)	2.73 (3.52)
FSS Fatigue Severity Scale. Scale appears to be 1-7 as is reported as a mean of different items in the questionnaire. Mean (SD)	4.82 (1.76)	4.89 (2.26)	5.23 (1.16)	5.18 (1.26)
HADS - anxiety Hospital Anxiety and Depression Scale. Scale not reported but is usually 0-21. Mean (SD)	8.53 (3.56)	7.09 (4.35)	6.4 (3.36)	6.09 (4.95)

Outcome	CogMed working memory training for working memory and attention, Baseline, N = 15	CogMed working memory training for working memory and attention, 6-month, N = 11	Treatment as usual - standard medical care, Baseline, N = 15	Treatment as usual - standard medical care, 6-month, N = 11
HADS - depression Hospital Anxiety and Depression Scale. Scale not reported but is usually 0-21. Mean (SD)	7.27 (3.99)	4.73 (4.03)	5.53 (3.14)	4.91 (3.15)
SF-36 Quality of life. Unclear if mental or physical composite or have combined the two. Scale not reported but usually 0-100. Mean (SD)	57.2 (19.01)	56.45 (23.79)	51.13 (17.46)	44.55 (12.78)
DEX Dysexecutive questionnaire - executive functioning. Scale not reported but is usually 0-80. Mean (SD)	27.67 (16.47)	23.09 (17.68)	23.27 (11.44)	20.55 (10.82)
CFQ Cognitive Failure Questionnaire. Scale not reported but is usually 0-100. Mean (SD)	44.53 (15.84)	42.36 (24.25)	39 (17.87)	36.45 (20.54)

Outcome	CogMed working memory training for working memory and attention, Baseline, N = 15	CogMed working memory training for working memory and attention, 6-month, N = 11	Treatment as usual - standard medical care, Baseline, N = 15	Treatment as usual - standard medical care, 6-month, N = 11
PDQ Perceived Deficits Questionnaire - measure of cognitive dysfunction. Scale not reported but is usually 0-80. Mean (SD)	40.53 (12.95)	37.82 (24.19)	33.47 (13.87)	30.73 (15.74)

1 PASAT - Polarity - Higher values are better
2 SDMT - Polarity - Higher values are better
3 DKEFS Color-Word Interference - Polarity - Higher values are better
4 CVLT2 Total Immediate Recall - Polarity - Higher values are better
5 BVMT-R Total Immediate Recall - Polarity - Higher values are better
6 WMS-III Spatial Span - forward - Polarity - Higher values are better
7 WMS-III Spatial Span - backward - Polarity - Higher values are better
8 WAIS-III Arithmetic - Polarity - Higher values are better
9 WAIS-III Letter-Number Sequencing - Polarity - Higher values are better
10 WAIS-III Digit Span - forward - Polarity - Higher values are better
11 WAIS-III Digit Span - backward - Polarity - Higher values are better
12 MSNQ - Polarity - Lower values are better
13 BDI-FS - Polarity - Lower values are better
14 FSS - Polarity - Lower values are better
15 HADS - anxiety - Polarity - Lower values are better
16 HADS - depression - Polarity - Lower values are better
17 SF-36 - Polarity - Higher values are better

DEX - Polarity - Lower values are better
CFQ - Polarity - Lower values are better
PDQ - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_PASAT_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_DKEFS Color-Word Interference_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT2 Total Immediate Recall_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_BVMT-R Total Immediate Recall_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_WMS-III Spatial Span-forward_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_WMS-III Spatial Span-backward_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WAIS-III Arithmetic_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WAIS-III Letter-Number Sequencing_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_WAIS-III Digit Span-forward_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_WAIS-III Digit Span-backward_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_MSNQ_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_BDI-FS_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

1 **Results_FSS_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Not specifically cognitive fatigue)*

2

3 **Results_HADS-anxiety_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_HADS-depression_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SF-36_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_DEX_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_CFQ_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PDQ_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Bove, 2021

Bibliographic Reference	Bove, R.; Rowles, W.; Zhao, C.; Anderson, A.; Friedman, S.; Langdon, D.; Alexander, A.; Sacco, S.; Henry, R.; Gazzaley, A.; Feinstein, A.; Anguera, J. A.; A novel in-home digital treatment to improve processing speed in people with multiple sclerosis: A pilot study; Multiple Sclerosis Journal; 2021; vol. 27 (no. 5); 778-789

Study details

Trial name / registration number	NCT03569618
Study location	USA
Study setting	Outpatient - recruited from University of California and Neuroinflammation Center
Study dates	Recruited between March and September 2018
Sources of funding	This research was supported by an unrestricted grant from Akili Interactive. Akili Interactive provided AKL-T03 and AKL-T09 without charge for the study.
Inclusion criteria	Diagnosis of clinically isolated syndrome or MS according to 2010 Revised McDonald criteria; adults with SDMT z-scores between -2 and 1; had WiFi at home; and visual acuity was 20/50 OU or better.
Exclusion criteria	Moderate-severe depression based on self- or clinician-report; and clinical relapse within last 30 days.

Recruitment / selection of participants	Recruited from the University of California San Francisco (UCSF) MS and Neuroinflammation Center between March and September 2018. Participants were either referred by their primary MS clinician or identified through review of their clinician's notes for mention of either patient subjective cognitive complaints or of observed abnormalities on testing.
Intervention(s)	**Sensory and motor tasks designed to improve processing speed:** In-home, tablet-based video game-like digital treatment (AKL-T03). Asked to complete 25 mins for 5 days each week for 6 weeks. Returned for second evaluation after 6 weeks. Persistence of effect evaluated by further assessments at 8 weeks without further intervention. AKL-T03 is an investigational medical device software developed by Akili Interactive. Uses Selective Stimulus Management Engine engaging patients in two simultaneous sensory and motor tasks and designed to engage frontal neural networks. Closed-loop system with algorithms adapting in real-time and between treatment sessions to automatically adjust level (or dose) for a personalised treatment experience adapted to each patient's needs. Allows real-time monitoring of progress and challenges patient continuously so it is never too easy or too difficult. Treatment locked out at 6 weeks. Average proportion of prescribed sessions played was 0.84.
Population subgroups	None
Comparator	**Active control digital game:** Administered on digital platform similar to AKL-T03, AKL-T09 is a game where aim is to connect letters on a grid and spell as many words as possible. Points earned by tracing words with two or more letters in any direction based on number of words formed, word length and use of uncommon letters with progressive difficulty. Active placebo control used to provide similar time on task and engagement. Average proportion of prescribed sessions played was 1.06.
Number of participants	44 randomised, 40 analysed in intention to treat population (unclear definition of this)
Duration of follow-up	Up to 8 weeks following the start of treatment (2 weeks after last session) - however, insufficient results provided for 8-week time-point.
Indirectness	Outcome - follow-up less than minimum of 3 months specified in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (>75%) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (median 3.5)

	• Severity of cognitive impairment (mild/moderate/severe) - unclear (those with SDMT z-score between -2 and 1 included) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (moderate to severe depression excluded) • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - intention to treat analysis (likely those with available data as n differs slightly for each outcome) stated to be used. n=40 returned for visit 2 (6 weeks) and included in intention to treat analysis. n=37 considered to be adherent (92.5%) as had completed at least 50% of prescribed sessions and included in per-protocol analyses. Reasons for study discontinuation included n=1 relapse, n=2 poor compliance to protocol and n=1 concurrent medical complication. n=39 returned for visit 3 at 8 weeks.

Study arms

Sensory and motor tablet-based tasks - intervention to improve processing speed (N = 23)

Active control tablet game (N = 21)

Characteristics

Arm-level characteristics

Characteristic	Sensory and motor tablet-based tasks - intervention to improve processing speed (N = 23)	Active control tablet game (N = 21)
% Female Sample size	n = 17 ; % = 73.9	n = 18 ; % = 85.7

Characteristic	Sensory and motor tablet-based tasks - intervention to improve processing speed (N = 23)	Active control tablet game (N = 21)
Mean age (SD) Mean (SD)	52.9 (14)	49.2 (10.9)
Hispanic Sample size	n = 3 ; % = 13	n = 1 ; % = 4.8
Non-Hispanic Sample size	n = 20 ; % = 87	n = 20 ; % = 95.2
White Sample size	n = 17 ; % = 73.9	n = 18 ; % = 85.7
American Indian/Alaska Native Sample size	n = 1 ; % = 4.3	n = 0 ; % = 0
Black/African American Sample size	n = 1 ; % = 4.3	n = 1 ; % = 4.8
More than one race Sample size	n = 1 ; % = 4.3	n = 0 ; % = 0
Unknown/not reported Sample size	n = 3 ; % = 13	n = 0 ; % = 0

Characteristic	Sensory and motor tablet-based tasks - intervention to improve processing speed (N = 23)	Active control tablet game (N = 21)
Comorbidities Custom value	NR	NR
Relapsing-remitting Sample size	n = 19 ; % = 82.6	n = 14 ; % = 66.7
Secondary progressive Sample size	n = 3 ; % = 13	n = 4 ; % = 19
Primary progressive Sample size	n = 1 ; % = 4.3	n = 1 ; % = 4.8
Clinically isolated syndrome Sample size	n = 0 ; % = 0	n = 1 ; % = 4.8
Undetermined Sample size	n = 0 ; % = 0	n = 1 ; % = 4.8
Self-injectable Sample size	n = 7 ; % = 30.4	n = 2 ; % = 9.5
Oral Sample size	n = 5 ; % = 21.7	n = 5 ; % = 23.8

Characteristic	Sensory and motor tablet-based tasks - intervention to improve processing speed (N = 23)	Active control tablet game (N = 21)
Infused Sample size	n = 7 ; % = 30.4	n = 9 ; % = 42.9
None Sample size	n = 4 ; % = 17.4	n = 5 ; % = 23.8
Disease duration (years) Mean (SD)	11.2 (7.9)	16.1 (7.8)
EDSS score Median (IQR)	3 (2.5 to 4.5)	3.5 (2.5 to 4)
T25FW test Mean (SD)	5.2 (1.5)	5.9 (3.3)
9HPT dominant Mean (SD)	25.4 (8.5)	24.9 (4.6)
9HPT non-dominant Mean (SD)	28.1 (12.2)	24.8 (7)
SDMT - correct Mean (SD)	39.2 (7.9)	42.7 (8.3)

Characteristic	Sensory and motor tablet-based tasks - intervention to improve processing speed (N = 23)	Active control tablet game (N = 21)
SDMT z score Mean (SD)	-1 (0.6)	-0.9 (0.6)
PASAT Mean (SD)	41.7 (11.6)	46.6 (10.7)
Brief Visuospatial Memory Test (BVMT) Mean (SD)	22.6 (4.3)	24.1 (6.8)
California Verbal Learning Test II (CVLT-II) Mean (SD)	56.4 (10.7)	56 (9.1)
Perceived Deficits Questionnaire-5 (PDQ-5) Mean (SD)	9.6 (2.7)	11.8 (3.4)
Center for Epidemiologic Studies Depression Scale (CES-D) Mean (SD)	10.7 (7.3)	14.4 (12.8)
State-Trait Anxiety Inventory (STAI) - State Mean (SD)	47.2 (6)	46.5 (9.2)
State-Trait Anxiety Inventory (STAI) - Trait	44.1 (2.8)	43.7 (3.6)

Characteristic	Sensory and motor tablet-based tasks - intervention to improve processing speed (N = 23)	Active control tablet game (N = 21)
Mean (SD)		
Modified Fatigue Impact Scale (MFIS) Mean (SD)	42.2 (14.4)	40.2 (18.8)

Outcomes

Study timepoints

- Baseline
- 6 week (6-weeks - end of intervention period (included as insufficient reporting of outcomes at 8 weeks))

Results - change from baseline

Outcome	Sensory and motor tablet-based tasks - intervention to improve processing speed, 6-week vs Baseline , N = 20	Active control tablet game, 6-week vs Baseline , N = 20
SDMT - number correct Symbol Digit Modalities Test. Measure of processing speed. Baseline values were 39.2 (7.9) and 42.7 (8.3), respectively. Mean (SD)	6.1 (4.62)	3.55 (7.51)
PASAT - number correct Paced Auditory Serial Addition Test. Measure of processing speed and	18	19

Outcome	Sensory and motor tablet-based tasks - intervention to improve processing speed, 6-week vs Baseline , N = 20	Active control tablet game, 6-week vs Baseline , N = 20
working memory. Baseline values were 41.7 (11.6) and 46.6 (10.7), respectively. Number analysed		
PASAT - number correct Paced Auditory Serial Addition Test. Measure of processing speed and working memory. Baseline values were 41.7 (11.6) and 46.6 (10.7), respectively. Mean (SD)	2.72 (5.41)	2.53 (7.19)
BVMT-R - number correct Brief Visuospatial Memory Test. Measures visual memory. Baseline values were 22.6 (4.3) and 24.1 (6.8), respectively. Mean (SD)	0.7 (4.47)	3.25 (5.23)
CVLT-II - number correct California Verbal Learning Test-II. Measures verbal learning and memory. Baseline values were 56.4 (10.7) and 56.0 (9.1), respectively. Mean (SD)	2.05 (9.14)	5.2 (8.6)
PDQ-5 5-item Perceived Deficits Questionnaire. Measures perceived deficits in terms of cognitive functioning. Scale not reported but usually 0-80. Baseline values were 9.6 (2.7) and 11.8 (3.4), respectively.	14	11

Outcome	Sensory and motor tablet-based tasks - intervention to improve processing speed, 6-week vs Baseline , N = 20	Active control tablet game, 6-week vs Baseline , N = 20
Number analysed		
PDQ-5 5-item Perceived Deficits Questionnaire. Measures perceived deficits in terms of cognitive functioning. Scale not reported but usually 0-80. Baseline values were 9.6 (2.7) and 11.8 (3.4), respectively. Mean (SD)	-0.57 (1.28)	-1.64 (1.63)
CES-D Center for Epidemiologic Studies Depression Scale. Measures depression. Scale not reported but is usually 0-60. Baseline values were 10.7 (7.3) and 14.4 (12.8), respectively. Number analysed	19	19
CES-D Center for Epidemiologic Studies Depression Scale. Measures depression. Scale not reported but is usually 0-60. Baseline values were 10.7 (7.3) and 14.4 (12.8), respectively. Mean (SD)	1.11 (6.14)	-0.9 (5.57)
STAI-S State-Trait Anxiety Inventory-State score. Measures anxiety-State. Scale not reported but usually 20-80. Baseline values were 47.2 (6.0) and 46.5 (9.2), respectively. Number analysed	19	19

Outcome	Sensory and motor tablet-based tasks - intervention to improve processing speed, 6-week vs Baseline , N = 20	Active control tablet game, 6-week vs Baseline , N = 20
STAI-S State-Trait Anxiety Inventory-State score. Measures anxiety-State. Scale not reported but usually 20-80. Baseline values were 47.2 (6.0) and 46.5 (9.2), respectively. Mean (SD)	0.05 (4.64)	0.21 (8.93)
STAI-T State-Trait Anxiety Inventory-Trait score. Measures anxiety-Trait. Scale not reported but usually 20-80. Baseline values were 44.1 (2.8) and 43.7 (3.6), respectively. Number analysed	17	17
STAI-T State-Trait Anxiety Inventory-Trait score. Measures anxiety-Trait. Scale not reported but usually 20-80. Baseline values were 44.1 (2.8) and 43.7 (3.6), respectively. Mean (SD)	0.77 (4.1)	0.35 (3.35)
MFIS Modified Fatigue Impact Scale. Scale not reported but is usually 0-84. Baseline values were 42.2 (14.4) and 40.2 (18.8), respectively. Number analysed	19	19

Outcome	Sensory and motor tablet-based tasks - intervention to improve processing speed, 6-week vs Baseline , N = 20	Active control tablet game, 6-week vs Baseline , N = 20
MFIS Modified Fatigue Impact Scale. Scale not reported but is usually 0-84. Baseline values were 42.2 (14.4) and 40.2 (18.8), respectively. Mean (SD)	-4.79 (6.27)	-2.95 (9.55)
Average proportion of prescribed sessions played Average	0.84	1.06

SDMT - number correct - Polarity - Higher values are better
PASAT - number correct - Polarity - Higher values are better
BVMT-R - number correct - Polarity - Higher values are better
CVLT-II - number correct - Polarity - Higher values are better
PDQ-5 - Polarity - Lower values are better
CES-D - Polarity - Lower values are better
STAI-S - Polarity - Lower values are better
STAI-T - Polarity - Lower values are better
MFIS - Polarity - Lower values are better
Average proportion of prescribed sessions played - Polarity - Higher values are better
Results only provided for 6 weeks (end of treatment) and not 8 weeks (2 weeks following end of intervention). Number analysed differed for each outcome and is indicated below if it was not n=20 in each group.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_SDMT_6 weeks change from baseline

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Reported at time-point <3 months minimum in protocol)*

Results_PASAT_6 weeks change from baseline

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Reported at time-point <3 months minimum in protocol)*

Results_BVMT_6 weeks change from baseline

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Reported at time-point <3 months minimum in protocol)*

Results_CVLT-II_6 weeks change from baseline

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Reported at time-point <3 months minimum in protocol)*

Results_PDQ-5_6 weeks change from baseline

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(Reported at time-point <3 months minimum in protocol)*

Results_CES-D_6 weeks change from baseline

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Reported at time-point <3 months minimum in protocol)*

1 **Results_STAI-S_6 weeks change from baseline**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Reported at time-point <3 months minimum in protocol)*

2

3 **Results_STAI-T_6 weeks change from baseline**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Reported at time-point <3 months minimum in protocol)*

Results_MFIS_6 weeks change from baseline

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Reported at time-point <3 months minimum in protocol. Also, not specifically cognitive fatigue.)*

Results_average proportion of sessions played_intervention period

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Brissart, 2020

Bibliographic Reference	Brissart, H.; Omorou, A. Y.; Forthoffer, N.; Berger, E.; Moreau, T.; De Seze, J.; Morele, E.; Debouverie, M.; Memory improvement in multiple sclerosis after an extensive cognitive rehabilitation program in groups with a multicenter double-blind randomized trial; Clinical Rehabilitation; 2020; vol. 34 (no. 6); 754-763

Study details

Trial name / registration number	NCT01659593
Study location	France
Study setting	Outpatient - recruited from university centres
Study dates	Recruited between September 2012 and December 2016
Sources of funding	No financial support received for research, authorship and/or publication of article

Inclusion criteria	People with MS diagnosis based on McDonald's criteria; 18-60 years old; EDSS score 6.0 or less; disease duration ≤30 years; cognitive status moderate (at least 2 cognitive functions of neuropsychological examination but not all); oral and written understanding of French; and affiliation to French health insurance system.
Exclusion criteria	Recent neuropsychological evaluation within 2 months prior to inclusion (to avoid re-test effect); no previous participation in a cognitive rehabilitation program; adult participants under guardianship; presence of other chronic or neurological disease and drug abuse; and corticoid treatment within 3 weeks prior to inclusion (limit bias as these treatments could affect cognition positively or negatively).
Recruitment / selection of participants	Recruited from four university centers between September 2012 and December 2016
Intervention(s)	ProCog-SEP cognitive rehabilitation: 13 group sessions over a period of 6 months each lasting 2 h (2 per month) conducted by different neuropsychologist to the one that performed initial assessment. Extended cognitive rehabilitation programme designed for people with MS using facilitation and reorganisation strategies. Functional reorganisation refers to aiming to improve cognitive functioning through treatments that they had not previously used or used infrequently. Combined with facilitation technique aiming to improve performance by building on preserved cognitive abilities. Programme includes psychoeducation advice and cognitive exercises targeting verbal and non-verbal episodic memory, working memory, short-term memory, executive functions and language.
Population subgroups	None
Comparator	Placebo programme: 13 2 h sessions over 6 months including non-cognitive exercises with discussion. No strategies or cognitive advice were provided. Pencil and paper exercises proposed but without memorisation, leaning and/or mental imagery.
Number of participants	128 randomised, 110 with baseline data (3 months post-randomisation) 101 with data at 6-9 months from baseline
Duration of follow-up	Up to 6-9 months from baseline
Indirectness	None

Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - unclear • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (mean 3.5) • Severity of cognitive impairment (mild/moderate/severe) - said to include those with moderate impairment • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (excluded other chronic or neurologic disease) • Computerised vs clinician led - clinician-led • Group vs individual - group Analysis - intention to treat analysis stated to be used however is more like modified intention to treat as excluded those dropping out or not continuing (n=101)

Study arms

ProCog-SEP extended cognitive rehabilitation program (N = 64)

Includes psychoeducational advices and cognitive exercises which target verbal and non-verbal episodic memory, working memory, short-term memory, executive functions, and language

Placebo programme - non-cognitive exercises and discussion (N = 64)

Characteristics

Arm-level characteristics

Characteristic	ProCog-SEP extended cognitive rehabilitation program (N = 64)	Placebo programme - non-cognitive exercises and discussion (N = 64)
% Female Sample size	n = 38 ; % = 73.1	n = 40 ; % = 81.6

Characteristic	ProCog-SEP extended cognitive rehabilitation program (N = 64)	Placebo programme - non-cognitive exercises and discussion (N = 64)
Mean age (SD) Custom value	NR	NR
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Mean age at onset of disease (years) Mean (SD)	47.2 (9)	44.9 (10)
EDSS score Mean (SD)	3.5 (1.5)	3.4 (1.7)
Mean disease duration (years) Mean (SD)	11.3 (7.5)	12.4 (7.5)
Progressive-relapsing remitting MS Sample size	n = 9 ; % = 17.3	n = 13 ; % = 26.5

1 Note that baseline values are given for those analysed (n=52 and n=49, respectively).

Outcomes

Study timepoints

- Baseline
- 6 month (Described as 6-9 months follow-up from baseline assessments.)

Results - raw data

Outcome	ProCog-SEP extended cognitive rehabilitation program , Baseline, N = 52	ProCog-SEP extended cognitive rehabilitation program , 6-month, N = 52	Placebo programme - non-cognitive exercises and discussion, Baseline, N = 49	Placebo programme - non-cognitive exercises and discussion, 6-month, N = 49
Selective Reminding Test - Mean free recall Measures episodic memory Mean (SD)	10.3 (1.9)	10.6 (2)	10.5 (2)	10.6 (1.8)
Selective Reminding Test - Learning Index Measures episodic memory Mean (SD)	53.8 (21.4)	60.7 (23.8)	55.6 (22.5)	54 (20.3)
Selective Reminding Test - Delayed Recall Measures episodic memory Mean (SD)	11.4 (3.2)	12.1 (3.3)	11.4 (3)	11.6 (3.1)

Outcome	ProCog-SEP extended cognitive rehabilitation program , Baseline, N = 52	ProCog-SEP extended cognitive rehabilitation program , 6-month, N = 52	Placebo programme - non-cognitive exercises and discussion, Baseline, N = 49	Placebo programme - non-cognitive exercises and discussion, 6-month, N = 49
10/36 Spatial Recall Test for episodic memory - Total Score Scale 0-30. Mean (SD)	17.2 (4.9)	18.6 (5)	16.6 (5.5)	17.1 (4.6)
10/36 Spatial Recall Test for episodic memory - Delayed Recall Scale 0-10. Mean (SD)	6.1 (2.3)	6.1 (2.3)	5.8 (2.4)	6.2 (2.4)
Digit Span - forward Measures short-term memory Mean (SD)	5.7 (1.1)	5.8 (1.2)	5.6 (1)	5.7 (1.1)
Digit span - backward Measure working memory Mean (SD)	4.2 (1.2)	4.8 (1.4)	4.4 (1.1)	4.5 (1.4)
Working Memory domain of Test of Attentional Performance - Omissions Measures working memory Mean (SD)	4.2 (2.9)	2.8 (2.8)	3 (2.2)	2.9 (2.3)

Outcome	ProCog-SEP extended cognitive rehabilitation program , Baseline, N = 52	ProCog-SEP extended cognitive rehabilitation program , 6-month, N = 52	Placebo programme - non-cognitive exercises and discussion, Baseline, N = 49	Placebo programme - non-cognitive exercises and discussion, 6-month, N = 49
Flexibility domain of Test of Attentional Performance - Correct answers Scale 0-100. Mean (SD)	89.3 (12.1)	91.4 (14.6)	92.7 (12.5)	96 (4.9)
Incompatibility domain of Test of Attentional Performance - Correct answers Scale 0-60. Measures inhibition. Mean (SD)	54 (9.8)	53.2 (12.4)	55.5 (8.2)	56.5 (8.4)
Verbal fluency - letter M Mean (SD)	12.2 (3.9)	13.1 (4.5)	12.2 (4.4)	12.5 (4)
Verbal fluency - Animals Mean (SD)	19.2 (5.4)	20.4 (5.4)	18.3 (4.6)	19 (5.9)
Code - assessing processing speed Mean (SD)	45.3 (9.7)	47.3 (9.6)	46.9 (13.6)	49.2 (12.8)

Outcome	ProCog-SEP extended cognitive rehabilitation program , Baseline, N = 52	ProCog-SEP extended cognitive rehabilitation program , 6-month, N = 52	Placebo programme - non-cognitive exercises and discussion, Baseline, N = 49	Placebo programme - non-cognitive exercises and discussion, 6-month, N = 49
DO80 - Total Score Picture-naming task evaluating language. Scale 0-80. Mean (SD)	77.3 (2.9)	77.9 (2.2)	77.1 (3.7)	77.5 (2.5)
DO80 - Time (seconds) Assesses language Mean (SD)	138.6 (46)	133.1 (49.1)	149.9 (61.8)	143.3 (57.2)
Adherence Defined as those that completed full programmes (attending at least 9/13 sessions and underwent neuropsychological assessment before and after intervention. No of events	n = NA ; % = NA	n = 50 ; % = 78.1	n = NA ; % = NA	n = 44 ; % = 68.8
Adherence Defined as those that completed full programmes (attending at least 9/13 sessions and underwent	NA	64	NA	64

Outcome	ProCog-SEP extended cognitive rehabilitation program , Baseline, N = 52	ProCog-SEP extended cognitive rehabilitation program , 6-month, N = 52	Placebo programme - non-cognitive exercises and discussion, Baseline, N = 49	Placebo programme - non-cognitive exercises and discussion, 6-month, N = 49
neuropsychological assessment before and after intervention. Number analysed				
MS International Quality of Life Questionnaire - Index Scale not reported but is usually 0-100 per domain. Index is mean of 9 subdomain scores. Mean (SD)	48.3 (22.8)	59.5 (12.3)	50.7 (21.6)	58.4 (16.6)

1 Selective Reminding Test - Mean free recall - Polarity - Higher values are better
2 Selective Reminding Test - Learning Index - Polarity - Higher values are better
3 Selective Reminding Test - Delayed Recall - Polarity - Higher values are better
4 10/36 Spatial Recall Test for episodic memory - Total Score - Polarity - Higher values are better
5 10/36 Spatial Recall Test for episodic memory - Delayed Recall - Polarity - Higher values are better
6 Digit Span - forward - Polarity - Higher values are better
7 Digit span - backward - Polarity - Higher values are better
8 Working Memory domain of Test of Attentional Performance - Omissions - Polarity - Lower values are better
9 Flexibility domain of Test of Attentional Performance - Correct answers - Polarity - Higher values are better
10 Incompatibility domain of Test of Attentional Performance - Correct answers - Polarity - Higher values are better
11 Verbal fluency - letter M - Polarity - Higher values are better
12 Verbal fluency - Animals - Polarity - Higher values are better

Code - assessing processing speed - Polarity - Higher values are better
DO80 - Total Score - Polarity - Higher values are better
DO80 - Time - Polarity - Lower values are better
MS International Quality of Life Questionnaire - Index - Polarity - Higher values are better
Final values reported for continuous outcomes.
N=64 were randomised to each group, but baseline values given for n=52 in intervention and n=49 in placebo group.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_selective reminding test mean free recall_6-9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_selective reminding test learning index_6-9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_selective reminding test delayed recall_6-9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_10/36 Spatial Recall Test for episodic memory - Total Score_6-9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_10/36 Spatial Recall Test for episodic memory - Delayed Recall_6-9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_Digit Span - forward_6-9 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_Digit Span - backward_6-9 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_Working Memory domain of Test of Attentional Performance - Omissions_6-9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_Flexibility domain of Test of Attentional Performance - Correct answers_6-9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_Incompatibility domain of Test of Attentional Performance - Correct answers_6-9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_Verbal fluency - letter M_6-9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_Verbal fluency - Animals_6-9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_Code - assessing processing speed_6-9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_DO80 Total Score_6-9 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_DO80 - Time_6-9 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1
2 **Adherence**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Would be more useful to have adherence to programme among those not lost to follow-up separately rather than combined with those that were lost to follow-up or withdrew)*

Results_MS International Quality of Life Questionnaire_6-9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Campbell, 2016

Bibliographic Reference	Campbell, J.; Langdon, D.; Cercignani, M.; Rashid, W.; A Randomised Controlled Trial of Efficacy of Cognitive Rehabilitation in Multiple Sclerosis: A Cognitive, Behavioural, and MRI Study; Neural Plasticity; 2016; vol. 2016; 4292585

Study details

Trial name / registration number	ISRCTN54901925.
Study location	UK
Study setting	Unclear - likely outpatient
Study dates	Invited to participate between February 2014 and February 2015
Sources of funding	Not reported
Inclusion criteria	Aged between 18 and 65 years; clinically definite MS according to McDonald criteria; EDSS score ≤6.5; cognitive impairment defined as scores below 5th percentile for normative data adjusted for age, sex and years of formal education on one or more of Brief International Cognitive Assessment for MS (BICAMS) tests (CVLT-II, BVMT-R and SDMT tests).
Exclusion criteria	History of significant psychiatric disorders; alcohol or substance abuse; visual acuity less than 6/18 corrected; oscillopsia; diplopia that would interfere with testing; had a MS relapse, received corticosteroids or changes made to psychoactive medications within the previous month.

Recruitment / selection of participants	Invited to participate between February 2014 and February 2015.
Intervention(s)	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules: 6 weeks of home-based computer-assisted cognitive rehabilitation using RehaCom software (45 min sessions three times weekly). Training in three modules involving working memory, visuospatial memory and divided attention. Difficulty tailored to individual's performance and increases automatically in line with progress. Divided attention module asked to drive simulated car using keyboard inputs with multiple distractions being navigated and speed and direction of vehicle adjusted according to road conditions. As complexity increases more distractors introduced. Working memory module involves remembering series of cards presented briefly on screen. As complexity increases, asked to remember only cards of a value or suit and number of items to remember increases. Higher levels involve remembering them in reverse order. Topological memory module involves visuospatial memory and involves various objects presented briefly on screen with patient asked to remember object and position in the sequence. As complexity increases number of items on screen increases and more abstract shapes introduced.
Population subgroups	None
Comparator	Control group: watched series of natural history DVDs of corresponding duration and frequency for 6 weeks.
Number of participants	38 randomised, 38 analysed at follow-up
Duration of follow-up	Up to 12 weeks following the end of a 6-week intervention (18 weeks)
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (71%) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (mean ~4.0 in both groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear (those below 5th percentile on one of three cognitive tests included) • Disease modifying treatment status (currently using and not currently using) - majority taking them (53%)

	• Mood disorders (presence or absence) - unclear (excluded if had history of psychiatric disorders) • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - appears to be intention to treat with those with no data removed as n=17 and n=14 included in the two groups at 18 weeks. N=2 in intervention group withdrew due to relapse (n=1) or not completing assessment due to time constraints (n=1). N=5 withdrew from control group due to time constraints meaning they did not complete assessment (n=1), relapse (n=1), unable to tolerate MRI (n=1), moving house (n=1) and no reason given (n=1).

Study arms

RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules (N = 19)

Control - natural history DVDs (N = 19)

Characteristics

Arm-level characteristics

Characteristic	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules (N = 19)	Control - natural history DVDs (N = 19)
% Female Sample size	n = 13 ; % = 68.4	n = 14 ; % = 73.6
Mean age (SD) Mean (SD)	46.21 (6.59)	48.53 (9.63)

Characteristic	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules (N = 19)	Control - natural history DVDs (N = 19)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Disease duration (years) Mean (SD)	10.53 (6.13)	12.68 (9.87)
EDSS score Mean (SD)	4.42 (1.75)	4.45 (1.77)
SDMT Mean (SD)	43.39 (7.39)	38.21 (11.39)
CLVT-II Mean (SD)	45.32 (9.56)	43.89 (9.73)
BVMT Mean (SD)	20.63 (5.77)	18.05 (7.37)
Relapsing-remitting Sample size	n = 14 ; % = 73.6	n = 13 ; % = 68.4

Characteristic	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules (N = 19)	Control - natural history DVDs (N = 19)
Secondary-progressive Sample size	n = 5 ; % = 26.3	n = 8 ; % = 42.1
Interferon (1b SC, 1A IM or 1A SC) Sample size	n = 5 ; % = 26.3	n = 2 ; % = 10.5
Fingolimod Sample size	n = 5 ; % = 26.3	n = 1 ; % = 5.3
Natalizumab Sample size	n = 2 ; % = 10.5	n = 4 ; % = 21.1
Teriflunomide Sample size	n = 0 ; % = 0	n = 1 ; % = 5.3
FAMS Functional Assessment of MS Mean (SD)	87.26 (23)	101.06 (31.98)
PAM-13 Patient Activation Measure-13 Mean (SD)	59.52 (18.42)	64.26 (15.65)

Characteristic	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules (N = 19)	Control - natural history DVDs (N = 19)
EQ-5D Mean (SD)	0.52 (0.18)	0.61 (0.19)
USE-MS Unidimensional Self-Efficacy Scale for MS Mean (SD)	48.26 (18.01)	59.74 (19.96)
MSNQ-S Multiple Sclerosis Neuropsychological Questionnaire Mean (SD)	36.89 (13.49)	34.68 (11.51)
HADS-depression Mean (SD)	9.47 (3.55)	8.47 (3.21)
HADS-anxiety Mean (SD)	9.26 (3.72)	9.37 (5.56)
FSS Mean (SD)	52.37 (10.4)	48.84 (13.59)

1

Outcomes

Study timepoints

- Baseline
- 18 week (18 weeks - 12-weeks following the last intervention session (6-week intervention period). 6-week time-point not extracted as 18 weeks better fits protocol.)

Results - change from baseline

Outcome	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules, 18-week vs Baseline, N = 17	Control - natural history DVDs, 18-week vs Baseline, N = 14
SDMT Symbol Digit Modalities Test. Baseline values were 43.39 (7.39) and 38.21 (11.39) Mean (SD)	3.35 (4.17)	4.57 (7.21)
CVLT-II California Verbal Learning Test. Baseline values were 45.32 (9.56) and 43.89 (9.73) Mean (SD)	6.94 (7.01)	7.5 (8.83)
BVMT Brief Visuospatial Memory Test. Baseline values were 20.63 (5.77) 18.05 (7.37) Mean (SD)	7.29 (5.07)	4.14 (5.32)

SDMT - Polarity - Higher values are better

CVLT-II - Polarity - Higher values are better
BVMT - Polarity - Higher values are better
N=17 and N=14, respectively, analysed in intervention and control groups at 18 weeks.

Results - raw data

Outcome	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules, Baseline, N = 17	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules, 18-week, N = 17	Control - natural history DVDs, Baseline, N = 14	Control - natural history DVDs, 18-week, N = 14
FAMS Functional Assessment of MS. Quality of life measure. Scale not reported but usually 0-176. Mean (SD)	85.24 (22.61)	89 (30.99)	102.79 (35.06)	101 (32.4)
PAM-13 Patient Activation Measure-13. Measures level of patient engagement in health. Scale not reported but usually 0-100. Mean (SD)	54.62 (17.13)	58.79 (15.52)	65.58 (14.66)	62.1 (15.9)
EQ-5D Scale appears to be 0-1. Mean (SD)	0.49 (0.13)	0.53 (0.2)	0.61 (0.22)	0.57 (0.27)
MSNQ-S Multiple Sclerosis	35.65 (13.56)	29.18 (15.14)	34.79 (12.34)	28.93 (13.13)

Outcome	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules, Baseline, N = 17	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules, 18-week, N = 17	Control - natural history DVDs, Baseline, N = 14	Control - natural history DVDs, 18-week, N = 14
Neuropsychological Questionnaire. Scale unclear but usually 0-60. Mean (SD)				
HADS-depression Hospital Anxiety and Depression Scale. Scale not reported but usually 0-21. Mean (SD)	9.82 (3.38)	9.35 (2.85)	9.21 (3.38)	8.79 (4.21)
HADS-anxiety Hospital Anxiety and Depression Scale. Scale not reported but usually 0-21. Mean (SD)	9.18 (3.8)	8.53 (4.38)	9.86 (5.74)	6.86 (4.93)
FSS Fatigue Severity Scale. Scale not reported but usually 9-63. Mean (SD)	52.12 (10.89)	52.53 (11.47)	49.43 (14.18)	49.29 (15.5)

Outcome	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules, Baseline, N = 17	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules, 18-week, N = 17	Control - natural history DVDs, Baseline, N = 14	Control - natural history DVDs, 18-week, N = 14
USE-MS Unidimensional Self-Efficacy scale for MS. Scale unclear. Mean (SD)	16 (5.85)	16.47 (5.7)	19 (6.72)	19.31 (8.7)
Completed at least 75% of prescribed sessions Custom value	NA	16/18 (88.9%)	NA	NR
Completed all prescribed sessions Custom value	NA	12/18 (66.7%)	NA	NR
0-back errors Measured on N-back test. Measures working memory. Mean (SD)	3.24 (3.42)	2.53 (3.64)	3.71 (4.92)	2.64 (2.5)
1-back errors Measured on N-back test. Measures working memory. Mean (SD)	2.71 (3.48)	3.06 (3.27)	4.57 (8.42)	2.14 (1.99)

Outcome	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules, Baseline, N = 17	RehaCom cognitive rehabilitation - divided attention, working memory and topological memory modules, 18-week, N = 17	Control - natural history DVDs, Baseline, N = 14	Control - natural history DVDs, 18-week, N = 14
2-back errors Measured on N-back test. Measures working memory. Mean (SD)	5.24 (4.82)	4.76 (5.76)	6 (9.83)	5.29 (3.83)

FAMS - Polarity - Higher values are better
PAM-13 - Polarity - Higher values are better
EQ-5D - Polarity - Higher values are better
MSNQ-S - Polarity - Lower values are better
HADS-depression - Polarity - Lower values are better
HADS-anxiety - Polarity - Lower values are better
FSS - Polarity - Lower values are better
USE-MS - Polarity - Higher values are better
0-back errors - Polarity - Lower values are better
1-back errors - Polarity - Lower values are better
2-back errors - Polarity - Lower values are better
Includes final values for continuous outcomes
Note that though there were N=19 per group at baseline, baseline values given here for the n=17 and n=14 analysed

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_SDMT change from baseline_18 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_BVMT change from baseline_18 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_FAMS_18 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PAM-13_18 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_EQ-5D_18 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_MSNQ-S_18 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_HADS-depression_18 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_HADS-anxiety_18 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_FSS_18 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(General fatigue rather than cognitive fatigue specifically)*

2

3 **Results_USE-MS_18 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_adherence 75% sessions_end of treatment

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_adherence all sessions_end of treatment**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

Results_0-back errors n-back_18 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_1-back errors n-back_18 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_2-back errors n-back_18 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT-II change from baseline_18 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Carr, 2014

Bibliographic Reference	Carr, S. E.; das Nair, R.; Schwartz, A. F.; Lincoln, N. B.; Group memory rehabilitation for people with multiple sclerosis: a feasibility randomized controlled trial; Clinical Rehabilitation; 2014; vol. 28 (no. 6); 552-61

Study details

Trial name / registration number	Not reported
Study location	UK
Study setting	Outpatient - recruited from those attending MS clinics
Study dates	Not reported
Sources of funding	Supported by a research grant from Biogen Idec Limited, Maidenhead, Berkshire
Inclusion criteria	Reported memory problems in daily life; were more than 12 months since diagnosis; able to give informed consent; able to speak and understand conversational English; and able to attend the outpatient unit where the treatment sessions were delivered
Exclusion criteria	Very severe memory problems who were considered by the consultant clinical psychologist or multiple sclerosis specialist nurse to not be able to cope with group sessions.
Recruitment / selection of participants	Identified from a register of patients who attended Central Surrey Health MS clinics. They were invited to take part in the study by letter, which contained information on the purpose of the study, including the focus on memory problems in daily life, and what participation would involve. Patients who were interested were asked to contact one of the researchers or to complete the consent form and return it in a pre-stamped envelope.
Intervention(s)	Group memory programme: group intervention consisting of 1.5 h sessions and homework over 10-week period (n=8 people per group). If sessions missed, they were invited to attend next session to catch up. Programme included both restitution and compensation strategies. Included one introductory session; three sessions on attention training; three sessions on internal memory strategies; two sessions on external memory aids; and one concluding session to bring

	together everything that had been learned and to reflect on the best strategies for each individual. Homework was recommended at the end of each session. Assistant psychologist delivered the treatment groups based on a manual. Session's video-recorded to check correspondence with manual.
Population subgroups	None
Comparator	Control group - usual care: received their usual care and all other rehabilitation (e.g., physiotherapy, occupational therapy) continued as usual.
Number of participants	48 randomised, number analysed depends on outcome as those with missing data not included
Duration of follow-up	4- and 8-months follow-up reported (1.5-5.5 months after end of sessions)
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority primary progressive or relapsing-remitting (33% each) • According to disability (EDSS <6 and EDSS ≥6) - unclear • Severity of cognitive impairment (mild/moderate/severe) - unclear (those with very severe problems excluded) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear • Computerised vs clinician led - clinician-led with homework • Group vs individual - group with homework Analysis - appears to have excluded those where no data available. n=7 in intervention and n=3 in control failed to return outcome questionnaires at 4 months and further n=2 and n=5 respectively failed to return questionnaires at 8 months. Number analysed differs slightly for different outcomes.

1

Study arms

Group memory programme - sessions on attention, internal memory strategies and external memory aids (N = 24)

Control - treatment as usual (N = 24)

Characteristics

Arm-level characteristics

Characteristic	Group memory programme - sessions on attention, internal memory strategies and external memory aids (N = 24)	Control - treatment as usual (N = 24)
% Female Sample size	n = 17 ; % = 71	n = 16 ; % = 67
Mean age (SD) Mean (SD)	55.8 (10.2)	52.9 (11.8)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Years since diagnosis Mean (SD)	16.3 (11.3)	12.3 (9.1)

Characteristic	Group memory programme - sessions on attention, internal memory strategies and external memory aids (N = 24)	Control - treatment as usual (N = 24)
Primary progressive Sample size	n = 6 ; % = 25	n = 10 ; % = 42
Secondary progressive Sample size	n = 4 ; % = 17	n = 4 ; % = 17
Relapsing-remitting Sample size	n = 7 ; % = 29	n = 9 ; % = 37
Benign Sample size	n = 2 ; % = 8	n = 0 ; % = 0
Unknown Sample size	n = 5 ; % = 21	n = 1 ; % = 4
Auditory memory N=23 and N=23 had data in the two groups Mean (SD)	95.8 (17.5)	100.7 (17.4)
Visual memory N=19 and N=21 had data in the two groups Mean (SD)	97.5 (12.5)	98.3 (17.4)

Characteristic	Group memory programme - sessions on attention, internal memory strategies and external memory aids (N = 24)	Control - treatment as usual (N = 24)
Visual working memory N=16 and N=16 had data in the two groups Mean (SD)	97.3 (17.3)	99.3 (15.9)
Immediate memory N=20 and N=21 had data in the two groups Mean (SD)	97.5 (14.2)	100.2 (19.1)
Delayed memory N=20 and N=21 had data in the two groups Mean (SD)	98.4 (15.5)	100.9 (18.1)
EMQ- self-report Everyday Memory Questionnaire Mean (SD)	27.3 (21.6)	30 (22.6)
EMQ - carer report Everyday Memory Questionnaire Mean (SD)	21.5 (19.5)	15.8 (17)

Characteristic	Group memory programme - sessions on attention, internal memory strategies and external memory aids (N = 24)	Control - treatment as usual (N = 24)
GHQ-28 General Health Questionnaire 28 Mean (SD)	23.5 (9.8)	25 (9)
MS Impact Scale Mean (SD)	66.7 (23.6)	76 (24.7)
Guys Neurological Disability Scale Mean (SD)	16.2 (7.9)	15.54 (6.73)

Outcomes

Study timepoints

- Baseline
- 4 month (4 months - ~1.5 months after end of intervention.)
- 8 month (8 months - ~5.5 months after end of intervention)

1 **Results - raw data**

Outcome	Group memory programme - sessions on attention, internal memory strategies and external memory aids, Baseline, N = 24	Group memory programme - sessions on attention, internal memory strategies and external memory aids, 4-month, N = 17	Group memory programme - sessions on attention, internal memory strategies and external memory aids, 8-month, N = 15	Control - treatment as usual, Baseline, N = 24	Control - treatment as usual, 4-month, N = 21	Control - treatment as usual, 8-month, N = 16
EMQ- self-report Everyday Memory Questionnaire. Scale 0-140. Mean (SD)	27.3 (21.6)	21.7 (13.1)	17.3 (11.2)	30 (22.6)	25.8 (19.9)	26.9 (19.3)
EMQ - carer report Everyday Memory Questionnaire. Scale 0-140. Number analysed	24	17	15	24	21	15
EMQ - carer report Everyday Memory Questionnaire. Scale 0-140. Mean (SD)	21.5 (19.5)	21.2 (19.9)	22 (23.9)	15.8 (17)	20.2 (17)	21.6 (20.1)
GHQ-28 General Health Questionnaire 28. Scale 0-84. Measure of	24	16	17	24	21	16

Outcome	Group memory programme - sessions on attention, internal memory strategies and external memory aids, Baseline, N = 24	Group memory programme - sessions on attention, internal memory strategies and external memory aids, 4-month, N = 17	Group memory programme - sessions on attention, internal memory strategies and external memory aids, 8-month, N = 15	Control - treatment as usual, Baseline, N = 24	Control - treatment as usual, 4-month, N = 21	Control - treatment as usual, 8-month, N = 16
psychological wellbeing (distress) Number analysed						
GHQ-28 General Health Questionnaire 28. Scale 0-84. Measure of psychological wellbeing (distress) Mean (SD)	23.5 (9.8)	23.7 (10.9)	18.4 (7)	25 (9)	22.7 (9.9)	25.3 (10.9)
MS Impact Scale-29 Quality of life. Scale 29-145. Number analysed	24	16	15	24	21	16
MS Impact Scale-29 Quality of life. Scale 29-145. Mean (SD)	66.7 (23.6)	77.2 (30.7)	68.3 (28)	76 (24.7)	69 (23.6)	74.6 (25.4)

Outcome	Group memory programme - sessions on attention, internal memory strategies and external memory aids, Baseline, N = 24	Group memory programme - sessions on attention, internal memory strategies and external memory aids, 4-month, N = 17	Group memory programme - sessions on attention, internal memory strategies and external memory aids, 8-month, N = 15	Control - treatment as usual, Baseline, N = 24	Control - treatment as usual, 4-month, N = 21	Control - treatment as usual, 8-month, N = 16
Satisfaction Proportion reporting that attending had made a difference to how they coped with memory difficulties. Reported during final session (10 weeks) rather than 4 months. Custom value	NA	15/18 (83.3%	NA	NA	NR	NA
Adherence Attendance out of 10 sessions. Reported at end of treatment rather than 4 months. Mean (SD)	NA (NA)	7.9 (0.23)	NA (NA)	NA (NA)	NR (NR)	NA (NA)

1 EMQ- self-report - Polarity - Lower values are better
2 EMQ - carer report - Polarity - Lower values are better
3 GHQ-28 - Polarity - Lower values are better
4 MS Impact Scale-29 - Polarity - Lower values are better
5 Adherence - Polarity - Higher values are better

Note that number analysed at each time-point differed depending on the outcome. Where the number analysed is different to that at the top of the table it has been indicated below for that specific outcome.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_EMQ self-report_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Resilts_EMQ self-report_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_EMQ carer report_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_EMQ carer report_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_GHQ-28_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_GHQ-28_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_MSIS-29_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_MSIS-29_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_satisfaction_end of treatment**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_adherence_end of treatment**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Charvet, 2015**

Bibliographic Reference	Charvet, L. E.; Shaw, M. T.; Haider, L.; Melville, P.; Krupp, L. B.; Remotely-delivered cognitive remediation in multiple sclerosis (MS): protocol and results from a pilot study; Multiple Sclerosis Journal Experimental Translational & Clinical; 2015; vol. 1; 2055217315609629

3

4 ## Study details

Trial name / registration number	Not reported
Study location	USA
Study setting	Outpatient - those seeking treatment for cognitive impairment as judged by referring neurologist

Study dates	Not reported
Sources of funding	Supported by Novartis AG with support from The Lourie Foundation Inc. The cognitive remediation program was provided by Lumos Labs, Inc.
Inclusion criteria	People seeking treatment for cognitive impairment as judged by referring neurologist; recently initiated on fingolimod treatment; English-speaking; between age of 18 and 70 years; relapsing-remitting MS; and stable disease.
Exclusion criteria	Other major medical conditions: and no recent relapse or associated steroid use in past month.
Recruitment / selection of participants	Enrolled participants seeking treatment for cognitive impairment due to MS, as judged by their referring neurologist. Recruited through the Stony Brook Medicine Multiple Sclerosis Comprehensive Care Center
Intervention(s)	Adaptive cognitive remediation programme: 12-week treatment period with cognitive exercises to be completed 5 times weekly (60 total days across three months). 30 min required per session. Technical support, coaching, and monitoring of computer use were completed remotely by a study technician. Lumosity platform, developed by Lumos Labs, Inc., was chosen as the active adaptive cognitive remediation program. Developed a study-specific portal and set of games that focused on the most common areas of impairment in MS, including speeded information processing and working memory. Games were visually engaging, using simple rules that were explained during a brief instructional phase before participants begin. All games were adaptive as they had the ability to increase difficulty based on the participant's improvement. The program tracked progress using various gameplay parameters, such as unique levels played, and improvements made in the game.
Population subgroups	None
Comparator	Active control - ordinary computer games: computer-based gaming program that would provide the experience of cognitive exercise associated with cognitive benefit but without the key components of the adaptive cognitive remediation programs (i.e., games not developed based on cognitive neuroscience principles to drive neural plasticity). Commercially available Hoyle puzzles and board games program. Participant was given a list of daily exercises to complete that would last the same game play time as the treatment condition. Participants in the active control condition were instructed to play two games for 15 minutes each, according to a set rotational sequence.
Number of participants	20 randomised, 20 analysed (does not mention any drop-out)

Duration of follow-up	Up to end of intervention (12 weeks)
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (median 2 or 2.5 in the two groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear (described as having mild-moderate impairments, proportion with each unclear) • Disease modifying treatment status (currently using and not currently using) - using (all had to have recently initiated fingolimod) • Mood disorders (presence or absence) - unclear (other major medical conditions excluded) • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - appears to be intention to treat as no missing data reported

Study arms

Adaptive cognitive remediation programme - Lumosity games including information processing speed and working memory (N = 11)

Active control - ordinary computer games (N = 9)

Cognitive tasks but without components of adaptive cognitive remediation programmes

Characteristics

Arm-level characteristics

Characteristic	Adaptive cognitive remediation programme - Lumosity games including information processing speed and working memory (N = 11)	Active control - ordinary computer games (N = 9)
% Female Sample size	n = 7 ; % = 63.6	n = 7 ; % = 77.7
Mean age (SD) Mean (SD)	38 (10.58)	42 (12.53)
White Sample size	n = 8 ; % = 72.7	n = 6 ; % = 66.7
Black Sample size	n = 2 ; % = 18.2	n = 1 ; % = 11.1
Hispanic Sample size	n = 0 ; % = 0	n = 1 ; % = 11.1
Non-Hispanic Sample size	n = 10 ; % = 90.9	n = 8 ; % = 88.8
Comorbidities Custom value	NR	NR

Characteristic	Adaptive cognitive remediation programme - Lumosity games including information processing speed and working memory (N = 11)	Active control - ordinary computer games (N = 9)
EDSS score Median (range)	2 (0-3)	2.5 (0-3.5)
WRAT-3 reading Wide range achievement test, third edition Mean (SD)	100.5 (10.42)	102.3 (6)
ECog Everyday cognition scale Mean (SD)	67.73 (18.55)	63.14 (18.97)
SDMT z score Mean (SD)	-0.45 (1.25)	-0.79 (1.01)

Outcomes

Study timepoints

- Baseline
- 12 week (12-weeks - end of treatment period)

Results - raw data

Outcome	Adaptive cognitive remediation programme - Lumosity games including information processing speed and working memory, Baseline, N = 11	Adaptive cognitive remediation programme - Lumosity games including information processing speed and working memory, 12-week, N = 11	Active control - ordinary computer games, Baseline, N = 9	Active control - ordinary computer games, 12-week, N = 9
WAIS-IV letter-numbering sequencing Wechsler adult intelligence scale, fourth edition. Reported as z-score only. Mean (SD)	-0.4 (0.7)	-0.04 (0.73)	0.09 (0.8)	-0.04 (0.72)
Visual span (Corsi blocks) Corsi block tapping test. Z-scores only. Mean (SD)	-0.65 (1)	-0.26 (0.68)	-0.48 (1.25)	-0.52 (0.67)
PASAT 2 second trials paced auditory serial addition test. z-score only Mean (SD)	-0.68 (1.21)	-0.28 (1.05)	-0.93 (1.27)	-0.48 (1.17)

Outcome	Adaptive cognitive remediation programme - Lumosity games including information processing speed and working memory, Baseline, N = 11	Adaptive cognitive remediation programme - Lumosity games including information processing speed and working memory, 12-week, N = 11	Active control - ordinary computer games, Baseline, N = 9	Active control - ordinary computer games, 12-week, N = 9
PASAT 3 second trials paced auditory serial addition test. z-score only Mean (SD)	-0.52 (1.61)	0.24 (0.99)	-0.89 (1.3)	-0.32 (0.88)
DKEFS trail 5 DelisKaplan executive function system. Reported as z-score only. Mean (SD)	0.7 (0.43)	0.64 (0.43)	0.52 (0.38)	0.63 (0.26)
DKEFS trails 2/3 combo DelisKaplan executive function system. Reported as z-score only. Mean (SD)	0.25 (0.72)	0.27 (0.77)	-0.2 (1.18)	0 (1.08)

Outcome	Adaptive cognitive remediation programme - Lumosity games including information processing speed and working memory, Baseline, N = 11	Adaptive cognitive remediation programme - Lumosity games including information processing speed and working memory, 12-week, N = 11	Active control - ordinary computer games, Baseline, N = 9	Active control - ordinary computer games, 12-week, N = 9
SRT learning trials selective reminding test. z-score only. Mean (SD)	-0.3 (1.23)	0.13 (1.45)	-0.15 (1.66)	-0.24 (0.86)
SRT delay selective reminding test. Reported as z-score only. Mean (SD)	0.51 (1.17)	0.59 (1.39)	0.67 (1.01)	0.3 (1.16)
BVMT-R learning trials brief visuospatial memory test, revised. z-score only. Mean (SD)	-0.8 (1.36)	-0.15 (1.64)	0.06 (1.37)	-0.25 (1.56)
BVMT-R delay brief visuospatial memory test, revised. z-score only. Mean (SD)	-0.94 (1.71)	-0.17 (1.69)	0.16 (0.93)	-0.33 (1.46)

Outcome	Adaptive cognitive remediation programme - Lumosity games including information processing speed and working memory, Baseline, N = 11	Adaptive cognitive remediation programme - Lumosity games including information processing speed and working memory, 12-week, N = 11	Active control - ordinary computer games, Baseline, N = 9	Active control - ordinary computer games, 12-week, N = 9
Adherence Compliance - % compliant to study requirements No of events	n = NA ; % = NA	n = 9 ; % = 81.8	n = NA ; % = NA	n = 7 ; % = 77.78

WAIS-IV letter-numbering sequencing - Polarity - Higher values are better
Visual span (Corsi blocks) - Polarity - Higher values are better
PASAT 2 second trials - Polarity - Higher values are better
PASAT 3 second trials - Polarity - Higher values are better
DKEFS trail 5 - Polarity - Higher values are better
DKEFS trails 2/3 combo - Polarity - Higher values are better
SRT learning trials - Polarity - Higher values are better
SRT delay - Polarity - Higher values are better
BVMT-R learning trials - Polarity - Higher values are better
BVMT-R delay - Polarity - Higher values are better
Final values for continuous outcomes

Results - change from baseline

Outcome	Adaptive cognitive remediation programme - Lumosity games including information processing speed and working memory, 12-week vs Baseline, N = 11	Active control - ordinary computer games, 12-week vs Baseline, N = 9
General cognitive composite Average from other cognitive test measures (WAIS-IV letter-numbering sequencing, visual span (Corsi blocks), SRT learning trials, BVMT-R learning trials). Z-score only. Mean (SD)	0.46 (0.59)	-0.14 (0.48)

General cognitive composite - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_WAIS-IV letter-numbering sequencing_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Visual span (Corsi blocks)_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_PASAT 2 second trials_12 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_PASAT 3 second trials_12 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_DKEFS trail 5_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_DKEFS 2/3 combo_12 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

Results_SRT learning trials_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SRT delay_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_BVMT-R learning trials_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_BVMT-R delay_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_adherence % compliance_12 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_general cognitive composite score_12 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Charvet, 2017

Bibliographic Reference	Charvet, L. E.; Yang, J.; Shaw, M. T.; Sherman, K.; Haider, L.; Xu, J.; Krupp, L. B.; Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial; PLoS ONE [Electronic Resource]; 2017; vol. 12 (no. 5); e0177177

Study details

Trial name / registration number	NCT02141386
Study location	USA
Study setting	Unclear - likely outpatient

Study dates	Recruitment began September 10, 2013 through June 5, 2015 with last data collection September 9, 2015
Sources of funding	Not reported
Inclusion criteria	Diagnosis of MS; scoring one or more standard deviations below published normative data on the Symbol Digit Modalities Test or SDMT; a reading recognition standard score of 85 or above on WRAT-3; learned English by 12 years of age; adequate visual, auditory, and motor capacity to operate computer software; no anticipated medication changes during the course of the three-month study period; and no relapses or steroids in the previous month.
Exclusion criteria	History of any developmental disorders, conditions other than MS associated with cognitive impairment, a primary psychiatric disorder, any serious medical conditions, alcohol or substance use disorder; and also, history of use of computer-based cognitive training developed by Posit Science (the developer of programme used in study).
Recruitment / selection of participants	Recruitment began September 10, 2013 through June 5, 2015 with last data collection September 9, 2015
Intervention(s)	Adaptive cognitive training programme: Training for 1 h per day, 5 days a week for 12 weeks (60 h target use over the period). Online adaptive cognitive training program developed by Posit Science Corporation. Research version of the BrainHQ program, and offered a portal dedicated to the study, central management of study participation and metrics, and a set of 15 exercises targeting speed, attention, working memory, and executive function through the visual and auditory domains. Each exercise was adaptive with a Bayesian algorithm operating on a trial-by-trial basis to increase the challenge as participants performed correctly and to reduce challenge as participants performed incorrectly. Each exercise employed multiple stimulus sets designed to span relevant dimensions of real-world stimuli. For example, auditory exercises employed stimuli related to human speech perception that were initially slowed and later speeded, while visual exercises initially employed simple high contrast stimuli and later provided stimuli that were naturalistic and low contrast. Participants required to attend to stimuli, detect novel stimuli and general receive a reward after a correct trial. Each daily training session consisted of four exercises chosen from an active set of six; when all of the content in an exercise was completed (typically over a number of days), that exercise was withdrawn from the schedule and the next exercise added to the active set of six. Participants had ongoing access to technical support as well as a scheduled weekly check-in phone call.
Population subgroups	None

Comparator	Active control condition: Training for 1 h per day, 5 days a week for 12 weeks (60 h target use over the period). software gaming suite developed by Hoyle Puzzle and Board Games (2008 version). Designed to account for nonspecific treatment effects including interactions with research personnel, and computer-based game-playing. Participants were provided a set gaming schedule and were instructed to play games in an arrangement that mirrored to the active condition, with a schedule of four games per session for 15 minutes each following a set rotational sequence. Games were selected for "face validity" as having cognitive benefit (e.g., word puzzles) but did not include the active condition's program design features to drive learning or maintain user challenge. Participants had ongoing access to technical support as well as a scheduled weekly check-in phone call.
Number of participants	135 randomised, 135 analysed (despite n=4 in intervention and n=1 in control discontinuing the intervention). Reasons for discontinuation were n=1 documented relapse, n=1 withdrawal, n=1 personal difficulties and n=1 no time to come for follow-up in intervention group and n=1 personal difficulties in control group.
Duration of follow-up	Up to the end of the treatment period (12 weeks).
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (66%) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (median 3.5) • Severity of cognitive impairment (mild/moderate/severe) - unclear (described as having mild-moderate impairments, proportion with each unclear) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (primary psychiatric disorder excluded) • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - appears to be intention to treat as all included in analysis despite some dropping out

1

Study arms

Adaptive cognitive training programme - BrainHQ program focusing on speed, attention, working memory and executive function (N = 74)

Active control - ordinary computer games (N = 61)

Cognitive tasks but without components of adaptive cognitive remediation programmes

Characteristics

Arm-level characteristics

Characteristic	Adaptive cognitive training programme - BrainHQ program focusing on speed, attention, working memory and executive function (N = 74)	Active control - ordinary computer games (N = 61)
% Female Sample size	n = 50 ; % = 67.57	n = 54 ; % = 88.52
Mean age (SD) Mean (SD)	48 (13)	52 (11)
White Sample size	n = 63 ; % = 85.14	n = 51 ; % = 83.61
Black/African American Sample size	n = 6 ; % = 8.11	n = 4 ; % = 6.56

Characteristic	Adaptive cognitive training programme - BrainHQ program focusing on speed, attention, working memory and executive function (N = 74)	Active control - ordinary computer games (N = 61)
Other/unknown Sample size	n = 5	n = 6 ; % = 9.84
Hispanic or Latino Sample size	n = 7 ; % = 9.86	n = 3 ; % = 5.26
Comorbidities Custom value	NR	NR
Relapsing-remitting Sample size	n = 51 ; % = 69	n = 39 ; % = 64
Primary progressive Sample size	n = 3 ; % = 4	n = 4 ; % = 7
Secondary progressive Sample size	n = 20 ; % = 27	n = 15 ; % = 25
Disease duration (years) Mean (SD)	11.9 (10.9)	13.5 (10)

Characteristic	Adaptive cognitive training programme - BrainHQ program focusing on speed, attention, working memory and executive function (N = 74)	Active control - ordinary computer games (N = 61)
EDSS score Median (IQR)	3.5 (4.0)	3.5 (4.0)
Screening SDMT z-score Mean (SD)	-2.1 (0.99)	-2.1 (1.01)

Outcomes

Study timepoints

- Baseline
- 12 week (12 weeks - end of treatment)

Results - change from baseline

Outcome	Adaptive cognitive training programme - BrainHQ program focusing on speed, attention, working memory and executive function, 12-week vs Baseline, N = 74	Active control - ordinary computer games , 12-week vs Baseline, N = 61
Neuropsychological composite score Battery of neuropsychological tests including PASAT, WAIS-IV Letter Number Sequence, WAIS-IV Digit Span Backwards, Selective Reminding Test, Brief Visuospatial Memory Test-Revised and Delis-Kaplan Executive Function	0.25 (0.45)	0.09 (0.37)

Outcome	Adaptive cognitive training programme - BrainHQ program focusing on speed, attention, working memory and executive function, 12-week vs Baseline, N = 74	Active control - ordinary computer games , 12-week vs Baseline, N = 61
System Trails. Baseline values were -0.77 (0.73) and -0.86 (0.77), respectively. Reported as a z-score. Mean (SD)		

1 Neuropsychological composite score - Polarity - Higher values are better
2 All of those randomised were analysed as intention to treat despite some missing from each group.
3 **Results - raw data**

Outcome	Adaptive cognitive training programme - BrainHQ program focusing on speed, attention, working memory and executive function, Baseline, N = NA	Adaptive cognitive training programme - BrainHQ program focusing on speed, attention, working memory and executive function, 12-week, N = 74	Active control - ordinary computer games , Baseline, N = NA	Active control - ordinary computer games , 12-week, N = 61
Compliance - defined as at least 6 compliant weeks 50% of target No of events	n = NA ; % = NA	n = 43 ; % = 58.11	n = NA ; % = NA	n = 48 ; % = 78.69
Compliance - defined as meeting or exceeding 30	n = NA ; % = NA	n = 44 ; % = 59.46	n = NA ; % = NA	n = 48 ; % = 78.69

Outcome	Adaptive cognitive training programme - BrainHQ program focusing on speed, attention, working memory and executive function, Baseline, N = NA	Adaptive cognitive training programme - BrainHQ program focusing on speed, attention, working memory and executive function, 12-week, N = 74	Active control - ordinary computer games , Baseline, N = NA	Active control - ordinary computer games , 12-week, N = 61
hours of training time 50% of target No of events				
Self-reported improvement in cognition during 12-week period Measured by participant scoring change: 0= the same, 1= improved and -1= declined No of events	n = NA ; % = NA	n = 42 ; % = 56.7	n = NA ; % = NA	n = 19 ; % = 31.1

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_neuropsychological composite score_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_compliance 6 compliant weeks_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_compliance reaching or exceeding 30 h_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_self-reported improvement in cognition_12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Chiaravalloti, 2018

Bibliographic Reference	Chiaravalloti, N. D.; Goverover, Y.; Costa, S. L.; DeLuca, J.; A Pilot Study Examining Speed of Processing Training (SPT) to Improve Processing Speed in Persons With Multiple Sclerosis; Frontiers in neurology [electronic resource].; 2018; vol. 9; 685

1 **Study details**

Trial name / registration number	NCT01838824
Study location	USA
Study setting	Outpatient - recruited through outpatient clinics, advertisements and through foundation database
Study dates	Study ran from 31/01/2012 to 02/02/2013
Sources of funding	Support from the National Multiple Sclerosis Society (pilot grant RG 4607-A) to NC and funding by the Kessler Foundation.
Inclusion criteria	Clinically definite MS; 18-65 years; free of exacerbations and steroid use for at least 1 month; and impaired processing speed at baseline (performance 1.5 SD below mean of published normative data on SDMT).
Exclusion criteria	Major psychiatric disorder; substance abuse; evidence of significant vision impairment from diplopia, nystagmus or scotomas upon testing (corrected vision in worse eye >20/60 assessed with Snellen Eye Test); or impaired language comprehension on the Token Test.
Recruitment / selection of participants	Recruited from MS Clinics, advertisements and through the Kessler Foundation database of research participants.
Intervention(s)	Speed of processing training (SPT): 10 computerised training sessions over a 5-week period. Initial sessions involve practice on three types of tasks presented on a computer (simple speed of processing, divided attention, and selective attention), with three different central demands (detection, identification, same/different). Training is customized to each participant's ability; an individual's entry point into SPT is determined by current level of PS, evaluated as the speed of stimulus presentation at which the person can correctly identify the stimulus 75% of the time. If this threshold is 30 ms or greater, SPT begins at the most basic level. Training sessions lasted approximately 30–45 min each depending on self-reported fatigue or an observable drop in performance. At level I practice single discrimination task at gradually increasing speeds. Involves either target present or absent, target identification or same/different judgements. Training continues with increasingly more complex discrimination tasks until can perform identification task correctly 75% of time at exposure duration of 17 ms - then progress to level II. Level II involves completing one of tasks described in level I and simultaneously locate a peripheral target. Demand of centre target can vary, and peripheral task demand changed by

	increasing or decreasing distance from centre target. The process of progressing from near peripheral targets to far targets is repeated, at faster speeds, and with increasing difficulty of the centre task. This is repeated until the participant can perform both the foveal identification task and the peripheral localization task (at the furthest eccentricity) with 75% accuracy, at a speed of 50 ms or less, before moving onto Level III. Level III involves selective attention training and requires discrimination task and location of peripheral target embedded among distracters. When the participant is able to perform the selected task correctly 75% of the time, a more demanding task is introduced by manipulating the complexity of the discrimination task, the display duration and/or target eccentricity. Practice continues until 75% correct performance is achieved at a 120 ms exposure, with peripheral targets at the most extreme eccentricity.
Population subgroups	None
Comparator	Control group: no treatment control condition.
Number of participants	21 randomised, 21 analysed (reported to be no dropout)
Duration of follow-up	End of treatment - 5 weeks
Indirectness	Outcome - follow-up <3 months minimum specified in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - unclear • Severity of cognitive impairment (mild/moderate/severe) - unclear (performance 1.5 standard deviations or more below the mean of published normative data on the oral Symbol Digit Modalities Test was inclusion criterion) • Disease modifying treatment status (currently using and not currently using) - majority were using one • Mood disorders (presence or absence) - unclear (those with major psychiatric disorder excluded) • Computerised vs clinician led - computerised • Group vs individual - individual

	Analysis - intention to treat as reported to be no dropouts

Study arms

Speed of processing training - focus on processing speed (N = 12)

Control - no treatment (N = 9)

Characteristics

Arm-level characteristics

Characteristic	Speed of processing training - focus on processing speed (N = 12)	Control - no treatment (N = 9)
% Female Sample size	n = 9 ; % = 67	n = 6 ; % = 67
Mean age (SD) Mean (SD)	46.42 (7.4)	52.11 (7.3)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Months since diagnosis	152 (59.2)	41 (26.9)

Characteristic	Speed of processing training - focus on processing speed (N = 12)	Control - no treatment (N = 9)
Mean (SD)		
Disease subtype - relapsing remitting MS Sample size	n = 12 ; % = 100	n = 9 ; % = 100
WASI vocabulary (pre-morbid IQ estimate) Wechsler Abbreviated Scale of Intelligence Mean (SD)	48.42 (12.9)	49.56 (12)
SDMT z-score Baseline processing speed ability Mean (SD)	-1.91 (0.79)	-2.38 (1.26)
Token test Mean (SD)	31.25 (2.6)	31.22 (2.3)
None Sample size	n = 3 ; % = 25	n = 3 ; % = 33.3
Copaxone Sample size	n = 4 ; % = 33.3	n = 4 ; % = 44.4
Avonex	n = 0 ; % = 0	n = 1 ; % = 11.1

Characteristic	Speed of processing training - focus on processing speed (N = 12)	Control - no treatment (N = 9)
Sample size		
Bestaseron Sample size	n = 1 ; % = 8.3	n = 1 ; % = 11.1
Aubagio Sample size	n = 1 ; % = 8.3	n = 0 ; % = 0
Rebif Sample size	n = 1 ; % = 8.3	n = 0 ; % = 0
Tysabri Sample size	n = 1 ; % = 8.3	n = 0 ; % = 0
Unknown / Other Sample size	n = 1 ; % = 8.3	n = 0 ; % = 0

Outcomes

Study timepoints

- Baseline
- 5 week (5 weeks - end of treatment period)

Results - raw data

Outcome	Speed of processing training - focus on processing speed, Baseline, N = 12	Speed of processing training - focus on processing speed, 5-week, N = 12	Control - no treatment, Baseline, N = 9	Control - no treatment, 5-week, N = 9
Digit Symbol Coding Subtest from the Wechsler Adult Intelligence Scale-III Measure of processing speed. Mean (SD)	5.83 (2.62)	7.5 (2.84)	5 (2.35)	5.44 (2.35)
Letter comparison Measure of processing speed (perceptual speed). Mean (SD)	8.4 (4.09)	8.13 (2.65)	6.89 (1.88)	6.78 (2.37)
Pattern comparison Measure of processing speed (perceptual speed). Mean (SD)	13.46 (3.34)	13.71 (3.18)	12.78 (3.18)	12.06 (4.28)
California Learning Verbal Test II (CVLT-II) - learning slope Measures verbal new learning and memory Mean (SD)	1.13 (0.66)	1.17 (0.61)	1.12 (0.43)	0.99 (0.4)
California Learning Verbal Test II (CVLT-II) - Short Delay Free Recall Measures verbal new learning and memory Mean (SD)	8.08 (3.5)	8.75 (4.27)	8.67 (4.36)	6.56 (3.54)

Outcome	Speed of processing training - focus on processing speed, Baseline, N = 12	Speed of processing training - focus on processing speed, 5-week, N = 12	Control - no treatment, Baseline, N = 9	Control - no treatment, 5-week, N = 9
Timed Instrumental Activities of Daily Living Test (TIADL) (Score incorporates speed and accuracy and is presented as a z-score only) performance-based measure of functional activities uses real everyday items comprising five tasks sampling common instrumental activities of daily living: (1) communication: finding a number in a phone book, (2) finance: counting change using coins, (3) nutrition: locating and reading ingredients from a food can, (4) shopping: locating items on a shelf, and (5) medicine: locating and reading directions from medicine bottles Mean (SD)	0.11 (1.02)	0.38 (0.76)	-0.02 (0.53)	-0.23 (0.45)

1 Digit Symbol Coding Subtest from the Wechsler Adult Intelligence Scale-III - Polarity - Higher values are better
2 Letter comparison - Polarity - Higher values are better
3 Pattern comparison - Polarity - Higher values are better
4 California Learning Verbal Test II (CVLT-II) - learning slope - Polarity - Higher values are better
5 California Learning Verbal Test II (CVLT-II) - Short Delay Free Recall - Polarity - Higher values are better
6 Timed Instrumental Activities of Daily Living Test (TIADL) - Polarity - Higher values are better

7

8

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_Digit Symbol Coding Subtest from the Wechsler Adult Intelligence Scale-III_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

1 **Results_letter comparison_5 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

2

3 **Results_pattern comparison_5 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_CVLT-II learning slope_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_CVLT-II Short Delay Free Recall_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_TIADL overall score_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Chiaravalloti, 2020

Bibliographic Reference	Chiaravalloti, N. D.; Moore, N. B.; DeLuca, J.; The efficacy of the modified Story Memory Technique in progressive MS; Multiple Sclerosis; 2020; vol. 26 (no. 3); 354-362

Study details

Trial name / registration number	NCT02301247
Study location	USA
Study setting	unclear - likely outpatient
Study dates	Recruitment ran from 1 September 2014 to 31 August 2016

Sources of funding	Support from Kessler Foundation, as well as grant support from the International Progressive Multiple Sclerosis Alliance (grant #PA0128) to N.D.C.
Inclusion criteria	New learning and memory impairment (1.5 SD+ compared to normative Open Trial Selective Reminding Test; age 30-68 years; free of exacerbations and steroid use for at least 1 month; no neurologic history other than MS; no history of major depressive disorder, schizophrenia, or bipolar disorder; no history of diagnosed substance use/dependence; intact vision; and intact language comprehension.
Exclusion criteria	None reported.
Recruitment / selection of participants	Recruitment ran from 1 September 2014 to 31 August 2016
Intervention(s)	Modified Story Memory Technique (mSMT): 10 sessions of the mSMT (2 times weekly for 5 weeks), with sessions lasting 45-60 min. The mSMT trains two related skills: imagery and context. Sessions 1-4 present the participants with stories for which they create visual imagery to aid memory. Sessions 5-8 present the participants with word lists for which they embed the words in a story and then visualize that story. Sessions 9 and 10 focus on applying the mSMT to real-world settings (directions, shopping). Treatment is manualised, and the therapist follows a scripted manual. Treatment was administered by a research assistant who was blinded to assessment results and study hypotheses.
Population subgroups	None
Comparator	Placebo control: control group met with the therapist at the same frequency as the treatment group, engaging in non-training-specific tasks to control for professional contact and disease alterations. Tasks included reading the same stories as the treatment group and answering questions about them. The only difference between the groups was that only the treatment group was exposed to the active ingredients of the mSMT (imagery, context).
Number of participants	30 randomised, 28 analysed at end of treatment (5 weeks)
Duration of follow-up	5 weeks - end of treatment (additional 3-month follow-up time-point reported but no useable data reported for this time-point vs. baseline). N=2 dropped out in the control group due to time commitment
Indirectness	Outcome - reported extractable outcomes at time-point <3 months minimum specified in protocol

Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority secondary-progressive (57%) • According to disability (EDSS <6 and EDSS ≥6) - unclear • Severity of cognitive impairment (mild/moderate/severe) - unclear (new learning and memory abilities that were at least 1.5 standard deviations below normative Open Trial Selective Reminding Test data) • Disease modifying treatment status (currently using and not currently using) - majority were using (71%) • Mood disorders (presence or absence) - likely absent (most conditions excluded) • Computerised vs clinician led - clinician-led • Group vs individual - individual Analysis - appears to be intention to treat with those with absent data not included in analysis (modified ITT)

Study arms

Modified Story Memory Technique - focus on new learning and memory (N = 15)

Placebo control - non-training-specific tasks (N = 15)

Characteristics

Arm-level characteristics

Characteristic	Modified Story Memory Technique - focus on new learning and memory (N = 15)	Placebo control - non-training-specific tasks (N = 15)
% Female Sample size	n = 11 ; % = 75	n = 7 ; % = 54

Characteristic	Modified Story Memory Technique - focus on new learning and memory (N = 15)	Placebo control - non-training-specific tasks (N = 15)
Mean age (SD) Mean (SD)	55.2 (9.13)	53.31 (10.74)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Months since diagnosis Mean (SD)	204.07 (143.16)	191.08 (84.9)
Primary progressive Sample size	n = 3 ; % = 20	n = 7 ; % = 53.8
Secondary progressive Sample size	n = 10 ; % = 66.7	n = 6 ; % = 46.2
Progressive-relapsing Sample size	n = 1 ; % = 6.7	n = 0 ; % = 0
Ambulation index Mean (SD)	4.67 (2.18)	4.89 (2.98)

Characteristic	Modified Story Memory Technique - focus on new learning and memory (N = 15)	Placebo control - non-training-specific tasks (N = 15)
WASI vocabulary (pre-morbid IQ estimate) Wechsler Abbreviated Scale of Intelligence Mean (SD)	49.53 (8.6)	51.23 (6)
SRT Trials to criterion (baseline learning abilities) Selective Reminding Test Mean (SD)	13.67 (2.85)	13.23 (3.09)
Chicago Multidimensional Depression Inventory Total T-score Mean (SD)	54.42 (16.77)	55.18 (11.71)
STAI - State Anxiety Standard Score Mean (SD)	53.17 (15.27)	56.11 (18.9)
None Sample size	n = 4 ; % = 26.7	n = 4 ; % = 30.8
Copaxone Sample size	n = 2 ; % = 13.3	n = 3 ; % = 23.1
Tecfidera Sample size	n = 1 ; % = 6.7	n = 2 ; % = 15.4

Characteristic	Modified Story Memory Technique - focus on new learning and memory (N = 15)	Placebo control - non-training-specific tasks (N = 15)
Intravenous immunoglobulin Sample size	n = 1 ; % = 6.7	n = 1 ; % = 7.7
Tysabri Sample size	n = 4 ; % = 26.7	n = 2 ; % = 15.4
Rituxan Sample size	n = 1 ; % = 6.7	n = 1 ; % = 7.7
Rebif Sample size	n = 1 ; % = 6.7	n = 0 ; % = 0
Beta-interferon Sample size	n = 1 ; % = 6.7	n = 0 ; % = 0

Note that patient characteristics are given for those analysed (n=15 vs. n=13) not those randomised (n=15 vs. n=15)

Outcomes

Study timepoints

- Baseline
- 5 week (5-weeks - end of treatment)

1 **Results - raw data**

Outcome	Modified Story Memory Technique - focus on new learning and memory, Baseline, N = 15	Modified Story Memory Technique - focus on new learning and memory, 5-week, N = 15	Placebo control - non-training-specific tasks, Baseline, N = 13	Placebo control - non-training-specific tasks, 5-week, N = 13
CVLT Learning Slope California Verbal Learning Test. Mean values not reported but can calculate from number analysed in RevMan. Baseline values reported but appear to be z-scores and possibly not same scale as what results are reported in: –0.6 (1.17) vs. –0.19 (1.13) Mean (95% CI)	NR (NR to NR)	NR (1.22 to 1.36)	NR (NR to NR)	NR (0.58 to 1.98)
Awareness of cognitive deficits Questionnaire (AQ) Scale unclear but possibly 17-85. Mean values not reported but can calculate from number analysed in RevMan. Baseline values not reported. Measure of subjective cognition. Mean (95% CI)	NR (NR to NR)	NR (13.05 to 18.63)	NR (NR to NR)	NR (8.37 to 14.79)
FrSBe Disinhibition After Illness Frontal Systems Behavior Scale. Scale unclear but possibly 15-75. Mean values not reported but can calculate from number analysed in RevMan. Baseline values reported but appear to be T-scores and possibly not same scale as what results are reported in: 52.73 (15.61) vs. 62.40 (18.86)	NR (NR to NR)	NR (25.72 to 29.21)	NR (NR to NR)	NR (23.07 to 26.57)

Outcome	Modified Story Memory Technique - focus on new learning and memory, Baseline, N = 15	Modified Story Memory Technique - focus on new learning and memory, 5-week, N = 15	Placebo control - non-training-specific tasks, Baseline, N = 13	Placebo control - non-training-specific tasks, 5-week, N = 13
Mean (95% CI)				

CVLT Learning Slope - Polarity - Higher values are better
Awareness of cognitive deficits Questionnaire (AQ) - Polarity - Higher values are better
FrSBe Disinhibition After Illness - Polarity - Lower values are better
Where reported, baseline values given for those analysed not those randomised.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_CVLT learning slope_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point less than minimum 3 months specified in protocol)*

Results_awareness of cognitive deficits questionnaire_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point less than minimum 3 months specified in protocol)*

1
2 **Results_FrSBe disinhibition after illness_5 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point less than minimum 3 months specified in protocol)*

Chiaravalloti, 2012

Bibliographic Reference	Chiaravalloti, N. D.; Wylie, G.; Leavitt, V.; Deluca, J.; Increased cerebral activation after behavioural treatment for memory deficits in MS; Journal of Neurology; 2012; vol. 259 (no. 7); 1337-46

Study details

Trial name / registration number	Not reported
Study location	USA
Study setting	Unclear, likely outpatient
Study dates	Not reported
Sources of funding	Funded by National Institutes of Health grants (Grant number R01 HD045798 and HD045798-S to N.D.C.); National Multiple Sclerosis Society (training grant-MB0003 to J.D.) and the Kessler Foundation
Inclusion criteria	Clinically definite MS according to McDonald criteria; right-handed; language comprehension intact (Token Test score >26); new learning and memory abilities at least 1.5 SD lower than mean of healthy control group based on Selective Reminding Test; and visual acuity to see test materials.
Exclusion criteria	History of major depressive disorder, schizophrenia or bipolar disorder I or II; and vision significantly impaired by scotomas (<20/60 corrected vision in worse eye), diplopia or nystagmus.

Recruitment / selection of participants	Not reported.
Intervention(s)	Modified Story Memory Technique - focus on memory: 10 sessions of Modified Story Memory Technique (mSMT). Twice weekly sessions for 5 weeks (45-60 min per session). Involves two related skills (imagery and context). Sessions 1-4 taught to utilise imagery to facilitate the learning of verbal information. Sessions 5-8 taught participants to utilise context to facilitate learning. Given the fact that real life rarely requires that one remember a list of words, sessions 9 and 10 focus on applying the mSMT to real-world settings. Real-life situations were addressed. If the participant could not describe two memory-taxing situations unique to their life, real-life situations were provided for them, from which they chose two situations they would most likely encounter, including (1) remembering a lengthy shopping list, (2) recalling a list of errands, and (3) recalling steps in driving directions. The treatment is highly manualized, and the therapist therefore followed a training manual with scripts provided.
Population subgroups	None
Comparator	Control group - placebo intervention sessions met with the treaters at the same frequency as the experimental group, but engaged in verbal tasks to control for professional contact and alterations in the disease process. Tasks consisted of reading the same stories that the experimental group used and answering questions. The placebo task was matched to the training task for duration of contact with the treater, and medium of presentation, specifically via computer.
Number of participants	16 randomised, 16 appear to be analysed as no dropouts reported
Duration of follow-up	End of treatment - 5 weeks.
Indirectness	Outcome - reported at <3 months minimum follow-up in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (69%) • According to disability (EDSS <6 and EDSS ≥6) - unclear • Severity of cognitive impairment (mild/moderate/severe) - unclear (new learning and memory abilities that were at least 1.5 standard deviations below the mean of a healthy control group an inclusion criterion)

	• Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - likely absent (most conditions excluded) • Computerised vs clinician led - mixed (met with clinicians but appears to be via computer) • Group vs individual - individual Analysis - appears to be intention to treat as no missing data reported

Study arms

Modified Story Memory Technique - focus on memory (N = 8)

Placebo control - verbal tasks without memory component (N = 8)

Characteristics

Arm-level characteristics

Characteristic	Modified Story Memory Technique - focus on memory (N = 8)	Placebo control - verbal tasks without memory component (N = 8)
% Female Sample size	n = 7 ; % = 87.5	n = 7 ; % = 87.5
Mean age (SD) Mean (SD)	49.25 (9.33)	46.75 (6.27)
Ethnicity	NR	NR

Characteristic	Modified Story Memory Technique - focus on memory (N = 8)	Placebo control - verbal tasks without memory component (N = 8)
Custom value		
Comorbidities Custom value	NR	NR
WASI vocabulary (estimate of premorbid IQ) Wechsler Abbreviated Scale of Intelligence Mean (SD)	8.67 (4.55)	11.88 (2.59)
Pre-treatment learning ability ORT-SRT trials to criterion Mean (SD)	10.75 (2.43)	11 (3.02)
Disease duration (Months) Mean (SD)	186.71 (116.95)	177.14 (66.49)
Months since symptom onset Mean (SD)	188.4 (168.3)	202.8 (56.45)
Months since last exacerbation Mean (SD)	30 (24.4)	11.5 (2.12)

Characteristic	Modified Story Memory Technique - focus on memory (N = 8)	Placebo control - verbal tasks without memory component (N = 8)
Ambulation index Mean (SD)	2.13 (1.73)	3.75 (1.39)
Disease subtype - relapsing-remitting MS Sample size	n = 5 ; % = 62.5	n = 6 ; % = 75

Outcomes

Study timepoints

- Baseline
- 5 week (5 weeks - end of treatment period)

Results - raw data

Outcome	Modified Story Memory Technique - focus on memory, Baseline, N = 8	Modified Story Memory Technique - focus on memory, 5-week, N = 8	Placebo control - verbal tasks without memory component, Baseline, N = 8	Placebo control - verbal tasks without memory component, 5-week, N = 8
CVLT short-delay recall - >10% improvement from baseline California Verbal Learning Test. 10% chosen based on literature relating to	n = NA ; % = NA	n = 6 ; % = 75	n = NA ; % = NA	n = 2 ; % = 25

Outcome	Modified Story Memory Technique - focus on memory, Baseline, N = 8	Modified Story Memory Technique - focus on memory, 5-week, N = 8	Placebo control - verbal tasks without memory component, Baseline, N = 8	Placebo control - verbal tasks without memory component, 5-week, N = 8
pharmacotherapy improvements generally seen. No of events				

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results CVLT short delay free recall improvement vs baseline_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Time-point <3 months minimum specified in protocol)*

Chmelarova, 2020

Bibliographic Reference	Chmelarova, D.; Fiala, L.; Dostal, M.; Lenz, J.; Intensive computer-assisted cognitive rehabilitation in persons with multiple sclerosis - results of a 12-week randomized study; Ceska a Slovenska Neurologie a Neurochirurgie; 2020; vol. 83 (no. 4); 408-415

Study details

Other publications associated with this study included in review	
Trial name / registration number	Not reported
Study location	Czech Republic
Study setting	Unclear - likely outpatient
Study dates	Not reported

Sources of funding	Not reported
Inclusion criteria	MS diagnosis: cognitive deficit at baseline (definition not reported); EDSS score 0-6.0; age 18-65 years; functionally dominant upper limb (to use keyboard); and access to a computer with internet connection
Exclusion criteria	History of drug or alcohol abuse; major psychiatric disorders; acute relapses; neurological disorders other than MS; and patients with ongoing rehabilitation.
Recruitment / selection of participants	Not reported
Intervention(s)	Happy Neuron Brain Jogging computer programme - multidomain cognitive programme: received training on it and then asked to work on it at home. Cognitive online training using Happy Neuron Brain Jogging computer program created by ABET HOLDING, a.s. part of French SBT group. Involves 20 different tasks related to memory, concentration, speech, logical thinking, special orientation and other abilities. Different levels of difficulty can be set meaning there is high variability in the exercise. Also include automatic coach able to select appropriate set of exercises to optimise benefits for patients. Training plan involved 4 times weekly sessions (30 min per session) for 8 consecutive weeks (32 training days on predetermined days with a specific training plan). Primary goals of treatment plan included following cognitive functions: memory, attention and concentration, speed and information processing, executive functions, expression and speed comparison and self-orientation and perception. All given training sheet including two exercises with requirement of repeating them three times. For the remaining time participants asked to undertake an exercise of their choice. Patients also informed that it is better to repeat the same exercise multiple times rather than many exercises only once. Required to complete all 32 training blocks. If needed, communication could be facilitated through a designated website. If sessions had not been completed, they were contacted in order to work out why and discuss how to continue with the training.
Population subgroups	None
Comparator	Control - no training: received no training but to control for placebo effect they were repeatedly contacted for 2 months (3 times in total) and asked to report their current psychological status by completing a prepared questionnaire.
Number of participants	43 randomised, 43 appear to have been analysed (no dropouts reported)

Duration of follow-up	8-weeks - end of treatment
Indirectness	Outcome - follow-up <3 months minimum specified in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - unclear • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (inclusion criterion) • Severity of cognitive impairment (mild/moderate/severe) - unclear (had to have cognitive deficit to be included - not defined) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (major psychiatric conditions excluded) • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - appears to be intention to treat as no missing appear to be present based on numbers analysed

Study arms

Happy Neuron Brain Jogging computer programme - multidomain cognitive programme (N = 26)

memory, concentration, speech, logical thinking, special orientation and other abilities

Control - no training (N = 17)

Characteristics

Arm-level characteristics

Characteristic	Happy Neuron Brain Jogging computer programme - multidomain cognitive programme (N = 26)	Control - no training (N = 17)
% Female Custom value	NR	NR
Mean age (SD) Mean (SD)	41.3 (6.5)	42.4 (9.2)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
EDSS score Mean (SD)	3.1 (1.4)	3.3 (2)

Outcomes

Study timepoints

- Baseline
- 8 week (8-weeks - end of treatment)

1 **Results - raw data**

Outcome	Happy Neuron Brain Jogging computer programme - multidomain cognitive programme, Baseline, N = 26	Happy Neuron Brain Jogging computer programme - multidomain cognitive programme, 8-week, N = 26	Control - no training, Baseline, N = 17	Control - no training, 8-week, N = 17
Immediate memory Scale not reported but possibly 40-152 Mean (SD)	98.9 (15)	107.8 (16.9)	103.4 (17.9)	97.7 (17.5)
Visuospatial/constructional Scale not reported but possibly 50-131 Mean (SD)	95.5 (16.9)	106.9 (10.9)	97.1 (13.3)	101.9 (15.3)
Language Scale not reported but possibly 40-134 Mean (SD)	101.9 (9.9)	107.7 (10.7)	99.8 (14)	100.4 (14.2)
Attention Scale not reported but possibly 40-150 Mean (SD)	83.4 (15.8)	94.8 (15.8)	85.1 (14.9)	81.4 (15.4)

Outcome	Happy Neuron Brain Jogging computer programme - multidomain cognitive programme, Baseline, N = 26	Happy Neuron Brain Jogging computer programme - multidomain cognitive programme, 8-week, N = 26	Control - no training, Baseline, N = 17	Control - no training, 8-week, N = 17
Delayed memory Scale not reported but possibly 40-133 Mean (SD)	98.2 (15.2)	108.4 (16.1)	96.8 (13.7)	98.8 (15)
Total score Scale unclear but possibly 40-160 Mean (SD)	93.7 (13.4)	107.3 (15.2)	89.6 (26.5)	94.9 (17.2)
Trail Making Test - A Mean (SD)	50.1 (16)	40 (14.8)	74.2 (47.1)	58.2 (38.3)
Trail Making Test - B Mean (SD)	91.5 (32.6)	81.3 (33.2)	120.7 (63)	121.1 (67.3)

1 RBANS - Polarity - Higher values are better
2 Trail Making Test - Polarity - Lower values are better
3 Final values

4

5

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_RBANS immediate memory_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Follow-up less than minimum 3 months specified in protocol)*

1 **Results_RBANS visuospatial/constructional_8 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Follow-up less than minimum 3 months specified in protocol)*

2

3 **Results_RBANS language_8 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Follow-up less than minimum 3 months specified in protocol)*

Results_RBANS attention_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Follow-up less than minimum 3 months specified in protocol)*

Results_RBANS delayed memory_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Follow-up less than minimum 3 months specified in protocol)*

Results_RBANS total score_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Follow-up less than minimum 3 months specified in protocol)*

Results_trail making test A_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Follow-up less than minimum 3 months specified in protocol)*

Results_trail making test B_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(Follow-up less than minimum 3 months specified in protocol)*

De Giglio, 2015

Bibliographic Reference	De Giglio, L.; De Luca, F.; Prosperini, L.; Borriello, G.; Bianchi, V.; Pantano, P.; Pozzilli, C.; A low-cost cognitive rehabilitation with a commercial video game improves sustained attention and executive functions in multiple sclerosis: a pilot study; Neurorehabilitation & Neural Repair; 2015; vol. 29 (no. 5); 453-61

Study details

Trial name / registration number	Not reported
Study location	Italy
Study setting	Outpatient - recruited from MS Centre
Study dates	Not reported
Sources of funding	LP received consulting fees from Merck Serono, Bayer Schering, and Biogen Idec and speaker honoraria from Biogen Idec, Teva, and Novartis. GB received consulting fees from Merck Serono and speaker honoraria from Bayer Schering, Biogen Idec, Teva, and Novartis. CP received consulting and lecture fees from Sanofi-Aventis, Biogen Idec, Bayer Schering, Merck Serono, and Novartis; he also received research funding from Sanofi-Aventis, Merck Serono, Bayer Schering, and Novartis
Inclusion criteria	MS diagnosed according to revised McDonald criteria; relapsing-remitting MS course; age between 18 and 50 years; at least 8 years of education; failure in at least 1 of the following tests: Stroop Test, PASAT 3-s presentation rate, and Symbol

	Digit Modalities Test (failure on PASAT and SDMT was defined as a score below the fifth percentile of normative data for the Italian population and failure on ST as an equivalent score below 3); regularly attending the MS Centre of S. Andrea Hospital in Rome; and willing to not change or start any disease-modifying drug or symptomatic medication for the entire duration of the study.
Exclusion criteria	Disease exacerbation in the previous 3 months; any motor or visual condition that could interfere with the performance of training; history of seizures; presence of depression and/or anxiety assessed by the Hamilton Depression Scale and the Hamilton Anxiety Scale (cut-off scores for exclusion of 7 and 9, respectively); Mini Mental State Examination equal to or below 24.17 to exclude severely cognitively impaired patients; patients with psychiatric illnesses; history of alcohol or substance abuse; history of medications that may interfere with attentional level; previous cognitive rehabilitation training; treatment with anticholinesterasics; and left-handed patients to ensure uniformity in the performance of ST18 (handedness was assessed by means of the Edinburgh inventory).
Recruitment / selection of participants	Consecutive series of patients diagnosed as affected by MS according to revised McDonald criteria10 and regularly attending the MS Centre of S. Andrea Hospital in Rome were recruited
Intervention(s)	Nintendo brain training game: 8-week training period with training in games of memory, attention, visuospatial processing, and calculations. The cognitive training was performed at home with the Italian version of the Dr Kawashima's Brain Training (DKBT). Instructed by a psychologist on how to use the console and how to perform the training. They were required to play 30 min daily, 5 days a week for 8 consecutive weeks. They were required also to follow the instructions of the game provided during the training from a virtual guide and to experience all the puzzles proposed. The number of puzzles proposed increased through time. Games included Calculations and Voice Calculations (solve simple mathematical questions that appear on the screen as quickly as possible and write the response on the touch screen or speak the response), Reading aloud (read aloud an excerpt from a classic story as quickly as possible), Low to high (memorise position of numbers appearing on the screen for a short period of time and indicate on the touch screen the position of numbers from lowest number to highest), Syllable count (count number of syllables in each phrase write the response on the screen), Head count (to keep track of the number of people inside a house after people leave and enter the house over time), Triangle math (solve equations involving 3 numbers and 2 mathematical operations as quickly as possible) and Time lapse (calculating the difference in time between 2 analogue clocks). Second visit with the same psychologist was performed 2 weeks after to check the correct use of the device and the correct execution of the training. In case of problems, the psychologist planned a third visit and phone calls were also scheduled every week.

Population subgroups	None
Comparator	Waitlist control group - no definition but presume continued usual care and received no additional intervention.
Number of participants	35 randomised, 34 analysed (n=1 in control group lost to follow-up and said to be not included in analysis)
Duration of follow-up	Up to end of intervention period - 8 weeks
Indirectness	Outcome - time-point <3-month minimum specified in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (median 2.0 or 3.25 in the two groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear (mild-moderate as severe cognitive problems said to be excluded, unclear proportion with each) • Disease modifying treatment status (currently using and not currently using) - unclear (changes or starting new drugs exclusion criterion but unclear proportion already on them) • Mood disorders (presence or absence) - likely absent (most conditions excluded) • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - modified intention to treat (n=1 lost to follow-up and not included in analysis)

Study arms

Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations (N = 18)

Waitlist control (N = 17)

Characteristics

Arm-level characteristics

Characteristic	Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations (N = 18)	Waitlist control (N = 17)
% Female Sample size	n = 14 ; % = 77.8	n = 12 ; % = 70.6
Mean age (SD) Mean (SD)	44.64 (7.63)	42.99 (9.42)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Disease duration (years) Mean (SE)	13.28 (8.28)	11.4 (7.45)
EDSS score Median (range)	3.25 (2-6)	2 (2-4)

Characteristic	Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations (N = 18)	Waitlist control (N = 17)
1 test Sample size	n = 9 ; % = 50	n = 6 ; % = 35.3
2 tests Sample size	n = 7 ; % = 38.9	n = 8 ; % = 47.1
3 tests Sample size	n = 2 ; % = 11.1	n = 3 ; % = 17.6

Outcomes

Study timepoints

- Baseline
- 8 week (8-weeks - end of treatment)

Results - raw data

Outcome	Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations, Baseline, N = 18	Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations, 8-week, N = 18	Waitlist control, Baseline, N = 17	Waitlist control, 8-week, N = 16
Stroop Test Assesses the ability to suppress habitual responses Mean (SD)	22.05 (7.19)	27.54 (7.44)	24.5 (7.09)	23.38 (8.64)
PASAT 3 seconds Paced Auditory Serial Additional Test Mean (SD)	24.83 (6.35)	36.28 (10.5)	32.12 (9.82)	31.69 (9.06)
SDMT Symbol Digit Modalities Test Mean (SD)	39.22 (9.68)	47.44 (11.47)	34.56 (8.03)	38.59 (8.6)
MFIS - cognitive Modified Fatigue Impact Scale. Scale usually 0-40. Total and physical scales also reported but primarily interested in cognitive subscale. Mean (SD)	16.41 (8.36)	11.06 (7.17)	19 (7.84)	18.06 (8.86)
Physical health composite Mean (SD)	60.09 (11.33)	62.7 (11.84)	57.04 (14.67)	62.72 (14.84)

Outcome	Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations, Baseline, N = 18	Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations, 8-week, N = 18	Waitlist control, Baseline, N = 17	Waitlist control, 8-week, N = 16
Mental health composite Mean (SD)	55.79 (20.2)	61.5 (12.9)	54.31 (15.4)	54.03 (16)
Treatment adherence % Only reported for intervention group as not applicable to control. Number of days in which the patient performed the training/ total number of days required Mean (range)	NA	96 (80-100)	NA	NR

1 Stroop Test - Polarity - Higher values are better
2 PASAT 3 seconds - Polarity - Higher values are better
3 SDMT - Polarity - Higher values are better
4 MFIS - cognitive - Polarity - Lower values are better
5 MSQoL-54 - Polarity - Higher values are better
6 Final values for continuous outcomes

7

8

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_Stroop test_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum specified in protocol)*

Results_PASAT 3 seconds_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum specified in protocol)*

Results_SDMT_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum specified in protocol)*

Results_MFIS cognitive_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum specified in protocol)*

Results_MSQOL-54 physical health_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum specified in protocol)*

Results_MSQOL-54 mental health_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum specified in protocol)*

Results_treatment adherence_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

De Giglio, 2016

Bibliographic Reference	De Giglio, L.; Tona, F.; De Luca, F.; Petsas, N.; Prosperini, L.; Bianchi, V.; Pozzilli, C.; Pantano, P.; Multiple Sclerosis: Changes in Thalamic Resting-State Functional Connectivity Induced by a Home-based Cognitive Rehabilitation Program; Radiology; 2016; vol. 280 (no. 1); 202-11

1 Study details

Trial name / registration number	Not reported
Study location	Italy
Study setting	Outpatient - recruited from MS Centre
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	MS diagnosed according to revised McDonald criteria; relapsing-remitting MS course; age between 18 and 50 years; right-handedness; and cognitive impairment with specific deficits in working memory, information processing speed, or sustained attention (failure on at least one of the following tests: PASAT 3-second presentation rate, SDMT, and the Stroop Test - failure on the PASAT and SDMT was defined as a score lower than the 10th percentile of normative data from the Italian population and failure on the ST as a score of less than 3); and willing to not change or start any medication for the entire study, except for the steroids required to treat MS exacerbations
Exclusion criteria	Disease exacerbation in the previous 3 months; any motor or visual condition that could interfere with the performance of training; history of seizures; presence of depression and/or anxiety assessed by the Hamilton Depression Scale and the Hamilton Anxiety Scale (cut-off scores for exclusion of 7 and 9, respectively); and Mini Mental State Examination equal to or below 24.17 to exclude severely cognitively impaired patients.
Recruitment / selection of participants	Consecutive series of patients with a diagnosis of MS according to the revised McDonald criteria (12) who were regularly attending the MS Center of S. Andrea Hospital (Rome, Italy) were recruited
Intervention(s)	Nintendo brain training game: 8-week training period with training in games of memory, attention, visuospatial processing, and calculations. The cognitive training was performed at home with the Italian version of the Dr Kawashima's Brain Training (DKBT). Instructed by a psychologist on how to use the console and how to perform the training. They were required to play 30 min daily, 5 days a week for 8 consecutive weeks. They were required also to follow the instructions of the game provided during the training from a virtual guide and to experience all the puzzles proposed. The number of puzzles proposed increased through time. Games included Calculations and Voice Calculations (solve simple mathematical

	questions that appear on the screen as quickly as possible and write the response on the touch screen or speak the response), Reading aloud (read aloud an excerpt from a classic story as quickly as possible), Low to high (memorise position of numbers appearing on the screen for a short period of time and indicate on the touch screen the position of numbers from lowest number to highest), Syllable count (count number of syllables in each phrase write the response on the screen), Head count (to keep track of the number of people inside a house after people leave and enter the house over time), Triangle math (solve equations involving 3 numbers and 2 mathematical operations as quickly as possible) and Time lapse (calculating the difference in time between 2 analogue clocks). Second visit with the same psychologist was performed 2 weeks after to check the correct use of the device and the correct execution of the training.
Population subgroups	None
Comparator	Waitlist control group - no definition but presume continued usual care and received no additional intervention.
Number of participants	24 randomised, 24 analysed (all completed follow-up)
Duration of follow-up	8-weeks - end of treatment
Indirectness	Outcome - time-point <3 months minimum specified in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (median score 2.0 for the whole population) • Severity of cognitive impairment (mild/moderate/severe) - unclear (mild-moderate as severe cognitive problems said to be excluded, unclear proportion with each) • Disease modifying treatment status (currently using and not currently using) - unclear (changes or starting new drugs exclusion criterion but unclear proportion already on them) • Mood disorders (presence or absence) - likely absent (most conditions excluded) • Computerised vs clinician led - computerised • Group vs individual - individual

	Analysis - intention to treat (all had follow-up and included in analysis)

Study arms

Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations (N = 12)

Waitlist control (N = 12)

Characteristics

Arm-level characteristics

Characteristic	Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations (N = 12)	Waitlist control (N = 12)
% Female Sample size	n = 8 ; % = 66.7	n = 6 ; % = 50
Mean age (SD) Mean (SD)	43.7 (7.6)	40.2 (10.1)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR

Characteristic	Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations (N = 12)	Waitlist control (N = 12)
Disease duration (years) Mean (SD)	12.9 (3.5)	13 (7.9)
EDSS score Median (range)	2 (2-4)	2 (2-7)

Outcomes

Study timepoints

- Baseline
- 8 week (8-weeks - end of treatment)

Results - raw data

Outcome	Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations, Baseline, N = 12	Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations, 8-week, N = 12	Waitlist control, Baseline, N = 12	Waitlist control, 8-week, N = 12
PASAT Paced Auditory Serial Addition Test Mean (SD)	35.5 (10.1)	46.4 (7.2)	32.2 (16.6)	37 (10.9)

Outcome	Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations, Baseline, N = 12	Nintendo brain training game - training in memory, attention, visuospatial processing, and calculations, 8-week, N = 12	Waitlist control, Baseline, N = 12	Waitlist control, 8-week, N = 12
SDMT Symbol Digit Modalities Test Mean (SD)	37.5 (9.5)	50.5 (17.9)	33.9 (8.6)	39 (12.6)
Stroop Test Assesses the ability to suppress habitual responses Mean (SD)	22.8 (4.9)	28.8 (4.9)	24.17 (5.5)	24.9 (8.1)

PASAT - Polarity - Higher values are better
SDMT - Polarity - Higher values are better
Stroop Test - Polarity - Higher values are better
Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_PASAT_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum specified in protocol)*

Results_SDMT_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum specified in protocol)*

Results_Stroop Test_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum specified in protocol)*

De la Torre, 2020

Bibliographic Reference	De la Torre GG; Mato I; Doval S; Espinosa R; Moya M; Cantero R; Gonzalez M; Gonzalez C; Garcia MA; Hermans G; González-Torre S; Mestre JM; Hidalgo V; Neurocognitive and emotional status after one-year of mindfulness-based intervention in patients with relapsing-remitting multiple sclerosis.; Applied neuropsychology. Adult; 2020

Study details

Trial name / registration number	Not reported
Study location	Spain
Study setting	Outpatient - those that had been referred to neurology unit of hospital after MS diagnosis

Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	Relapsing-remitting MS diagnosis regardless of degree of functional deterioration; and >18 years of age. Cognitive impairment not explicitly stated to be an inclusion criterion, but possible that those selected by neuropsychologists were those who were thought would benefit most from attempt to improve cognitive abilities (very few inclusion criteria mentioned).
Exclusion criteria	Presenting with severe cognitive deterioration.
Recruitment / selection of participants	Recruited from those referred to neurology unit of a university hospital - selected for the work by hospital's neuropsychologists.
Intervention(s)	Mindfulness intervention +pharmacological treatment: 8 weekly (2 h) group sessions of mindfulness using 'Mindfulness-Based Cognitive Therapy for Depression' programme based on Jon Kabat-Zinn's programme adapted for patients with depression. Focused on common problems and worries people with MS have such as functional independent living level, mood, uncertainty and work. Training focused on understanding and becoming aware of the present moment. Guided meditation used to teach participants to become more aware of physical sensations such as breathing and to train the mind to become aware of the body and the emotion they experienced at the present moment. Also used cognitive strategies aimed at recognising and paying attention to pleasant and unpleasant thoughts and feelings by working on acceptance and non-judgemental attitude towards the experience. Carried out in three cycles, within each cycle group of 10 people met for 2 months with each cycle being 2 weeks apart. Meetings outside of working ours to improve attendance. Participants also committed to series of exercises at home at least 1 h per day for 6 days a week (listening to guided meditations as well as doing written exercises related to aspects in each session). Assume usual pharmacological treatment continued for the pharmacological component mentioned in this group.
Population subgroups	None
Comparator	Control - no mindfulness intervention. Described as pharmacological treatment only and assume usual pharmacological treatment continued as no further details provided.
Number of participants	60 randomised, assume 60 analysed as no drop out mentioned

Duration of follow-up	Up to 12 months - unclear whether this represents 10 months after the end of the intervention or whether the at-home components were continued for the whole 12 months (suggests group sessions only lasted for 2 months but no mention of at-home exercise duration).
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - unclear • Severity of cognitive impairment (mild/moderate/severe) - unclear (unclear if all had impairment at baseline as not explicitly mentioned as an inclusion criterion) • Disease modifying treatment status (currently using and not currently using) - using (based on figure in paper majority appear to have been using one) • Mood disorders (presence or absence) - unclear • Computerised vs clinician led - clinician-led • Group vs individual - mixed (group sessions as well as at-home exercises/tasks) Analysis - assumed intention to treat as no missing data apparent

Study arms

Mindfulness (focus is on cognitive outcomes not solely psychological outcomes) + pharmacological treatment (N = 30)

Control - pharmacological treatment only (N = 30)

Characteristics

Arm-level characteristics

Characteristic	Mindfulness (focus is on cognitive outcomes not solely psychological outcomes) + pharmacological treatment (N = 30)	Control - pharmacological treatment only (N = 30)
% Female Sample size	n = 22 ; % = 73.3	n = 18 ; % = 60
Mean age (SD) Mean (SD)	44.3 (10.34)	48.8 (8.76)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month (12-months - unclear if 10 months following the end of the intervention (group sessions lasted for 2 months) or whether some components of the intervention (e.g., at-home tasks) continued for the whole 12-month period)

1 **Results - raw data**

Outcome	Mindfulness (focus is on cognitive outcomes not solely psychological outcomes) + pharmacological treatment, Baseline, N = 30	Mindfulness (focus is on cognitive outcomes not solely psychological outcomes) + pharmacological treatment, 12-month, N = 30	Control - pharmacological treatment only, Baseline, N = 30	Control - pharmacological treatment only, 12-month, N = 30
Attention Mean (SD)	4.43 (1.45)	5.03 (1.69)	3.8 (1.77)	4.87 (2.4)
Long-term memory Mean (SD)	6.47 (3)	7.87 (2.78)	5.3 (3.43)	6.1 (3.74)
Short-term memory Mean (SD)	28.03 (6.71)	29.43 (6.64)	26 (7.66)	27.17 (9.48)
Recognition Mean (SD)	21.9 (2.99)	22.23 (2.67)	19.97 (4.8)	20 (5.13)
Learning Mean (SD)	3.97 (2.19)	3.97 (1.96)	3.7 (2.04)	3.37 (1.65)
SDMT Symbol Digit Modalities Test Mean (SD)	37.73 (14.2)	40.97 (15.57)	31.9 (17.55)	33.43 (13.42)

Outcome	Mindfulness (focus is on cognitive outcomes not solely psychological outcomes) + pharmacological treatment, Baseline, N = 30	Mindfulness (focus is on cognitive outcomes not solely psychological outcomes) + pharmacological treatment, 12-month, N = 30	Control - pharmacological treatment only, Baseline, N = 30	Control - pharmacological treatment only, 12-month, N = 30
Words (FAS) Mean (SD)	32.67 (13.38)	37.13 (13.21)	28.93 (13.62)	30.37 (11.17)
Names of animals Mean (SD)	17.23 (4.65)	18.03 (5.52)	16.07 (7.93)	15.73 (6.45)
2 seconds Mean (SD)	30.5 (9.93)	35.5 (13.89)	22.57 (10.54)	23.1 (11.57)
3 seconds Mean (SD)	33.6 (10.33)	37.2 (11.93)	26.03 (11.37)	26.23 (12.26)
Beck Depression Inventory Scale usually 0-63. Mean (SD)	17.83 (11.42)	14 (7.52)	13.37 (13.23)	18.67 (10.68)
State-Trait Anxiety Inventory Unclear if state or trait. Scale usually 20-80.	60.87 (33.36)	38.97 (23)	NR (NR)	41.77 (23.52)

Outcome	Mindfulness (focus is on cognitive outcomes not solely psychological outcomes) + pharmacological treatment, Baseline, N = 30	Mindfulness (focus is on cognitive outcomes not solely psychological outcomes) + pharmacological treatment, 12-month, N = 30	Control - pharmacological treatment only, Baseline, N = 30	Control - pharmacological treatment only, 12-month, N = 30
Mean (SD)				
Independence - functional Independence measure (FIM) + functional assessment measure (FAM) Measure of independence in daily life. Scale usually 30-210 Mean (SD)	24.72 (8.65)	50.17 (16.64)	28.42 (11.49)	53.25 (18.65)

Wechsler Memory Scale - III Spanish Version - Polarity - Higher values are better
SDMT - Polarity - Higher values are better
COWAT verbal fluency test - Polarity - Higher values are better
PASAT - Polarity - Higher values are better
Beck Depression Inventory - Polarity - Lower values are better
State-Trait Anxiety Inventory - Polarity - Lower values are better
Independence - functional Independence measure (FIM) + functional assessment measure (FAM) - Polarity - Higher values are better
Final values for continuous outcomes.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_WMS attention_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WMS long-term memory_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WMS short-term memory_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_recognition_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WMS learning_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_COWAT - words (FAS)_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_COWAT - names of animals_12 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_PASAT 2 seconds_12 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_PASAT 3 seconds_12 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_BDI_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_STAI anxiety_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_functional independence (FIM + FAM)_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Ernst, 2016

Bibliographic Reference	Ernst, A.; Sourty, M.; Roquet, D.; Noblet, V.; Gounot, D.; Blanc, F.; De Seze, J.; Manning, L.; Functional and structural cerebral changes in key brain regions after a facilitation programme for episodic future thought in relapsing-remitting multiple sclerosis patients; Brain & Cognition; 2016; vol. 105; 34-45

Study details

Trial name / registration number	Not reported
Study location	France
Study setting	Unclear - likely outpatient
Study dates	Not reported
Sources of funding	Funding from 'Fondation pour la Recherche sur la Sclérose en Plaques' and Ministry of National Education and Research.
Inclusion criteria	Relapsing-remitting MS; EDSS score ≤4.0; no recent MS symptom exacerbation; right-handiness; absence of major signs of depression according to Montgomery and Asberg Depression Rating Scale (score ≤15.0); and impaired episodic future thought performance (mild-moderate cognitive impairment in attention and/or executive functions; mean number of internal details ≤19).

Exclusion criteria	Not reported
Recruitment / selection of participants	Selected from a group of patients involved in a broader study on autobiographical memory and episodic future thinking (Ernst 2015)
Intervention(s)	Mental visual imagery programme: based on the ability to mentally construct scenes and follows a goal-directed approach. Encompassed six two-hour sessions (once or twice per week), organised in four steps, with mental visualisation exercises of increasing difficulty, during which the neuropsychologist provides a continuous guidance. The screening step aims at probing basic visual imaging abilities and is based on three subtests from the 'Imagery and Perception Battery'. None of the patients showed difficulties to perform these tasks, (ii) The external visualisation includes 10 names of objects to be imagined and described, (iii) The construction phase consists in figuring out complex scenes, bringing into play several characters. Five verbal items were proposed with for each one, a first training step and a subsequent scene, sharing thematic similarities; (iv) the self-visualisation step follows the same procedure, but patients are asked to imagine themselves within a given scenario as they are living the scene.
Population subgroups	None
Comparator	Verbal control programme: based on the role of narrative structure, which provides a scaffold for the evocation of personal events, but which distinctly plays a minor role in mental time travel compared to mental visual imagery. Construct discussions about texts (extracted from websites) with the neuropsychologist's guidance, through steps of increasing difficulty: (i) the external discussion comprises 20 texts and aims at identifying influential variables on text understanding (e.g., clarity, vocabulary used, etc.). (ii) The discussion construction comprises five items, with for each of them, a training and construction steps. So, the two texts of each item were thematically related to enable the reliance on the first to construct the second text, (iii) The self-involved discussion is similar to the previous step, but the exchange is focused on the patient's personal opinion.
Number of participants	17 randomised, unclear number analysed
Duration of follow-up	Unclear - possibly 6-8 weeks (intervention duration) based on previous study
Indirectness	Outcome - time-point <3 months minimum specified in protocol

Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (score <4.0 inclusion criterion) • Severity of cognitive impairment (mild/moderate/severe) - mild - reported in study to have mild cognitive impairments • Disease modifying treatment status (currently using and not currently using) - using (both groups reported to be on 1.0 (0.0) DMD treatment overall • Mood disorders (presence or absence) - unclear (depression excluded) • Computerised vs clinician led - clinician led • Group vs individual - individual Analysis - unclear (number analysed unclear but no dropouts mentioned)

Study arms

Mental visual imagery - focus on attention and executive functions (N = 10)

Verbal control programme (N = 7)

Characteristics

Arm-level characteristics

Characteristic	Mental visual imagery - focus on attention and executive functions (N = 10)	Verbal control programme (N = 7)
% Female Sample size	n = 6 ; % = 60	n = 6 ; % = 85.7

Characteristic	Mental visual imagery - focus on attention and executive functions (N = 10)	Verbal control programme (N = 7)
Mean age (SD) Mean (SD)	38.4 (10.94)	34.71 (8.44)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
EDSS score Mean (SD)	2.45 (1.73)	1.85 (1.18)
Duration of MS (years) Mean (SD)	11.1 (11.03)	8.85 (5.27)
Number of disease-modifying drug treatments Mean (SD)	1 (0)	1 (0)

Outcomes

Study timepoints

- Baseline
- 6 week (6-8 weeks - likely end of intervention based on similar study by same authors)

Results - raw data

Outcome	Mental visual imagery - focus on attention and executive functions, Baseline, N = 10	Mental visual imagery - focus on attention and executive functions, 6-week, N = 10	Verbal control programme, Baseline, N = 7	Verbal control programme, 6-week, N = 7
Amount of details provided Measure of mental visualisation ability. This measure extracted as most relevant measure based on study aims. Mean (SD)	5.6 (1.86)	5.86 (2.28)	6.93 (0.72)	6.41 (2.2)

Amount of details provided - Polarity - Higher values are better

Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_number of details provided_end of treatment

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Time-point <3 months minimum in protocol)*

1

2 **Filippi, 2012**

Bibliographic Reference	Filippi, M.; Riccitelli, G.; Mattioli, F.; Capra, R.; Stampatori, C.; Pagani, E.; Valsasina, P.; Copetti, M.; Falini, A.; Comi, G.; Rocca, M. A.; Multiple sclerosis: effects of cognitive rehabilitation on structural and functional MR imaging measures--an explorative study; Radiology; 2012; vol. 262 (no. 3); 932-40

3

4 ## Study details

Trial name / registration number	Not reported

Study location	Italy
Study setting	Unclear - possibly outpatient
Study dates	Enrolled between November 2008 and January 2010
Sources of funding	Not reported
Inclusion criteria	Relapsing-remitting MS; EDSS score ≤4.0; no clinical exacerbations; no disease-modifying treatments during year before study enrolment; deficits in both PASAT (z-scores <-1.5) and Wisconsin Card Sorting Test (z scores <-1.5 in any of test measures); right handedness; normal or corrected-to-normal vision; and no concomitant therapy with antidepressants, psychoactive drugs or steroids.
Exclusion criteria	Ongoing major psychiatric and/or medical disorder; substance abuse; Mini-Mental State Examination score of less than 24; and occurrence of a relapse during the study (n=2 excluded)
Recruitment / selection of participants	Enrolled between November 2008 and January 2010
Intervention(s)	RehaCom cognitive training: performed with the supervision of one neuropsychologist. Intensive computer-assisted cognitive rehabilitation of attention, information processing, and executive functions for 12 weeks, performed by using a software that is part of the RehaCom package. Each session lasted for 1 hour, with a frequency of three sessions per week. The “Plan a Day” procedure trained the patient's ability to organize, plan, and develop solution strategies by employing realistic simulations of a set of scheduled dates and duties to be organized at specific places in a small city map. Times for planning and schedules were registered for each patient at each session, and only improvement and acquisition of sufficient planning abilities for fulfilling all the appointments required were used to ameliorate the level in the subsequent treatment session. In "Divided Attention," the patient was required to simulate the actions of a train driver, carefully observing the control panel of the train and the countryside. Several distractions, including crossing animals and train speed, were added with increasing levels of difficulty. Specific speed information training, consisting of a modified PASAT task with numbers, words, and months of the year, was combined with each "Divided Attention" session.
Population subgroups	None
Comparator	Control - no training: control group patients did not receive any rehabilitation

Number of participants	20 said to be randomised, though suggests some excluded post-randomisation, 20 analysed at 3 months (end of treatment)
Duration of follow-up	3 months - end of intervention period
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (score <4.0 inclusion criterion) • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - possibly not using (excluded those that had used them within last year) • Mood disorders (presence or absence) - unclear (excluded major psychiatric conditions) • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - possibly intention to treat as all 20 said to be randomised analysed, but wording suggests some that were randomised may have been excluded during the study due to relapse occurring

Study arms

RehaCom cognitive training - focus on executive function, attention and speed of information processing (N = 10)

Control - no cognitive training (N = 10)

Characteristics

Arm-level characteristics

Characteristic	RehaCom cognitive training - focus on executive function, attention and speed of information processing (N = 10)	Control - no cognitive training (N = 10)
% Female Sample size	n = 10 ; % = 100	n = 10 ; % = 100
Mean age (SD) Mean (range)	44.8 (28-60)	46.7 (25-64)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Disease duration (years) Median (range)	15.5 (1-28)	13.5 (1-28)
EDSS score Median (range)	2.5 (1.0-4.0)	2.0 (1.5-4.0)

Outcomes

Study timepoints

- Baseline
- 3 month (3 months - end of intervention)
- 9 month (9 months - 6 months after the end of the 3-month intervention)

Results - raw data

Outcome	RehaCom cognitive training - focus on executive function, attention and speed of information processing, Baseline, N = 10	RehaCom cognitive training - focus on executive function, attention and speed of information processing, 3-month, N = 10	RehaCom cognitive training - focus on executive function, attention and speed of information processing, 9-month, N = 9	Control - no cognitive training, Baseline, N = 10	Control - no cognitive training, 3-month, N = 10	Control - no cognitive training, 9-month, N = 9
2 seconds Mean (SD)	7.6 (10.1)	17.7 (15)	18 (13.5)	3.9 (8.3)	4.9 (9.4)	6.8 (10.6)
3 seconds Mean (SD)	12.9 (14)	30.8 (17)	29.5 (14.5)	11 (11.9)	9.7 (16.4)	15.2 (18.5)
Total errors Mean (SD)	66.7 (19.3)	28 (11.8)	30.1 (15.1)	55.7 (15.3)	41.3 (20.7)	49.5 (20.5)
Perseverative responses Mean (SD)	60.7 (15.1)	25.5 (11)	24.2 (8.3)	52.2 (21.7)	39.8 (27.5)	36.8 (24.6)

Outcome	RehaCom cognitive training - focus on executive function, attention and speed of information processing, Baseline, N = 10	RehaCom cognitive training - focus on executive function, attention and speed of information processing, 3-month, N = 10	RehaCom cognitive training - focus on executive function, attention and speed of information processing, 9-month, N = 9	Control - no cognitive training, Baseline, N = 10	Control - no cognitive training, 3-month, N = 10	Control - no cognitive training, 9-month, N = 9
Perseverative errors Mean (SD)	47.2 (9.8)	18.1 (6.4)	19.8 (8.6)	42.7 (14.6)	29 (19.5)	32.22 (15.1)
COWA/P controlled oral word association test with phonemic cues Mean (SD)	26.9 (7.9)	34.4 (11.2)	31.3 (7.7)	30.6 (9.2)	30 (11.2)	31.1 (9.9)
COWA/S controlled oral word association test with semantic cues Mean (SD)	32.6 (8.5)	37.6 (12.4)	38.8 (9.8)	33 (10.1)	35 (8)	31.5 (10.1)
TEA median for auditory stimulus Test of Everyday Attention Mean (SD)	683.1 (232.9)	750.3 (171.4)	672.7 (123.7)	714.6 (230.9)	612.8 (117.2)	500.1 (302.4)

Outcome	RehaCom cognitive training - focus on executive function, attention and speed of information processing, Baseline, N = 10	RehaCom cognitive training - focus on executive function, attention and speed of information processing, 3-month, N = 10	RehaCom cognitive training - focus on executive function, attention and speed of information processing, 9-month, N = 9	Control - no cognitive training, Baseline, N = 10	Control - no cognitive training, 3-month, N = 10	Control - no cognitive training, 9-month, N = 9
TEA median for visual stimulus Test of Everyday Attention Mean (SD)	1074.5 (250.8)	959.1 (132.4)	962.7 (133.5)	1079.4 (329)	1048.7 (193.4)	734.5 (434.7)
TEA total omitted stimuli Test of Everyday Attention Mean (SD)	7.3 (3.8)	4.5 (1.8)	NR (NR)	5.3 (5.6)	4.6 (3)	NR (NR)
TEA total errors Test of Everyday Attention Mean (SD)	9.6 (9.1)	4.8 (4.3)	NR (NR)	5.7 (5.3)	6.1 (6.1)	NR (NR)
SRT/CTRL Selective Reminding Test for verbal	19.8 (12.8)	21.8 (13.7)	23.3 (15.8)	17.7 (8.3)	16.3 (11.6)	21.1 (14.6)

Outcome	RehaCom cognitive training - focus on executive function, attention and speed of information processing, Baseline, N = 10	RehaCom cognitive training - focus on executive function, attention and speed of information processing, 3-month, N = 10	RehaCom cognitive training - focus on executive function, attention and speed of information processing, 9-month, N = 9	Control - no cognitive training, Baseline, N = 10	Control - no cognitive training, 3-month, N = 10	Control - no cognitive training, 9-month, N = 9
learning/consistent long-term retrieval Mean (SD)						
SRT/DR Selective Reminding Test for verbal learning/delayed retrieval Mean (SD)	6.9 (1.7)	7.3 (2.5)	7.7 (2.3)	5.2 (2.25)	5.7 (2.83)	6.3 (2.55)
10/36 SPART LTR 10/36 Spatial Recall Test long-term retrieval Mean (SD)	14.8 (3.5)	16 (5)	15.1 (3.5)	16.5 (4.7)	16.3 (4.4)	15.5 (4.6)
10/36 SPART DR 10/36 Spatial Recall Test delayed recall Mean (SD)	4.8 (1.8)	4.7 (2.2)	5.2 (2.4)	5.2 (2.3)	5.4 (2.3)	5.4 (2.3)

Outcome	RehaCom cognitive training - focus on executive function, attention and speed of information processing, Baseline, N = 10	RehaCom cognitive training - focus on executive function, attention and speed of information processing, 3-month, N = 10	RehaCom cognitive training - focus on executive function, attention and speed of information processing, 9-month, N = 9	Control - no cognitive training, Baseline, N = 10	Control - no cognitive training, 3-month, N = 10	Control - no cognitive training, 9-month, N = 9
SDMT Symbol Digit Modalities Test Mean (SD)	30.8 (11.4)	32.7 (10.9)	35 (12)	35 (14.8)	34.8 (18.2)	34.7 (16.3)
SRT-LTS Selective Reminding Test long-term storage Mean (SD)	28.4 (10.1)	32.2 (13.7)	35.8 (11.6)	26 (10.7)	25.2 (11.3)	30.2 (11.7)
Montgomery–Asberg Depression Scale Scale usually 0-60. Mean (SD)	14.8 (10.7)	5.9 (5.7)	7.3 (6.2)	12.5 (8.9)	14.7 (8.9)	17.1 (12.9)
Multiple Sclerosis Quality of Life Unclear scale. Mean (SD)	177.44 (45.51)	188.44 (47.92)	198.5 (40.36)	174.33 (33.1)	157.56 (22.1)	171.13 (33.4)

1 PASAT - Polarity - Higher values are better

Wisconsin Card Sorting Test - Polarity - Lower values are better
COWA/P - Polarity - Higher values are better
COWA/S - Polarity - Higher values are better
TEA median for auditory stimulus - Polarity - Higher values are better
TEA median for visual stimulus - Polarity - Higher values are better
TEA total omitted stimuli - Polarity - Lower values are better
TEA total errors - Polarity - Lower values are better
SRT/CTRL - Polarity - Higher values are better
SRT/DR - Polarity - Higher values are better
10/36 SPART LTR - Polarity - Higher values are better
10/36 SPART DR - Polarity - Higher values are better
SDMT - Polarity - Higher values are better
SRT-LTS - Polarity - Higher values are better
Montgomery–Asberg Depression Scale - Polarity - Lower values are better
Multiple Sclerosis Quality of Life - Polarity - Higher values are better
Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_PASAT 2 seconds_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT 3 seconds_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_WCST total errors_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

1 **Results_WCST perseverative responses_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_WCST perseverative errors_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_COWA/P_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_COWA/S_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_TEA median auditory stimulus_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_TEA visual stimulus_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_TEA total omitted stimuli_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_TEA total errors_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

Results_SRT/CTRL_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SRT/DR_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_10/36 SRT LTR_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_10/36 SRT DR_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_SDMT_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_PASAT 2 seconds_9 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT 3 seconds_9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_WCST total errors_9 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

1 **Results_perseverative responses_9 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_WCST perseverative errors_9 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_COWA/P_9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_COWA/S_9 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

Results_TEA median auditory stimulus_9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_TEA median visual stimulus_9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SRT/CTRL_9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SRT/DR_9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_10/36 SPART LTR_9 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_10/36 SPART DR_9 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_SRT/LTS_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

1 **Results_SRT/LTS_9 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_Montgomery-Asberg Depression Scale_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Montgomery-Asberg Depression Scale_9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_MS Quality of Life_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_MS Quality of Life_9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Flachenecker, 2017

Bibliographic Reference	Flachenecker, P.; Meissner, H.; Frey, R.; Guldin, W.; Neuropsychological Training of Attention Improves MS-Related Fatigue: Results of a Randomized, Placebo-Controlled, Double-Blind Pilot Study; European Neurology; 2017; vol. 78 (no. 56); 312-317

1 **Study details**

Trial name / registration number	Not reported
Study location	Germany
Study setting	Inpatient - admitted to inpatient rehabilitation at Neurological Rehabilitation Centre Quellenhof
Study dates	Admitted between November 2009 and April 2010
Sources of funding	Not reported
Inclusion criteria	Diagnosis of MS according to 2005 McDonald criteria; age at least 18 years; experiencing fatigue (as complained by patients); and abnormal results in neuropsychological testing of intensity of attention (T-values of mean reaction times <40).
Exclusion criteria	Relapse and/or received corticosteroids within 30 days of inclusion; experienced overt depression and/or cognitive deficits; and exhibited factors that might influence neuropsychological testing (sedating medication, visual disturbances, hand paresis or intercurrent infections).
Recruitment / selection of participants	Those admitted to inpatient rehabilitation at Neurological Rehabilitation Centre Quellenhof between November 2009 and April 2010
Intervention(s)	Neuropsychological training involving reaction time tasks: 2-week computerised neuropsychological training twice daily for 30 min on five days per week. Supervised by neuropsychologist. Also received usual, goal-oriented, specifically tailored rehabilitation programme. Performed simple reaction time tasks using software packages 'Reaktion' and 'Jeton' by Petra Rigling REHA Software. Each consists of 4 different programmes that allows neuropsychologist to vary demands in two dimensions (time constraints and difficulty) to gradually adapt training tasks according to performance of patient.
Population subgroups	None
Comparator	Control - unspecific neuropsychological training without time components: 2-week computerised neuropsychological training twice daily for 30 min on five days per week. Supervised by neuropsychologist. Also received usual, goal-oriented, specifically tailored rehabilitation programme. Software packages 'Bilder', 'Garten', 'Mosaik', 'Partino' and 'Vario' by Petra

	Rigling REHA Software were used. Designed to improve distinct cognitive functions such as selective attention, cognitive flexibility and working memory. Main principle was that there are less time components and patients could work on it without time pressure (unlike intervention group). Training adjusted by neuropsychologist to possibilities and improvements of the patient.
Number of participants	32 randomised, 30 analysed (n=2 excluded in intervention group due to receiving sedating medication during intervention period)
Duration of follow-up	2-weeks - end of treatment period
Indirectness	Outcome - less than minimum of 3 months specified in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (50%) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (mean in two groups <6.0) • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - using (majority reported to be using immunotherapy in both groups) • Mood disorders (presence or absence) - unclear (depression excluded) • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - modified intention to treat (some that met exclusion criteria during study excluded)

Study arms

Neuropsychological training involving reaction time tasks (N = 16)

Control - unspecific neuropsychological training without time components (N = 16)

Characteristics

Arm-level characteristics

Characteristic	Neuropsychological training involving reaction time tasks (N = 16)	Control - unspecific neuropsychological training without time components (N = 16)
% Female Sample size	n = 8 ; % = 58	n = 14 ; % = 88
Mean age (SD) Mean (SD)	43.3 (7.3)	45.2 (7.1)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Disease duration (years) Mean (SD)	6.5 (4)	9.4 (7)
EDSS score Mean (SD)	3.8 (1.3)	4.7 (1.3)

Characteristic	Neuropsychological training involving reaction time tasks (N = 16)	Control - unspecific neuropsychological training without time components (N = 16)
Relapsing-remitting subtype Sample size	n = 6 ; % = 43	n = 9 ; % = 56
Immunotherapy Sample size	n = 11 ; % = 79	n = 10 ; % = 63
Alertness (m/s) Mean (SD)	389 (88)	388 (126)
WEIMus score Wurzburg Fatigue Inventory for MS Mean (SD)	43.4 (10.6)	47.6 (11.7)

Baseline values and results given for those analysed (n=14 vs. n=16) rather than those randomised (n=16 vs. n=16)

Outcomes

Study timepoints

- Baseline
- 2 week (2 weeks - end of treatment)

Results - raw data

Outcome	Neuropsychological training involving reaction time tasks, Baseline, N = 14	Neuropsychological training involving reaction time tasks, 2-week, N = 14	Control - unspecific neuropsychological training without time components, Baseline, N = 16	Control - unspecific neuropsychological training without time components, 2-week, N = 16
Alertness - T-value indicating normal results (≥40) No of events	n = 0 ; % = 0	n = 9 ; % = 64	n = 0 ; % = 0	n = 6 ; % = 38
WEIMuS score indicating fatigue (above cut-off value of 32) No of events	n = 12 ; % = 86	n = 6 ; % = 43	n = 15 ; % = 94	n = 11 ; % = 69
Adherence - completed scheduled training sessions of 10 h total No of events	n = NA ; % = NA	n = 10 ; % = 71	n = NA ; % = NA	n = 8 ; % = 50

Despite n=16 being randomised to each group, data only provided for n=14 vs. n=16 at baseline and end of treatment

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_alertness t-value indicating normal results_2 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Time-point <3 months minimum in protocol)*

Results_fatigue score above cut-off value indicating fatigue_2 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Time-point <3 months minimum in protocol. Also, general fatigue rather than specifically cognitive fatigue.)*

Results_adherence to training_2 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Gich, 2015

Bibliographic Reference	Gich, J.; Freixanet, J.; Garcia, R.; Vilanova, J. C.; Genis, D.; Silva, Y.; Montalban, X.; Ramio-Torrenta, L.; A randomized, controlled, single-blind, 6-month pilot study to evaluate the efficacy of MS-Line!: a cognitive rehabilitation programme for patients with multiple sclerosis; Multiple Sclerosis; 2015; vol. 21 (no. 10); 1332-43

Study details

Trial name / registration number	Not reported

Study location	Spain
Study setting	Outpatient - selected from hospital database
Study dates	Not reported
Sources of funding	Financial support was provided by Biogen Idec, Merck Serono, Bayer Healthcare, Teva Pharmaceutical Industries, 'La Caixa' (Spain), Fundación Obra Socia Caja Madrid (Spain) and Acadèmia de Ciències Mèdiques i de la Salut de Catalunya i de Balears (Spain).
Inclusion criteria	Aged 20–60 years; had clinically defined MS according to the Poser criteria; have had at least a primary education (8 years); and mild cognitive impairment as determined by the neuropsychological assessment (for each of the tests, scores were considered to be impaired if they were 1.5 SD or more below the mean of normative data; cognitive impairment was defined as: mild, between one and three impaired cognitive tests; moderate, four to seven impaired tests; and severe, eight or more impaired tests)
Exclusion criteria	Severe psychiatric disorders; a history of traumatic brain injury; having taken steroids or immunosuppressor medications during the previous month; and having received other cognitive rehabilitation treatment during the previous 6 months.
Recruitment / selection of participants	Randomly chosen from the database of the hospital's MS unit using a random numbers table. Sent information sheet describing study and request to attend a briefing. Following briefing application forms completed and informed consent signed.
Intervention(s)	MS Line! cognitive rehabilitation programme: two 75-minute sessions per week of cognitive rehabilitation with MS-Line! for a 6-month period. Performed at the Dr Josep Trueta University Hospital. Each session combined 25 minutes of written, manipulative and computer-based materials. Patients and family members also had to do a short daily cognitive exercise together at home lasting no more than 5 minutes (chosen from Soma 4, five-piece Tangram, Space Shuttle and Peg-Solitaire Hoppers). Written (e.g., mathematical problems, crosswords and word search puzzles), manipulative (e.g., spatial games with blocks, origami) and computer-based (e.g., logic and reasoning games, working memory games) materials included in MS-Line! were designed and developed by a multidisciplinary team consisting of software engineers, mathematicians, psychologists and linguists. All materials had different levels of difficulty, and clues to resolve the problems were provided.
Population subgroups	None

Comparator	Control - no intervention: Patients in the control group received no treatment.
Number of participants	43 randomised, 41 analysed (n=1 per group discontinued study for unknown reasons)
Duration of follow-up	6 months - end of intervention period
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (>80% in both groups) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (score ~3.0 in both groups) • Severity of cognitive impairment (mild/moderate/severe) - moderate (majority had moderate impairment at baseline) • Disease modifying treatment status (currently using and not currently using) - using (majority, 65%, using these at baseline) • Mood disorders (presence or absence) - unclear (severe psychiatric disorders excluded) • Computerised vs clinician led - clinician led • Group vs individual - individual Analysis - modified intention to treat with some that dropped out excluded

Study arms

MS Line! cognitive rehabilitation programme (N = 22)

Control - no intervention (N = 21)

Characteristics

Arm-level characteristics

Characteristic	MS Line! cognitive rehabilitation programme (N = 22)	Control - no intervention (N = 21)
% Female Sample size	n = 16 ; % = 72.7	n = 13 ; % = 61.9
Mean age (SD) Mean (SD)	45.5 (9.6)	44 (8.3)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Relapsing-remitting MS Sample size	n = 21 ; % = 95.5	n = 17 ; % = 80.9
Secondary progressive MS Sample size	n = 1 ; % = 4.5	n = 4 ; % = 19.1
Time since first symptoms (years) Mean (SD)	13.4 (8.5)	13.2 (7.3)
Time since diagnosis (years)	9.8 (6.2)	10.7 (6.8)

Characteristic	MS Line! cognitive rehabilitation programme (N = 22)	Control - no intervention (N = 21)
Mean (SD)		
Mild Sample size	n = 6 ; % = 27.3	n = 5 ; % = 23.8
Moderate Sample size	n = 11 ; % = 50	n = 11 ; % = 52.4
Severe Sample size	n = 5 ; % = 22.7	n = 5 ; % = 23.8
EDSS score Mean (SD)	2.6 (1.7)	2.8 (1.8)
Pharmacological treatment at baseline Sample size	n = 14 ; % = 63.6	n = 14 ; % = 66.7
IFN beta-1b sc Sample size	n = 4 ; % = 28.6	n = 4 ; % = 28.6
Natalizumab Sample size	n = 2 ; % = 14.3	n = 2 ; % = 14.3
Glatiramer acetate Sample size	n = 2 ; % = 14.3	n = 4 ; % = 28.6

Characteristic	MS Line! cognitive rehabilitation programme (N = 22)	Control - no intervention (N = 21)
IFN-beta-1a IM Sample size	n = 2 ; % = 14.3	n = 1 ; % = 7.1
IFN-beta-1a sc Sample size	n = 3 ; % = 21.4	n = 3 ; % = 21.4
Investigational drug Sample size	n = 1 ; % = 7.1	n = 0 ; % = 0

Outcomes

Study timepoints

- Baseline
- 6 month (6 months - end of intervention period)

Results - ANCOVA results for intervention vs. control for change from baseline scores

Outcome	MS Line! cognitive rehabilitation programme vs Control - no intervention, 6-month vs Baseline, N2 = 20, N1 = 21
SRT-T Selective reminding test – total: sum of trials I–VI Mean (95% CI)	1.63 (-2.76 to 6.01)

Outcome	MS Line! cognitive rehabilitation programme vs Control - no intervention, 6-month vs Baseline, N2 = 20, N1 = 21
SRT-LTS Selective reminding test – long-term storage Mean (95% CI)	-0.69 (-8.76 to 7.37)
SRT-CLTR Selective reminding test – consistent long-term retrieval Mean (95% CI)	1.74 (-3.11 to 11.52)
SRT/DR Selective reminding test – delayed recall Mean (95% CI)	0.66 (-0.57 to 1.88)
10/36 SPART-T 10/36 Spatial Recall Test - total Mean (95% CI)	5.62 (2.88 to 8.36)
10/36 SPART-DR Spatial recall test – delayed recall Mean (95% CI)	2.21 (0.86 to 3.56)
SDMT Symbol digit modalities test Mean (95% CI)	3.28 (-2.48 to 9.04)

Outcome	MS Line! cognitive rehabilitation programme vs Control - no intervention, 6-month vs Baseline, N2 = 20, N1 = 21
PASAT Paced auditory serial addition test Mean (95% CI)	3.01 (-1.91 to 7.92)
Word List Generation Test Mean (95% CI)	3.6 (0.83 to 6.37)
FAS test - verbal fluency Mean (95% CI)	1.55 (-3.48 to 6.58)
Forward digit span Subtest on Wechsler adult intelligence scale III. Measures working memory Mean (95% CI)	0.43 (-0.34 to 1.2)
Backward digit span Subtest on Wechsler adult intelligence scale III. Measures working memory Mean (95% CI)	0.92 (-0.2 to 2.04)
Block design Subtest on Wechsler adult intelligence scale III. Measures perceptual organisation Mean (95% CI)	4.35 (-1.01 to 9.72)

Outcome	MS Line! cognitive rehabilitation programme vs Control - no intervention, 6-month vs Baseline, N2 = 20, N1 = 21
Letter-number sequencing Subtest on Wechsler adult intelligence scale III. Measures working memory Mean (95% CI)	1.48 (0.06 to 2.89)
Boston Naming Test Mean (95% CI)	2.58 (1.16 to 4)
Trail Making Test - A Mean (95% CI)	-13.98 (-24.42 to -3.55)
Trail Making Test - B Mean (95% CI)	-13.97 (-34.4 to 6.47)
HADS - anxiety Scale usually 0-21. Mean (95% CI)	-1.92 (-3.92 to 0.09)
HADS - depression Scale usually 0-21. Mean (95% CI)	-1.51 (-3.18 to 0.17)

1 SRT-T - Polarity - Higher values are better

SRT-LTS - Polarity - Higher values are better

SRT-CLTR - Polarity - Higher values are better

SRT/DR - Polarity - Higher values are better

10/36 SPART-T - Polarity - Higher values are better

10/36 SPART-DR - Polarity - Higher values are better

SDMT - Polarity - Higher values are better

PASAT - Polarity - Higher values are better

Word List Generation Test - Polarity - Higher values are better

FAS test - verbal fluency - Polarity - Higher values are better

Forward digit span - Polarity - Higher values are better

Backward digit span - Polarity - Higher values are better

Block design - Polarity - Higher values are better

Letter-number sequencing - Polarity - Higher values are better

Boston Naming Test - Polarity - Higher values are better

Trail Making Test - A - Polarity - Lower values are better

Trail Making Test - B - Polarity - Lower values are better

HADS - anxiety - Polarity - Lower values are better

HADS - depression - Polarity - Lower values are better

Baseline values not reported for outcome measures.

Results - raw data

Outcome	MS Line! cognitive rehabilitation programme, Baseline, N = 22	MS Line! cognitive rehabilitation programme, 6-month, N = 22	Control - no intervention, Baseline, N = 21	Control - no intervention, 6-month, N = 21
Adherence Defined as attending at least 80% of hospital sessions and completed at least 80% of daily exercises. Similar measure could not be reported for control group No of events	n = NA ; % = NA	n = 8 ; % = 36.4	n = NA ; % = NA	n = NA ; % = NA

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_SRT-T_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SRT-LTS_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SRT-CLTR_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_SRT-DR_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_10/36 SPART-T_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_10/36 SPART-DR_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Word List Generation Test_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_FAS test verbal fluency_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_forward digit span_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_backward digit span_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_block deisgn_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_letter-number sequencing_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Boston Naming Test_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Trail Making Test-A_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_Trail Making Test-B_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_HADS - anxiety_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_HADS - depression_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_adherence_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Goverover, 2018

Bibliographic Reference	Goverover, Y.; Chiaravalloti, N.; Genova, H.; DeLuca, J.; A randomized controlled trial to treat impaired learning and memory in multiple sclerosis: The self-GEN trial; Multiple Sclerosis; 2018; vol. 24 (no. 8); 1096-1104

Study details

Trial name / registration number	self-GEN trial. NCT02032589.
Study location	USA
Study setting	Unclear - possibly outpatient
Study dates	Recruitment ran from 19 December 2013 to 15 July 2015
Sources of funding	Supported by the National Multiple Sclerosis Society (Grant No. PP2098).
Inclusion criteria	Clinically definite MS; documented memory impairment based on selective memory test (SRT; those scoring at least 0.5 SD less than the mean of healthy control group); between ages of 31 and 65 years; free from history of neurological injuries or illnesses other than MS; no reported history of alcohol or drug abuse and/or major psychiatric illnesses; sufficient vision assessed by paragraph reading; English as primary language; at least 1 month post the most recent exacerbation; and free of corticosteroid use.

Exclusion criteria	No further criteria reported.
Recruitment / selection of participants	Participants were recruited through advertisements, support groups, and a database at Kessler Foundation. Recruitment ran from 19 December 2013 to 15 July 2015.
Intervention(s)	Self-generation learning programme focused on memory: six 60 min sessions of individualised treatment (two per week over 3 weeks), each including four parts: 1. items that were to be learned were presented in provided and self-generated conditions (order was counterbalanced within session). In the self-generated condition, the items were presented with a sentence, word pair, or picture. However, the word or the item to be learned was missing, as indicated by a blank line; participants were asked to fill in the blank with the most logical choice. For the provided condition, items to be learned were provided with a sentence/step/word-pair underlined, and participants were asked to remember the underlined item. Task presentations were followed by immediate free recall, in which participants were asked to verbally recall the items they learned. 2. participants asked which of the previous two they remembered better and what helped them to remember that list better. After answering, recall results were presented to participants and researcher explained by self-generation has potential to enhance memory and recall. 3. parts 1 and 2 repeated with similar but different stimuli. 4. participants presented with new items/words to remember and asked how self-generation strategy can be used. Then asked to apply self-generation strategy to recall the items. Asked to recall the items/words learned immediately after learning. After part 4, participants asked to complete short journal summarising the activity session, what was learned and what was helpful. Each of six sessions followed same format but presented different stimuli to be learned as follows: 1. words within sentences; 2. paired associated words; 3. names; 4. dates, appointments and object locations; 5. cooking and finances; and 6. choice of a personal task to learn (included creating an email account, storing information on i-cloud or learning a new language).
Population subgroups	None
Comparator	Control - memory tasks without self-generation element: placebo control met with the researcher at the same frequency and for the same duration as the treatment group and performed the same memory tasks. However, they were not exposed to the active ingredients of the treatment: self-generated learning and transfer instructions. They were asked to simply remember items. Included three components within each of the sessions. Participants were presented with (1) items to be learned in a provided condition only and were asked to recall them. (2) Similar but different stimuli to learn in a provided condition. (3) New items to be remembered: participants were asked to learn and recall them later (same as the self-GEN

	groups). For the sixth session, participants were given a finance management task to perform and did not choose a personal task to learn.
Number of participants	35 randomised, 35 appear to have been analysed
Duration of follow-up	3-4 weeks - end of intervention period (measured within a week of completion)
Indirectness	Outcome - time-point <3 months minimum in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (>60% in both groups) • According to disability (EDSS <6 and EDSS ≥6) - unclear (only PDDS reported - 2.9 or 3.8 in the two groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (major psychiatric conditions excluded) • Computerised vs clinician led - clinician led • Group vs individual - individual Analysis - intention to treat likely as no dropouts mentioned

Study arms

Self-generation learning programme focused on memory (N = 19)

Control - memory tasks without self-generation element (N = 16)

Characteristics

Arm-level characteristics

Characteristic	Self-generation learning programme focused on memory (N = 19)	Control - memory tasks without self-generation element (N = 16)
% Female Sample size	n = 13 ; % = 70	n = 13 ; % = 80
Mean age (SD) Mean (SD)	50.15 (9.12)	48.5 (8.8)
Caucasian Sample size	n = 11 ; % = 60	n = 8 ; % = 50
African American Sample size	n = 8 ; % = 40	n = 5 ; % = 31.3
Hispanic Sample size	n = 0 ; % = 0	n = 3 ; % = 18.8
Comorbidities Custom value	NR	NR
Time since diagnosis (years) Mean (SD)	11.1 (6.5)	11.4 (7.1)

Characteristic	Self-generation learning programme focused on memory (N = 19)	Control - memory tasks without self-generation element (N = 16)
Relapsing-remitting Sample size	n = 12 ; % = 63.2	n = 12 ; % = 75
Secondary progressive Sample size	n = 2 ; % = 10.5	n = 2 ; % = 12.5
Primary progressive Sample size	n = 5 ; % = 26.3	n = 2 ; % = 12.5
PDDS Patient Determined Disease Steps Mean (SD)	3.8 (1.8)	2.9 (1.4)
SRT % of words recalled over six learning trials Selective memory/reminding test Mean (SD)	65.5 (14.6)	62.9 (15.8)

Outcomes

Study timepoints

- Baseline
- 3 week (3-4 weeks - end of intervention)

Results - raw data

Outcome	Self-generation learning programme focused on memory, Baseline, N = 19	Self-generation learning programme focused on memory, 3-week, N = 19	Control - memory tasks without self-generation element, Baseline, N = 16	Control - memory tasks without self-generation element, 3-week, N = 16
CVLT-II raw (five trials sum) California Verbal Learning Test 2nd Edition Mean (SD)	50.5 (11.8)	53.5 (10.5)	45.5 (9.9)	52.1 (10.6)
CVLT-II raw (long delay) California Verbal Learning Test 2nd Edition Mean (SD)	10.1 (3.9)	11.6 (3.4)	8.8 (3.7)	10.5 (4)
CMT raw (immediate) Contextual Memory Test Mean (SD)	13.5 (2.8)	15.6 (2.6)	12.3 (2.7)	11.6 (2.7)
CMT raw (delayed) Contextual Memory Test Mean (SD)	12.1 (3)	14 (3.3)	11 (3.1)	10.38 (3.3)
MIST prospective memory Memory for Intentions Test Mean (SD)	29.9 (27.6)	63.4 (20.6)	39.3 (33.4)	48.8 (30)

Outcome	Self-generation learning programme focused on memory, Baseline, N = 19	Self-generation learning programme focused on memory, 3-week, N = 19	Control - memory tasks without self-generation element, Baseline, N = 16	Control - memory tasks without self-generation element, 3-week, N = 16
MFQ Memory Functioning Questionnaire. Scale possibly 64-448 Mean (SD)	245.1 (51.5)	250.2 (47)	217.1 (48.6)	209.4 (56.3)
Self-awareness - Awareness Questionnaire (AQ) Scale usually 17-85. Lower indicates more awareness of cognitive deficits. Mean (SD)	6.9 (7.1)	8.6 (8.1)	5.7 (3.6)	4.8 (4.8)
Self-Regulation Skills interview Scale 0-10. Assesses self-awareness and strategy use. Mean (SD)	32.7 (8.9)	29.2 (7.3)	30.5 (7.8)	31.7 (6.1)
Verbal fluency (total across three letters) - executive function Mean (SD)	39.25 (12.4)	40.25 (14.1)	36.9 (15.9)	35.7 (14.5)

Outcome	Self-generation learning programme focused on memory, Baseline, N = 19	Self-generation learning programme focused on memory, 3-week, N = 19	Control - memory tasks without self-generation element, Baseline, N = 16	Control - memory tasks without self-generation element, 3-week, N = 16
Actual Reality™ Task - total errors Assesses functional performance Mean (SD)	5.8 (2.4)	4.4 (2.7)	6.9 (2.6)	6.8 (4.9)
Actual Reality™ Task - cognitive score Mean (SD)	4 (1.8)	3.2 (2.3)	5 (1.7)	4.1 (3)
Functional behavioural profile (FBP) Self-reported. Scale possibly 0-108. Mean (SD)	95.4 (15.2)	101.5 (10.5)	91.8 (18.4)	88.9 (16.3)
FAMS Functional Assessment of Multiple Sclerosis. Quality of life. Scale usually 0-176 Mean (SD)	100.3 (32.3)	102.5 (27.5)	101.7 (30.9)	98.3 (31.5)

Outcome	Self-generation learning programme focused on memory, Baseline, N = 19	Self-generation learning programme focused on memory, 3-week, N = 19	Control - memory tasks without self-generation element, Baseline, N = 16	Control - memory tasks without self-generation element, 3-week, N = 16
STAI (trait) - anxiety State-Trait Anxiety Inventory. Scale usually 20-80 Mean (SD)	39.8 (14.1)	39.4 (12.6)	40.7 (11.1)	41.4 (10.5)
Depression (CDMI) Chicago Multiscale Depression Inventory. Scale possibly 42-210. Mean (SD)	61.73 (19.7)	53.1 (15.8)	61.9 (17.3)	63.2 (15.4)
Satisfaction with life scale Scale usually 5-35. Mean (SD)	19.1 (7.1)	19.19 (18.3)	18.7 (7.4)	18.3 (8.3)

1 CVLT-II raw (five trials sum) - Polarity - Higher values are better
2 CVLT-II raw (long delay) - Polarity - Higher values are better
3 CMT raw (immediate) - Polarity - Higher values are better
4 CMT raw (delayed) - Polarity - Higher values are better
5 MIST prospective memory - Polarity - Higher values are better
6 MFQ - Polarity - Higher values are better
7 Self-awareness - Awareness Questionnaire (AQ) - Polarity - Lower values are better
8 Self-Regulation Skills interview - Polarity - Lower values are better
9 Verbal fluency (total across three letters) - executive function - Polarity - Higher values are better
10 Actual Reality™ Task - total errors - Polarity - Lower values are better

Actual Reality™ Task - cognitive score - Polarity - Lower values are better
Functional behavioural profile (FBP) - Polarity - Higher values are better
FAMS - Polarity - Higher values are better
STAI (trait) - anxiety - Polarity - Lower values are better
Depression (CDMI) - Polarity - Lower values are better
Satisfaction with life scale - Polarity - Higher values are better
Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_CVLT-II five trials sum_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_CVLT-II long delay_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

1 **Results_CMT immediate_3 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

2

3 **Results_CMT delayed_3 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_MIST prospective memory_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_MFQ_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_self-awareness questionnaire_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_self-regulation skills interview_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_verbal fluency - executive function_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_actual reality total errors_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_actual reality cognitive score_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_FBP_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_FAMS_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_STAI trait anxiety_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_CDMI depression_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_satisfaction with life scale_3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Grasso, 2017

Bibliographic Reference	Grasso, M. G.; Broccoli, M.; Casillo, P.; Catani, S.; Pace, L.; Pompa, A.; Rizzi, F.; Troisi, E.; Evaluation of the Impact of Cognitive Training on Quality of Life in Patients with Multiple Sclerosis; European Neurology; 2017; vol. 78 (no. 12); 111-117

Study details

Trial name / registration number	Not reported
Study location	Italy
Study setting	Inpatient - those admitted to Santa Lucia Foundation for multidisciplinary rehabilitation
Study dates	Screened between January 2015 and May 2016
Sources of funding	Not reported
Inclusion criteria	Meeting McDonald diagnosis criteria for MS
Exclusion criteria	Age <18 years or >65 years; education <8 years; ongoing major psychiatric disorders; exacerbations in 3 months prior to enrolment; immunomodulant or immunosuppressant treatment started 3 months before enrolment; cognitive rehabilitation in 6 months before enrolment; MMSE score >24 (those with up to mild impairment only included); and psychotropic drugs and

	drugs for spasticity, tremor, bladder disturbances and fatigue could not be prescribed (if already being taken, doses and schedules needed to remain constant over study period).
Recruitment / selection of participants	Recruited from those admitted to Santa Lucia Foundation for rehabilitation. Consecutive patients screened between January 2015 and May 2016.
Intervention(s)	Cognitive training + multidisciplinary rehabilitation: 3 times weekly for 3 months by qualified cognitive rehabilitation specialist. Individualised, goal-oriented multidisciplinary inpatient programme performed, which for this group included cognitive training. Each patient assessed to determine needs for rehabilitation programme. Standard rehabilitation programme involved 3 h daily for 5 days per week, including 2 daily physiotherapy sessions (aimed at improving movements on paretic side and at upper-limb exercises as well as improving balance, standing, sitting and transferring. Cognitive training involved intensive computer-assisted cognitive rehabilitation for attention, information processing and executive functions. Based on Attention Processing Training program (APT) - consists of group of hierarchically organised tasks that exercise different components of attention that are commonly impaired after brain injury including sustained, selective, alternating and divided attention. Tasks place increasing demands on complex attentional control and working memory systems.
Population subgroups	None
Comparator	Control - multidisciplinary rehabilitation without cognitive training: Individualised, goal-oriented multidisciplinary inpatient programme performed, which for this group included cognitive training. Each patient assessed to determine needs for rehabilitation programme. Standard rehabilitation programme involved 3 h daily for 5 days per week, including 2 daily physiotherapy sessions (aimed at improving movements on paretic side and at upper-limb exercises as well as improving balance, standing, sitting and transferring. Control group received standard occupational therapy sessions instead of computer-assisted cognitive rehabilitation 3 times weekly for 3 months so that intervention group did not receive additional rehabilitation time than the control group - underwent nonspecific computer training consisting of series of nonspecific exercises including text and newspaper article reading and comprehension, description of pictures etc.
Number of participants	34 randomised, assume 34 analysed as no dropout mentioned
Duration of follow-up	Up to 6 months (3 months following the end of intervention)

Indirectness	Population - cognitive impairment doesn't appear to have been a requirement for every participant included
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (47.1%) followed by secondary progressive (44%) • According to disability (EDSS <6 and EDSS ≥6) - >6.0 (mean score 7.5) • Severity of cognitive impairment (mild/moderate/severe) - unclear (at most mild impairment but many may not have impairment at baseline) • Disease modifying treatment status (currently using and not currently using) - unclear (new use excluded) • Mood disorders (presence or absence) - unclear • Computerised vs clinician led - mix clinician led/computerised • Group vs individual - individual Analysis - unclear (number analysed unclear but no dropouts mentioned)

Study arms

Cognitive training + multidisciplinary rehabilitation (N = 17)

Control - multidisciplinary rehabilitation without cognitive training (N = 17)

Characteristics

Arm-level characteristics

Characteristic	Cognitive training + multidisciplinary rehabilitation (N = 17)	Control - multidisciplinary rehabilitation without cognitive training (N = 17)
% Female	n = 11 ; % = 64.7	n = 11 ; % = 64.7

Characteristic	Cognitive training + multidisciplinary rehabilitation (N = 17)	Control - multidisciplinary rehabilitation without cognitive training (N = 17)
Sample size		
Mean age (SD) Mean (SD)	59.55 (7.2)	58.67 (10.3)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Relapsing-remitting Sample size	n = 8 ; % = 47.1	n = 8 ; % = 47.1
Secondary progressive Sample size	n = 7 ; % = 41.1	n = 8 ; % = 47.1
Primary progressive Sample size	n = 2 ; % = 11.8	n = 1 ; % = 5.8
Disease duration (years) Mean (SD)	21.64 (9.4)	21.9 (6.9)
MMSE score at baseline	21.55 (1.8)	21.67 (2.5)

Characteristic	Cognitive training + multidisciplinary rehabilitation (N = 17)	Control - multidisciplinary rehabilitation without cognitive training (N = 17)
Mean (SD)		
EDSS score at baseline Mean (SD)	7.54 (0.8)	7.5 (0.8)
Barthel index at baseline Mean (SD)	39 (20.8)	41.33 (16.6)
Rivermead Mobility Index at baseline Mean (SD)	2.36 (1.3)	2.78 (2.5)
Montgomery and Asberg Depression Rating Scale at baseline Mean (SD)	20 (9.1)	21.33 (10.1)
Length of stay Mean (SD)	107.36 (25.1)	83.67 (29.2)

Outcomes

Study timepoints

- Baseline
- 3 month (3 months - End of intervention - discharge (extracted for depression and Barthel Index outcomes as no 6-month data provided for this outcome))
- 6 month (6 months - 3 months after end of intervention period)

Results - raw data

Outcome	Cognitive training + multidisciplinary rehabilitation, Baseline, N = 17	Cognitive training + multidisciplinary rehabilitation, 3-month, N = 17	Cognitive training + multidisciplinary rehabilitation, 6-month, N = 17	Control - multidisciplinary rehabilitation without cognitive training, Baseline, N = 17	Control - multidisciplinary rehabilitation without cognitive training, 3-month, N = 17	Control - multidisciplinary rehabilitation without cognitive training, 6-month, N = 17
SRT-LTS Selective Reminding Test Long-Term Storage Mean (SD)	29 (8.1)	NA (NA)	34.1 (6.7)	30.5 (7.3)	NA (NA)	33.7 (7.4)
SRT-D Selective Reminding Test - Delayed Mean (SD)	3 (5.4)	NA (NA)	4.1 (4.1)	3.3 (4.3)	NA (NA)	3.1 (1.7)
SPART Spatial Recall Test Mean (SD)	12.9 (7.1)	NA (NA)	13.7 (6.7)	14.1 (4.3)	NA (NA)	14.7 (7.1)

Outcome	Cognitive training + multidisciplinary rehabilitation, Baseline, N = 17	Cognitive training + multidisciplinary rehabilitation, 3-month, N = 17	Cognitive training + multidisciplinary rehabilitation, 6-month, N = 17	Control - multidisciplinary rehabilitation without cognitive training, Baseline, N = 17	Control - multidisciplinary rehabilitation without cognitive training, 3-month, N = 17	Control - multidisciplinary rehabilitation without cognitive training, 6-month, N = 17
SPART-D Spatial Recall Test - delayed Mean (SD)	6.2 (3.1)	NA (NA)	6.1 (5.1)	5.9 (4.1)	NA (NA)	6 (4.8)
SDMT Symbol Digit Modalities Test Mean (SD)	18.2 (7.1)	NA (NA)	18.3 (6.7)	17.9 (4.8)	NA (NA)	19.1 (7.3)
PASAT 3 seconds Paced Auditory Serial Addition Test Mean (SD)	17.4 (6.1)	NA (NA)	18.5 (9.7)	16.9 (6.4)	NA (NA)	17.9 (8.1)
PASAT 2 seconds Paced Auditory	15.9 (6.3)	NA (NA)	16.9 (5.6)	16.2 (5.7)	NA (NA)	17.7 (7.3)

Outcome	Cognitive training + multidisciplinary rehabilitation, Baseline, N = 17	Cognitive training + multidisciplinary rehabilitation, 3-month, N = 17	Cognitive training + multidisciplinary rehabilitation, 6-month, N = 17	Control - multidisciplinary rehabilitation without cognitive training, Baseline, N = 17	Control - multidisciplinary rehabilitation without cognitive training, 3-month, N = 17	Control - multidisciplinary rehabilitation without cognitive training, 6-month, N = 17
Serial Addition Test Mean (SD)						
Word List Generation Mean (SD)	10 (7.1)	NA (NA)	12.5 (8.9)	13.1 (7.7)	NA (NA)	14.1 (9.1)
Stroop Test Mean (SD)	27.1 (8.4)	NA (NA)	21.5 (7.1)	28.3 (7.1)	NA (NA)	30.5 (13.4)
Montgomery and Asberg Depression Rating Scale Scale possibly 0-60. Mean (SD)	20 (9.1)	16.73 (6.8)	NR (NR)	21.33 (10.1)	20.44 (10)	NR (NR)
Barthel Index - measure of activities of	39 (20.8)	39 (20.8)	NR (NR)	41.33 (16.6)	44.22 (19.6)	*empty data*

Outcome	Cognitive training + multidisciplinary rehabilitation, Baseline, N = 17	Cognitive training + multidisciplinary rehabilitation, 3-month, N = 17	Cognitive training + multidisciplinary rehabilitation, 6-month, N = 17	Control - multidisciplinary rehabilitation without cognitive training, Baseline, N = 17	Control - multidisciplinary rehabilitation without cognitive training, 3-month, N = 17	Control - multidisciplinary rehabilitation without cognitive training, 6-month, N = 17
daily living (ADL) Scale 0-100. Mean (SD)						

SRT-LTS - Polarity - Higher values are better
SRT-D - Polarity - Higher values are better
SPART - Polarity - Higher values are better
SPART-D - Polarity - Higher values are better
SDMT - Polarity - Higher values are better
PASAT 3 seconds - Polarity - Higher values are better
PASAT 2 seconds - Polarity - Higher values are better
Word List Generation - Polarity - Higher values are better
Stroop Test - Polarity - Higher values are better
Montgomery and Asberg Depression Rating Scale - Polarity - Lower values are better
Barthel Index - measure of activities of daily living (ADL) - Polarity - Higher values are better
Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_SRT-LTS_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_SRT-D_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_SPART_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_SPART-D_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT 3 seconds_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT 2 seconds_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_Word List Generation_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_Stroop Test_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_Montgomery Asberg Depression Scale_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_Barthel Index activities of daily living_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

3

Hancock, 2015

Bibliographic Reference	Hancock, L. M.; Bruce, J. M.; Bruce, A. S.; Lynch, S. G.; Processing speed and working memory training in multiple sclerosis: a double-blind randomized controlled pilot study; Journal of Clinical & Experimental Neuropsychology: Official Journal of the International Neuropsychological Society; 2015; vol. 37 (no. 2); 113-27

Study details

Other publications associated with this study included in review	• Hancock, Laura Mitchell (2014) Processing speed and working memory training in multiple sclerosis: A blinded randomized controlled trial. Dissertation Abstracts International: Section B: The Sciences and Engineering 74(10be): nopaginationspecified - **outcomes and characteristics extracted from this paper as did not appear to exclude those that did not meet 80% adherence criterion, whereas these were excluded in the 2015 paper**
Trial name / registration number	Not reported
Study location	USA
Study setting	Outpatient - recruited from MS specialty clinic and metropolitan community
Study dates	Recruitment for the study began in 08/2011, and the last study participant completed all study appointments in 10/2012
Sources of funding	Funded by University of Kansas Endowment: Boelte Family Fund for Multiple Sclerosis.
Inclusion criteria	MS diagnosis; no history of alcohol/drug abuse; no nervous system disorder other than MS; no sensory impairments that might interfere significantly with cognitive testing or training; no developmental history of learning disability or attention-deficit/hyperactivity disorder; no relapse and/or corticosteroid use within four weeks of initial assessment; absence of severe physical/neurological impairment that would make testing or training insurmountable; a working home computer with internet access; between the ages of 18 and 60 years; and presence of subjectively reported cognitive complaints
Exclusion criteria	No further criteria reported

Recruitment / selection of participants	Recruited from both a large MS specialty clinic at the University of Kansas Medical Center and from the Kansas City metropolitan community
Intervention(s)	Processing speed and working memory training: computerised cognitive training in their homes using Posit Science InSight and Brain Twister visual n-back programs. The Brain Twister software includes a visual n-back task to train working memory. Asked to engage in training six days per week, for 30-minute intervals, for a six-week period. They spent three days per week engaged in processing speed training and three days per week engaged in working memory training. Received detailed instructions regarding which modules to complete and how to use the software. Additionally, they received contact information for a research assistant who could assist them with technical or logistical software problems as they engaged in the training process. Processing tasks used were PositScience's Sweet Seeker and Road Tour - presented in game format where points were earned for performance. **For the active training group, game continually challenged participants by increasing speed of stimuli presentation and making discriminations more difficult.** Working memory tasks were PositScience's Master Gardener and the Brain Twister N-Back Task - played single modality visual n-back game. **Active training group tasks increased in difficulty.**
Population subgroups	None
Comparator	Sham training group: computerised cognitive training in their homes using Posit Science InSight and Brain Twister visual n-back programs. The Brain Twister software includes a visual n-back task to train working memory. Asked to engage in training six days per week, for 30-minute intervals, for a six-week period. They spent three days per week engaged in processing speed training and three days per week engaged in working memory training. Received detailed instructions regarding which modules to complete and how to use the software. Additionally, they received contact information for a research assistant who could assist them with technical or logistical software problems as they engaged in the training process. Processing tasks used were PositScience's Sweet Seeker and Road Tour - presented in game format where points were earned for performance. **For sham control, games stayed at a simple introductory level of difficulty.** Working memory tasks were PositScience's Master Gardener and the Brain Twister N-Back Task - played single modality visual n-back game. **Sham control group tasks did not increase in difficulty and played a 0-back version of the game (n-back task in sham group created specifically for this study).**
Number of participants	71 randomised, 40 analysed at end of treatment (n=21 withdrew - 30% work demands, 25% not being able to do the training consistently, 25% family demands and 20% loss to follow-up)

Duration of follow-up	6 weeks - end of treatment
Indirectness	Outcome - follow-up <3 months minimum specified in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting in both groups (>60%) • According to disability (EDSS <6 and EDSS ≥6) - unclear • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - modified intention to treat (2014 paper), with those lost to follow-up or withdrawing excluded (2015 paper additionally excludes those not meeting adherence criterion)

Study arms

Processing speed and working memory training - tasks increasing in difficulty (N = 34)

Sham training - constant difficulty level processing speed and working memory tasks (N = 37)

Characteristics

Arm-level characteristics

Characteristic	Processing speed and working memory training - tasks increasing in difficulty (N = 34)	Sham training - constant difficulty level processing speed and working memory tasks (N = 37)
% Female Sample size	n = 18 ; % = 90	n = 17 ; % = 85
Mean age (SD) Mean (SD)	48.45 (8.1)	49.15 (10.41)
European-American Sample size	n = 17 ; % = 85	n = 19 ; % = 95
Comorbidities Custom value	NR	NR
Relapsing-remitting MS Sample size	n = 13 ; % = 65	n = 15 ; % = 75
Disease duration (Months) Mean (SD)	126.75 (65.25)	167.1 (94.4)

Said to have analysed N=20 per group, assuming characteristics given for this population rather than number randomised

Outcomes

Study timepoints

- Baseline
- 6 week (6-weeks - end of treatment period)

Results - raw data

Outcome	Processing speed and working memory training - tasks increasing in difficulty, Baseline, N = 20	Processing speed and working memory training - tasks increasing in difficulty, 6-week, N = 20	Sham training - constant difficulty level processing speed and working memory tasks, Baseline, N = 20	Sham training - constant difficulty level processing speed and working memory tasks, 6-week, N = 20
PASAT Paced Auditory Serial Addition Test Mean (SD)	76.95 (18.47)	88.05 (21.59)	74.61 (24.64)	76.67 (22.4)
SDMT Symbol Digit Modalities Test Mean (SD)	48.45 (11.12)	50.85 (11.52)	49.15 (16.72)	50.5 (15.14)
Stroop Test Mean (SD)	33 (6.94)	35.6 (7.52)	30.37 (7.86)	32.16 (7.54)
Letter-number sequencing	10.15 (2.35)	11.15 (2.39)	10.7 (3.2)	10.95 (2.91)

Outcome	Processing speed and working memory training - tasks increasing in difficulty, Baseline, N = 20	Processing speed and working memory training - tasks increasing in difficulty, 6-week, N = 20	Sham training - constant difficulty level processing speed and working memory tasks, Baseline, N = 20	Sham training - constant difficulty level processing speed and working memory tasks, 6-week, N = 20
Mean (SD)				
Digits backward Mean (SD)	4.95 (1.88)	5.05 (1.73)	4.8 (1.82)	5.1 (2.25)
Raven's Advanced Progressive Matrices Test of fluid intelligence. Mean (SD)	8.84 (4.13)	9.32 (3.47)	9.31 (4.03)	10.44 (4.35)
BVMT Brief Visuospatial Memory Test Trials 1–3 Mean (SD)	18.1 (4.84)	21.45 (4.87)	18.63 (7.09)	20.05 (6.81)
COWAT Controlled Oral Word Associations Test Mean (SD)	37.1 (9.68)	42.15 (15.23)	39.5 (15.54)	37.95 (14.23)
Conners' Continuous Performance Task Commissions T-score	53.06 (8.84)	48 (9.85)	50.81 (11.7)	49.5 (12.3)

Outcome	Processing speed and working memory training - tasks increasing in difficulty, Baseline, N = 20	Processing speed and working memory training - tasks increasing in difficulty, 6-week, N = 20	Sham training - constant difficulty level processing speed and working memory tasks, Baseline, N = 20	Sham training - constant difficulty level processing speed and working memory tasks, 6-week, N = 20
Sustained attention and response inhibition. Speed measured. Mean (SD)				
AVLT Auditory Verbal Learning Task Trials 1–5. Mean (SD)	48.05 (9.42)	52.65 (9.55)	42.3 (9.63)	45.95 (11.49)
STAI - state State-Trait Personality Inventory. Scale usually 20-80. Mean (SD)	46.15 (5.08)	45.6 (6.29)	43.93 (7.41)	44.33 (5.73)
STAI - trait State-Trait Personality Inventory. Scale usually 20-80. Mean (SD)	44.72 (3.97)	45.5 (5.11)	43.57 (6.45)	44.64 (5.71)

Outcome	Processing speed and working memory training - tasks increasing in difficulty, Baseline, N = 20	Processing speed and working memory training - tasks increasing in difficulty, 6-week, N = 20	Sham training - constant difficulty level processing speed and working memory tasks, Baseline, N = 20	Sham training - constant difficulty level processing speed and working memory tasks, 6-week, N = 20
BDI-FS Beck Depression Inventory Fast Screen. Scale 0-21. Mean (SD)	4.42 (2.8)	4 (2.79)	3.47 (3.68)	2.6 (2.47)
MFIS Modified Fatigue Impact Scale. Scale usually 0-84. Mean (SD)	45.6 (12)	43.95 (17.45)	51.8 (16.81)	43.6 (18.98)
MSQoL-54 MS Quality of Life Questionnaire. Scale usually 0-100. Mean (SD)	66.75 (9.97)	70.5 (12.77)	71.33 (19.45)	75.45 (15.12)
Adherence - % training completed (objective report) Mean (SD)	NA (NA)	94.63 (12.58)	NA (NA)	95.3 (12.01)

Outcome	Processing speed and working memory training - tasks increasing in difficulty, Baseline, N = 20	Processing speed and working memory training - tasks increasing in difficulty, 6-week, N = 20	Sham training - constant difficulty level processing speed and working memory tasks, Baseline, N = 20	Sham training - constant difficulty level processing speed and working memory tasks, 6-week, N = 20
Satisfaction - proportion very satisfied with overall experience in study Measured using 4-point Likert scale No of events	n = NA ; % = NA	n = 12 ; % = 61	n = NA ; % = NA	n = 17 ; % = 83

PASAT - Polarity - Higher values are better
SDMT - Polarity - Higher values are better
Stroop Test - Polarity - Higher values are better
Letter-number sequencing - Polarity - Higher values are better
Digits backward - Polarity - Higher values are better
Raven's Advanced Progressive Matrices - Polarity - Higher values are better
BVMT - Polarity - Higher values are better
COWAT - Polarity - Higher values are better
Conners' Continuous Performance Task Commissions T-score - Polarity - Higher values are better
AVLT - Polarity - Higher values are better
STAI - state - Polarity - Lower values are better
STAI - trait - Polarity - Lower values are better
BDI-FS - Polarity - Lower values are better
MFIS - Polarity - Lower values are better
MSQoL-54 - Polarity - Higher values are better

Adherence - % training completed (objective report) - Polarity - Higher values are better
Final values for continuous outcomes
Despite n=34 and n=37 being randomised to intervention and control, only n=20 per group were analysed

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_PASAT_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_SDMT_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_Stroop test_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_Letter-number sequencing_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_Digits backward_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_Raven's advanced progressive matrices_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_BVMT_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_COWAT_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_Conner's continuous performance task_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_AVLT_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_STAI-state_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_STAI-trait_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_BDI-FS_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_MFIS_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_MSQOL-54_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_adherence % training completed objective report_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_satisfaction_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Hancock, 2014

Bibliographic Reference	Hancock, Laura Mitchell; Processing speed and working memory training in multiple sclerosis: A blinded randomized controlled trial; Dissertation Abstracts International: Section B: The Sciences and Engineering; 2014; vol. 74 (no. 10be); nopaginationspecified-

Study details

Secondary publication of another included study- see primary study for details	• Hancock, L. M., Bruce, J. M., Bruce, A. S. et al. (2015) Processing speed and working memory training in multiple sclerosis: a double-blind randomized controlled pilot study. Journal of Clinical & Experimental Neuropsychology: Official Journal of the International Neuropsychological Society 37(2): 113-27

Hanssen, 2016

Bibliographic Reference	Hanssen, K. T.; Beiske, A. G.; Landro, N. I.; Hofoss, D.; Hessen, E.; Cognitive rehabilitation in multiple sclerosis: a randomized controlled trial; Acta Neurologica Scandinavica; 2016; vol. 133 (no. 1); 30-40

Study details

Trial name / registration number	Not reported
Study location	Norway
Study setting	Inpatient - people undergoing inpatient rehabilitation
Study dates	Not reported
Sources of funding	Received financial support from the following legacies associated with the Norwegian MS Society: Per. B. Larsens Legater and Hørlands legat. The project was also awarded funding from MSCH and the Kristiansand and vicinity MS Association.
Inclusion criteria	Subjective complaints about cognitive problems; motivation for working with cognitive problems to increase coping in everyday life; adequate language skills to participate in group discussions without any need for an interpreter; no central

	nervous system injury or disease other than MS; no psychopathology that would negatively interfere with participation in the cognitive rehabilitation; and no general cognitive impairment defined as a scores from 24 and below on the Mini Mental State Examination
Exclusion criteria	No further criteria reported
Recruitment / selection of participants	Recruited from participants undergoing multidisciplinary inpatient rehabilitation programmes of 4-week duration that were offered for people with MS
Intervention(s)	Cognitive sessions + multidisciplinary rehabilitation: Cognitive rehabilitation in addition to usual rehabilitation offered by the centre. Cognitive rehabilitation involved guidance through the process of formulating Goal Attainment Scaling (GAS) goals for coping with cognitive problems in everyday life. GAS is a method for quantifying the attainment of individualised goals set in rehabilitation (five different levels - lower values indicate worse goal attainment compared to expectations, for example -2 indicates goal attainment worse than expected, 0 as expected and +2 much better than expected). During first week, neuropsychological assessment performed with a feedback session. To facilitate metacognitive awareness, cognitive strengths and symptoms were discussed with the patient and related to everyday challenges. Cognitive strengths and symptoms summarised in a form that contained general advice for coping with cognitive problems and sections in which the patient could enter goals and operationalize behaviours required to reach them. The form was continually updated by the patient, under supervision of the neuropsychologist and the occupational therapist, as the goal setting proceeded during the rehabilitation stay. Before discharge, the most important goals were converted into GAS goals. During inpatient stay, took part in three cognitive group (3-6 participants) sessions to increase awareness of their cognitive strengths, problems and coping strategies. Sessions conducted by study neuropsychologist and study occupational therapist. Sessions included lectures, practical exercises, and discussions. Main theme of first session was cognitive functions and principles of goal setting. The second session included a lecture about executive functions, a group exercise related to planning, and a discussion of strategies for keeping track of appointments and belongings. The third session dealt with how cognitive symptoms can affect communication, how to cope with such challenges, and how to communicate about MS. Second and third weeks of rehabilitation stay involved individual sessions with a neuropsychologist and occupational therapist. Motivational interviewing and cognitive behavioural therapy methods used to support goal setting process. For 3 months following discharge, six biweekly phone calls were arranged to focus on attainment of GAS goals set during rehabilitation period.

Population subgroups	None
Comparator	Control - multidisciplinary rehabilitation only: offered neuropsychological assessment, including feedback, and otherwise participated in the ordinary 4-week rehabilitation program of individual follow-up by a multidisciplinary team: neurologist, physiotherapist, social worker, occupational therapist, and nursing staff. Physical activities and lectures about MS-related topics were offered daily. As part of the ordinary rehabilitation program, participants in the control group had the opportunity to consult a clinical psychologist and attend lectures on cognitive and psychological aspects of MS.
Number of participants	120 randomised, 103 analysed at 4 months post-start of rehabilitation, 101 analysed at 7 months post-start of rehab (3- and 6-months following discharge, respectively)
Duration of follow-up	Up to 7 months following start of rehabilitation (6 months post-discharge)
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (49%) followed by secondary progressive (28%) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (mean score ~4.0 in both groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (psychopathology that could interfere with cognitive rehabilitation excluded) • Computerised vs clinician led - clinician led • Group vs individual - individual/group mixture Analysis - possibly modified intention to treat with those with missing data not included

1

Study arms

Cognitive sessions + multidisciplinary rehabilitation - focus on goal attainment scaling (executive function) (N = 60)

Control - multidisciplinary rehabilitation only (N = 60)

Characteristics

Arm-level characteristics

Characteristic	Cognitive sessions + multidisciplinary rehabilitation - focus on goal attainment scaling (executive function) (N = 60)	Control - multidisciplinary rehabilitation only (N = 60)
% Female Sample size	n = 40 ; % = 66.7	n = 48 ; % = 80
Mean age (SD) Mean (range)	53.9 (33-70)	52.5 (32-71)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Years since diagnosis Mean (SD)	10.6 (7.7)	12 (9.7)

Characteristic	Cognitive sessions + multidisciplinary rehabilitation - focus on goal attainment scaling (executive function) (N = 60)	Control - multidisciplinary rehabilitation only (N = 60)
EDSS score Mean (SD)	4.4 (1.7)	4.2 (1.7)
Primary progressive MS Sample size	n = 18 ; % = 30	n = 10 ; % = 16.7
Relapsing-remitting MS Sample size	n = 27 ; % = 45	n = 32 ; % = 53.3
Secondary progressive MS Sample size	n = 15 ; % = 25	n = 18 ; % = 30
IQ Mean (SD)	111.8 (12.5)	111.8 (10.7)

Outcomes

Study timepoints

- Baseline
- 4 month (4 months - 3 months post-discharge)
- 7 month (6 months post-discharge)

Results - raw data

Outcome	Cognitive sessions + multidisciplinary rehabilitation - focus on goal attainment scaling (executive function), Baseline, N = 60	Cognitive sessions + multidisciplinary rehabilitation - focus on goal attainment scaling (executive function), 4-month, N = 51	Cognitive sessions + multidisciplinary rehabilitation - focus on goal attainment scaling (executive function), 7-month, N = 54	Control - multidisciplinary rehabilitation only, Baseline, N = 60	Control - multidisciplinary rehabilitation only, 4-month, N = 51	Control - multidisciplinary rehabilitation only, 7-month, N = 48
BRIEF-A - General Executive Composite, T-score Behavior Rating Inventory of Executive Function – Adult version. For T-scores, score of 50 represents mean - each 10-point difference indicates difference of 1 SD from mean (of normative population scores) Mean (SD)	61.1 (11)	56.4 (11.7)	56.3 (11.8)	60 (10.6)	56.7 (11.7)	55.2 (11.5)

Outcome	Cognitive sessions + multidisciplinary rehabilitation - focus on goal attainment scaling (executive function), Baseline, N = 60	Cognitive sessions + multidisciplinary rehabilitation - focus on goal attainment scaling (executive function), 4-month, N = 51	Cognitive sessions + multidisciplinary rehabilitation - focus on goal attainment scaling (executive function), 7-month, N = 54	Control - multidisciplinary rehabilitation only, Baseline, N = 60	Control - multidisciplinary rehabilitation only, 4-month, N = 51	Control - multidisciplinary rehabilitation only, 7-month, N = 48
BRIEF-A - Metacognition Index, T-score Behavior Rating Inventory of Executive Function – Adult version. For T-scores, score of 50 represents mean - each 10-point difference indicates difference of 1 SD from mean (of normative population scores) Mean (SD)	62.7 (11.3)	58.2 (11.8)	57.7 (11.9)	61 (10.5)	57.8 (10.7)	56.7 (10.9)
MSIS-29 - psychological subscale Norwegian version	21.3 (7)	18.3 (6.9)	18.3 (7.2)	20.9 (6.6)	19.9 (7.7)	20.6 (8)

Outcome	Cognitive sessions + multidisciplinary rehabilitation - focus on goal attainment scaling (executive function), Baseline, N = 60	Cognitive sessions + multidisciplinary rehabilitation - focus on goal attainment scaling (executive function), 4-month, N = 51	Cognitive sessions + multidisciplinary rehabilitation - focus on goal attainment scaling (executive function), 7-month, N = 54	Control - multidisciplinary rehabilitation only, Baseline, N = 60	Control - multidisciplinary rehabilitation only, 4-month, N = 51	Control - multidisciplinary rehabilitation only, 7-month, N = 48
used. Quality of life. Scale 9-45. Mean (SD)						
HSCL-25 total score Hopkins Symptom Checklist- 25. Measures psychological health. Scale 1-4. Mean (SD)	1.76 (0.53)	1.6 (0.49)	1.62 (0.47)	1.75 (0.42)	1.74 (0.5)	1.65 (0.53)

1 BRIEF-A - General Executive Composite, T-score - Polarity - Lower values are better
2 BRIEF-A - Metacognition Index, T-score - Polarity - Lower values are better
3 MSIS-29 - psychological subscale - Polarity - Lower values are better
4 HSCL-25 total score - Polarity - Lower values are better
5 Final values for continuous outcomes

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Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_BRIEF-A General Executive Composite_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_BRIEF-A General Executive Composite_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_BRIEF-A Metacognition Index_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_BRIEF-A Metacognition Index_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_MSIS-29 psychological_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_MSIS-29 psychological_7 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_HSCL-25 total score_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_HSCL-25 total score_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Janssen, 2015

Bibliographic Reference	Janssen, A.; Boster, A.; Lee, H.; Patterson, B.; Prakash, R. S.; The effects of video-game training on broad cognitive transfer in multiple sclerosis: A pilot randomized controlled trial; Journal of Clinical & Experimental Neuropsychology: Official Journal of the International Neuropsychological Society; 2015; vol. 37 (no. 3); 285-302

Study details

Trial name / registration number	Not reported
Study location	USA
Study setting	Outpatient - recruited from local community
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	20/40 visual acuity or better; dominant right-handedness as measured by the Edinburgh Handedness Inventory; absence of depression as measured by a score of 18 or less on the Beck Depression Inventory–II; absence of relapse and corticosteroid use for the last 30 days; age 30–59 years; a score higher than 23 on the Mini Mental Status Examination; videogame usage of less than 4 hours/week; absence of any other neurological or psychological disorders; and a score greater than 1 on the Expanded Disability Status Scale.
Exclusion criteria	No further criteria reported
Recruitment / selection of participants	Recruited from the local community via advertisements in the media, North American Research Commission on MS, promotional flyers, Research Match, the National MS Society and the Multiple Sclerosis Treatment Centre affiliated with the research laboratory's larger institution
Intervention(s)	Video-game training with cognitive-focused Space Fortress game: the first assessment included an introduction to the Space Fortress game. Participants shown instructional videos outlining all rules, tips for success, and instructions for the Space Fortress game. To ensure that each participant understood the rules governing the Space Fortress game, a 15-

	question quiz was administered directly after the instructional videos, and further clarification was provided, if necessary. Space Fortress game used to implement **hybrid-variable priority training.** Designed by cognitive psychologists to examine the influence of various training strategies on skill acquisition rates. First 10 one-hour training sessions required participants to practice part-task training. This learning approach divided the Space Fortress game into 14-part tasks, each about 2 min long, which focused on different aspects of the game. Initially three full-emphasis games (games not altered from original Space Fortress format) followed by 14 part-task games and another three full-emphasis games. Following 10 one-hour sessions consisted of variable priority training - highlighted different aspects of the game, with varying emphasis on each sub score to minimize overall cognitive load, while integrating previously trained part-tasks. Participants completed six variable priority games, with a varying, counterbalanced emphasis order of points, control, speed, velocity, and total scores, bookended by three full emphasis games at the beginning and end of each session.
Population subgroups	None
Comparator	Waitlist control: contacted every two weeks to ensure good health and compliance with study guidelines. Participants were requested to refrain from engaging in any other experimental trials and were required to attend two training sessions at Weeks 4 and 8 to obtain comparison game-play data for skill acquisition analysis.
Number of participants	34 randomised, 28 analysed (intervention, n=2 lost to relapse and n=1 excluded due to prolonged training; waitlist, n=2 lost to attrition and n=1 excluded due to prolonged waitlist control period).
Duration of follow-up	Up to 8 weeks - end of intervention
Indirectness	Outcome - time-point <3-month minimum in protocol Population - having a cognitive impairment was not an inclusion criterion
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting MS • According to disability (EDSS <6 and EDSS ≥6) - >6.0 (mean score 2.7 and 2.9 in the two groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear (having an impairment was not an inclusion criterion) • Disease modifying treatment status (currently using and not currently using) - unclear

	• Mood disorders (presence or absence) - unclear • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - per protocol (those with missing data excluded and also excluded some that did not complete within specified time)

Study arms

Hybrid-variable priority training (HVT) - Video-game training with cognitive-focused Space Fortress game (N = 17)

Waitlist control (N = 17)

Characteristics

Arm-level characteristics

Characteristic	Hybrid-variable priority training (HVT) - Video-game training with cognitive-focused Space Fortress game (N = 17)	Waitlist control (N = 17)
% Female Sample size	n = 10 ; % = 71.4	n = 11 ; % = 78.6
Mean age (SD) Mean (SD)	49.43 (6.4)	44.93 (8.8)
Ethnicity	NR	NR

Characteristic	Hybrid-variable priority training (HVT) - Video-game training with cognitive-focused Space Fortress game (N = 17)	Waitlist control (N = 17)
Custom value		
Comorbidities Custom value	NR	NR
EDSS score Mean (SD)	2.86 (1.3)	2.68 (1.7)
Disease duration (years) Mean (SD)	13 (6.7)	10.93 (7.4)

Note that baseline characteristics are given for the n=14 analysed in each group, not the n=17 randomised per group.

Outcomes

Study timepoints

- Baseline
- 8 week (8-weeks - post-training time-point)

1 **Results - raw data**

Outcome	Hybrid-variable priority training (HVT) - Video-game training with cognitive-focused Space Fortress game, Baseline, N = 14	Hybrid-variable priority training (HVT) - Video-game training with cognitive-focused Space Fortress game, 8-week, N = 14	Waitlist control, Baseline, N = 14	Waitlist control, 8-week, N = 14
PASAT 2 seconds Paced Auditory Serial Addition Test. Attention/executive function measure. Mean (SD)	33.93 (12.1)	35.36 (14.03)	33.43 (12.67)	34.14 (12.7)
PASAT 3 seconds Paced Auditory Serial Addition Test. Attention/executive function measure. Mean (SD)	44.21 (12.88)	48.86 (13.45)	43.07 (12.19)	45.64 (10.63)
SDMT Oral Symbol Digit Modalities Test. Attention/executive function measure. Mean (SD)	43.79 (11.68)	45.07 (12.09)	42.43 (11.15)	40.21 (10.85)
SRT LTS Selective Reminding Test - Long-Term Storage. Assesses verbal memory.	50.43 (17.18)	47.36 (19.77)	44.43 (19.52)	51.14 (11.29)

Outcome	Hybrid-variable priority training (HVT) - Video-game training with cognitive-focused Space Fortress game, Baseline, N = 14	Hybrid-variable priority training (HVT) - Video-game training with cognitive-focused Space Fortress game, 8-week, N = 14	Waitlist control, Baseline, N = 14	Waitlist control, 8-week, N = 14
Mean (SD)				
SRT-CLTR Selective Reminding Test - Consecutive Long-Term Retrieval. Assesses verbal memory. Mean (SD)	44.71 (19.79)	39.43 (21.14)	31.79 (23.67)	38.29 (20.53)
SRT Delayed Selective Reminding Test - Delayed Recall. Assesses verbal memory. Mean (SD)	9.07 (2.65)	8.86 (2.41)	8.07 (3)	9.29 (2.02)
10/36 Spatial Recall - Correct Visual memory Mean (SD)	18.79 (5.95)	22 (6.15)	23.5 (5.03)	19.43 (6.78)
10/36 Spatial Recall Delayed Mean (SD)	7.07 (3.27)	7.57 (3.01)	7.64 (2.41)	6.5 (3.57)
Word List Generation Test Verbal fluency	28.43 (7.31)	27.79 (9.25)	26.5 (8.3)	28.07 (6.12)

Outcome	Hybrid-variable priority training (HVT) - Video-game training with cognitive-focused Space Fortress game, Baseline, N = 14	Hybrid-variable priority training (HVT) - Video-game training with cognitive-focused Space Fortress game, 8-week, N = 14	Waitlist control, Baseline, N = 14	Waitlist control, 8-week, N = 14
Mean (SD)				

PASAT 2 seconds - Polarity - Higher values are better
PASAT 3 seconds - Polarity - Higher values are better
SDMT - Polarity - Higher values are better
SRT LTS - Polarity - Higher values are better
SRT-CLTR - Polarity - Higher values are better
10/36 Spatial Recall - Correct - Polarity - Higher values are better
10/36 Spatial Recall Delayed - Polarity - Higher values are better
Word List Generation Test - Polarity - Higher values are better
Final values for continuous outcomes
Despite n=17 being randomised to each group, study likely gives baseline values for the n=14 analysed in each group, as was the case for baseline characteristics

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_PASAT 2 seconds_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_PASAT 3 seconds_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_SDMT_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_SRT-LTS_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

1 **Results_SRT-CLTR_8 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

2

3 **Results_SRT Delayed_8 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_10/36 Spatial Recall - correct_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_10/36 Spatial Recall - delayed_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_Word List Generation Test_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Krch, 2019

Bibliographic Reference	Krch, D.; Lequerica, A.; Aguayo Arelis, A.; Rabago Barajas, B. V.; Arango-Lasprilla, J. C.; Chiaravalloti, N. D.; Efficacy of the Spanish modified Story Memory Technique in Mexicans with multiple sclerosis: A pilot randomized controlled trial; Neurorehabilitation; 2019; vol. 45 (no. 3); 349-358

Study details

Trial name / registration number	NCT03453125
Study location	Mexico
Study setting	Outpatient - recruited from Foundation for MS in Mexico (Guadalajara)
Study dates	Recruitment period from 1st April 2015 to 31st November 2015
Sources of funding	Grant from National Institute on Disability, Independent Living and Rehabilitation Research (NIDILRR - centre within Administration for Community Living of Department of Health and Human Services).
Inclusion criteria	Aged 18-70 years; free of exacerbations for at least 1 month prior to participation; intact language comprehension (Verbal Comprehension subscales of Bilingual Aphasia Test); impaired new learning (measured by failing to achieve perfect recall on 2 consecutive trials by trial 7 on Open Trial administration of Selective Reminding Test); and no significant neurological history other than MS.
Exclusion criteria	Currently using steroids, benzodiazepines or neuroleptics; significant history of major depressive disorder, schizophrenia or bipolar disorder that could affect learning; and scotomas, diplopia or nystagmus that may affect seeing stimuli.
Recruitment / selection of participants	Recruited from Foundation for MS in Guadalajara.

Intervention(s)	Modified Story Memory Technique (mSMT) for learning in MS: translated from English to Spanish version by bilingual researcher. 10-session computer-assisted manualised intervention delivered in presence of a trainer. Imagery used in first 4 sessions and use of context trained in sessions 5-8, with generalisation of newly learned skills to everyday activities in the final 2 sessions. Training sessions ~45 min duration two times weekly for 5 weeks.
Population subgroups	None
Comparator	Placebo control: Manualised and delivered by computer in presence of a trainer. Stimulus content and presentation of control sessions matched to the treatment sessions - exposed to same stories and target words but were not taught how to apply imagery and context to the material. Training sessions ~45 min duration two times weekly for 5 weeks.
Number of participants	20 randomised, 20 analysed
Duration of follow-up	5-weeks - end of treatment period
Indirectness	Outcome - time-point <3 months minimum in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - unclear • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (depression and bipolar excluded) • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - intention to treat (appear to be no dropouts)

1

Study arms

Modified Story Memory Technique (mSMT) for learning in MS (N = 10)

Placebo control - similar training but without being taught how to apply imagery and context (N = 10)

Characteristics

Arm-level characteristics

Characteristic	Modified Story Memory Technique (mSMT) for learning in MS (N = 10)	Placebo control - similar training but without being taught how to apply imagery and context (N = 10)
% Female Sample size	n = 5 ; % = 50	n = 5 ; % = 50
Mean age (SD) Mean (SD)	33.8 (12.3)	39.5 (10.8)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Months since diagnosis Mean (SD)	70.1 (55.8)	65.2 (39.5)

Characteristic	Modified Story Memory Technique (mSMT) for learning in MS (N = 10)	Placebo control - similar training but without being taught how to apply imagery and context (N = 10)
Months since most recent exacerbation Mean (SD)	11.2 (3.2)	13.2 (2.4)

Outcomes

Study timepoints

- Baseline
- 5 week (5-weeks - end of intervention period)

Results - raw data

Outcome	Modified Story Memory Technique (mSMT) for learning in MS, Baseline, N = 10	Modified Story Memory Technique (mSMT) for learning in MS, 5-week, N = 10	Placebo control - similar training but without being taught how to apply imagery and context, Baseline, N = 10	Placebo control - similar training but without being taught how to apply imagery and context, 5-week, N = 10
HVLT-R Total Learning Trials 1-3 Hopkins Verbal Learning Test-Revised. Assesses verbal learning and memory. Only 95% CI reported and mean can be calculated from CI and number analysed. Baseline values for raw scores not reported but z-scores reported to be -0.92 (0.87) and -0.02	NR	22.66-27.88	NR	19.33-24.54

Outcome	Modified Story Memory Technique (mSMT) for learning in MS, Baseline, N = 10	Modified Story Memory Technique (mSMT) for learning in MS, 5-week, N = 10	Placebo control - similar training but without being taught how to apply imagery and context, Baseline, N = 10	Placebo control - similar training but without being taught how to apply imagery and context, 5-week, N = 10
(0.98) - significant difference at baseline but 95% CI values given are possibly those adjusted for baseline values. 95% CI				
Memory Functioning Questionnaire - Spanish version Self-reported measure of memory complaints. Scale 31-217. Only 95% CI reported and mean can be calculated from CI and number analysed. Baseline values for raw scores reported as mean (SD): 109.0 (18.33) vs. 108.60 (16.79). 95% CI values given are possibly those adjusted for baseline values. 95% CI	NR	99.36-112.44	NR	104.26-117.34
Life satisfaction - Satisfaction With Life Scale Scale usually 5-35. Only 95% CI reported and mean can be calculated from CI and number analysed. Baseline values for raw scores reported as mean (SD): 23.20 (6.03) vs. 19.70 (5.31). 95% CI values given are possibly those adjusted for baseline values.	NR	21.04-26.14	NR	17.76-22.86

Outcome	Modified Story Memory Technique (mSMT) for learning in MS, Baseline, N = 10	Modified Story Memory Technique (mSMT) for learning in MS, 5-week, N = 10	Placebo control - similar training but without being taught how to apply imagery and context, Baseline, N = 10	Placebo control - similar training but without being taught how to apply imagery and context, 5-week, N = 10
95% CI				
Patient-reported Baseline values for raw scores reported as mean (SD): 101.40 (9.88) VS. 95.80 (9.59). 95% CI values given are possibly those adjusted for baseline values. 95% CI	NR	92.14-104.53	NR	91.47-103.86
Family-reported Baseline values for raw scores reported as mean (SD): 104.20 (11.0) vs. 103.0 (11.94). 95% CI values given are possibly those adjusted for baseline values. 95% CI	NR	100.12-104.70	NR	102.50-107.08

1 HVLT-R Total Learning Trials 1-3 - Polarity - Higher values are better
2 Memory Functioning Questionnaire - Spanish version - Polarity - Lower values are better
3 Life satisfaction - Satisfaction With Life Scale - Polarity - Higher values are better
4 Patient Competency Rating Scale (PCRS) - Polarity - Higher values are better
5 Final values for continuous outcomes

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Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_HVLT-R Total Learning Trials 1-3_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_memory functioning questionnaire_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_life satisfaction_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_patient competency scale - patient-reported_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_patient competency scale - family-reported_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Lamargue, 2020

Bibliographic Reference	Lamargue, D.; Koubiyr, I.; Deloire, M.; Saubusse, A.; Charre-Morin, J.; Moroso, A.; Coupe, P.; Brochet, B.; Ruet, A.; Effect of cognitive rehabilitation on neuropsychological and semiecological testing and on daily cognitive functioning in multiple sclerosis: The REACTIV randomized controlled study; Journal of the Neurological Sciences; 2020; vol. 415; 116929

Study details

Trial name / registration number	NCT01207856
Study location	France
Study setting	Outpatients - recruited during outpatient visits
Study dates	Not reported
Sources of funding	Funded by ARSEP Foundation (Association pour la Recherche contre la Sclerose en Plaques), ANR-10-LABX-57 Translational Research and Advanced Imaging Cluster of Excellence and a grant from Merck.
Inclusion criteria	MS according to McDonald criteria of any phenotype; age 18-55 years; disease duration >6 months and ≤15.0 years; right-handedness; having a driver's license; and cognitive criterion of mild cognitive impairment (at least 3 scores <1 SD on tests measuring information processing speed, attention, working memory and executive function); complaining of discomfort in daily lives due to cognitive problems.
Exclusion criteria	Previous history of other neurological or psychiatric disorders; visual, oculomotor, auditory or motor impairments precluding ability to perform computerised tasks; addictive behaviour; MS attack and/or corticosteroid pulse therapy in 2 months prior to screening; severe cognitive deficits or dementia (Mini-Mental Status Examination <27); moderate-severe visuospatial incapacity (raw score <28 on copy trial of Rey-Osterrieth Figure Test); and moderate-severe depression (BDI >27).

Recruitment / selection of participants	People complaining of discomfort in their daily lives due to cognitive problems during routine outpatient visits for MS were recruited.
Intervention(s)	REACTIV specific cognitive rehabilitation covering multiple cognitive domains: Total of 50 sessions (45 min duration each) delivered three times weekly for 4 months. Supervised by specifically trained speech therapists or neuropsychologists. Individual sessions only. Designed for mild-moderate impairment and focused on certain fundamental cognitive processes: information processing speed (using feedback from reaction times in computerised and timed tasks); attention (particularly selective, sustained and divided attention); executive function (mainly inhibition and flexibility processes, control processes, the allocation and coordination of attentional resources or checking strategies); working memory (particularly central executive and storage capacity; and metacognition. Progressive programme including general framework with work on attention, information processing and executive function that was tailored to level of deficits for each patient. Progression controlled by validation of consecutive levels of difficulty. REACTIV used wide range of exercises of increasing complexity to limit familiarisation, maintain interest and novelty and stimulate attention, including computerised standardised exercises, pen and pencil exercises and rehabilitation games. Tasks performed across different modalities (visual or auditory, verbal or non-verbal, written or oral or motor). Provided time for work focusing on difficulties in daily life and for metacognitive deep thinking.
Population subgroups	None
Comparator	Non-specific cognitive intervention: Total of 50 sessions (45 min duration each) delivered three times weekly for 4 months. Supervised by specifically trained speech therapists or neuropsychologists. Focused on information about disease, its symptoms and management, relaxation, physical activity coaching and global cognitive stimulation (including 10 sessions with focus on semantic memory, autobiographical memory and verbal and visual episodic memory).
Number of participants	35 randomised, 35 randomised at 4- and 8-month time-points (end of intervention and 4-month post-intervention completion)
Duration of follow-up	Outcomes reported at 4- and 8-month time-points (end of intervention and 4-month post-intervention completion)
Indirectness	None

Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (83%) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (median score 2.0 and 3.0 in two groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear (mild-moderate included, proportion with each unclear) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - likely absent (history of psychiatric disorders excluded) • Computerised vs clinician led - mix clinician led/computerised • Group vs individual - individual Analysis - intention to treat (all of those randomised analysed)

Study arms

REACTIV specific cognitive rehabilitation covering multiple cognitive domains (N = 18)

Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory (N = 17)

Characteristics

Arm-level characteristics

Characteristic	REACTIV specific cognitive rehabilitation covering multiple cognitive domains (N = 18)	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory (N = 17)
% Female	n = 12 ; % = 66.6	n = 14 ; % = 82.4

Characteristic	REACTIV specific cognitive rehabilitation covering multiple cognitive domains (N = 18)	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory (N = 17)
Sample size		
Mean age (SD) Mean (SD)	43.8 (5.6)	38.3 (8.2)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Disease duration (years) Mean (SD)	6.7 (3.1)	6.5 (5.5)
EDSS score Median (range or interquartile range)	3.0 (1-8)	2.0 (0-4)
Relapsing-remitting Sample size	n = 14 ; % = 77.8	n = 15 ; % = 88.2

Characteristic	REACTIV specific cognitive rehabilitation covering multiple cognitive domains (N = 18)	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory (N = 17)
Secondary progressive Sample size	n = 3 ; % = 16.7	n = 1 ; % = 5.9
Primary progressive Sample size	n = 1 ; % = 5.6	n = 1 ; % = 5.9

Outcomes

Study timepoints

- Baseline
- 4 month (4-months - end of intervention period)
- 8 month (8-months - 4-months following end of intervention period)

Results - raw data

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
SDMT Symbol Digit Modalities Test. Correct answers in 90 seconds. Measure of information processing speed. Mean (SD)	51.7 (10.2)	57.8 (10.2)	58.7 (10.3)	52 (8.8)	57.2 (9.1)	59.4 (10)
Without warning Mean (SD)	334.1 (208.9)	250.1 (45.1)	251.1 (38.9)	274.2 (38.1)	273.3 (38.6)	267.2 (38.4)
With warning Mean (SD)	335.7 (238.4)	248.2 (45.5)	262.5 (75.1)	250.2 (26.3)	261.9 (41.2)	250 (31)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
Without warning Mean (SD)	40 (0)	40 (0)	40 (0)	40 (0)	40 (0)	40 (0)
With warning Mean (SD)	40 (0)	40 (0)	40 (0)	40 (0)	40 (0)	40 (0)
With a target Mean (SD)	3499.5 (1241.8)	3325.3 (1291.4)	2860.2 (906.8)	3344.2 (552.8)	3023.5 (786)	2789.2 (628.7)
Without a target Mean (SD)	6101.2 (2076.1)	6460.1 (2882.9)	5596.6 (1995.7)	6089.2 (1500.2)	5723.4 (1837.3)	5456.7 (1467.1)
With a target Mean (SD)	39.1 (7.4)	43.6 (4.4)	40.8 (6)	35.5 (9.4)	40.3 (7.8)	43.1 (4.4)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
Without a target Mean (SD)	49.8 (0.4)	49.8 (0.4)	49.8 (0.5)	49.8 (0.4)	50 (0)	49.8 (0.4)
Divided Attention (visual attention) - Test of Attentional Performances subtest - reaction time Measure of information processing speed/attention Mean (SD)	888.7 (136.7)	803.6 (97.3)	809.3 (145.2)	884.9 (111)	856.9 (120.7)	829.2 (98.1)
Simple task condition Mean (SD)	888.7 (136.7)	803.6 (97.3)	809.3 (145.2)	884.9 (111)	856.9 (120.7)	829.2 (98.1)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
Dual-task condition Mean (SD)	904.4 (145.2)	824.8 (115.5)	782.9 (116.7)	818.9 (91.4)	800.5 (91.8)	811.2 (79.7)
Simple task condition Mean (SD)	15.4 (1.8)	15.9 (1.3)	15.7 (2.2)	15.8 (1.5)	16.2 (1.4)	15.8 (1.4)
Dual-task condition Mean (SD)	15.5 (1.6)	16.3 (0.8)	16 (1)	15.8 (2.2)	16.1 (1.2)	15.8 (1.1)
Simple task condition Mean (SD)	646.2 (151.2)	525.4 (90.6)	558.4 (64.2)	572.7 (126.4)	560.1 (119.8)	561.5 (124.4)
Dual-task condition Mean (SD)	704.3 (210.5)	574.4 (102.3)	596.9 (106.5)	642.5 (149.5)	583.6 (98.6)	588.4 (101.4)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
Simple task condition Mean (SD)	15.4 (1.9)	16 (0)	15.8 (0.4)	15.8 (0.5)	15.5 (1)	15.8 (0.4)
Dual-task condition Mean (SD)	14.8 (2.9)	15.7 (0.6)	15.7 (0.8)	14.7 (1.4)	15.3 (1.5)	15.3 (1.7)
N-back - Test of Attentional Performances subtest - reaction time Measure of working memory Mean (SD)	781.2 (208.9)	703.3 (120.8)	648.3 (103.5)	724.2 (146.9)	753.1 (209.8)	698.5 (214.7)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
N-back - Test of Attentional Performances subtest - correct answers Measure of working memory Mean (SD)	12.5 (1.8)	13.7 (1)	13.7 (1.4)	13.4 (1.8)	13.2 (1.6)	13.6 (1.4)
Colour naming Mean (SD)	73.1 (22.8)	61.6 (9.4)	60.8 (9.3)	75.2 (16.2)	66.5 (9.9)	64.1 (11.2)
Word reading Mean (SD)	55.4 (24.4)	50.3 (14.4)	46.8 (7.3)	51.4 (9.2)	48.5 (7.5)	48.4 (8.4)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
Interference Mean (SD)	59.7 (29.9)	44.6 (26.3)	38.4 (14.2)	50.2 (14.9)	38.2 (15.8)	40.2 (16.5)
Part A Mean (SD)	44.4 (25.9)	34.9 (11.5)	31 (8.3)	34.1 (8.1)	30.2 (9.9)	28.3 (10.6)
Part B Mean (SD)	89.6 (32.8)	69.6 (19.2)	67.1 (24.4)	80.8 (17.1)	63.5 (16.5)	57.2 (17.9)
Baddeley's Dual Task forward span - correct answers Assesses working memory/attention. Mean (SD)	5.1 (1)	5.8 (0.9)	5.7 (1)	5.5 (1)	5.5 (1.1)	5.4 (1.1)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
Semantic Mean (SD)	28.2 (6.5)	29.6 (7.6)	29.6 (6.5)	29 (7.7)	30.8 (7.8)	31.5 (7.6)
Phonemic Mean (SD)	18.8 (5.7)	20.6 (5.8)	21.3 (6.1)	21.2 (5)	21.2 (4.3)	22.1 (4.5)
Backward span - correct answers measures working memory Mean (SD)	3.8 (0.8)	4.1 (1.1)	4.7 (1)	3.8 (0.8)	3.7 (0.9)	4.2 (1)
Leaning trials - List A Mean (SD)	61.2 (7.7)	63.7 (6)	67.8 (6.4)	62.5 (8.6)	65.7 (10.2)	66.1 (7.8)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
Learning trials - List B Mean (SD)	7.6 (2.3)	7.9 (2.2)	8 (2.4)	8.3 (2.4)	8.3 (2.3)	8 (2.9)
Immediate recall Mean (SD)	12.1 (2.4)	13.7 (2)	13.5 (2.4)	13 (2.8)	13.5 (2.4)	14.1 (2)
Delayed recall Mean (SD)	12.9 (2.5)	14.2 (1.7)	14.4 (2)	13.6 (1.8)	14.1 (1.8)	14.4 (1.8)
Immediate cued recall Mean (SD)	12.9 (1.8)	14.3 (1.7)	14.6 (1.9)	13.5 (1.8)	13.8 (1.8)	14.2 (1.9)
Delayed cued recall	13.2 (2.4)	14 (1.9)	14.8 (1.6)	13.6 (1.9)	14.2 (1.8)	14.6 (1.5)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
Mean (SD)						
Recognition Mean (SD)	15.2 (1.5)	15.4 (1)	15.7 (0.7)	15.5 (0.8)	15.7 (0.6)	15.8 (0.4)
Rey complex figure - correct answers Measures visuoconstruction and episodic memory Mean (SD)	33.6 (2.4)	34.5 (1.5)	34.7 (1.1)	33.5 (2.6)	33.9 (2)	33.7 (1.4)
Rey complex figure - time Measures	184.2 (76.5)	192.2 (67.1)	173 (55.2)	195.9 (90.2)	162.7 (73)	158.9 (69.5)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
visuoconstruction and episodic memory Mean (SD)						
DO80 naming task - correct answers Mean (SD)	78.1 (1.1)	78.2 (1.5)	79 (1.3)	77.9 (1.3)	78.1 (1.9)	78.7 (1.3)
Daily Cognitive Activities Questionnaire (DCAQ) Self-report. Scale 0-60. 12-item results extracted as no baseline values given for 17-item version and	40.3 (23.9)	55.9 (14.1)	NR (NR)	43.4 (16.4)	49.2 (16.9)	NR (NR)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
17-item one not mentioned in methods. Mean (SD)						
Beck Depression Inventory Scale usually 0-63. Mean (SD)	16.4 (7.4)	10.5 (7.3)	NR (NR)	15.6 (7.7)	9.5 (6.7)	NR (NR)
STAI - A (state?) State-Trait Anxiety Inventory. Scale usually 20-80. Mean (SD)	36.6 (12.6)	36.9 (16.1)	NR (NR)	32.9 (6.8)	32.2 (8.4)	NR (NR)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
STAI - B (trait?) State-Trait Anxiety Inventory. Scale usually 20-80. Mean (SD)	47 (10.7)	42.5 (12.1)	NR (NR)	45.7 (8)	39.4 (9.2)	NR (NR)
MFIS - cognitive Modified Fatigue Impact Scale. Scale usually 0-40. Mean (SD)	24.4 (7.7)	17.2 (7.9)	NR (NR)	25.2 (7.4)	17.5 (9.9)	NR (NR)
Physical composite Mean (SD)	50.3 (17.2)	58.1 (16.7)	NR (NR)	52.2 (14.9)	55.8 (20.5)	NR (NR)

Outcome	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, Baseline, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 4-month, N = 18	REACTIV specific cognitive rehabilitation covering multiple cognitive domains, 8-month, N = 18	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, Baseline, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 4-month, N = 17	Non-specific cognitive intervention - information about disease, relaxation, physical activity coaching and global cognitive stimulation with special focus on memory, 8-month, N = 17
Mental composite Mean (SD)	50 (22.8)	59.9 (17.7)	NR (NR)	53 (18.6)	57.8 (20.2)	NR (NR)

SDMT - Polarity - Higher values are better
Alertness - Test of Attentional Performances subtest - reaction time - Polarity - Lower values are better
Alertness - Test of Attentional Performances subtest - correct answers - Polarity - Higher values are better
Visual scanning - Test of Attentional Performances subtest - reaction time - Polarity - Lower values are better
Visual scanning - Test of Attentional Performances subtest - correct answers - Polarity - Higher values are better
Divided Attention (visual attention) - Test of Attentional Performances subtest - reaction time - Polarity - Lower values are better
Divided Attention (visual attention) - Test of Attentional Performances subtest - correct answers - Polarity - Higher values are better
Divided Attention (auditory attention) - Test of Attentional Performances subtest - reaction time - Polarity - Lower values are better
Divided Attention (auditory attention) - Test of Attentional Performances subtest - correct answers - Polarity - Higher values are better
N-back - Test of Attentional Performances subtest - reaction time - Polarity - Lower values are better
N-back - Test of Attentional Performances subtest - correct answers - Polarity - Higher values are better
Stroop Test (time) - Polarity - Lower values are better
Trail Making Test (time) - Polarity - Lower values are better
Baddeley's Dual Task forward span - correct answers - Polarity - Higher values are better

Fluency - correct answers - Polarity - Higher values are better
Backward span - correct answers - Polarity - Higher values are better
CVLT - correct answers - Polarity - Higher values are better
Rey complex figure - correct answers - Polarity - Higher values are better
Rey complex figure - time - Polarity - Lower values are better
DO80 naming task - correct answers - Polarity - Higher values are better
Daily Cognitive Activities Questionnaire (DCAQ) - Polarity - Higher values are better
Beck Depression Inventory - Polarity - Lower values are better
STAI - A (state?) - Polarity - Lower values are better
STAI - B (trait?) - Polarity - Lower values are better
MFIS - cognitive - Polarity - Lower values are better
SF-36 - Polarity - Higher values are better
Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_SDMT_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_alertness TAP reaction time without warning_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_alertness TAP reaction time without warning_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_alertness TAP reaction time with warning_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1
2 **Results_alertness TAP reaction time with warning_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3
4 **Results_alertness TAP correct answers without warning_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_alertness TAP correct answers without warning_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_alertness TAP correct answers with warning_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_alertness TAP correct answers with warning_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_visual scanning TAP reaction time with a target_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_visual scanning TAP reaction time with a target_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_visual scanning TAP reaction time without a target_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_visual scanning TAP reaction time without a target_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_visual scanning TAP correct answers with a target_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_visual scanning TAP correct answers with a target_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_visual scanning TAP correct answers without a target_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_visual scanning TAP correct answers without a target_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (visual) TAP reaction time - simple task condition_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (visual) TAP reaction time - simple task condition_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (visual) TAP reaction time - dual task condition_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (visual) TAP reaction time - dual task condition_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (auditory) TAP reaction time - simple task condition_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (auditory) TAP reaction time - simple task condition_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (auditory) TAP reaction time - dual task condition_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (auditory) TAP reaction time - dual task condition_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (visual) TAP correct answers - simple task condition_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (visual) TAP correct answers - simple task condition_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (visual) TAP correct answers - dual task condition_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (visual) TAP correct answers - dual task condition_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (auditory) TAP correct answers - simple task condition_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (auditory) TAP correct answers - simple task condition_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (auditory) TAP correct answers - dual task condition_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Divided attention (auditory) TAP correct answers - dual task condition_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_N-back reaction time_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_N-back reaction time_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_N-back correct answers_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_N-back correct answers_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Stroop Test Color Naming_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_Stroop Test Color Naming_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

1 **Results_Stroop Test Word Reading_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_Stroop Test Word Reading_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Stroop Test Interference_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Stroop Test Interference_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Trail Making Test - A_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Trail Making Test - A_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_Trail Making Test - B_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Trail Making Test - B_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Baddeley's Dual Task forward span correct answers_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Baddeley's Dual Task forward span correct answers_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1
2 **Results_Fluency - semantic_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3
4 **Results_Fluency - semantic_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Fluency - phonemic_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_Fluency - phonemic_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_Backward Span_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_Backward Span_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT learning trials list A_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT learning trials list A_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT learning trials list B_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT learning trials list B_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT immediate recall_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_CVLT immediate recall_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_CVLT delayed recall_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT delayed recall_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT immediate cued recall_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT immediate cued recall_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT delayed cued recall_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT delayed cued recall_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_CVLT recognition_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_CVLT recognition_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Rey complex figure correct answers_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1
2 **Results_Rey complex figure correct answers_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3
4 **Results_Rey complex figure time_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Rey complex figure time_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_DO80 naming task_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_DO80 naming task_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_Daily Cognitive Activities Questionnaire_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Beck Depression Inventory_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_STAI-A (state?)_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_STAI-B (trait?)_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_MFIS cognitive_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SF-36 physical composite_4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_SF-36 mental composite_4 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

Lincoln, 2020

Bibliographic Reference	Lincoln, N. B.; Bradshaw, L. E.; Constantinescu, C. S.; Day, F.; Drummond, A. E.; Fitzsimmons, D.; Harris, S.; Montgomery, A. A.; das Nair, R.; Group cognitive rehabilitation to reduce the psychological impact of multiple sclerosis on quality of life: the CRAMMS RCT; Health Technology Assessment (Winchester, England); 2020; vol. 24 (no. 4); 1-182

Study details

Secondary publication of another included study- see primary study for details	• Lincoln, N. B., Bradshaw, L. E., Constantinescu, C. S. et al. (2020) Cognitive rehabilitation for attention and memory in people with multiple sclerosis: a randomized controlled trial (CRAMMS). Clinical Rehabilitation 34(2): 229-241

Lincoln, 2020

Bibliographic Reference	Lincoln, N. B.; Bradshaw, L. E.; Constantinescu, C. S.; Day, F.; Drummond, A. E.; Fitzsimmons, D.; Harris, S.; Montgomery, A. A.; das Nair, R.; Group, Cramms Trial Collaborative; Cognitive rehabilitation for attention and memory in people with multiple sclerosis: a randomized controlled trial (CRAMMS); Clinical Rehabilitation; 2020; vol. 34 (no. 2); 229-241

Study details

Other publications associated with this study included in review	• Lincoln, N. B., Bradshaw, L. E., Constantinescu, C. S. et al. (2020) Group cognitive rehabilitation to reduce the psychological impact of multiple sclerosis on quality of life: the CRAMMS RCT. Health Technology Assessment (Winchester, England) 24(4): 1-182

Trial name / registration number	CRAMMS study. ISRCTN09697576/14/08/2014.
Study location	UK
Study setting	Outpatient - identified through hospitals, charities and UK MS Register
Study dates	Participants were recruited between 13 March 2015 and 23 March 2017
Sources of funding	Funded by the National Institute for Health Research Health Technology Assessment programme (project number 12/190/05)
Inclusion criteria	Aged 18–69 years; diagnosed with relapsing–remitting or progressive multiple sclerosis; diagnosed at least three months prior to the screening assessment; reported having cognitive problems defined as >27 on the patient version of the Multiple Sclerosis Neuropsychological Screening Questionnaire; impaired on at least one of the Brief Repeatable Battery of Neuropsychological tests (defined as performance >1 SD below the mean of healthy controls, corrected for age and education); able to attend group sessions; able to speak English sufficiently to complete the cognitive assessments; gave written informed consent
Exclusion criteria	Had vision or hearing problems, such that they were unable to complete the cognitive assessments; had concurrent severe medical or psychiatric conditions, which prevented them from engaging in treatment; were involved in other psychological intervention trials
Recruitment / selection of participants	Participants were identified through United Kingdom National Health Service hospitals, charities (e.g., MS Society) and the United Kingdom MS Register. The trial was conducted in five sites in England.
Intervention(s)	Group cognitive programme with main focus on memory + usual care: Cognitive rehabilitation was provided by an Assistant Psychologist to groups of 4-6 with meetings almost weekly for 10 sessions. Content of sessions defined in treatment manual. Included restitution strategies to retrain attention and memory functions and strategies to improve encoding and retrieval. Compensation strategies taught included the use of internal mnemonics (such as chunking) and external devices (such as diaries and mobile phones) and ways of coping with attention and memory problems. Attendance was recorded. If participants missed a session, they could attend early for the following session to catch up on the content they had missed. Homework assignments facilitated individualisation of care and generalization of cognitive strategies to daily life. Usual care involved general advice from multiple sclerosis nurse specialists and occupational therapists on how to manage any

	cognitive difficulties. All participants were notified of information available on the webpages of multiple sclerosis charities, which include suggestions for coping with cognitive problems. All other clinical services, and support from specialist charities, were available as part of usual care.
Population subgroups	Reports data separately for some of the population subgroups in health economic paper (including type of MS)
Comparator	Usual care only: Usual care involved general advice from multiple sclerosis nurse specialists and occupational therapists on how to manage any cognitive difficulties. All participants were notified of information available on the webpages of multiple sclerosis charities, which include suggestions for coping with cognitive problems. All other clinical services, and support from specialist charities, were available as part of usual care.
Number of participants	449 randomised, 404 analysed at 6 months and 387 analysed at 12 months (intervention: n=13 withdrew consent, n=12 lost to follow-up, n=1 returned questionnaire >15 months post-randomisation, n=3 visit completed but questionnaire not done, n=1 MSIS-psychological could not be scored and n=1 unknown; control, n=16 withdrew consent, n=10 lost to follow-up, n=3 returned questionnaire >15 months post-randomisation and n=2 visit completed but questionnaire not done)
Duration of follow-up	Up to 12 months post-randomisation (9-10 months after end of intervention)
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (65% both groups) • According to disability (EDSS <6 and EDSS ≥6) - unclear • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (major psychiatric conditions excluded) • Computerised vs clinician led - clinician led • Group vs individual - group Analysis - modified attention to treat with those with no data excluded

Study arms

Group cognitive programme with main focus on memory + usual care (N = 245)

Usual care only (N = 204)

Characteristics

Arm-level characteristics

Characteristic	Group cognitive programme with main focus on memory + usual care (N = 245)	Usual care only (N = 204)
% Female Sample size	n = 178 ; % = 73	n = 148 ; % = 73
Mean age (SD) Mean (SD)	49.9 (9.8)	48.9 (10)
White Sample size	n = 237 ; % = 97	n = 195 ; % = 96
Non-white Sample size	n = 8 ; % = 3	n = 9 ; % = 4
Comorbidities Custom value	NR	NR

Characteristic	Group cognitive programme with main focus on memory + usual care (N = 245)	Usual care only (N = 204)
Years since diagnosis Mean (SD)	12.1 (8)	11.1 (8.7)
Relapsing-remitting Sample size	n = 159 ; % = 65	n = 132 ; % = 65
Primary progressive Sample size	n = 22 ; % = 9	n = 24 ; % = 12
Secondary progressive Sample size	n = 64 ; % = 26	n = 48 ; % = 24

Outcomes

Study timepoints

- Baseline
- 6 month (6-months - 3-4 months after intervention)
- 12 month (12-months - 9-10 months after intervention)

1 **Results - difference relative to control group**

Outcome	Group cognitive programme with main focus on memory + usual care vs Usual care only, Baseline, N2 = 204, N1 = 245	Group cognitive programme with main focus on memory + usual care vs Usual care only, 6 month, N2 = 187, N1 = 217	Group cognitive programme with main focus on memory + usual care vs Usual care only, 12 month, N2 = 173, N1 = 214
Psychological Mean (SD) baseline values were: 23.3 (5.8) vs. 24.7 (6.0) Number analysed	NA	217 vs. 187	214 vs. 173
Psychological Mean (SD) baseline values were: 23.3 (5.8) vs. 24.7 (6.0) Mean (95% CI)	NR (NR to NR)	-0.9 (-1.7 to -0.1)	-0.6 (-1.5 to 0.3)
Physical Mean (SD) baseline values were: 52.0 (13.6) vs. 53.4 (13.1) Number analysed	NA	215 vs. 187	214 vs. 173
Physical Mean (SD) baseline values were: 52.0 (13.6) vs. 53.4 (13.1) Mean (95% CI)	NR (NR to NR)	-0.6 (-2.2 to 0.9)	-0.1 (-1.8 to 1.5)

Outcome	Group cognitive programme with main focus on memory + usual care vs Usual care only, Baseline, N2 = 204, N1 = 245	Group cognitive programme with main focus on memory + usual care vs Usual care only, 6 month, N2 = 187, N1 = 217	Group cognitive programme with main focus on memory + usual care vs Usual care only, 12 month, N2 = 173, N1 = 214
Participant-reported Mean (SD) baseline values were: 45.0 (22.8) vs. 47.1 (23.2) Number analysed	NA	214 vs. 181	210 vs. 168
Participant-reported Mean (SD) baseline values were: 45.0 (22.8) vs. 47.1 (23.2) Mean (95% CI)	NR (NR to NR)	-5.3 (-8.7 to -1.9)	-4.4 (-7.8 to -0.9)
Relative-reported Mean (SD) baseline values were: 34.7 (23.4) vs. 38.2 (25.9) Number analysed	NA	184 vs. 152	164 vs. 142
Relative-reported Mean (SD) baseline values were: 34.7 (23.4) vs. 38.2 (25.9) Mean (95% CI)	NR (NR to NR)	-5.4 (-9.1 to -1.7)	-5.5 (-9.6 to -1.5)
General Health Questionnaire-30 (GHQ-30) Scale usually 0-90. Assessment of mental wellbeing. Mean (SD)	NA	212 vs. 183	209 vs. 167

Outcome	Group cognitive programme with main focus on memory + usual care vs Usual care only, Baseline, N2 = 204, N1 = 245	Group cognitive programme with main focus on memory + usual care vs Usual care only, 6 month, N2 = 187, N1 = 217	Group cognitive programme with main focus on memory + usual care vs Usual care only, 12 month, N2 = 173, N1 = 214
baseline values were: 36.5 (14.2) vs. 39.7 (15.8) Number analysed			
General Health Questionnaire-30 (GHQ-30) Scale usually 0-90. Assessment of mental wellbeing. Mean (SD) baseline values were: 36.5 (14.2) vs. 39.7 (15.8) Mean (95% CI)	NR (NR to NR)	-3.4 (-5.9 to -0.8)	-3.4 (-6.2 to -0.6)
Fatigue Severity Scale Scale used likely 1-7. Mean (SD) baseline values were: 1.4 (1.4) vs. 1.3 (1.3) Number analysed	NA	214 vs. 185	210 vs. 168
Fatigue Severity Scale Scale used likely 1-7. Mean (SD) baseline values were: 1.4 (1.4) vs. 1.3 (1.3) Mean (95% CI)	NR (NR to NR)	-0.1 (-0.3 to 0.2)	-0.3 (-0.5 to 0)

Outcome	Group cognitive programme with main focus on memory + usual care vs Usual care only, Baseline, N2 = 204, N1 = 245	Group cognitive programme with main focus on memory + usual care vs Usual care only, 6 month, N2 = 187, N1 = 217	Group cognitive programme with main focus on memory + usual care vs Usual care only, 12 month, N2 = 173, N1 = 214
EQ-5D visual analogue Scale usually 0-100. Mean (SD) baseline values were: 59.9 (21.2) vs. 59.6 (20.3) Number analysed	NA	224 vs. 187	209 vs. 173
EQ-5D visual analogue Scale usually 0-100. Mean (SD) baseline values were: 59.9 (21.2) vs. 59.6 (20.3) Mean (95% CI)	NR (NR to NR)	2.6 (-0.9 to 6)	2.6 (-0.9 to 6)
Total Mean (SD) baseline values were: 40.6 (11) vs. 40.2 (10.5) Number analysed	NA	220 vs. 182	206 vs. 170
Total Mean (SD) baseline values were: 40.6 (11) vs. 40.2 (10.5) Mean (95% CI)	NR (NR to NR)	1.6 (0.1 to 3)	0.6 (-0.9 to 2.1)

Outcome	Group cognitive programme with main focus on memory + usual care vs Usual care only, Baseline, N2 = 204, N1 = 245	Group cognitive programme with main focus on memory + usual care vs Usual care only, 6 month, N2 = 187, N1 = 217	Group cognitive programme with main focus on memory + usual care vs Usual care only, 12 month, N2 = 173, N1 = 214
Delay Mean (SD) baseline values were: 5.8 (2.8) vs. 5.7 (2.8) Number analysed	NA	220 vs. 182	206 vs. 170
Delay Mean (SD) baseline values were: 5.8 (2.8) vs. 5.7 (2.8) Mean (95% CI)	NR (NR to NR)	0.2 (-0.2 to 0.6)	0.4 (0.1 to 0.8)
Total Mean (SD) baseline values were: 18.1 (4.5) vs. 18.3 (4.9) Number analysed	NA	217 vs. 182	206 vs. 170
Total Mean (SD) baseline values were: 18.1 (4.5) vs. 18.3 (4.9) Mean (95% CI)	NR (NR to NR)	-0.6 (-1.5 to 0.3)	-0.1 (-1 to 0.8)
Delay Mean (SD) baseline values were: 6.0 (2.2) vs. 6.3 (2.1)	NA	217 vs. 182	206 vs. 170

Outcome	Group cognitive programme with main focus on memory + usual care vs Usual care only, Baseline, N2 = 204, N1 = 245	Group cognitive programme with main focus on memory + usual care vs Usual care only, 6 month, N2 = 187, N1 = 217	Group cognitive programme with main focus on memory + usual care vs Usual care only, 12 month, N2 = 173, N1 = 214
Number analysed			
Delay Mean (SD) baseline values were: 6.0 (2.2) vs. 6.3 (2.1) Mean (95% CI)	NR (NR to NR)	0 (-0.4 to 0.4)	-0.1 (-0.5 to 0.2)
SDMT Symbol Digit Modalities Test. Mean (SD) baseline values were: 36.3 (11.5) vs. 37.8 (12.1) Number analysed	NA	220 vs. 181	205 vs. 170
SDMT Symbol Digit Modalities Test. Mean (SD) baseline values were: 36.3 (11.5) vs. 37.8 (12.1) Mean (95% CI)	NR (NR to NR)	1.3 (-0.6 to 3.2)	0.4 (-1.7 to 2.5)
Easy Mean (SD) baseline values were: 31.6 (16.2) vs. 31.3 (16.4) Number analysed	NA	217 vs. 178	205 vs. 169

Outcome	Group cognitive programme with main focus on memory + usual care vs Usual care only, Baseline, N2 = 204, N1 = 245	Group cognitive programme with main focus on memory + usual care vs Usual care only, 6 month, N2 = 187, N1 = 217	Group cognitive programme with main focus on memory + usual care vs Usual care only, 12 month, N2 = 173, N1 = 214
Easy Mean (SD) baseline values were: 31.6 (16.2) vs. 31.3 (16.4) Mean (95% CI)	NR (NR to NR)	0 (-2.4 to 2.5)	-0.6 (-3.1 to 1.9)
Hard Mean (SD) baseline values were: 17.3 (16.5) vs. 15.9 (15.8) Number analysed	NA	217 vs. 178	205 vs. 169
Hard Mean (SD) baseline values were: 17.3 (16.5) vs. 15.9 (15.8) Mean (95% CI)	NR (NR to NR)	-0.3 (-2.9 to 2.2)	-1.9 (-4.8 to 1)
Word fluency Mean (SD) baseline values were: 24.8 (8.8) vs. 25.1 (8.9) Number analysed	NA	219 vs. 182	206 vs. 169
Word fluency Mean (SD) baseline values were: 24.8 (8.8) vs. 25.1 (8.9)	NR (NR to NR)	0 (-1.3 to 1.3)	-0.2 (-1.5 to 1.2)

Outcome	Group cognitive programme with main focus on memory + usual care vs Usual care only, Baseline, N2 = 204, N1 = 245	Group cognitive programme with main focus on memory + usual care vs Usual care only, 6 month, N2 = 187, N1 = 217	Group cognitive programme with main focus on memory + usual care vs Usual care only, 12 month, N2 = 173, N1 = 214
Mean (95% CI)			
Doors and people (overall age scaled score) Mean (SD) baseline values were: 7.0 (3.7) vs. 7.0 (3.9) Number analysed	NA	221 vs. 181	206 vs. 168
Doors and people (overall age scaled score) Mean (SD) baseline values were: 7.0 (3.7) vs. 7.0 (3.9) Mean (95% CI)	NR (NR to NR)	0.4 (-0.1 to 0.9)	0.6 (0 to 1.1)
Trail Making Test (B-A) Mean (SD) baseline values were: 71.7 (41.0) vs. 69.6 (41.4) Number analysed	NA	218 vs 179	205 vs. 165
Trail Making Test (B-A) Mean (SD) baseline values were: 71.7 (41.0) vs. 69.6 (41.4) Mean (95% CI)	NR (NR to NR)	-0.3 (-6.8 to 6.2)	-3.2 (-10 to 3.6)

Outcome	Group cognitive programme with main focus on memory + usual care vs Usual care only, Baseline, N2 = 204, N1 = 245	Group cognitive programme with main focus on memory + usual care vs Usual care only, 6 month, N2 = 187, N1 = 217	Group cognitive programme with main focus on memory + usual care vs Usual care only, 12 month, N2 = 173, N1 = 214
Carer Strain Index Scale unclear - possibly 0-13. Baseline values not reported Number analysed	NA	173 vs. 154	159 vs. 141
Carer Strain Index Scale unclear - possibly 0-13. Baseline values not reported Mean (95% CI)	NR (NR to NR)	-0.9 (-2.2 to 0.4)	-0.4 (-1.6 to 0.8)
Any employment 82/245 (33%) vs. 69/204 (34%) said to be in employment or education at baseline Number analysed	NA	224 vs. 187	209 vs. 173
Any employment 82/245 (33%) vs. 69/204 (34%) said to be in employment or education at baseline Odds ratio/95% CI	NR (NR to NR)	0.88 (0.55 to 1.39)	0.99 (0.6 to 1.63)

1 MSIS-29 - Polarity - Lower values are better
2 Everyday Memory Questionnaire (EMQ) - Polarity - Lower values are better

General Health Questionnaire-30 (GHQ-30) - Polarity - Lower values are better
Fatigue Severity Scale - Polarity - Lower values are better
EQ-5D visual analogue - Polarity - Higher values are better
Selective reminding test - Polarity - Higher values are better
10/36 Spatial Recall Test - Polarity - Higher values are better
SDMT - Polarity - Higher values are better
Paced Serial Addition Test (PASAT?) - Polarity - Higher values are better
Word fluency - Polarity - Higher values are better
Doors and people (overall age scaled score) - Polarity - Higher values are better
Trail Making Test (B-A) - Polarity - Lower values are better
Carer Strain Index - Polarity - Lower values are better
Final values for continuous outcomes
Note that number analysed varies depending on the outcome and where it differs to those in the table heading have been indicated separately for each result. Adjusted differences adjusted for site, multiple sclerosis type, gender and baseline score as covariates. Missing baseline scores were imputed for the analysis using the mean score at each site.

Results - raw data

Outcome	Group cognitive programme with main focus on memory + usual care , Baseline, N = 245	Group cognitive programme with main focus on memory + usual care , 6-month, N = 217	Group cognitive programme with main focus on memory + usual care , 12-month, N = 214	Usual care only, Baseline, N = 204	Usual care only, 6-month, N = 187	Usual care only, 12-month, N = 173
Adherence - attended at least 3 sessions Defined as minimum that was considered likely to affect change. Note this	n = 208 ; % = 84.9	n = NA ; % = NA	n = NA ; % = NA	n = NR ; % = NR	n = NA ; % = NA	n = NA ; % = NA

Outcome	Group cognitive programme with main focus on memory + usual care , Baseline, N = 245	Group cognitive programme with main focus on memory + usual care , 6-month, N = 217	Group cognitive programme with main focus on memory + usual care , 12-month, N = 214	Usual care only, Baseline, N = 204	Usual care only, 6-month, N = 187	Usual care only, 12-month, N = 173
was at end of intervention. No of events						

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_MSIS-29 psychological_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_MSIS-29 psychological_12 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

1 **Results_MSIS-29 physical_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_MSIS-29 physical_12 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_EMQ participant-reported_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_EMQ participant-reported_12 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

1 **Results_EMQ relative-reported_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_EMQ relative-reported_12 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_general health questionnaire_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_general health questionnaire_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_Fatigue Severity Scale_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(not specifically cognitive fatigue)*

2

3 **Results_Fatigue Severity Scale_12 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(not specifically cognitive fatigue)*

Results_EQ-5D visual analogue_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_EQ-5D visual analogue_12 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

Results_SMT total_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SMT total_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SMT delay_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1
2 **Results_SMT delay_12 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3
4 **Results_10/36 spatial recall total_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_10/36 spatial recall total_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_10/36 spatial recall delay_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_10/36 spatial recall delay_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT easy_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT easy_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT hard_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT hard_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_verbal fluency_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_verbal fluency_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_doors and people test_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_doors and people test_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Trail Making Test B-A_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Trail Making Test B-A_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_carer strain index_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

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3 **Results_carer strain index_12 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_any employment_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_any employment_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_adherence at least 3 sessions_end of intervention

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Manglani, 2020

Bibliographic Reference	Manglani, H. R.; Samimy, S.; Schirda, B.; Nicholas, J. A.; Prakash, R. S.; Effects of 4-week mindfulness training versus adaptive cognitive training on processing speed and working memory in multiple sclerosis; Neuropsychology; 2020; vol. 34 (no. 5); 591-604

1 **Study details**

Other publications associated with this study included in review	• Schirda, B., Duraney, E., Lee, H. K. et al. (2020) Mindfulness training for emotion dysregulation in multiple sclerosis: A pilot randomized controlled trial. Rehabilitation Psychology 65(3): 206-218
Trial name / registration number	NCT02717429
Study location	USA
Study setting	Outpatient - recruited from community
Study dates	Study recruitment took place from September 2015 through March 2017. Four waves of training began in October 2015, March 2016, September 2016, and March 2017, respectively.
Sources of funding	Supported by the National Multiple Sclerosis Society
Inclusion criteria	Clinical diagnosis of any MS subtype; aged 30 –59 years; absence of relapse in the last 30 days; no other diagnosed neurological disorders (e.g., dementia, Parkinson's disease, traumatic brain injury); score 23 on the Mini-Mental Status Examination; corrected visual acuity of 20/40 or better; no recent (in the previous year) or long-term experience with mindfulness meditation or cognitive training; and access to a computer and internet at home.
Exclusion criteria	No further criteria reported.
Recruitment / selection of participants	Advertisements were sent via listserv to members of our laboratory's participant database, the National Multiple Sclerosis Society, and local MS support groups.
Intervention(s)	Adaptive cognitive training covering multiple domains: training in group sessions at Ohio State University for 2 h each week over 4 weeks. Two doctoral students in clinical psychology, supervised by a licensed psychologist, facilitated these group sessions. Sessions included a combination of didactics, group discussion, and practice with the training materials. Participants were asked to supplement the training with 40 min of at-home practice on the remaining 6 days of the week and to log their practice time daily. Designed using component of previous cognitive training programmes with

	demonstrated efficacy, including adaptive difficulty and training in the basic building blocks of cognition, such as processing speed and attention, followed by higher-order cognitive domains, including executive functioning and working memory. Participants trained in these cognitive domains in the following order: processing speed (Week 1); attention (Week 2); executive function, including working memory (Weeks 3 and 4). The first hour of each group session was dedicated to didactics, wherein facilitators presented research findings on known cognitive limitations in PwMS and invited participants to share their personal experiences with this. Following this didactic portion, participants played four computer games lasting approximately 10 min each on the Posit Science BrainHQ website, and in-between games were provided brief instruction from facilitators. An algorithm matched the level of difficulty in each game to participants' current skill level, such that participants were continuously challenged as their performance improved. Mindfulness-based training: training in group sessions at Ohio State University for 2 h each week over 4 weeks. Two doctoral students in clinical psychology, supervised by a licensed psychologist, facilitated these group sessions, with the exception of one group where it was facilitated by a single student. Sessions included a combination of didactics, group discussion, and practice with the training materials. Participants were asked to supplement the training with 40 min of at-home practice on the remaining 6 days of the week and to log their practice time daily. Based on Jon Kabat-Zinn's 8-week programme, 4-week programme used in this study was designed to provide training in the skills and principles of mindfulness in an abbreviated form. First 3 weeks of the programme included breath awareness, body scan, and sitting meditation practices, with a particular emphasis on thoughts, emotions, and sensations, each designed to cultivate sustained attention. In the final week, participants practiced open monitoring of the breath, thoughts, emotions, and bodily sensations, which required concentrative attention. Over time, participants transitioned from focused-attention practices to open-monitoring practices, which required greater self-directed attentional monitoring of the present moment and invited them to bring awareness to unfolding thoughts, emotions, and sensations, moment by moment.
Population subgroups	None
Comparator	Waitlist control: did not engage in any training and invited to complete pre- and post-training assessment sessions.
Number of participants	61 randomised across the three groups, 50 analysed (cognitive training, discontinued due to n=1 relapse, n=1 illness in family, n=1 unclear; mindfulness, discontinued due to n=1 relapse, n=1 lost interested and n=2 were no shows; control,

	discontinued due to n=1 illness in family, n=1 family death, n=1 length of post-training assessment session and n=1 lost interest).
Duration of follow-up	4 weeks - end of intervention period
Indirectness	Outcome - time-point <3 months minimum specified in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (>95% both groups) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (mean scores <6.0 in both groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear (may not have been a requirement to have any impairment at baseline) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear • Computerised vs clinician led - mixed - clinician led with some computerised training • Group vs individual - group Analysis - modified intention to treat (appears to have analysed those with data at follow-up)

Study arms

Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory) (N = 20)

Waitlist control (N = 21)

Mindfulness-based training (N = 20)

Characteristics

Arm-level characteristics

Characteristic	Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory) (N = 20)	Waitlist control (N = 21)	Mindfulness-based training (N = 20)
% Female Sample size	n = 16 ; % = 80	n = 15 ; % = 71.4	n = 16 ; % = 80
Mean age (SD) Mean (SD)	44.8 (8.76)	46 (8.35)	46.5 (7.45)
Caucasian/white Sample size	n = 15 ; % = 75	n = 14 ; % = 66.7	n = 15 ; % = 75
African American/Black Sample size	n = 2 ; % = 10	n = 6 ; % = 28.6	n = 5 ; % = 25
Biracial Sample size	n = 1 ; % = 5	n = 1 ; % = 4.8	n = 0 ; % = 0
Other Sample size	n = 1 ; % = 5	n = 0 ; % = 0	n = 0 ; % = 0
Comorbidities Custom value	NR	NR	NR

Characteristic	Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory) (N = 20)	Waitlist control (N = 21)	Mindfulness-based training (N = 20)
Disease duration (years) Mean (SD)	12.3 (8.34)	11.3 (7.85)	10.1 (5.88)
EDSS score Mean (SD)	4.4 (1.07)	4.02 (1.51)	4.63 (1.29)
Relapsing-remitting Sample size	n = 20 ; % = 100	n = 20 ; % = 95	n = 19 ; % = 95
Primary progressive Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 5
Unknown Sample size	n = 0 ; % = 0	n = 1 ; % = 5	n = 0 ; % = 0

Outcomes

Study timepoints

- Baseline
- 4 week (4-weeks - end of intervention period)

Results - raw data

Outcome	Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory), Baseline, N = 20	Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory), 4-week, N = 17	Waitlist control, Baseline, N = 21	Waitlist control, 4-week, N = 17	Mindfulness-based training, Baseline, N = 20	Mindfulness-based training, 4-week, N = 16
SRT-LTS Selective Reminding Test Long-Term Storage Mean (SD)	40.8 (14.1)	43.3 (13.9)	38.7 (18.7)	44.2 (19.7)	43.1 (20.7)	50.9 (18)
SRT-CLTR Selective Reminding Test Consistent Long-Term Retrieval Mean (SD)	33.4 (14.2)	33.3 (16.6)	32.9 (21)	36.3 (23.3)	36.1 (23.4)	45.4 (23.1)
SRT-D Selective Reminding Test Delayed. Mean (SD)	8.4 (2.3)	7.59 (2.94)	7.83 (3.14)	7.53 (3.84)	8.2 (3.21)	8.75 (3.11)
10/36 SPART Immediate	20.1 (5.1)	20.3 (7.03)	20.4 (4.35)	23.1 (5.01)	21.4 (5.25)	21.9 (6.52)

Outcome	Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory), Baseline, N = 20	Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory), 4-week, N = 17	Waitlist control, Baseline, N = 21	Waitlist control, 4-week, N = 17	Mindfulness-based training, Baseline, N = 20	Mindfulness-based training, 4-week, N = 16
10/36 Spatial Recall Test Mean (SD)						
10/36 SPART-D 10/36 Spatial Recall Test-Delayed Mean (SD)	7.7 (2.23)	6.88 (2.91)	7.24 (2.53)	8.24 (2.02)	7.1 (2.4)	7.25 (2.86)
SDMT Symbol Digit Modalities Test Mean (SD)	52.6 (13.4)	53.2 (13.5)	52.3 (15.1)	53.5 (15.2)	52.3 (13.9)	61.1 (15.6)
PASAT 2 seconds Paced Auditory Serial Addition Test Mean (SD)	33.9 (10.2)	38.9 (8.61)	36.2 (9.95)	42.1 (9.87)	34.6 (11.8)	38.3 (12)

Outcome	Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory), Baseline, N = 20	Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory), 4-week, N = 17	Waitlist control, Baseline, N = 21	Waitlist control, 4-week, N = 17	Mindfulness-based training, Baseline, N = 20	Mindfulness-based training, 4-week, N = 16
PASAT 3 seconds Paced Auditory Serial Addition Test Mean (SD)	44 (10.8)	51.1 (8.52)	46.9 (10)	52.7 (6.73)	45.7 (12.4)	48.3 (12.7)
Word List Generation Mean (SD)	34.8 (8.5)	33.9 (8.58)	28.9 (9.02)	32 (8.12)	28.7 (8.91)	29.8 (8.07)
Beck Depression Inventory-II Scale usually 0-63. Mean (SD)	12.4 (7.85)	11.4 (9.28)	13.7 (12.9)	10.2 (10.1)	10.8 (9.6)	8.13 (7.55)
Penn State Worry Questionnaire. Scale usually 16-80. Mean (SD)	51.5 (13.2)	48.5 (11.8)	45.3 (16.2)	42.6 (17.5)	49.1 (17)	43.9 (16.1)
Difficulties in Emotion Regulation	4.78	5.01	4.66	4.88	4.78	5.01

Outcome	Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory), Baseline, N = 20	Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory), 4-week, N = 17	Waitlist control, Baseline, N = 21	Waitlist control, 4-week, N = 17	Mindfulness-based training, Baseline, N = 20	Mindfulness-based training, 4-week, N = 16
Scale (DERS) Scale unclear. Standard error						
Difficulties in Emotion Regulation Scale (DERS) Scale unclear. Mean (95% CI)	75.8 (66.2 to 85.3)	74.5 (64.7 to 84.4)	71.8 (62.6 to 81.1)	75 (65.3 to 84.7)	82.2 (72.7 to 91.7)	68.8 (58.8 to 78.8)
Quality of life - WHO Quality of Life and Satisfaction With Life Scale composite z-score for composite of these two scales reported (due to correlation between them) Standard error	0.21	0.21	0.21	0.21	0.21	0.22

Outcome	Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory), Baseline, N = 20	Adaptive cognitive training covering multiple domains (processing speed, attention, executive function and working memory), 4-week, N = 17	Waitlist control, Baseline, N = 21	Waitlist control, 4-week, N = 17	Mindfulness-based training, Baseline, N = 20	Mindfulness-based training, 4-week, N = 16
Quality of life - WHO Quality of Life and Satisfaction With Life Scale composite z-score for composite of these two scales reported (due to correlation between them) Mean (95% CI)	-0.14 (-0.55 to 0.29)	0.056 (-0.37 to 0.48)	0.15 (-0.26 to 0.56)	0.16 (-0.26 to 0.57)	0.0094 (-0.33 to 0.51)	0.45 (0.022 to 0.88)
Adherence - completing all four weekly sessions No of events	n = NA ; % = NA	n = 13 ; % = 65	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = 15 ; % = 75

1 SRT-LTS - Polarity - Higher values are better
2 SRT-CLTR - Polarity - Higher values are better
3 SRT-D - Polarity - Higher values are better
4 10/36 SPART Immediate - Polarity - Higher values are better
5 10/36 SPART-D - Polarity - Higher values are better
6 SDMT - Polarity - Higher values are better

PASAT 2 seconds - Polarity - Higher values are better
PASAT 3 seconds - Polarity - Higher values are better
Word List Generation - Polarity - Higher values are better
Beck Depression Inventory-II - Polarity - Lower values are better
Penn State Worry Questionnaire. - Polarity - Lower values are better
Difficulties in Emotion Regulation Scale (DERS) - Polarity - Lower values are better
Quality of life - WHO Quality of Life and Satisfaction With Life Scale composite - Polarity - Higher values are better
Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_SRT-LTS_4 weeks_adaptive cognitive training vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_SRT-CLTR_4 weeks_adaptive cognitive training vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_SRT-D_4 weeks_adaptive cognitive training vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month*

Section	Question	Answer
		minimum specified in protocol)

Results_10/36 SPART Immediate_4 weeks_adaptive cognitive training vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

1 **Results_10/36 SPART-D_4 weeks_adaptive cognitive training vs. control**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

2

3 **Results_SDMT_4 weeks_adaptive cognitive training vs. control**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_PASAT 2 seconds_4 weeks_adaptive cognitive training vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_PASAT 3 seconds_4 weeks_adaptive cognitive training vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_Word List Generation_4 weeks_adaptive cognitive training vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_Beck Depression Inventory-II_4 weeks_adaptive cognitive training vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_Penn State Worry Questionnaire_4 weeks_adaptive cognitive training vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_DERS_4 weeks_adaptive cognitive training vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month*

Section	Question	Answer
		minimum specified in protocol)

Results_quality of life_4 weeks_adaptive cognitive training vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_adherence_4 weeks_adaptive cognitive training vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_SRT-LTS_4 weeks_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_SRT-LTS_4 weeks_mindfulness vs. adaptive cognitive training

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_SRT-CLTR_4 weeks_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_SRT-CLTR_4 weeks_mindfulness vs. adaptive cognitive training

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_SRT-D_4 weeks_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_SRT-D_4 weeks_mindfulness vs. adaptive cognitive training

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month*

Section	Question	Answer
		minimum specified in protocol)

Results_SPART Immediate_4 weeks_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

1 **Results_SPART Immediate_4 weeks_mindfulness vs. adaptive cognitive training**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

2

3 **Results_10/36 SPART-D_4 weeks_mindfulness vs. control**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_10/36 SPART-D_4 weeks_mindfulness vs. adaptive cognitive training

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_SDMT_4 weeks_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_SDMT_4 weeks_mindfulness vs. adaptive cognitive training

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_PASAT 2 seconds_4 weeks_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_PASAT 2 seconds_4 weeks_mindfulness vs. adaptive cognitive training

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_PASAT 3 seconds_4 weeks_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month*

Section	Question	Answer
		minimum specified in protocol)

Results_PASAT 3 seconds_4 weeks_mindfulness vs. adaptive cognitive training

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

1 **Results_Word List Generation_4 weeks_mindfulness vs. control**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

2

3 **Results_Word List Generation_4 weeks_mindfulness vs. adaptive cognitive training**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_Beck Depression Inventory_4 weeks_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_Beck Depression Inventory_4 weeks_mindfulness vs. adaptive cognitive training

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_Penn State Worry Questionnaire_4 weeks_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_Penn State Worry Questionnaire_4 weeks_mindfulness vs. adaptive cognitive training

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_DERS_4 weeks_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results_DERS_4 weeks_mindfulness vs. adaptive cognitive training

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month*

Section	Question	Answer
		minimum specified in protocol)

Results_quality of life_4 weeks_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

1 **Results_quality of life_4 weeks_mindfulness vs. adaptive cognitive training**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

2

3 **Results_adherence_4 weeks_mindfulness vs. control**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_adherence_4 weeks_mindfulness vs. adaptive cognitive training

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Mani, 2018**

Bibliographic Reference	Mani, A.; Chohedri, E.; Ravanfar, P.; Mowla, A.; Nikseresht, A.; Efficacy of group cognitive rehabilitation therapy in multiple sclerosis; Acta Neurologica Scandinavica; 2018; vol. 137 (no. 6); 589-597

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4 **Study details**

Trial name / registration number	IRCT2016090929714N1
Study location	Iran
Study setting	Outpatient - those referred to a Neurology clinic
Study dates	Those referred to clinic between November 2016 and February 2017 invited to participate
Sources of funding	Funded by the Vice Chancellery for Research Affairs at Shiraz University of Medical Sciences, Shiraz, Iran
Inclusion criteria	Relapsing-remitting MS diagnosis; age 20-45 years; normal IQ (>90 on Raven Progressive Matrix Test); at least sixth-grade education; and minimal cognitive impairment based on Addenbrooke's cognitive examination (scores >70 - patients with severe cognitive deficits not included).

Exclusion criteria	MS flare-up within previous 6 months; any chronic illness that may affect neuropsychological system (such as neurologic, rheumatologic, infectious, or endocrine diseases as well as chronic renal/liver failure); significant primary psychiatric disorder; severe ambulation disability; pregnancy; and native language other than Farsi.
Recruitment / selection of participants	Those referred to Emam Reza Neurology Clinic at Shiraz University of Medical Sciences in Shiraz, Iran, between November 2016 and February 2017 were invited to participate in the study
Intervention(s)	Group cognitive rehabilitation: two 2 h sessions of group cognitive rehabilitation per week for 4 weeks. Compensatory, problem-based, and integrated approach based on learning theory and an information processing model to enhance general cognitive function. Total of 8 related sessions with each involving a home training assignment to apply learning to everyday life. Consisted of four main steps: psychoeducation, attention, memory, and executive function enhancement. First session involved being educated about how MS affects cognitive performance and learning about information processing model with everyday examples given for each step (then asked to write an essay about effects of MS on everyday cognitive functioning at home). Second session began with discussion of homework assignment, followed by explaining effects of mood on cognition and relaxation training as a strategy to control stress and anxiety (home assignments involved patients chronicling daily activities in 24 h and 7-day charts. Third session started with discussion of homework assignment followed by compensatory attention rehabilitation section (focused on sustained, shifting and divided attention - verbal and visual examples in training for each type of attention provided). Sessions four to seven focused on memory rehabilitation (memory processing model explained, encoding-enhancement strategies taught for example use of internal aids, and trained to use mnemonics, cueing and chunking to facilitate storage of information, methods of loci and spaced retrieval also explained to improve memory retrieval and taught to use external aids such as calendars and reminders). Eighth session began with description of executive functions and then proceeded to instruction on how previous interventions, such as self-regulation, affected this domain. Patients used their 24-hour charts of daily activities from previous sessions to improve self-regulation. They received feedback from the therapist and from other group members. Patients also learned problem-solving, decision-making, and time management techniques.
Population subgroups	None
Comparator	Control - psychoeducation and information-sharing: two 2 h non-therapeutic group sessions per week for 4 weeks. Based on psychoeducation, which was considered a sham intervention compared to the cognition-targeted group intervention received by patients in the intervention group. Control group meetings were designed as dynamic, interpersonal relationship

	training that was integrated with expressions of patients' daily life experiences regarding their disease and the sharing of scientific information about MS. These group meetings had no content related to that assessed on the outcome measures. For 3 months after the last intervention session, patients received phone call follow-ups twice a week encouraging them to use learned techniques in their everyday lives.
Number of participants	34 randomised, 30 analysed (n=2 in control group and n=1 in intervention group failed to complete 3-month study protocol and n=1 in intervention group had incomplete data at follow-up)
Duration of follow-up	Up to 3 months (2 months after the end of the intervention)
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - unclear • Severity of cognitive impairment (mild/moderate/severe) - unclear (mild/moderate included as severe was an exclusion criterion) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (possibly excluded as significant primary psychiatric disorder excluded) • Computerised vs clinician led - clinician led • Group vs individual - group Analysis - per protocol (excluded some that did not adhere to protocol, n=3)

Study arms

Group cognitive rehabilitation - psychoeducation, attention, memory and executive function (N = 17)

Control - psychoeducation and information-sharing (N = 17)

Characteristics

Arm-level characteristics

Characteristic	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function (N = 17)	Control - psychoeducation and information-sharing (N = 17)
% Female Sample size	n = 17 ; % = 100	n = 17 ; % = 100
Mean age (SD) Mean (SD)	35.29 (5.22)	35.82 (5.25)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Donepezil Sample size	n = 9 ; % = 53	n = 8 ; % = 47
Memantin Sample size	n = 8 ; % = 47	n = 9 ; % = 53

Outcomes

Study timepoints

- Baseline
- 3 month (3-months (2-months after the end of the intervention).)
- 4 week (4-weeks - end of treatment period (for one of attention outcomes as only reported at 4 weeks))

Results - raw data

Outcome	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, Baseline, N = 15	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, 3-month, N = 15	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, 4-week, N = 15	Control - psychoeducation and information-sharing, Baseline, N = 15	Control - psychoeducation and information-sharing, 3-month, N = 15	Control - psychoeducation and information-sharing, 4-week, N = 15
Addenbrooke's cognitive examination General cognitive function (orientation, attention, memory, verbal fluency, language and visuospatial ability). Scale usually 0-100.	81.41 (7.85)	93.33 (5.03)	NA (NA)	79.91 (8.34)	86.4 (6.49)	NA (NA)

Outcome	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, Baseline, N = 15	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, 3-month, N = 15	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, 4-week, N = 15	Control - psychoeducation and information-sharing, Baseline, N = 15	Control - psychoeducation and information-sharing, 3-month, N = 15	Control - psychoeducation and information-sharing, 4-week, N = 15
Mean (SD)						
Wisconsin Card Sorting Test (WCST) - Perseverative errors Executive function measure. Mean (SD)	9.64 (8.72)	4.16 (3.85)	NA (NA)	9.6 (3.99)	12.2 (4.33)	NA (NA)
Wisconsin Card Sorting Test (WCST) - Category completed Executive function measure. Mean (SD)	2.64 (1.9)	4.25 (2)	NA (NA)	2 (1.15)	2.4 (1.3)	NA (NA)
Wisconsin Card Sorting Test	18.64 (4.41)	15.08 (5.61)	NA (NA)	22.07 (5.47)	19.8 (6)	NA (NA)

Outcome	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, Baseline, N = 15	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, 3-month, N = 15	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, 4-week, N = 15	Control - psychoeducation and information-sharing, Baseline, N = 15	Control - psychoeducation and information-sharing, 3-month, N = 15	Control - psychoeducation and information-sharing, 4-week, N = 15
(WCST) - Non-perseverative errors Executive function measure. Mean (SD)						
Wisconsin Card Sorting Test (WCST) - Total time taken Executive function measure Mean (SD)	413.64 (159.07)	308.1 (100.44)	NA (NA)	415.26 (151.32)	340.8 (77.93)	NA (NA)
BRIEF-A - Global executive function Behavior rating inventory of executive function-adult.	125.2 (32.36)	97.41 (6.61)	NA (NA)	125.99 (18.22)	124 (7.03)	NA (NA)

Outcome	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, Baseline, N = 15	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, 3-month, N = 15	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, 4-week, N = 15	Control - psychoeducation and information-sharing, Baseline, N = 15	Control - psychoeducation and information-sharing, 3-month, N = 15	Control - psychoeducation and information-sharing, 4-week, N = 15
Self-report questionnaire. Measure of executive function. Scale 75-525 Mean (SD)						
Memory Functioning Questionnaire (MFQ) - general rating Scale unclear as values are lower than the range usually is (64-448). Mean (SD)	46.1 (7.3)	51.28 (4.31)	NA (NA)	44.37 (7.72)	44.41 (8.01)	NA (NA)
Visual memory	12.26 (5.33)	16.58 (2.93)	NA (NA)	10 (4.03)	12 (3.94)	NA (NA)

Outcome	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, Baseline, N = 15	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, 3-month, N = 15	Group cognitive rehabilitation - psychoeducation, attention, memory and executive function, 4-week, N = 15	Control - psychoeducation and information-sharing, Baseline, N = 15	Control - psychoeducation and information-sharing, 3-month, N = 15	Control - psychoeducation and information-sharing, 4-week, N = 15
Mean (SD)						
Verbal memory Mean (SD)	16.93 (4.78)	19.32 (3.18)	NA (NA)	15.53 (4.24)	14.05 (5.1)	NA (NA)

Addenbrooke's cognitive examination - Polarity - Higher values are better
Wisconsin Card Sorting Test (WCST) - Perseverative errors - Polarity - Lower values are better
Wisconsin Card Sorting Test (WCST) - Category completed - Polarity - Higher values are better
Wisconsin Card Sorting Test (WCST) - Non-perseverative errors - Polarity - Lower values are better
Wisconsin Card Sorting Test (WCST) - Total time taken - Polarity - Lower values are better
BRIEF-A - Global executive function - Polarity - Lower values are better
Memory Functioning Questionnaire (MFQ) - general rating - Polarity - Lower values are better
Weschler Memory Scale-Revised (WMS-R) - Polarity - Higher values are better
Final values for continuous outcomes
Despite n=17 being randomised to each group; analysis was performed on n=15 in each group.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_Addenbrooke's cognitive examination_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WCST perseverative errors_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WCST category completed_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_WCST non-perseverative errors_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WCST total time taken_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WCST_BRIEF-A Global Executive Function_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_memory functioning questionnaire general rating_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_WMS-R visual memory_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_WMS-R verbal memory_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Martin, 2014

Bibliographic Reference	Martin, K.; Lincoln, N.; das Nair, R.; Group-based memory rehabilitation for people with multiple sclerosis: subgroup analysis of the ReMiND trial; International journal of therapy & rehabilitation; 2014; vol. 21 (no. 12); 590-596

Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	• das Nair, R. and Lincoln, N. B. (2012) Evaluation of rehabilitation of memory in neurological disabilities (ReMiND): a randomized controlled trial. Clinical Rehabilitation 26(10): 894-903

Trial name / registration number	ReMIND study
Study location	UK
Study setting	Outpatient - recruited through community
Study dates	Not reported
Sources of funding	Research was supported by grants from The Stroke Association, Remedi (2006/05), Universities UK (Overseas Research Students Award Scheme), and the University of Nottingham.
Inclusion criteria	Over 18 years old; reported memory problems; and diagnosed with stroke, TBI or MS, which was verified by a clinician (note this paper focuses on MS subpopulation)
Exclusion criteria	Did not speak English; did not live within 50 miles of Nottingham or Derby; uncorrected visual or hearing impairments which prevented them from completing the assessments; overall profile score of >1 on the Rivermead Behavioural Memory Test Extended (defined as no impairment)
Recruitment / selection of participants	Advertised through clinicians and charities, such as the Multiple Sclerosis Society.
Intervention(s)	Compensatory memory training (use of external aids): intervention was carried out by research assistants who were trained by a Clinical Psychologist. Each session lasted approximately 1.5 hours with a 10–15-minute break. All sessions began with a summary of the previous session and an outline of the current session, and finished with a review of the session, assignment of homework and a preview of the next session. Each programme contained 10 sessions, one per week for 10 weeks. The purpose of the homework was to give the participants an opportunity to practice strategies learned in the session in daily life. Treatment manuals developed based on existing programmes and in consultation with practitioners. Participants in both of the intervention programmes (restitution and compensation) were taught the use of internal memory aids and errorless learning techniques. Compensation group were also taught how to use external memory aids (e.g., diaries).

	Restitution memory training (training in coding, organisation and retrieval of information - internal aids): intervention was carried out by research assistants who were trained by a Clinical Psychologist. Each session lasted approximately 1.5 hours with a 10–15-minute break. All sessions began with a summary of the previous session and an outline of the current session, and finished with a review of the session, assignment of homework and a preview of the next session. Each programme contained 10 sessions, one per week for 10 weeks. The purpose of the homework was to give the participants an opportunity to practice strategies learned in the session in daily life. Treatment manuals developed based on existing programmes and in consultation with practitioners. Participants in both of the intervention programmes (restitution and compensation) were taught the use of internal memory aids and errorless learning techniques. Those in the restitution group completed exercises to practice encoding and retrieval, and also included attention-retraining exercises, such as letter and number cancellation. Participants in the restitution group were also taught how to encode and retrieve specific information (e.g., remembering people's names by paying attention not only to the acoustic and orthographic presentation of the name but by creating a visual image of the name).
Population subgroups	None
Comparator	Self-help control group not taught any memory strategies, but were taught relaxation techniques and ways in which they could cope with their condition.
Number of participants	39 randomised,
Duration of follow-up	Up to 7-month follow-up (5- and 7-month time-points - 2-3 and 4-5 months following end of intervention)
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - unclear • According to disability (EDSS <6 and EDSS ≥6) - unclear • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear • Computerised vs clinician led - clinician-led

	• Group vs individual - group Analysis - intention to treat (appear to be no dropouts and stated intention to treat used)

Study arms

Compensatory memory training (use of external aids) (N = 12)

Restitution memory training (training in coding, organisation and retrieval of information - internal aids) (N = 17)

Self-help control group (N = 10)

Characteristics

Arm-level characteristics

Characteristic	Compensatory memory training (use of external aids) (N = 12)	Restitution memory training (training in coding, organisation and retrieval of information - internal aids) (N = 17)	Self-help control group (N = 10)
% Female Sample size	n = 9 ; % = 75	n = 13 ; % = 76	n = 7 ; % = 70
Mean age (SD) Mean (SD)	48.3 (10.8)	45.2 (7.5)	47.7 (10.9)

Characteristic	Compensatory memory training (use of external aids) (N = 12)	Restitution memory training (training in coding, organisation and retrieval of information - internal aids) (N = 17)	Self-help control group (N = 10)
Ethnicity Custom value	NR	NR	NR
Comorbidities Custom value	NR	NR	NR
Time since disease (Months) Mean (SD)	131.5 (98.2)	100.8 (93.6)	95.7 (55.1)

Outcomes

Study timepoints

- Baseline
- 5 month (5-months - 2-3 months after end of intervention)
- 7 month (7-months - 4-5 months after end of intervention)

1 **Results - raw data**

Outcome	Compensatory memory training (use of external aids), Baseline, N = 12	Compensatory memory training (use of external aids), 5-month, N = 17	Compensatory memory training (use of external aids), 7-month, N = 10	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), Baseline, N = 12	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), 5-month, N = 17	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), 7-month, N = 12	Self-help control group, Baseline, N = 11	Self-help control group, 5-month, N = 17	Self-help control group, 7-month, N = 10
Everyday Memory Questionnaire Scale unclear - usually 0-140. Subjective assessment of memory. Median (SD)	NR	43.0 (18.7)	39.0 (19.2)	NR	36.0 (25.3)	30.0 (25.2)	NR	38.0 (18.9)	41.0 (20.6)
Everyday Memory Questionnaire Scale unclear - usually 0-140. Subjective	NA	11	11	NA	16	16	NA	10	10

Outcome	Compensatory memory training (use of external aids), Baseline, N = 12	Compensatory memory training (use of external aids), 5-month, N = 17	Compensatory memory training (use of external aids), 7-month, N = 10	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), Baseline, N = 12	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), 5-month, N = 17	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), 7-month, N = 12	Self-help control group, Baseline, N = 11	Self-help control group, 5-month, N = 17	Self-help control group, 7-month, N = 10
assessment of memory. Number analysed									
Rivermead Behavioural Memory Questionnaire - Extended Scale unclear. Median (SD)	NR	27.0 (7.7)	26.5 (6.1)	NRN	26.0 (7.6)	29.0 (7.9)	NR	24.5 (9.8)	22.5 (9.3)
General Health Questionnaire Scale unclear.	NR	2.0 (3.8)	2.5 (3.6)	*empty data*	4.0 (3.8)	7.0 (4.4)	NR	3.0 (4.0)	2.0 (3.8)

Outcome	Compensatory memory training (use of external aids), Baseline, N = 12	Compensatory memory training (use of external aids), 5-month, N = 17	Compensatory memory training (use of external aids), 7-month, N = 10	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), Baseline, N = 12	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), 5-month, N = 17	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), 7-month, N = 12	Self-help control group, Baseline, N = 11	Self-help control group, 5-month, N = 17	Self-help control group, 7-month, N = 10
Mental health measure. Median (SD)									
Extended Activities of Daily Living Scale usually 0-66. Median (SD)	NR	53.0 (11.9)	54.0 (11.9)	NR	47.0 (12.9)	48.5 (10.9)	NR	50.0 (14.1)	55.0 (12.4)
Extended Activities of Daily Living Scale usually 0-66.	NA	16	16	NA	9	9	NA	10	10

Outcome	Compensatory memory training (use of external aids), Baseline, N = 12	Compensatory memory training (use of external aids), 5-month, N = 17	Compensatory memory training (use of external aids), 7-month, N = 10	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), Baseline, N = 12	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), 5-month, N = 17	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), 7-month, N = 12	Self-help control group, Baseline, N = 11	Self-help control group, 5-month, N = 17	Self-help control group, 7-month, N = 10
Number analysed									
Wimbledon Self-Report Scale Assesses mood. Scale usually 0-30. Median (SD)	NR	16.0 (4.1)	16,5 (3.9)	NR	21.0 (7.6)	22.0 (7.2)	NR	18.0 (7.9)	20.0 (7.4)
Wimbledon Self-Report Scale Assesses mood. Scale usually 0-30.	NA	10	10	NA	15	15	NA	7	7

Outcome	Compensatory memory training (use of external aids), Baseline, N = 12	Compensatory memory training (use of external aids), 5-month, N = 17	Compensatory memory training (use of external aids), 7-month, N = 10	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), Baseline, N = 12	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), 5-month, N = 17	Restitution memory training (training in coding, organisation and retrieval of information - internal aids), 7-month, N = 12	Self-help control group, Baseline, N = 11	Self-help control group, 5-month, N = 17	Self-help control group, 7-month, N = 10
Number analysed									

Everyday Memory Questionnaire - Polarity - Lower values are better
Rivermead Behavioural Memory Questionnaire - Extended - Polarity - Higher values are better
General Health Questionnaire - Polarity - Lower values are better
Extended Activities of Daily Living - Polarity - Higher values are better
Wimbledon Self-Report Scale - Polarity - Lower values are better
Final values for continuous outcomes
Note number analysed varies depending on outcome and indicated below for each outcome that differs to the numbers given in table heading.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_Everyday Memory Questionnaire_compensatory vs. restitution_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Everyday Memory Questionnaire_compensatory vs. restitution_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Everyday Memory Questionnaire_compensatory vs. control_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Everyday Memory Questionnaire_compensatory vs. control_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_Everyday Memory Questionnaire_restitution vs. control_5 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_Everyday Memory Questionnaire_restitution vs. control_7 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Rivermead Behavioural Memory Questionnaire_compensatory vs. restitution_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Rivermead Behavioural Memory Questionnaire_compensatory vs. restitution_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Rivermead Behavioural Memory Questionnaire_compensatory vs. control_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Rivermead Behavioural Memory Questionnaire_compensatory vs. control_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Rivermead Behavioural Memory Questionnaire_restitution vs. control_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Rivermead Behavioural Memory Questionnaire_restitution vs. control_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_General Health Questionnaire_compensatory vs. restitution_5 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_General Health Questionnaire_compensatory vs. restitution_7 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_General Health Questionnaire_compensatory vs. control_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_General Health Questionnaire_compensatory vs. control_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_General Health Questionnaire_restitution vs. control_5 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_General Health Questionnaire_restitution vs. control_7 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Extended Activities of Daily Living_compensatory vs. restitution_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Extended Activities of Daily Living_compensatory vs. restitution_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_Extended Activities of Daily Living_compensatory vs. control_5 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_Extended Activities of Daily Living_compensatory vs. control_7 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Extended Activities of Daily Living_restitution vs. control_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Extended Activities of Daily Living_restitution vs. control_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_Wimbledon Self-Report Scale_compensatory vs. restitution_5 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_Wimbledon Self-Report Scale_compensatory vs. restitution_7 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Wimbledon Self-Report Scale_compensatory vs. control_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Wimbledon Self-Report Scale_compensatory vs. control_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Wimbledon Self-Report Scale_restitution vs. control_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Wimbledon Self-Report Scale_restitution vs. control_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Mattioli, 2016

Bibliographic Reference	Mattioli, F.; Bellomi, F.; Stampatori, C.; Provinciali, L.; Compagnucci, L.; Uccelli, A.; Pardini, M.; Santuccio, G.; Fregonese, G.; Pattini, M.; Allegri, B.; Clerici, R.; Lattuada, A.; Montomoli, C.; Corso, B.; Gallo, P.; Riccardi, A.; Ghezzi, A.; Roscio, M.; Tola, M. R.; Calanca, C.; Baldini, D.; Trafficante, D.; Capra, R.; Two Years Follow up of Domain Specific Cognitive Training in Relapsing Remitting Multiple Sclerosis: A Randomized Clinical Trial; Frontiers in Behavioral Neuroscience; 2016; vol. 10; 28

Study details

Secondary publication of another included study- see primary study for details	• Mattioli, F., Stampatori, C., Bellomi, F. et al. (2014) A RCT Comparing Specific Intensive Cognitive Training to Aspecific Psychological Intervention in RRMS: The SMICT Study. Frontiers in neurology [electronic resource]. 5: 278

Mattioli, 2014

Bibliographic Reference	Mattioli, F.; Stampatori, C.; Bellomi, F.; Danni, M.; Compagnucci, L.; Uccelli, A.; Pardini, M.; Santuccio, G.; Fregonese, G.; Pattini, M.; Allegri, B.; Clerici, R.; Lattuada, A.; Montomoli, C.; Corso, B.; Capra, R.; A RCT Comparing Specific Intensive Cognitive Training to Aspecific Psychological Intervention in RRMS: The SMICT Study; Frontiers in neurology [electronic resource].; 2014; vol. 5; 278

Study details

Other publications associated with this study included in review	• Mattioli, F., Bellomi, F., Stampatori, C. et al. (2016) Two Years Follow up of Domain Specific Cognitive Training in Relapsing Remitting Multiple Sclerosis: A Randomized Clinical Trial. Frontiers in Behavioral Neuroscience 10: 28
Trial name / registration number	SMICT study. NP:560.
Study location	Italy
Study setting	Unclear - likely outpatient. 10 Italian MS Centres.
Study dates	Patients' enrolment started on June 2010 and ended 31 December 2011.
Sources of funding	Not reported
Inclusion criteria	Diagnosed as affected with MS, according to Poser et al. criteria with a relapsing remitting course; have been prescribed interferon beta 1A 44 mcg three times/week no later than 6 months before, in order to have the most homogeneous drug regimen in patients; impaired (age corrected z-score≤1.5 SD to norms) in at least one of the following test of the Italian version of the Rao's Brief Repeatable Battery: Paced Auditory Serial Addition Task (PASAT 200, PASAT 300), Symbol Digit

	modality Test (SDMT), Spatial Recall Test (SPART) 10/36, and Delayed Recall (SPART D), Selective Reminding Test Long-Term storage (SRT LTS), Consistent Long-Term Retrieval (SRT CLTR), Delayed Recall (SRT DR) (23), Controlled Oral Words Association (COWA) with the Phoneme (P) and Category (C) modalities (12), and Stroop test;
Exclusion criteria	Dementia (excluded by means of anamnestic reports as well as MMSE >24 in patients), previous or present psychiatric disorders (requiring pharmacological treatment) and clinically evident relapse in the previous 6 months.
Recruitment / selection of participants	Recruited from 10 Italian MS Centres
Intervention(s)	Specific cognitive training - differed depending on the cognitive impairments experienced: scheduled duration was 15 consecutive weeks (2 60 min sessions per week) by an expert neuropsychologist, different from the evaluating one. If missed three sessions, then excluded from study. Administered according to the impaired neuropsychological function: Plan a Day software of the Rehacom was used if a patient resulted impaired in executive function (poor score was in the Stroop test or in the COWA P or COWA/C); Memory software of the same package was used if the patient was impaired in either the SRT or SPART verbal or spatial memory measures, and attention/speeded information processing training if they were impaired in this domain (pathological PASAT 200, PASAT 300, SDMT). If a patient was impaired in more than one domain, all the single domain trainings were balanced in the hourly session each time. Exercises complexity was adapted each time to the severity of each single patient's impairment in the selected domain, with the aim that the exercise had to be challenging in each treatment session. Plan a day trains ability to organise, plan and develop solution strategies using realistic situations. For memory, patients asked to give answers to multiple choice or open questions about tales of increasing length. Information processing training involved increasing velocity previously shown to be effective in people with brain injuries - modified PASAT task with numbers, words and months of the year.
Population subgroups	None
Comparator	Non-specific intervention - psychoeducation with no cognitive skill training: conducted by the psychologist by using conversation about the patient's disease perception, his/her work, family, and hobbies, with the aim not to specifically exercise a cognitive ability, avoiding treating depression or to have any behavioural or psychoanalytic approach. All the psychologists were trained by attending 10 consecutive training meetings with the psychologists of the coordinator centre.
Number of participants	41 randomised, 41 analysed at 1-year follow-up

Duration of follow-up	1-year follow-up (possibly 8-9 months after end of intervention)
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (median 2.0 in both groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear (said to be moderate based on number of tests the population had impairments in) • Disease modifying treatment status (currently using and not currently using) - using (all had to be using interferon beta 1A) • Mood disorders (presence or absence) - possibly absent (excluded psychiatric disorders where medication was being used for them) • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - intention to treat (appear to be no dropouts)

Study arms

Specific cognitive training - differed depending on the cognitive impairments experienced (N = 22)

Non-specific intervention - psychoeducation with no cognitive skill training (N = 19)

Characteristics

Arm-level characteristics

Characteristic	Specific cognitive training - differed depending on the cognitive impairments experienced (N = 22)	Non-specific intervention - psychoeducation with no cognitive skill training (N = 19)
% Female Sample size	n = 13 ; % = 59.1	n = 11 ; % = 57.9
Mean age (SD) Median (IQR)	45 (38 to 50)	43 (34 to 53)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Disease duration (Months) Median (IQR)	23.5 (12 to 120)	36 (12 to 96)
Relapses during previous year Median (IQR)	1 (0 to 2)	1 (1 to 2)
EDSS score	2 (2 to 3)	2 (1 to 3.5)

Characteristic	Specific cognitive training - differed depending on the cognitive impairments experienced (N = 22)	Non-specific intervention - psychoeducation with no cognitive skill training (N = 19)
Median (IQR)		

Outcomes

Study timepoints

- Baseline
- 1 year (1-year follow-up - possibly 8-9 months after end of intervention)

Results - change from baseline

Outcome	Specific cognitive training - differed depending on the cognitive impairments experienced, 1 year vs Baseline, N = 22	Non-specific intervention - psychoeducation with no cognitive skill training, 1 year vs Baseline, N = 19
PASAT 3 seconds Paced Auditory Serial Addition Test. P=0.46 between groups. Median (IQR)	6 (2 to 10)	4 (0 to 9)
PASAT 2 seconds Paced Auditory Serial Addition Test. P=0.42 between groups. Median (IQR)	8 (0 to 10)	3 (0 to 8)
SPART 10/36 10/36 Spatial Recall Test for visuo-spatial	4 (1 to 7)	0 (-1 to 5)

Outcome	Specific cognitive training - differed depending on the cognitive impairments experienced, 1 year vs Baseline, N = 22	Non-specific intervention - psychoeducation with no cognitive skill training, 1 year vs Baseline, N = 19
learning – long-term retrieval. P=0.0395 between groups. Median (IQR)		
SPARTDR Spatial Recall Test for visuo-spatial learning – delayed recall. P=0.36 between groups Median (IQR)	1 (0 to 4)	0 (-1 to 3)
SRT-LTS Selective Reminding Test – Long-Term storage. P=0.34 between groups Median (IQR)	10 (4 to 16)	6 (0 to 17)
SRT-CLTR Selective Reminding Test – Consistent Long-Term Retrieval. P=0.22 between groups Median (IQR)	7.5 (2 to 16)	4 (-4 to 12)
SRT/DR Selective Reminding Test – delayed recall. P=0.0076 between groups	1.5 (1 to 3)	0 (-1 to 1)

Outcome	Specific cognitive training - differed depending on the cognitive impairments experienced, 1 year vs Baseline, N = 22	Non-specific intervention - psychoeducation with no cognitive skill training, 1 year vs Baseline, N = 19
Median (IQR)		
Symbol digit modalities test SDMT. P=0.24 between groups Median (IQR)	3 (1 to 7)	1 (0 to 5)
COWA/P Controlled Oral Words Association – Phoneme. P=0.36 between groups Median (IQR)	3 (-1 to 8)	1 (-2 to 4)
COWAC Controlled Oral Words Association – Category. P=0.20 between groups Median (IQR)	3.5 (2 to 7)	2 (-2 to 6)
Stroop Test P=0.96 between groups Median (IQR)	2 (-1 to 7)	2 (-1 to 5)
MS Quality of Life-54 Scale usually 0-100. P=0.98 between groups Median (IQR)	0 (-12 to 9)	1 (-9 to 7)

Outcome	Specific cognitive training - differed depending on the cognitive impairments experienced, 1 year vs Baseline, N = 22	Non-specific intervention - psychoeducation with no cognitive skill training, 1 year vs Baseline, N = 19
Montgomery–Asberg Depression Rating Scale Scale usually 0-60. P=0.72 between groups Median (IQR)	-0.5 (-3 to 1)	0 (-4 to 1)
Modified fatigue impact scale Scale usually 0-84 if total score reported. . P=0.52 between groups Median (IQR)	-2.5 (-8 to 0)	-1 (-9 to 4)

PASAT 3 seconds - Polarity - Higher values are better
PASAT 2 seconds - Polarity - Higher values are better
SPART 10/36 - Polarity - Higher values are better
SPARTDR - Polarity - Higher values are better
SRT-LTS - Polarity - Higher values are better
SRT-CLTR - Polarity - Higher values are better
SRT/DR - Polarity - Higher values are better
Symbol digit modalities test - Polarity - Higher values are better
COWA/P - Polarity - Higher values are better
COWAC - Polarity - Higher values are better
Stroop Test - Polarity - Higher values are better
MS Quality of Life-54 - Polarity - Higher values are better
Montgomery–Asberg Depression Rating Scale - Polarity - Lower values are better
Modified fatigue impact scale - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_PASAT 3 seconds_1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT 2 seconds_1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_SPART 10/36_1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_SPART-DR_1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_SRT-LTS_1 year**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_SRT-CLTR_1 year**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_SRT-DR_1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_COWA-P_1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_COWA-C_1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_Stroop Test_1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_MSQoL-54_1 year**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_Montgomery-Asberg Depression Rating Scale_1 year**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Modified Fatigue Impact Scale_1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(not specifically cognitive fatigue)*

Messinis, 2020

Bibliographic Reference	Messinis, L.; Kosmidis, M. H.; Nasios, G.; Konitsiotis, S.; Ntoskou, A.; Bakirtzis, C.; Grigoriadis, N.; Patrikelis, P.; Panagiotopoulos, E.; Gourzis, P.; Malefaki, S.; Papathanasopoulos, P.; Do Secondary Progressive Multiple Sclerosis patients benefit from Computer- based cognitive neurorehabilitation? A randomized sham-controlled trial; Multiple Sclerosis and Related Disorders; 2020; vol. 39; 101932

Study details

Trial name / registration number	Not reported
Study location	Greece
Study setting	Outpatient - informed of study by consulting neurologists
Study dates	Recruitment and enrolment performed between January 2018 and February 2019
Sources of funding	Reported not to have received any specific funding
Inclusion criteria	Diagnosis of secondary progressive MS based on McDonald criteria, without any relapses or MRI activity in the last 12 months (none were receiving disease-modifying therapy and no activity was observed throughout the study); patients aged between 25 and 60; educational level of at least 6 years (primary school graduates in Greece); EDSS score no higher than 7; cognitive deficit on at least two domains of the Central Nervous System Vital Sign neuropsychological screening battery

	(performance 1.5 SD below healthy control group data); native Greek speakers; provision of written informed consent to take part in the study; normal or corrected hearing and vision; and IQ score of ≥80 on the Greek-validated Wechsler Abbreviated Scale of Intelligence or normal intelligence as assessed by clinical evaluation.
Exclusion criteria	Ongoing major psychiatric disorders (e.g. psychotic symptoms or disorders, illegal drug use or alcohol abuse); presence of another neurological disorder (e.g., dementia, stroke, epilepsy, and traumatic brain injury resulting in a loss of consciousness for more than 30 minutes); Mini-Mental State Examination score ≥ 24; treated with cognitive rehabilitation in the 12 months prior to enrolment; initiation of psychotropic medications or medications for spasticity, tremor, bladder disturbances, and fatigue (if already taking such medications, doses and schedules had to be held constant during the study period).
Recruitment / selection of participants	Recruitment and enrolment performed between January 2018 and February 2019. Patients attending either the outpatient neurology department at the University Hospital of Patras in Greece or the MS centre at AHEPA University Hospital in Thessaloniki. Recruited by consulting neurologists.
Intervention(s)	Cognitive rehabilitation using RehaCom: 24 individualised domain and task-specific sessions (45 min over an 8-week period - 3 sessions per week) performed at home by the patient on their own or with supervision of a caregiver. RehaCom Cognitive Therapy software was used. As most of those included were impaired in more than one cognitive domain but mostly on episodic memory, information processing speed/attention, and executive functions, the intervention was balanced over the 8-week period in order to train all domains equally. Attention - 'attention and concentration' and 'divided attention' modules. Memory - 'topological memory' and 'verbal memory' modules. Executive function - 'logical reasoning' and 'shopping' modules/tasks. To ensure patients and caregivers understood procedures and instructions, they were trained by psychologists at respective MS clinics. Caregivers present during each session for entire period but told not to provide any assistance regarding their performance. Psychologists visited patient homes and present during first training sessions to solve any problems or difficulty. Phone calls every week to encourage patient adherence/compliance and provide solutions to problems. Conducted on desktop computers with separate screens.
Population subgroups	None
Comparator	Sham cognitive intervention: usual care + sham cognitive intervention. Non-specific computerised activities including solving puzzles, reading and understanding magazines and newspapers, shopping games, brain teasers etc. were used. Patients performed at home in presence of caregiver for 45 min, three times weekly for 8 weeks. Caregivers informed not to provide any assistance relating to performance. Psychologists visited patient homes during first training session to ensure

	PCs functioning and assisted patients in finding activities on the internet. Phone calls every week to encourage patient adherence/compliance and provide solutions to problems. Also continued standard clinical care - taking their prescribed medication and all other related treatments (e.g., physiotherapy, psychotherapy), and all other clinical or referral services were available to them as usual for the entire period.
Number of participants	36 randomised, 36 analysed at end of treatment (8 weeks)
Duration of follow-up	8 weeks - end of intervention period
Indirectness	Outcome - time-point <3 months minimum in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all secondary progressive MS • According to disability (EDSS <6 and EDSS ≥6) - borderline (median 5.5 in one group and 6.0 in the other) • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - not using (reported that none were taking these) • Mood disorders (presence or absence) - unclear (major psychiatric disorders excluded) • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - intention to treat (appear to be no dropouts)

Study arms

Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training (N = 19)

Control - usual care + sham computer exercises (N = 17)

Characteristics

Arm-level characteristics

Characteristic	Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training (N = 19)	Control - usual care + sham computer exercises (N = 17)
% Female Sample size	n = 12 ; % = 63.2	n = 12 ; % = 70.6
Mean age (SD) Mean (SD)	46.47 (4.1)	45.29 (3.9)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Disease duration (years) Mean (SD)	21.15 (5.1)	20.76 (4.1)
EDSS score Median (IQR)	5.5 (4.5 to 7)	6 (5 to 7)

Outcomes

Study timepoints

- Baseline
- 8 week (8-weeks - end of intervention period)

Results - change from baseline

Outcome	Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training, 8-week vs Baseline, N = 19	Control - usual care + sham computer exercises, 8-week vs Baseline, N = 17
SDMT Symbol Digit Modalities Test. Baseline values were: 34.94 (10.0) vs. 33.23 (9.6) Mean (SD)	5.47 (3.51)	-1.7 (3.13)
Greek Verbal Learning Test Baseline values were: 50.00 (10.1) vs. 48.29 (8.1) Mean (SD)	8.1 (5.76)	-0.94 (2.72)
BVMT-RT Brief Visuospatial Memory Test-Revised Total Recall. Baseline values were: 15.10(4.7) vs. 15.58 (4.8) Mean (SD)	3.78 (1.87)	0.29 (2.25)

Outcome	Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training, 8-week vs Baseline, N = 19	Control - usual care + sham computer exercises, 8-week vs Baseline, N = 17
EQ-5D Visual Analogue Scale Scale usually 0-100. Baseline values were: 50.74 (16.2) vs. 55.29 (14.6) Mean (SD)	9.42 (4.79)	-1.17 (7.6)
Modified Fatigue Impact Scale - Cognitive Scale usually 0-40. Baseline values were: 28.10 (3.8) vs. 28.76 (3.1) Mean (SD)	-5.68 (3.26)	-0.88 (2.26)
Beck Depression Inventory - Fast Screen Scale usually 0-21. Baseline values were: 6.26 (3.1) vs. 6.47 (3.50) Mean (SD)	-2.57 (2.36)	0.29 (2.82)

1 SDMT - Polarity - Higher values are better
2 Greek Verbal Learning Test - Polarity - Higher values are better
3 BVMT-RT - Polarity - Higher values are better
4 EQ-5D Visual Analogue Scale - Polarity - Higher values are better
5 Modified Fatigue Impact Scale - Cognitive - Polarity - Lower values are better
6 Beck Depression Inventory - Fast Screen - Polarity - Lower values are better

7

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_SDMT_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_Greek verbal learning test_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_BVMT-RT_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_EQ-5D visual analogue scale_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results MFIS cognitive_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Resutls_Beck Depression Inventory_8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Messinis, 2017

Bibliographic Reference	Messinis, L.; Nasios, G.; Kosmidis, M. H.; Zampakis, P.; Malefaki, S.; Ntoskou, K.; Nousia, A.; Bakirtzis, C.; Grigoriadis, N.; Gourzis, P.; Papathanasopoulos, P.; Efficacy of a Computer-Assisted Cognitive Rehabilitation Intervention in Relapsing-Remitting Multiple Sclerosis Patients: A Multicenter Randomized Controlled Trial; Behavioural Neurology; 2017; vol. 2017; 5919841

Study details

Trial name / registration number	Not reported
Study location	Greece
Study setting	Outpatient - from outpatient clinic or community
Study dates	Recruitment between March 2014 and December 2015
Sources of funding	Not reported
Inclusion criteria	Diagnosis of relapsing-remitting MS based on McDonald criteria; patients aged between 21 and 60; educational level of at least 6 years (primary school graduates in Greece); EDSS score of between 0–5; cognitive deficit on at least one domain of the Central Nervous System Vital Sign neuropsychological screening battery (performance between the 2nd and 8th percentile based on CNSVS demographically corrected normative data); native Greek speakers; provision of written informed consent to take part in the study; normal or corrected hearing and vision; and Q score of ≥80 on the Greek-validated Wechsler Abbreviated Scale of Intelligence.
Exclusion criteria	Ongoing major psychiatric disorders (e.g., psychotic symptoms or disorders, illegal drugs, or alcohol abuse); (presence of another neurological disorder (e.g., dementia, stroke, epilepsy, and traumatic brain injury resulting in a loss of consciousness for more than 30 minutes); Mini-Mental State Examination score ≥ 24; one or more exacerbations in the 3 months prior to enrolment and immunological or immunosuppressant treatment initiated within 4 months prior to enrolment or treated with cognitive rehabilitation in the 12 months prior to enrolment; initiation of psychotropic medications or medications for spasticity, tremor, bladder disturbances, and fatigue (if already taking such medications, doses and schedules had to be held constant during the study period).
Recruitment / selection of participants	Between March of 2014 and December of 2015 patients attending either the outpatient neurology department at the University Hospital of Patras in Greece or the “Society of friends of patients with multiple sclerosis” situated in Ioannina were referred for assessment at outpatient memory and neuropsychological unit
Intervention(s)	Cognitive rehabilitation using RehaCom software: 20 individualised 1 h sessions over a 10-week period (2 sessions per week). The rehabilitation program was conducted by trained clinicians, either speech and language therapists or

	psychologists, and supervised by a clinical neuropsychologist, on a desktop computer with a large screen. RehaCom Cognitive Therapy software was used. As most of those included were impaired in more than one cognitive domain but mostly on episodic memory, information processing speed/attention, and executive functions, the intervention was balanced over the 10-week period in order to train all domains equally. Attention - 'attention and concentration' and 'divided attention' modules. Memory - 'topological memory' and 'verbal memory' modules. Executive function - 'logical reasoning' and 'shopping' modules/tasks.
Population subgroups	None
Comparator	Control - usual care: standard clinical care. Continued taking their prescribed medication and all other related treatments (e.g., physiotherapy, psychotherapy), and all other clinical or referral services were available to them as usual for the entire 10 weeks that the intervention group received cognitive training.
Number of participants	58 randomised, 58 randomised at 10 weeks (end of treatment). 6-month time-point reported but only provides data for the intervention group (non-comparative data).
Duration of follow-up	10 weeks - end of treatment period
Indirectness	Outcome - time-point <3-month minimum specified in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (0-5 inclusion criterion) • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - using (majority of >65% in both groups using) • Mood disorders (presence or absence) - unclear (major psychiatric disorders excluded) • Computerised vs clinician led - computerised • Group vs individual - individual

	Analysis - intention to treat (appear to be no dropouts)

Study arms

Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training (N = 32)

Control - usual care (N = 26)

Characteristics

Arm-level characteristics

Characteristic	Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training (N = 32)	Control - usual care (N = 26)
% Female Sample size	n = 22 ; % = 68.75	n = 18 ; % = 69.24
Mean age (SD) Mean (SD)	46.03 (7.97)	45.15 (9.65)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR

Characteristic	Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training (N = 32)	Control - usual care (N = 26)
EDSS score Median (range)	3.0 (1.5-5.5)	3.5 (1.0-5.0)
Disease duration (years) Median (range)	13.31 (11.46-15.17)	11.27 (9.39-13.14)
Interferon Sample size	n = 25 ; % = 78.12	n = 17 ; % = 65.38
Fingolimod Sample size	n = 2 ; % = 6.25	n = 3 ; % = 11.53
Natalizumab Sample size	n = 5 ; % = 15.63	n = 6 ; % = 23.07

Outcomes

Study timepoints

- Baseline
- 10 week (10-weeks - end of intervention period)

1 **Results - raw data**

Outcome	Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training , Baseline, N = 32	Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training , 10-week, N = 32	Control - usual care, Baseline, N = 26	Control - usual care, 10-week, N = 26
SRT-LTS Selective Reminding Test Long-Term Storage Mean (SD)	36.72 (5.94)	43.47 (8.09)	36.42 (5.08)	36.38 (5.06)
SRT/DR Selective Reminding Test-Delayed Recall Mean (SD)	6.09 (1.82)	8.22 (1.75)	7.15 (1.25)	7.12 (7.12)
BVMT-RT Brief Visuospatial Memory Test-Revised Total Recall Mean (SD)	21.4 (5.85)	24.5 (6.02)	22.5 (7.8)	20.8 (6.85)
Verbal Fluency Test - Phonemic Mean (SD)	31.88 (8.2)	33.13 (7.01)	29.81 (8.46)	29.95 (7.88)
Verbal Fluency Test - Semantic Mean (SD)	41.03 (8.16)	43.56 (8.34)	40.5 (9.44)	39.58 (9.83)

Outcome	Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training , Baseline, N = 32	Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training , 10-week, N = 32	Control - usual care, Baseline, N = 26	Control - usual care, 10-week, N = 26
SDMT Symbol Digit Modalities Test Mean (SD)	36.91 (8.36)	40.03 (7.08)	37.42 (10.87)	37.43 (9.85)
Trail Making Test - Part A Mean (SD)	73.5 (23.35)	59.53 (18.49)	69.27 (20.3)	68.88 (20.32)
Trail Making Test - Part B Mean (SD)	145.81 (46.29)	113.28 (51.47)	111.54 (37.89)	110.96 (36.6)
Stroop Neuropsychological Screening Test Mean (SD)	59.8 (15.5)	63.5 (13.25)	58.7 (17.3)	57.6 (14.2)
Satisfaction Measured for different domains using Likert scales but results only given as a narrative summary Custom value	NA	*empty data*	NA	NR

Outcome	Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training , Baseline, N = 32	Cognitive rehabilitation using RehaCom - executive function, attention, memory and information processing speed training , 10-week, N = 32	Control - usual care, Baseline, N = 26	Control - usual care, 10-week, N = 26
Benefits and recommending to someone else with MS Custom value	NA	n=30 reported large personal benefits gained, improvement in cognition and would recommend it	NA	NR
Benefits in terms of everyday life activities Custom value	NA	n=28 reported large benefits in terms of everyday life activities	NA	NR
Adherence - completing 10-week intervention No of events	n = NA ; % = NA	n = 32 ; % = 100	n = NA ; % = NA	n = NA ; % = NA

SRT-LTS - Polarity - Higher values are better
SRT/DR - Polarity - Higher values are better
BVMT-RT - Polarity - Higher values are better
Verbal Fluency Test - Phonemic - Polarity - Higher values are better
Verbal Fluency Test - Semantic - Polarity - Higher values are better
SDMT - Polarity - Higher values are better
Trail Making Test - Part A - Polarity - Higher values are better
Trail Making Test - Part B - Polarity - Higher values are better
Stroop Neuropsychological Screening Test - Polarity - Higher values are better
Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_SRT-LTS_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

1 **Results_SRT-DR_10 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

2

3 **Results_BVMT-RT_10 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_Verbal fluency test - phonemic_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_Verbal fluency test - semantic_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_SDMT_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_Trail Making Test Part A_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_Trail Making Test Part B_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_Stroop Test_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_satisfaction benefits and recommending_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_satisfaction everyday life activities_10 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

Results_adherence_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Mousavi, 2020

Bibliographic Reference	Mousavi, S.; Zare, H.; Etemadifar, M.; Evaluating the effectiveness of cognitive rehabilitation on everyday memory in multiple sclerosis patients; Neuropsychological Rehabilitation; 2020; vol. 30 (no. 6); 1013-1023

Study details

Secondary publication of another included study- see primary study for details	• Mousavi, S., Zare, H., Etemadifar, M. et al. (2018) Memory rehabilitation for the working memory of patients with multiple sclerosis (MS). Journal of Clinical & Experimental Neuropsychology: Official Journal of the International Neuropsychological Society 40(4): 405-410

Mousavi, 2018

Bibliographic Reference	Mousavi, S.; Zare, H.; Etemadifar, M.; Taher Neshatdoost, H.; Memory rehabilitation for the working memory of patients with multiple sclerosis (MS); Journal of Clinical & Experimental Neuropsychology: Official Journal of the International Neuropsychological Society; 2018; vol. 40 (no. 4); 405-410

Study details

Other publications associated with this study included in review	• Mousavi, S.; Zare, H.; Etemadifar, M. (2020) Evaluating the effectiveness of cognitive rehabilitation on everyday memory in multiple sclerosis patients. Neuropsychological Rehabilitation 30(6): 1013-1023 - provides 'everyday memory' outcome which appears to be a different outcome to 'working memory' described in this 2018 paper
Trial name / registration number	Not reported
Study location	Iran
Study setting	Outpatient - recruited from an MS centre

Study dates	Entire study period lasted from August 2015 to December 2016 (selection and screening to end of programme)
Sources of funding	Not reported
Inclusion criteria	Age 18– 69 years,' the ability to read and write; Multiple sclerosis neuropsychological screening questionnaire ≤ 27; achieving 2 standard deviations lower than the healthy people on the scale of brief repeatable battery of neuropsychological test; EDSS < 4; General Health Questionnaire score < 22; and not having medical and severe psychiatric problems at the same time.
Exclusion criteria	No further criteria reported.
Recruitment / selection of participants	Patients were selected from Isfahan's centre for MS
Intervention(s)	Cognitive group memory programme - including various techniques: received the memory rehabilitation program for 8 weeks (1 h per week) in groups of four people. Training in compensatory strategies, explanations on different types of internal and external memory aids, mnemonics, mental reviews and error-free learning. Memory problem adaptation methods offered based on individual difficulties and predetermined objectives. Treatment delivered by MS centre's psychologist that had been trained in rehabilitation. Each group had same person deliver the programme. Also received usual care of offering information regarding cognitive problems.
Population subgroups	None
Comparator	For the purpose of this review, placebo and control groups which were reported as two separate comparators in the paper were combined into a single comparator group to be compared with the memory rehabilitation intervention. Placebo: received body relaxation techniques during weekly sessions. Also received usual care of offering information regarding cognitive problems.

	Control: given ordinary information regarding cognitive problems in MS - usual care with no additional intervention.
Number of participants	60 randomised, 60 analysed at 13 weeks (5 weeks after end of intervention)
Duration of follow-up	Up to 13 weeks (5 weeks after end of 8-week intervention period)
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority (82%) relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (score <4.0 inclusion criterion) • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - possibly absent (severe psychiatric problems and score <22 on General Health Questionnaire excluded) • Computerised vs clinician led - clinician led • Group vs individual - group Analysis - intention to treat (appear to be no dropouts)

Study arms

Cognitive group memory programme - including various techniques (N = 20)

Control - placebo (relaxation techniques) and control (information only with usual care) combined into single control group (N = 40)

Characteristics

Study-level characteristics

Characteristic	Study (N = 60)
% Female Sample size	n = 35 ; % = 58
Relapsing-remitting Sample size	n = 49 ; % = 82
Secondary progressive Sample size	n = 11 ; % = 18

Arm-level characteristics

Characteristic	Cognitive group memory programme - including various techniques (N = 20)	Control - placebo (relaxation techniques) and control (information only with usual care) combined into single control group (N = 40)
Mean age (SD) Mean	40.55	40.95
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR

Characteristic	Cognitive group memory programme - including various techniques (N = 20)	Control - placebo (relaxation techniques) and control (information only with usual care) combined into single control group (N = 40)
Disease duration (years) Mean	6.20	7.18

Outcomes

Study timepoints

- Baseline
- 13 week (13-weeks - 5 weeks following end of the 8-week intervention period (8-week time-point not extracted as 13 weeks better matches protocol))

Results - raw data

Outcome	Cognitive group memory programme - including various techniques, Baseline, N = 20	Cognitive group memory programme - including various techniques, 13-week, N = 20	Control - placebo (relaxation techniques) and control (information only with usual care) combined into single control group, Baseline, N = 40	Control - placebo (relaxation techniques) and control (information only with usual care) combined into single control group, 13-week, N = 40
Everyday Memory Questionnaire Scale 0-175. Frequency of memory failure assessed. Mean (SD)	122.85 (1.04)	121.2 (1.57)	122.08 (1.47)	120.9 (1.44)

Outcome	Cognitive group memory programme - including various techniques, Baseline, N = 20	Cognitive group memory programme - including various techniques, 13-week, N = 20	Control - placebo (relaxation techniques) and control (information only with usual care) combined into single control group, Baseline, N = 40	Control - placebo (relaxation techniques) and control (information only with usual care) combined into single control group, 13-week, N = 40
Working memory - possibly Wechsler Memory Scale–III Mean (SD)	20.1 (2.36)	22.85 (3.08)	20.5 (2.19)	20.65 (3.34)

Everyday Memory Questionnaire - Polarity - Lower values are better
Working memory - possibly Wechsler Memory Scale–III - Polarity - Higher values are better
Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_Everyday Memory Questionnaire_13 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Results_working memory_13 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Naeeni Davarani, 2020

Bibliographic Reference	Naeeni Davarani, M.; Arian Darestani, A.; Hassani-Abharian, P.; Vaseghi, S.; Zarrindast, M. R.; Nasehi, M.; RehaCom rehabilitation training improves a wide-range of cognitive functions in multiple sclerosis patients; Applied Neuropsychology; 2020; vol. adult; 1-11

Study details

Trial name / registration number	Not reported
Study location	Iran
Study setting	Outpatient - selected from those had been referred to rehabilitation clinic
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	People with MS referred to specialised rehabilitation clinic (Brain and cognition Clinic); 18-65 years old; and no sensory aphasia, speech comprehension impairment, hemianopia, visual disturbances or mechanical/neuromuscular disorder in the hands.
Exclusion criteria	No further criteria reported.
Recruitment / selection of participants	Recruited from those referred to Brain and Cognition Clinic
Intervention(s)	RehaCom cognitive software - (working memory, attention, processing speed, response control, executive functions and spatial awareness): 5-week intervention period where RehaCom cognitive rehabilitation software was used twice weekly (60 min sessions). Following modules used: 'working memory' training working memory, ability to memorise and manipulate

	information that is presented and then removed; 'responsiveness', which trains attention, response control and processing speed; 'divided attention 2' and 'attention and concentration' which train selective attention, divided attention, visual scanning and response control to visual and acoustic information; 'logical reasoning' which trains executive functions and problem-solving; and ' spatial operations 3D' which trains spatial awareness and spatial attention. These employed for all patients. RehaCom has auto-adaptive ability meaning level of complexity and difficulty of task automatically increased or decreased depending on participant function.
Population subgroups	None
Comparator	Control - no intervention: no intervention was received in the control group.
Number of participants	60 randomised, 54 appear to have been analysed (unclear reasons for those missing from analysis)
Duration of follow-up	Up to 10 weeks (5-weeks after the end of the 5-week intervention period)
Indirectness	Outcome - time-point <3-month minimum specified in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - unclear • According to disability (EDSS <6 and EDSS ≥6) - unclear • Severity of cognitive impairment (mild/moderate/severe) - unclear (referred to cognition clinic but severity unclear) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (did not exclude those with depression or anxiety) • Computerised vs clinician led - computerised • Group vs individual - individual Analysis - unclear - some missing from analysis and unclear reasons for exclusion

1

Study arms

RehaCom cognitive software - (working memory, attention, processing speed, response control, executive functions and spatial awareness (N = 30)

Control - no intervention (N = 30)

Characteristics

Arm-level characteristics

Characteristic	RehaCom cognitive software - (working memory, attention, processing speed, response control, executive functions and spatial awareness (N = 30)	Control - no intervention (N = 30)
% Female Sample size	n = 23	n = 21 ; % = 81
Mean age (SD) Mean (SD)	39.31 (6.1)	37.55 (8.99)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR

Note that baseline characteristics are given for n=28 and n=26 that appear to have been analysed in the two groups, respectively.

Outcomes

Study timepoints

- Baseline
- 10 week (10-weeks - 5-weeks after the end of the 5-week intervention period)

Results - raw data

Outcome	RehaCom cognitive software - (working memory, attention, processing speed, response control, executive functions and spatial awareness, Baseline, N = 26	RehaCom cognitive software - (working memory, attention, processing speed, response control, executive functions and spatial awareness, 10-week, N = 26	Control - no intervention, Baseline, N = 28	Control - no intervention, 10-week, N = 28
Visual attention Mean (SD)	81.36 (19.4)	88.31 (17.31)	78.38 (29.38)	76.73 (27.58)
Auditory attention Mean (SD)	75.43 (25.83)	84.58 (21.46)	72.31 (22.3)	71.27 (22.02)
Visual response control Mean (SD)	92.61 (17.83)	98.19 (17.96)	88.81 (21.21)	86.58 (20.41)
Auditory response control Mean (SD)	78.86 (18.09)	86.92 (14.56)	73.69 (23.77)	71.19 (22.55)
Visual comprehension	86.68 (21.35)	93.77 (20.14)	82.23 (26.53)	80.81 (25.92)

Outcome	RehaCom cognitive software - (working memory, attention, processing speed, response control, executive functions and spatial awareness, Baseline, N = 26	RehaCom cognitive software - (working memory, attention, processing speed, response control, executive functions and spatial awareness, 10-week, N = 26	Control - no intervention, Baseline, N = 28	Control - no intervention, 10-week, N = 28
Mean (SD)				
Auditory comprehension Mean (SD)	76.39 (32.2)	87.27 (24.36)	77.5 (25.79)	75.69 (23.46)
Visual persistence attention Mean (SD)	96.54 (16.21)	99.77 (24.17)	92.58 (20.93)	88.19 (17.96)
Auditory persistence attention Mean (SD)	94.57 (10.71)	102.88 (10.33)	92.96 (17.04)	88.62 (14.62)
Visual sensory-motor attention Mean (SD)	88.71 (14.32)	96.08 (12.14)	86 (23.15)	83.77 (22.37)
Auditory sensory-motor attention Mean (SD)	102.32 (21.78)	107.58 (20.2)	102.65 (25.03)	97.88 (21.19)
Fine motor hyperactivity Mean (SD)	68.32 (31.76)	77.62 (27.92)	65.46 (31.15)	63.92 (28.49)

Outcome	RehaCom cognitive software - (working memory, attention, processing speed, response control, executive functions and spatial awareness, Baseline, N = 26	RehaCom cognitive software - (working memory, attention, processing speed, response control, executive functions and spatial awareness, 10-week, N = 26	Control - no intervention, Baseline, N = 28	Control - no intervention, 10-week, N = 28
Judgement of Line Orientation Visuospatial and motor skills. Scale 0-30. Mean (SD)	18.96 (3.57)	20.69 (2.85)	19.65 (4)	18.77 (3.43)
Verbal - DKEFS-D Mean (SD)	24.22 (10.25)	29.46 (10.59)	25.23 (11.85)	24.85 (10.96)
Non-verbal (DKEFS-T) Mean (SD)	6.15 (2.54)	7.85 (2.56)	6.54 (2.85)	6.46 (2.77)
SDMT Symbol Digit Modalities Test. Concentration, agility of motor vision, visual scanning and speed of information processing. Mean (SD)	34.46 (4.19)	38.5 (3.79)	32.96 (5.25)	32.92 (5.1)
PASAT Paced Auditory Serial Addition Test. Capacity and rate of information processing, working	37.25 (9.2)	41.85 (8.86)	36.85 (9.77)	36.54 (9.48)

Outcome	RehaCom cognitive software - (working memory, attention, processing speed, response control, executive functions and spatial awareness, Baseline, N = 26	RehaCom cognitive software - (working memory, attention, processing speed, response control, executive functions and spatial awareness, 10-week, N = 26	Control - no intervention, Baseline, N = 28	Control - no intervention, 10-week, N = 28
memory, and sustained and divided attention. Mean (SD)				

Integrated Auditory Visual-2 (IVA-2) - Polarity - Higher values are better
Judgement of Line Orientation - Polarity - Higher values are better
Delis-Kaplan Executive Function System (D-KEFS) - card sorting test - Polarity - Higher values are better
SDMT - Polarity - Higher values are better
PASAT - Polarity - Higher values are better
Note that despite n=30 being randomised to each group, n=26 and n=28 appear to have been analysed in the two groups, respectively. Paper suggests results are change scores, but looking at the values and comparing against scale ranges they appear to have given final values for each time-point but used analysis to assess changes across time-points.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_IVA-2 visual attention_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_IVA-2 auditory attention_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_IVA-2 visual response control_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_IVA-2 auditory response control_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_IVA-2 visual comprehension_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_IVA-2 auditory comprehension_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_IVA-2 visual persistence attention_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_IVA-2 auditory persistence attention_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_IVA-2 visual sensory-motor attention_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_IVA-2 auditory sensory-motor attention_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_IVA-2 fine motor hyperactivity_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_judgement of line orientation_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_DKEFS verbal_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_DKEFS non-verbal_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_SDMT_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_PASAT_10 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

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2 **Nazaribadie, 2020**

Bibliographic Reference	Nazaribadie, M.; Ghaleiha, A.; Ahmadpanah, M.; Mazdeh, M.; Matinnia, N.; Zarabian, M. K.; Effectiveness of detached mindfulness intervention on cognitive functions in multiple sclerosis patients, results from a randomized controlled study; Pakistan Journal of Medical and Health Sciences; 2020; vol. 14 (no. 4); 2022-2029

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1 **Study details**

Other publications associated with this study included in review	• Nazaribadie, M., Ghaleiha, A., Ahmadpanah, M. et al. (2021) Metacognitive model of mindfulness can improve executive function in multiple sclerosis patients. Pakistan Journal of Medical and Health Sciences 15(1): 590-597
Trial name / registration number	IRCT2016112728119N5
Study location	Iran
Study setting	Outpatient
Study dates	Conducted between December 2016 and April 2018
Sources of funding	Funded as part of a Ph.D thesis at Hamadan University of Medical Sciences.
Inclusion criteria	outpatients clinically diagnosed with MS (ICD 10: G35); information processing dysfunction (one paper reports this was based on PASAT test but the other states it was based on Wisconsin Card Sorting Test); aged 18-45 years; EDSS score ≤4.0; no history of mental (psychosis) and physical disorders; not clinically depressed; diploma or higher education; and attended at least two of the scheduled study sessions.
Exclusion criteria	No further criteria reported.
Recruitment / selection of participants	Conducted at outpatient clinic of Farshchian Hospital and Hamadan MS Association between December 2016 and April 2018.
Intervention(s)	Detached mindfulness: performed in group sessions by psychologists over eight sessions with one session per week (60-70 min per session). Each group included 5-7 participants. Described as metacognitive model of detached mindfulness.

	All participants also received pharmacological treatment consisting of interferon beta-1a (Avonex 30 min, Cinnovex 30 mg or Actovex 30 mg) weekly.
Population subgroups	None
Comparator	Control - referred to outpatient clinic for MS once weekly. Received medical treatment and counselling about complications of MS as well as coping with these complications and the socio-therapeutic factors. Social communication with the patient regularly maintained allowing social contact to be maintained. All participants also received pharmacological treatment consisting of interferon beta-1a (Avonex 30 min, Cinnovex 30 mg or Actovex 30 mg) weekly.
Number of participants	60 randomised, 53 analysed (n=3 and n=4 lost in each group, reasons include personal reasons in n=1, unclear in n=4, disliking offered treatment in n=1 and n=1 due to pregnancy)
Duration of follow-up	16 weeks - longest follow-up was 8 weeks after the end of the 8-week intervention period
Indirectness	None
Additional comments	Appears to be modified intention to treat as excluded those lost to follow-up

Study arms

Detached mindfulness + interferon treatment (N = 30)

Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms (N = 30)

Characteristics

Arm-level characteristics

Characteristic	Detached mindfulness + interferon treatment (N = 30)	Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms (N = 30)
% Female Sample size	% = 66.7	% = 53.8
Mean age (SD) Mean (SD)	33.48 (8.59)	31.42 (6.58)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Relapsing-remitting Sample size	% = 55.6	% = 57.7
Secondary progressive Sample size	% = 44.4	% = 42.3
EDSS score Mean (SD)	2.92 (0.74)	2 (0.63)

Characteristic	Detached mindfulness + interferon treatment (N = 30)	Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms (N = 30)
Duration of disease (years) Mean (SD)	5.22 (2.57)	5.11 (2.99)

Outcomes

Study timepoints

- Baseline
- 16 week (16 weeks - 8 weeks after the end of the 8-week intervention period)

Results - raw data

Outcome	Detached mindfulness + interferon treatment, Baseline, N = 30	Detached mindfulness + interferon treatment, 16-week, N = 27	Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms, Baseline, N = 30	Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms, 16-week, N = 26
Wechsler Adult Intelligence Scale-Revised (WAIS-R) - symbol coding test Measure of information processing and working memory Mean (SD)	44.03 (7.77)	50.4 (9.26)	45.03 (10.03)	45.88 (10.58)

Outcome	Detached mindfulness + interferon treatment, Baseline, N = 30	Detached mindfulness + interferon treatment, 16-week, N = 27	Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms, Baseline, N = 30	Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms, 16-week, N = 26
Wechsler Adult Intelligence Scale-Revised (WAIS-R) - digit span test Measure of information processing and working memory Mean (SD)	5.66 (1.46)	6.74 (1.53)	5.5 (1.42)	5.38 (1.2)
Recall Mean (SD)	17.66 (5.15)	24.77 (5.29)	19.26 (5.11)	22.8 (3.28)
Copy Mean (SD)	35.85 (0.53)	36 (0)	35.92 (0.27)	36 (0)
PASAT 3 seconds Paced Auditory Serial Addition Test. Assesses information processing and attention Mean (SD)	32.88 (11.18)	44.11 (10.1)	31.8 (11.18)	33.61 (14.75)
PASAT 2 seconds Paced Auditory Serial	27.92 (8.19)	37.88 (7.97)	28.76 (7.51)	31.69 (10.07)

Outcome	Detached mindfulness + interferon treatment, Baseline, N = 30	Detached mindfulness + interferon treatment, 16-week, N = 27	Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms, Baseline, N = 30	Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms, 16-week, N = 26
Addition Test. Assesses information processing and attention Mean (SD)				
Wisconsin Card Sorting Test - category Measure of executive function Mean (SD)	2.07 (1.75)	4.18 (2.05)	2.15 (1.43)	3.53 (2.02)
Wisconsin Card Sorting Test - perseveration Measure of executive function Mean (SD)	9.33 (5.29)	3.22 (2.65)	9.88 (5.06)	8 (5.45)
Wisconsin Card Sorting Test - conception responses Measure of executive function Mean (SD)	2.44 (2.8)	4.81 (2.09)	2 (2.26)	3.92 (2.72)

Outcome	Detached mindfulness + interferon treatment, Baseline, N = 30	Detached mindfulness + interferon treatment, 16-week, N = 27	Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms, Baseline, N = 30	Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms, 16-week, N = 26
Wisconsin Card Sorting Test - total correct Measure of executive function Mean (SD)	27.92 (8.19)	37.88 (7.97)	28.76 (7.51)	31.69 (10.07)
Wisconsin Card Sorting Test - number of errors Measure of executive function Mean (SD)	30.7 (9.52)	17.85 (7.5)	30.8 (7.18)	25.26 (9.61)
Wisconsin Card Sorting Test - other errors Measure of executive function Mean (SD)	21.48 (5.5)	13.96 (6.22)	20.23 (4.23)	16.61 (6.12)
Wisconsin Card Sorting Test - first trial category Measure of executive function Mean (SD)	25.51 (22.19)	9.88 (8.81)	18.88 (14.91)	13.84 (14.27)

Outcome	Detached mindfulness + interferon treatment, Baseline, N = 30	Detached mindfulness + interferon treatment, 16-week, N = 27	Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms, Baseline, N = 30	Control + interferon treatment - outpatient visit with medical and counseling and coping mechanisms, 16-week, N = 26
Hamilton Anxiety Scale Scale 0-56. Mean (SD)	17 (4.42)	6.44 (4.06)	15.96 (6.31)	13 (5.83)

Wechsler Adult Intelligence Scale-Revised (WAIS-R) - symbol coding test - Polarity - Higher values are better
Wechsler Adult Intelligence Scale-Revised (WAIS-R) - digit span test - Polarity - Higher values are better
Rey Complex Figure test - Polarity - Higher values are better
PASAT 3 seconds - Polarity - Higher values are better
PASAT 2 seconds - Polarity - Higher values are better
Wisconsin Card Sorting Test - category - Polarity - Higher values are better
Wisconsin Card Sorting Test - perseveration - Polarity - Lower values are better
Wisconsin Card Sorting Test - conception responses - Polarity - Higher values are better
Wisconsin Card Sorting Test - total correct - Polarity - Higher values are better
Wisconsin Card Sorting Test - number of errors - Polarity - Lower values are better
Wisconsin Card Sorting Test - other errors - Polarity - Lower values are better
Wisconsin Card Sorting Test - first trial category - Polarity - Lower values are better
Hamilton Anxiety Scale - Polarity - Lower values are better
Note that some outcomes are reported in the primary paper and others reported in a secondary paper published in 2021.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_WAIS-R symbol coding test_16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WAIS-R digit span test_16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Rey's complex figure test recall_16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Rey's complex figure test copy_16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_PASAT 3 seconds_16 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

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3 **Results_PASAT 2 seconds_16 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WCST category_16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WCST perseveration_16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_WCST conception responses_16 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_WCST total correct_16 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_WCST number of errors_16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_WCST other errors_16 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

1 **Results_WCST first trial category_16 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_Hamilton Anxiety Scale_16 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Nazaribadie, 2021

Bibliographic Reference	Nazaribadie, M.; Ghaleiha, A.; Ahmadpanah, M.; Mazdeh, M.; Matinnia, N.; Zarabian, M. K.; Metacognitive model of mindfulness can improve executive function in multiple sclerosis patients; Pakistan Journal of Medical and Health Sciences; 2021; vol. 15 (no. 1); 590-597

Study details

Secondary publication of another included study- see primary study for details	• Nazaribadie, M., Ghaleiha, A., Ahmadpanah, M. et al. (2020) Effectiveness of detached mindfulness intervention on cognitive functions in multiple sclerosis patients, results from a randomized controlled study. Pakistan Journal of Medical and Health Sciences 14(4): 2022-2029

Parisi, 2014

Bibliographic Reference	Parisi, L.; Rocca, M. A.; Mattioli, F.; Copetti, M.; Capra, R.; Valsasina, P.; Stampatori, C.; Filippi, M.; Changes of brain resting state functional connectivity predict the persistence of cognitive rehabilitation effects in patients with multiple sclerosis; Multiple Sclerosis; 2014; vol. 20 (no. 6); 686-94

Study details

Secondary publication of another included study- see primary study for details	• Filippi, M., Riccitelli, G., Mattioli, F. et al. (2012) Multiple sclerosis: effects of cognitive rehabilitation on structural and functional MR imaging measures--an explorative study. Radiology 262(3): 932-40

Perez-Martin, 2017

Bibliographic Reference	Perez-Martin, M. Y.; Gonzalez-Platas, M.; Eguia-Del Rio, P.; Croissier-Elias, C.; Jimenez Sosa, A.; Efficacy of a short cognitive training program in patients with multiple sclerosis; Neuropsychiatric Disease & Treatment; 2017; vol. 13; 245-252

Study details

Trial name / registration number	Not reported

Study location	Spain - Canary Islands (Tenerife and Lanzarote)
Study setting	Outpatient - MS patients treated at Service of Neurology of two tertiary hospitals recruited
Study dates	The study was conducted between October 2013 and June 2015
Sources of funding	Reported to be no funding sources.
Inclusion criteria	MS diagnosis according to the revised McDonald criteria; being older than 18 years; having an Expanded Disability Status Scale score ≤7.0 to prevent the inclusion of patients who may have difficulty traveling to the centre in the rehabilitation phase; subjective complaints about cognitive problems; and objective cognitive impairment defined as a performance of 1.5 standard deviation lower than the mean in a control group in at least two cognitive tests (determined by the neuropsychological assessment).
Exclusion criteria	Diagnosis of current or past severe psychiatric disorder; relapse or had taken steroids within the 3 months prior to inclusion based on their clinical history; previously participated in any cognitive rehabilitation program; met the criteria for the diagnosis of dementia
Recruitment / selection of participants	An incidental sample obtained from the population of patients with MS treated at the Service of Neurology of two tertiary hospitals was recruited
Intervention(s)	Cognitive rehabilitation: received cognitive training for a total of 12 weekly consecutive sessions, each lasting 60–75 min. Focused on attention, processing speed, memory and executive functions through computerized and paper and pencil tasks designed by the members of the research team (all tasks were different to evaluation procedures to prevent the effect of practice). All sessions were standardised for all patients. Sessions included 10 minutes to evaluate the generalisation of prior training to activities of daily life and control and/or correction of assignment notebooks delivered in the previous session and 50 minutes of working with the patients. The last 10–15 minutes consisted of feedback on the performance and relevance of the work and a review of work done at home during the week. Booklet with tasks to complete at home given after each session - minimum of 10 and maximum of 30 exercises designed to reinforce material covered in sessions and prevent cognitive inactivity between sessions. Compliance <80% with home-tasks was an exclusion criterion from analysis. The last booklet contained a set of guidelines and general advice on the influence of habits and lifestyles on cognitive functions, practical exercises for working memory and the ability to concentrate as well as suggestions on planning and physical activity.

Population subgroups	None
Comparator	Waitlist control: received no treatment, only received information about their cognitive status and a booklet containing set of guidelines and general advice on influence of habits and lifestyles on cognitive functions. Group was contacted once a week.
Number of participants	62 randomised, 62 analysed.
Duration of follow-up	3 months - end of intervention period.
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (>90% both groups) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (mean <3.0 in both groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear (said to include those with mild-moderate cognitive impairment level) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (severe psychiatric conditions excluded) • Computerised vs clinician led - mixed/unclear (mix of computerised and paper tasks but performed in clinic) • Group vs individual - individual Analysis - appears to be intention to treat as all randomised were analysed

Study arms

Cognitive rehabilitation - computerised and paper tasks focusing on attention, processing speed, memory and executive functions (N = 30)

Control - waitlist control (N = 32)

Characteristics

Arm-level characteristics

Characteristic	Cognitive rehabilitation - computerised and paper tasks focusing on attention, processing speed, memory and executive functions (N = 30)	Control - waitlist control (N = 32)
% Female Sample size	n = 18 ; % = 56.3	n = 14 ; % = 76.7
Mean age (SD) Mean (SD)	44.93 (9.89)	40.88 (8.5)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Relapsing-remitting Sample size	n = 27 ; % = 90	n = 30 ; % = 93.7
Secondary progressive Sample size	n = 2 ; % = 6.7	n = 0 ; % = 0

Characteristic	Cognitive rehabilitation - computerised and paper tasks focusing on attention, processing speed, memory and executive functions (N = 30)	Control - waitlist control (N = 32)
Primary progressive Sample size	n = 1 ; % = 3.3	n = 2 ; % = 6.3
Disease duration (years) Mean (SD)	11.5 (8.05)	9.59 (7.4)
EDSS score Mean (SD)	2.78 (1.98)	2.11 (1.36)

Outcomes

Study timepoints

- Baseline
- 3 month (3-months - end of intervention period)

Results - raw data

Outcome	Cognitive rehabilitation - computerised and paper tasks focusing on attention, processing speed, memory and executive functions, Baseline, N = 30	Cognitive rehabilitation - computerised and paper tasks focusing on attention, processing speed, memory and executive functions, 3-month, N = 30	Control - waitlist control, Baseline, N = 32	Control - waitlist control, 3-month, N = 32
SRT-LTS Long-term storage Mean (SD)	26.37 (15.56)	41.4 (14.91)	28.91 (13.27)	34 (16.26)
SRT-CLTR Consistent long-term retrieval Mean (SD)	17.57 (13.94)	32.03 (18.26)	22.03 (13.89)	24.53 (16.28)
SRT/DR Delayed recall Mean (SD)	5.87 (2.56)	8.03 (2.79)	6.03 (2.87)	6.22 (2.86)
SPART-total Mean (SD)	20.7 (4.81)	22.77 (5.56)	20.47 (4.5)	21.38 (4.14)
SPARTDR Delayed recall Mean (SD)	6.5 (2.11)	7.87 (2.21)	7.59 (1.76)	7.63 (1.81)
SDMT Symbol Digit Modalities Test.	42 (12.72)	46.47 (13.3)	47.53 (11.09)	47.93 (10.34)

Outcome	Cognitive rehabilitation - computerised and paper tasks focusing on attention, processing speed, memory and executive functions, Baseline, N = 30	Cognitive rehabilitation - computerised and paper tasks focusing on attention, processing speed, memory and executive functions, 3-month, N = 30	Control - waitlist control, Baseline, N = 32	Control - waitlist control, 3-month, N = 32
Measure of complex attention and processing speed Mean (SD)				
PASAT 3 seconds Paced Auditory Serial Addition Test. Assesses sustained attention and working memory Mean (SD)	24.5 (14.56)	29.7 (15.48)	31.18 (14.41)	30.44 (16.08)
FAS - phonetic fluency Mean (SD)	28.37 (10.13)	32.23 (9.67)	31.88 (9.69)	33.13 (11.21)
Animals Mean (SD)	17.7 (5.05)	19.23 (4.45)	19 (4.48)	19.63 (5.51)
MSNQ Multiple Sclerosis Neuropsychological Questionnaire. Scale usually 0-60. Mean (SD)	29.83 (11.99)	23.87 (11.83)	24.28 (11.57)	25.63 (11.83)

Outcome	Cognitive rehabilitation - computerised and paper tasks focusing on attention, processing speed, memory and executive functions, Baseline, N = 30	Cognitive rehabilitation - computerised and paper tasks focusing on attention, processing speed, memory and executive functions, 3-month, N = 30	Control - waitlist control, Baseline, N = 32	Control - waitlist control, 3-month, N = 32
Fatigue Severity Scale Scale usually 9-63. Mean (SD)	34.73 (21.97)	30.51 (20.22)	28.89 (21.79)	29.21 (21.94)
HADS - anxiety Hospital Anxiety and Depression Scale. Scale usually 0-21. Mean (SD)	8.1 (4.18)	5.97 (3.15)	6.5 (3.39)	7.41 (3.44)
HADS - depression Hospital Anxiety and Depression Scale. Scale usually 0-21. Mean (SD)	7.47 (3.29)	5.57 (3.93)	5.75 (3.63)	6.13 (3.49)
Physical composite Mean (SD)	46.43 (17.83)	52.99 (19.2)	63.75 (17.27)	63.24 (16.98)
Mental composite Mean (SD)	47.88 (20.19)	56.39 (18.7)	62.16 (16.27)	67.32 (17.06)

1 SRT - Polarity - Higher values are better

10/36 SPART - Polarity - Higher values are better
SDMT - Polarity - Higher values are better
PASAT 3 seconds - Polarity - Higher values are better
COWAT - Polarity - Higher values are better
MSNQ - Polarity - Lower values are better
Fatigue Severity Scale - Polarity - Lower values are better
HADS - anxiety - Polarity - Lower values are better
HADS - depression - Polarity - Lower values are better
MSQoL-54 - Polarity - Higher values are better
Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_SRT-LTS_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SRT-CLTR_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_SRT-DR_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_10/36 SPART total_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_10/36 SPART-DR_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT 3 seconds_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_COWAT FAS - phonetic fluency_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_COWAT animals_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_MNSQ_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_FFS_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_HADS anxiety_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_HADS depression_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_MSQoL-54 physical composite_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_MSQoL-54 mental composite_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Pusswald, 2014

Bibliographic Reference	Pusswald, G.; Mildner, C.; Zebenholzer, K.; Auff, E.; Lehrner, J.; A neuropsychological rehabilitation program for patients with Multiple Sclerosis based on the model of the ICF; Neurorehabilitation; 2014; vol. 35 (no. 3); 519-27

Study details

Trial name / registration number	Not reported
Study location	Austria
Study setting	Outpatient - recruited MS outpatients from Department of Neurology at single centre and from the community
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	MS diagnosed by neurologist according to McDonald criteria; no psychiatric disorders; no other neurological disease; no dementia (MMSE >26); no loss of visual acuity; no clinical exacerbations in past 30 days and therefore no corticosteroid therapy in past 30 days.
Exclusion criteria	No further criteria reported

Recruitment / selection of participants	Recruited from MS outpatients at Department of Neurology of Medical University of Vienna and from local MS society
Intervention(s)	Cognitive training - computerised attention training + psychosocial group sessions: cognitive functional training, including specific computer-based home training of divided attention (3 times weekly for 30 min over 5 weeks). Training sessions recorded in individual training diary. Software used was 'Fresh Minder 2', which provides users with feedback and involves the 'Divided Attention' programme consisting of three software packages. This group also received psychosocial group sessions covering other cognitive areas - weekly group sessions for 90 min over 5 weeks. Included several cognitive rehabilitation techniques (e.g., simple behavioural coping strategies such as time management, setting priorities, planning, relaxation techniques, social skills training like conversion-tracking skills, memory retraining including face-name recall, visual imagery or errorless learning and enhancement of emotional health and social function (e.g., stress reduction). Manual used for each session. Trained in these strategies by two neuropsychologists. Therapy book maintained by each participant including information about cognitive functions and advice for training.
Population subgroups	None
Comparator	Control - no training: did not undergo any specific training during the trial period.
Number of participants	40 randomised, 40 analysed (said to have all completed study)
Duration of follow-up	5-weeks - end of intervention period (3-month time-point mentioned but no results provided)
Indirectness	Population - does not appear to be an inclusion criterion requiring there to be cognitive deficits at baseline Outcome - time-point <3 months minimum specified in the protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (83%) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (mean <6.0 in both groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear (cognitive impairment does not appear to have been an inclusion criterion)

	• Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - possibly absent (psychiatric disorders excluded) • Computerised vs clinician led - mixed (mix of computerised tasks and group sessions in clinic) • Group vs individual - mixed (individual and group components involved) Analysis - intention to treat (appears to be no missing data)

Study arms

Cognitive training - computerised attention training + psychosocial group sessions (coping methods and compensatory techniques, etc.) (N = 20)

Control - no training (N = 20)

Characteristics

Study-level characteristics

Characteristic	Study (N = 40)
Relapsing-remitting Sample size	n = 33 ; % = 82.5
Secondary progressive Sample size	n = 6 ; % = 15
Primary progressive	n = 1 ; % = 2.5

Characteristic	Study (N = 40)
Sample size	

Arm-level characteristics

Characteristic	Cognitive training - computerised attention training + psychosocial group sessions (coping methods and compensatory techniques, etc.) (N = 20)	Control - no training (N = 20)
% Female Sample size	n = 15 ; % = 75	n = 16 ; % = 80
Mean age (SD) Mean (SD)	42.6 (1)	45.3 (7.1)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Disease duration (years) Mean (SD)	15.1 (10.4)	12.6 (8.8)
EDSS score Mean (SD)	3 (1.7)	4 (2.07)

Outcomes

Study timepoints

- Baseline
- 5 week (5-weeks - end of intervention period)

Results - raw data

Outcome	Cognitive training - computerised attention training + psychosocial group sessions (coping methods and compensatory techniques, etc.), Baseline, N = 20	Cognitive training - computerised attention training + psychosocial group sessions (coping methods and compensatory techniques, etc.), 5-week, N = 20	Control - no training, Baseline, N = 20	Control - no training, 5-week, N = 20
Simple Mean (SD)	277.1 (45)	250.6 (29)	289.2 (43.2)	269.8 (20)
Cued Mean (SD)	272 (37.7)	242.8 (29.2)	283.8 (39.7)	264.3 (19.3)
Acoustic Mean (SD)	623.6 (89.1)	575.5 (105.2)	660.9 (82)	605.1 (119.8)
Visual Mean (SD)	878.4 (115)	806 (91.7)	887.8 (90.9)	865.5 (48.7)
Verbal memory	13.06 (3.29)	14.5 (3.3)	13.63 (3.2)	14.38 (3.5)

Outcome	Cognitive training - computerised attention training + psychosocial group sessions (coping methods and compensatory techniques, etc.), Baseline, N = 20	Cognitive training - computerised attention training + psychosocial group sessions (coping methods and compensatory techniques, etc.), 5-week, N = 20	Control - no training, Baseline, N = 20	Control - no training, 5-week, N = 20
Mean (SD)				
Verbal retrieval Mean (SD)	5.39 (1.57)	6.11 (1.7)	5.75 (1.48)	5.88 (1.24)
Verbal fluency Mean (SD)	14.61 (4.2)	14.72 (3.9)	15.5 (2.8)	14.88 (2.9)
Interferences Mean (SD)	11.9 (6.14)	9.19 (6.2)	11.72 (5.51)	12.01 (6.42)

1 TAP Alertness - reaction time - Polarity - Lower values are better
2 TAP Divided Attention - reaction time - Polarity - Lower values are better
3 MUSIC - Polarity - Higher values are better
4 Final values for continuous outcomes

5

6

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_TAP Alertness simple_5 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol and appears to be no specific cognitive impairment required for inclusion)*

1 **Results_TAP Alertness cued_5 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol and appears to be no specific cognitive impairment required for inclusion)*

2

1 **Results_TAP Divided Attention acoustic_5 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol and appears to be no specific cognitive impairment required for inclusion)*

2

1 **Results_TAP Divided Attention visual_5 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol and appears to be no specific cognitive impairment required for inclusion)*

2

1 **Results_MUSIC verbal memory_5 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol and appears to be no specific cognitive impairment required for inclusion)*

2

1 **Results_MUSIC verbal retrieval_5 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol and appears to be no specific cognitive impairment required for inclusion)*

2

1 **Results_MUSIC verbal fluency_5 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol and appears to be no specific cognitive impairment required for inclusion)*

2

1 **Results_MUSIC interferences_5 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol and appears to be no specific cognitive impairment required for inclusion)*

2

Rahmani, 2020

Bibliographic Reference	Rahmani, M.; Rahimian Boogar, I.; Talepasand, S.; Nokani, M.; Comparing the Effectiveness of Computer-Based, Manual-based, and Combined Cognitive Rehabilitation on Cognitive Functions in Relapsing-Remitting Multiple Sclerosis Patients; Iranian Journal of Neuroscience; 2020; vol. 11 (no. 1); 99-110

Study details

Trial name / registration number	Not reported
Study location	Iran
Study setting	Unclear - likely outpatient
Study dates	Selected by convenience sampling between July 2016 and March 2017
Sources of funding	Published as part of PhD thesis at Higher Education Centre at Semnan University
Inclusion criteria	Relapsing-remitting MS; aged 18-45 years; Expanded Disability Status Scale score of ≤3.5; Mini-Mental State Examination score of 10-20; and at least a moderate literacy level.
Exclusion criteria	Pregnancy during the study or decision to become pregnant at the beginning of the study; the lack of regular medical check-up or follow-up treatment; MS attack in the last month and during the study; psychotic/major psychopathological comorbidities; major medical comorbidities; and hearing or speaking difficulties
Recruitment / selection of participants	Recruited patients with relapsing-remitting MS in Arak City, Iran, from July 2016 to March 2017.
Intervention(s)	**Cognitive rehabilitation - for the purpose of this review, computer-based, manual and combined groups were combined into a single intervention to be compared with a control group:** all groups were scheduled to have 21 sessions (1 h, once weekly) of cognitive rehabilitation over 5 months. Content of all three groups included memory (immediate or working memory; short-term memory; remote or long-term memory or the type of remembered information,

	including verbal; spatial; and motor skills), information processing speed (formulate an appropriate response, processing sentences and making sense of conversations, processing of visual information in a short distance, processing auditory, and the processing of incoming information), attention (selective attention, divided attention, alternating attention, and sustained attention), executive functions (planning and organizing sequencing, e.g. completing complex tasks, flexible thinking, motivation/ drive, self-monitoring, problem-solving, self-correction, diminished abstract reasoning, poor decision making, & distractibility). In addition, these protocols comprised related psychoneurological skills, including linguistic functions and visual perceptual functions. Involved four steps: 1. remediation (retraining impaired functions), 2. substitution (reorganising functions), 3. accommodation (promoting use of preserved functions) and 4. assimilation (learning compensation strategies). Implemented by three MSc in clinical psychology that had been trained and supervised by the researcher in Arak Payam Noor University Counseling Center **Computer-based group:** Captain's Log Computerised Training System. Developed by Brain Train Company, which involves 2000 different programmes at different levels aiming to improve various cognition functions, including precision, concentration, working memory, instant memory, short-term auditory and visual memory, visual and auditory processing speed, auditory and visual perception, sensorimotor coordination, hand-eye coordination, visual processing, micromotion control, problem-solving skills, executive functions and speed of response. **Manual-based group:** Pars Cognitive Rehabilitation Package used, including programs for Neurocognitive Joyful Attentive Training Intervention (developed by Nejati 2016) in Cognitive Neuroscience Centre at Shahid Beheshti University. This includes exercises for improving attention and working memory. Also includes pen-paper programme for improving executive functions and consists of hierarchically-organised group of assignments that reinforce different aspects of executive functions. Hierarchical process meaning initial concepts of cognitive domains (e.g., conceptualising, planning and memory) are targeted through frequent exercises and then skills training and higher-level functions are targeted by the intervention. Difficulty of exercises increase based on user's response beyond sessions. Assignments are organised based on various functions of attention, working memory, and inhibition. These assignments can be repeated until the patient reaches the desired level. Therapist present to improve assignment level. Manual programme involved Pars Cognitive

	Rehabilitation Package described as well as being based on cognitive rehabilitation guideline by Kellay and O'Sullivan 2015 and hierarchical model of cognitive rehabilitation by Sohlberg and Mateer. **Combined group:** constructed based on both Captain's Log Computerised Cognitive Training System and the Pars Cognitive Rehabilitation Package described in the computer-based and manual-based groups above, respectively.
Population subgroups	None
Comparator	**Control - for the purpose of this review two separate control groups reported in the paper (placebo and control) were combined into a single control group to compare against an intervention group.** **Placebo:** received a physical rehabilitation intervention only. Physical rehabilitation intervention in the placebo group was conducted by a sports and health specialist in Arak City. No further details provided. **No intervention control:** control group that received no intervention.
Number of participants	60 randomised, unclear analysed (assumed 60 as no drop-out mentioned)
Duration of follow-up	5-month (end of intervention period) and 7-month (2 months after end of intervention period) time-points reported
Indirectness	Population - does not appear to be an inclusion criterion relating to cognitive impairment being present
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting MS • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (EDSS up to 3.5 an inclusion criterion)

	• Severity of cognitive impairment (mild/moderate/severe) - unclear (cognitive impairment does not appear to be an inclusion criterion) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (psychotic/major psychopathological conditions were excluded) • Computerised vs clinician led - mixed (combined various groups for purpose of this review - computerised, manual and a mixed group) • Group vs individual - individual Analysis - assume intention to treat as no mention of any missing data

Study arms

Cognitive rehabilitation (computer-based, manual and combined groups combined into a single interventio) (N = 36)

Control (placebo group receiving physical intervention and control with no intervention combined) (N = 24)

Characteristics

Study-level characteristics

Characteristic	Study (N = 60)
Disease duration (years) Range	2 to 7

Arm-level characteristics

Characteristic	Cognitive rehabilitation (computer-based, manual and combined groups combined into a single interventio) (N = 36)	Control (placebo group receiving physical intervention and control with no intervention combined) (N = 24)
% Female Sample size	n = 36 ; % = 100	n = 24 ; % = 100
Mean age (SD) Mean (SD)	29.14 (7.23)	30.43 (8.14)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR

Outcomes

Study timepoints

- Baseline
- 5 month (5-months - end of intervention period)
- 7 month (7-months - 2 months after the end of the 5-month intervention period)

Results - raw data

Outcome	Cognitive rehabilitation (computer-based, manual and combined groups combined into a single intervention,), Baseline, N = 36	Cognitive rehabilitation (computer-based, manual and combined groups combined into a single intervention,), 5-month, N = 36	Cognitive rehabilitation (computer-based, manual and combined groups combined into a single intervention,), 7-month, N = 36	Control (placebo group receiving physical intervention and control with no intervention combined), Baseline, N = 24	Control (placebo group receiving physical intervention and control with no intervention combined), 5-month, N = 24	Control (placebo group receiving physical intervention and control with no intervention combined), 7-month, N = 24
Working memory Likely assessed with PASAT - Paced Auditory Serial Addition Test Mean (SD)	19.26 (2.7)	22.89 (3.08)	21.89 (3.06)	19.21 (3.07)	19.56 (3.26)	19.46 (3.41)
Selective attention Likely assessed with Stroop Colour and Word Test. Mean (SD)	12.08 (1.66)	9.13 (1.56)	9.77 (1.54)	12.09 (1.71)	11.96 (1.55)	11.96 (1.33)
Executive function	13.33 (1.65)	10.19 (1.62)	10.91 (1.48)	13.42 (2.08)	13.29 (2.42)	13.33 (2.41)

Outcome	Cognitive rehabilitation (computer-based, manual and combined groups combined into a single intervention,), Baseline, N = 36	Cognitive rehabilitation (computer-based, manual and combined groups combined into a single intervention,), 5-month, N = 36	Cognitive rehabilitation (computer-based, manual and combined groups combined into a single intervention,), 7-month, N = 36	Control (placebo group receiving physical intervention and control with no intervention combined), Baseline, N = 24	Control (placebo group receiving physical intervention and control with no intervention combined), 5-month, N = 24	Control (placebo group receiving physical intervention and control with no intervention combined), 7-month, N = 24
Likely assessed with Wisconsin Card Sorting Test. Mean (SD)						
Information processing speed Unclear how this was measured - possibly PASAT or Stroop Colour and Word Test. Mean (SD)	1126.8 (73.25)	1041.4 (53.69)	1071.8 (60.06)	1122.7 (62.89)	1122.5 (81.28)	1122.8 (81.26)

1 Working memory - Polarity - Higher values are better
2 Selective attention - Polarity - Lower values are better

Executive function - Polarity - Lower values are better
Information processing speed - Polarity - Lower values are better
Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_working memory_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_working memory_7 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_selective attention_5 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_selective attention_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Results_executive function_5 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

1 **Results_executive function_7 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_information processing speed_5 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_information processing speed_7 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Richard, 2013

Bibliographic Reference	Richard, Nadine Marie; Rehabilitation of executive dysfunction in multiple sclerosis: Cognitive, behavioural and neurophysiological effects of goal management training; Dissertation Abstracts International: Section B: The Sciences and Engineering; 2013; vol. 78 (no. 9be); nopaginationspecified-

Study details

Trial name / registration number	Not reported
Study location	Canada
Study setting	Outpatient - recruited from MS clinics
Study dates	Not reported
Sources of funding	Not reported - part of a thesis
Inclusion criteria	Aged at least 18 years; fluent in English; able to provide informed consent to all procedures; no history of developmental disorder; neither history of nor current substance abuse; diagnosis of MS with no concurrent or previous neurological disorder; no psychiatric disorder (other than mood, personality, or behaviour change following the onset of MS); no other medical condition suspected to influence cognition; no current benzodiazepine or neuroleptic medication use; no relapse

	during the study period or the two months prior; sufficient motor and sensory functioning (e.g., as determined by neurological examination, with an Expanded Disability Severity Scale score ≤ 8) – with correction or assistance as required – to complete assessment activities; preliminary indication of functionally significant attention or executive deficits (e.g., from clinical presentation, chart information from the referring institutional clinic and/or patient self-report); objective evidence of functionally significant attention or executive deficits (as determined by the baseline neuropsychological evaluation); ability to complete all study activities, including attendance at 9 weekly training sessions, individual progress meetings and post-training assessments; and sufficient arousal capacity, awareness of deficits and motivation to engage in the interventions. Apart from those listed above, patients were not excluded for undergoing treatment for MS or concurrent mood disorder, but were asked to report any change in treatment status (no changes reported during study period).
Exclusion criteria	No further criteria reported.
Recruitment / selection of participants	All participants were recruited through one of two MS centres.
Intervention(s)	Goal management programme: weekly 2 h sessions over course of 9 weeks. Led by author with support from additional trainer (occupational therapist experienced in working with MS patients or a post-doctoral fellow completing supervised psychological practice hours). Designed to be highly interactive, combining lectures on key topics with discussions relating to participants' experiences with in-class activities and homework. This intervention focused on information and activities to build skills in goal awareness, attentional control and self-regulation, while providing a socially supportive atmosphere to practice and discuss progress with these skills. Comprised 9-modules - engaged in a set of "present-mindedness" exercises aimed at gradually building attentional awareness and control (mindfulness-based strategies) combined with key goal management training strategies (1. accessible education about executive functions, including attention and working memory, 2. building self-awareness of when and why "slips" (errors, forgetfulness) occur, 3. self-regulatory strategies learned in the context of functional tasks and participants' daily life situations, and 4. training in the use of compensatory aids (organizers, mnemonics) within the overall self-regulatory strategy training). Intervention targeted at executive dysfunction tailored to participant needs and real-life situations. Group based programme with groups of 4-5 people. Participants who missed a scheduled group session completed an individual make-up session by the trainer prior to the next scheduled group module. Also provided two private 30-minute appointments with the author (scheduled after the third and sixth training sessions) to discuss their progress and any concerns or questions about program content, activities and assignments.

Population subgroups	None
Comparator	Active control - brain health workshop (psychoeducation): weekly 2 h sessions over course of 9 weeks. Led by author with support from additional trainer (occupational therapist experienced in working with MS patients or a post-doctoral fellow completing supervised psychological practice hours). Designed to be highly interactive, combining lectures on key topics with discussions relating to participants' experiences with in-class activities and homework. This control intervention contained information and activities to increase participants' knowledge of brain function, cognition and MS, while providing social support and lifestyle recommendations (e.g., energy conservation, nutrition and exercise, stress reduction). Psychoeducational programme about the brain, cognition and functional changes associated with MS. Differs from goal management training and other targeted cognitive rehabilitation protocol as though these educational programmes may increase awareness of potential deficits in cognition, they don't provide specific tools to help patients improve these deficits. Combined education about various domains of cognition, their relation to brain functioning and potential effects of MS. To achieve a degree of patient-centred discussion and personal relevance comparable to the intervention group, time was spent on group discussions of participant experiences related to topic material. Homework assignments were also designed to be comparable in terms of length and involvement to those within the intervention group (included readings, brain challenge exercises similar to those in population brain fitness materials, self-assessment scales and log-keeping). Participants who missed a scheduled group session completed an individual make-up session by the trainer prior to the next scheduled group module. Also provided two private 30-minute appointments with the author (scheduled after the third and sixth training sessions) to discuss their progress and any concerns or questions about program content, activities and assignments.
Number of participants	28 randomised, 27 analysed post-test (9 weeks) and 23 analysed at ~8 months (6-month follow-up after the end of the intervention period).
Duration of follow-up	Up to 6 months after the end of the intervention period
Indirectness	Outcome for 9-week time-point - time-point <3-month minimum specified in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (61%) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (median <6.0 in both groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear

	• Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear • Computerised vs clinician led - clinician led • Group vs individual - group Analysis - those with data (available case analysis) appear to have been reported in paper

Study arms

Goal management programme (N = 14)

Active control - psychoeducation (Brain Health Workshop) (N = 14)

Characteristics

Arm-level characteristics

Characteristic	Goal management programme (N = 14)	Active control - psychoeducation (Brain Health Workshop) (N = 14)
% Female Custom value	NR	NR
Mean age (SD) Mean (SD)	50.1 (8)	52.4 (10.6)
Ethnicity Custom value	*empty data*	NR

Characteristic	Goal management programme (N = 14)	Active control - psychoeducation (Brain Health Workshop) (N = 14)
Comorbidities Custom value	NR	NR
Relapsing-remitting Sample size	n = 7 ; % = 63.6	n = 7 ; % = 58.3
Progressive Sample size	n = 4 ; % = 36.4	n = 5 ; % = 41.7
Disease duration (years) Mean (SD)	12.8 (8.5)	14 (11.1)
EDSS score Median	3.0	5.0

Baseline characteristics given for n=11 and n=12, respectively, which was the number analysed at follow-up time-point (6-months after end of intervention) and not for those randomised.

Outcomes

Study timepoints

- Baseline
- 9 week (9-weeks - end of intervention period)
- 8 month (~8 months - 6 months after the end of the 9-week intervention period)

1 **Results - raw data**

Outcome	Goal management programme , Baseline, N = 14	Goal management programme , 9-week, N = 13	Goal management programme , 8-month, N = 11	Active control - psychoeducation (Brain Health Workshop), Baseline, N = 14	Active control - psychoeducation (Brain Health Workshop), 9-week, N = 14	Active control - psychoeducation (Brain Health Workshop), 8-month, N = 12
Sustained Attention to Response Task (SART) - Commission errors (% no-go trials) Measure of sustained attention; inhibitory control (executive function). Failure to inhibit responses on no-go trials. Mean (SD)	47.7 (38.4)	39.4 (29.6)	42 (28)	32.4 (14.6)	28.3 (22)	32 (21.3)
Sustained Attention to Response Task (SART) - Omission errors (% go trials) Measure of sustained attention; inhibitory control (executive function). Failure to respond on go trials. Mean (SD)	5.4 (5.1)	4.4 (4.7)	3.6 (3.3)	5 (6.1)	4.2 (5)	2.9 (3.3)

Outcome	Goal management programme , Baseline, N = 14	Goal management programme , 9-week, N = 13	Goal management programme , 8-month, N = 11	Active control - psychoeducation (Brain Health Workshop), Baseline, N = 14	Active control - psychoeducation (Brain Health Workshop), 9-week, N = 14	Active control - psychoeducation (Brain Health Workshop), 8-month, N = 12
Sustained Attention to Response Task (SART) - mean reaction time across go trials (msec) Measure of sustained attention; inhibitory control (executive function) Mean (SD)	435.6 (126.4)	447.8 (108.8)	423 (116.1)	456.1 (66.4)	454 (80.4)	433.8 (79.3)
Elevator counting with distraction Mean (SD)	6.6 (3.2)	7.6 (2.8)	7.6 (2.8)	5.9 (3.3)	5.7 (3.2)	6.7 (2.3)
Visual elevator Mean (SD)	7.5 (2.5)	8.4 (2.5)	8.7 (1.6)	7.5 (1.3)	8 (2.2)	9.2 (1)
Elevator counting with reversal Mean (SD)	4.6 (2.7)	5.5 (3)	4.8 (3)	4.5 (3)	4.3 (3.3)	3.7 (3)

Outcome	Goal management programme , Baseline, N = 14	Goal management programme , 9-week, N = 13	Goal management programme , 8-month, N = 11	Active control - psychoeducation (Brain Health Workshop), Baseline, N = 14	Active control - psychoeducation (Brain Health Workshop), 9-week, N = 14	Active control - psychoeducation (Brain Health Workshop), 8-month, N = 12
DKEFS Tower test - achievement score Delis-Kaplan Executive Function Scale. Measures planning, working memory (sequencing) (executive function) Mean (SD)	6.9 (3.9)	7.6 (2.9)	7.8 (2.4)	6.9 (3.1)	8.9 (3)	8.3 (2.1)
Hotel Test - Tasks attempted Measures monitoring; attention; prospective memory (executive function) Mean (SD)	4.2 (1.2)	4.7 (0.5)	4.9 (0.3)	4.2 (1.1)	4.3 (1)	4.6 (0.7)
Hotel Test - deviation from optimal task time (seconds) Measures monitoring; attention; prospective	495.7 (260.9)	403.6 (111.7)	345.3 (116.1)	509.8 (290.3)	458.3 (170.9)	406.2 (144.1)

Outcome	Goal management programme , Baseline, N = 14	Goal management programme , 9-week, N = 13	Goal management programme , 8-month, N = 11	Active control - psychoeducation (Brain Health Workshop), Baseline, N = 14	Active control - psychoeducation (Brain Health Workshop), 9-week, N = 14	Active control - psychoeducation (Brain Health Workshop), 8-month, N = 12
memory (executive function) Mean (SD)						
Goal attainment post-intervention - proportion achieving or exceeding target goal Measures Success and satisfaction with goal attainment No of events	n = NA ; % = NA	n = 7 ; % = 53.8	n = NR ; % = NR	n = NA ; % = NA	n = 3 ; % = 21.4	n = NR ; % = NR
Cognitive Failures Questionnaire (CFQ) Measures absentmindedness in everyday life. Scale usually 0-100. Mean (SD)	44.9 (17.6)	42.3 (11.3)	41.7 (13.5)	44.4 (13.4)	37.3 (13.4)	35.8 (14.5)

Outcome	Goal management programme , Baseline, N = 14	Goal management programme , 9-week, N = 13	Goal management programme , 8-month, N = 11	Active control - psychoeducation (Brain Health Workshop), Baseline, N = 14	Active control - psychoeducation (Brain Health Workshop), 9-week, N = 14	Active control - psychoeducation (Brain Health Workshop), 8-month, N = 12
Self-reported Mean (SD)	23 (13.2)	19 (9.3)	20.1 (8.9)	23.3 (12.3)	17.2 (9.2)	16.9 (10.9)
Informant-reported Mean (SD)	25.9 (18.1)	21.5 (18.8)	15.7 (10.4)	22.7 (16)	22.5 (17.7)	18.4 (13.2)
POMS - Total Mood Disturbance Scale usually 0-200. Measure of mood. Mean (SD)	52.9 (39.2)	34.9 (20.1)	36.3 (20.9)	34.3 (23)	23 (21.1)	20.5 (24.1)
PSQI - Global Sleep Disturbance Pittsburgh Sleep Quality Index. Scale usually 0-21. Mean (SD)	9.6 (3.5)	7 (4.1)	7.9 (3.3)	9.2 (5.4)	7.2 (5.6)	6.6 (3.8)
Adherence - attendance rate for group sessions	NA	95.2%	NA	NA	94.4%	NA

Outcome	Goal management programme , Baseline, N = 14	Goal management programme , 9-week, N = 13	Goal management programme , 8-month, N = 11	Active control - psychoeducation (Brain Health Workshop), Baseline, N = 14	Active control - psychoeducation (Brain Health Workshop), 9-week, N = 14	Active control - psychoeducation (Brain Health Workshop), 8-month, N = 12
Overall group attendance rate						

Sustained Attention to Response Task (SART) - Commission errors (% no-go trials) - Polarity - Lower values are better
Sustained Attention to Response Task (SART) - Omission errors (% go trials) - Polarity - Lower values are better
Sustained Attention to Response Task (SART) - mean reaction time across go trials - Polarity - Lower values are better
Test of Everyday Attention (TEA) - Polarity - Higher values are better
DKEFS Tower test - achievement score - Polarity - Higher values are better
Hotel Test - Tasks attempted - Polarity - Higher values are better
Hotel Test - deviation from optimal task time - Polarity - Lower values are better
Cognitive Failures Questionnaire (CFQ) - Polarity - Lower values are better
DEX - total score - Polarity - Lower values are better
POMS - Total Mood Disturbance - Polarity - Lower values are better
PSQI - Global Sleep Disturbance - Polarity - Lower values are better
Adherence - attendance rate for group sessions - Polarity - Higher values are better
Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_SART commission errors_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_SART commission errors_9 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SART omission errors_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_SART omission errors_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_SART mean reaction time_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

1 **Results_SART mean reaction time_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_TEA elevator counting with distraction_9 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_TEA elevator counting with distraction_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_TEA visual elevator_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_TEA visual elevator_9 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

2

3 **Results_TEA elevator counting with reversal_9 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_TEA elevator counting with reversal_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_DKEFS Tower Test achievement score_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_DKEFS Tower Test achievement score_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_Hotel Task tasks attempted_9 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

2

3 **Results_Hotel Task tasks attempted_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_Hotel Task deviation from optimal time_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_Hotel Task deviation from optimal time_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_achieving or exceeding goals_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

1 **Results_CFQ_9 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

2

3 **Results_CFQ_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_DEX self-report_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_DEX self-report_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_DEX informant-reported_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

1 **Results_DEX informant-reported_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_POMS total mood disturbance_9 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_POMS total mood disturbance_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PSQI sleep disturbance_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months minimum in protocol)*

Results_PSQI sleep disturbance_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results_adherence - attendance group sessions_9 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Rilo, 2018

Bibliographic Reference	Rilo, O.; Pena, J.; Ojeda, N.; Rodriguez-Antiguedad, A.; Mendibe-Bilbao, M.; Gomez-Gastiasoro, A.; DeLuca, J.; Chiaravalloti, N.; Ibarretxe-Bilbao, N.; Integrative group-based cognitive rehabilitation efficacy in multiple sclerosis: a randomized clinical trial; Disability & Rehabilitation; 2018; vol. 40 (no. 2); 208-216

1 **Study details**

Trial name / registration number	NCT02287454
Study location	Spain
Study setting	Outpatient - recruited through neurologists
Study dates	The recruitment and enrolment were conducted in several periods from January to March 2013, from January to April 2014, and from May to September 2015.
Sources of funding	Supported by the Spanish Ministry of Economy and Competitiveness
Inclusion criteria	Clinically definite MS according to McDonald criteria; patients aged between 20 and 60 years; with relapsing-remitting, secondary progressive or primary progressive MS; and with or without cognitive deficits
Exclusion criteria	Presence of dementia as defined by a Mini Mental State Examination Test score lower than 24; having suffered an exacerbation during the month prior to the cognitive assessment; being treated with corticosteroids during study participation; the presence of another relevant neurological disorder; history of stroke or traumatic brain injury resulting in a loss of consciousness for more than 30 min; and the presence of psychiatric disorders.
Recruitment / selection of participants	The recruitment and enrolment were conducted in several periods from January to March 2013, from January to April 2014, and from May to September 2015. Informed of opportunity to participate in the study by their neurologists from Cruces and Basurto University Hospitals, in Biscay, Spain
Intervention(s)	Manual cognitive rehabilitation using REHACOP: group cognitive rehabilitation for 3 months (3 1 h sessions per week, 39 sessions total) -5 also had private cognitive rehabilitation sessions on top of this during their participation in the study (mean 10 sessions, 45 min each) mainly focusing on short term memory. REHACOP is an integrative cognitive rehabilitation programme based on the principles of restoration, compensation and optimisation. Treatment begins with remediation of basic cognitive processes, gradually advancing to more complex cognitive domains, and finishes with daily living complex tasks that integrate the utilization of several more basic cognitive domains. Allows for individual or group format and is composed of up to 300 paper and pen tasks divided into eight consecutive modules: attention, learning and memory, language, executive functions, social cognition, social skills, activities of daily living, and psycho-education. Processing speed is also trained in the first four modules, because several tasks are timed. Tasks within each module are hierarchically

	arranged by ability subtypes and difficulty levels to ensure an increasing level of cognitive demand. Two neuropsychologists, trained in the administration of the protocol, conducted the cognitive rehabilitation using the same materials and instructions. The neuropsychologists provided instructions of each paper–pencil task to the whole group, and subsequently, patients individually performed the task. Once the correction process was finished, patients could share with the remaining members of the group the difficulties encountered and the strategies employed during the task. Four weeks training in attention, three weeks focused on learning and memory, three weeks focused on language, three weeks focused on executive functioning and one week on training in social cognition. Also performed tasks at home three times a week during the learning and memory module to promote the generalization of the use of learning strategies to daily life activities.
Population subgroups	None
Comparator	Waitlist control group - waitlist control with no intervention.
Number of participants	44 randomised, 42 analysed
Duration of follow-up	3 months - end of intervention period
Indirectness	Population - does not appear to have required participants to have a cognitive impairment at baseline to be included
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (>70% in both groups) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (mean <6.0 in both groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear (does not appear to have required cognitive impairment to be included) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (likely absent as psychiatric conditions excluded) • Computerised vs clinician led - clinician led • Group vs individual - group

	Analysis - those with data (available case analysis) appear to have been reported in paper

Study arms

Manual cognitive rehabilitation using REHACOP (focused on attention, processing speed, learning and memory, language, executive functioning, and social cognition) (N = 22)

Waitlist control (N = 22)

Characteristics

Arm-level characteristics

Characteristic	Manual cognitive rehabilitation using REHACOP (focused on attention, processing speed, learning and memory, language, executive functioning, and social cognition) (N = 22)	Waitlist control (N = 22)
% Female Sample size	n = 13 ; % = 61.9	n = 14 ; % = 66.67
Mean age (SD) Mean (SD)	43.9 (9.51)	43.67 (6.89)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR

Characteristic	Manual cognitive rehabilitation using REHACOP (focused on attention, processing speed, learning and memory, language, executive functioning, and social cognition) (N = 22)	Waitlist control (N = 22)
Disease duration (years) Mean (SD)	9.95 (7.84)	10.67 (5.79)
Relapsing-remitting Sample size	n = 15 ; % = 71.43	n = 17 ; % = 80.95
Primary progressive Sample size	n = 1 ; % = 4.76	n = 0 ; % = 0
Secondary progressive Sample size	n = 5 ; % = 23.81	n = 4 ; % = 19.05
EDSS score Mean (SD)	3.52 (1.59)	2.5 (1.85)

Baseline characteristics are given for those analysed (n=21 per group) and not those randomised (n=22 per group)

Outcomes

Study timepoints

- Baseline

- 3 month (3-months - end of intervention period)

Results - raw data

Outcome	Manual cognitive rehabilitation using REHACOP (focused on attention, processing speed, learning and memory, language, executive functioning, and social cognition), Baseline, N = 21	Manual cognitive rehabilitation using REHACOP (focused on attention, processing speed, learning and memory, language, executive functioning, and social cognition), 3-month, N = 21	Waitlist control, Baseline, N = 21	Waitlist control, 3-month, N = 21
Brief Test of Attention Mean (SD)	12.43 (3.53)	12.81 (4.2)	15.14 (4.05)	15.1 (3.71)
Backward Digits subtest of the Wechsler Adult Intelligence Scale III; Measured working memory Mean (SD)	5.14 (1.77)	6.43 (1.75)	6.1 (1.58)	6.24 (1.73)
SDMT Symbol Digit Modalities Test. Measured processing speed. Mean (SD)	36.67 (9.23)	42.62 (12.46)	46.43 (13.46)	47.52 (13)
Salthouse Perceptual Comparison Test	20.52 (5.37)	25.38 (7.21)	26.19 (8.91)	27.38 (9.29)

Outcome	Manual cognitive rehabilitation using REHACOP (focused on attention, processing speed, learning and memory, language, executive functioning, and social cognition), Baseline, N = 21	Manual cognitive rehabilitation using REHACOP (focused on attention, processing speed, learning and memory, language, executive functioning, and social cognition), 3-month, N = 21	Waitlist control, Baseline, N = 21	Waitlist control, 3-month, N = 21
Measured processing speed. Mean (SD)				
Trail-Making Test Part A Measured processing speed. Mean (SD)	50.9 (23.12)	45.24 (16.63)	37.38 (14.59)	40.43 (18.23)
Hopkins Verbal Learning Test-Revised - learning Measured verbal learning and memory Mean (SD)	20.95 (3.89)	24.48 (4.63)	24.86 (3.58)	24.81 (4.42)
Hopkins Verbal Learning Test-Revised - recall Measured verbal learning and memory	7.19 (2.73)	8.71 (2.67)	8.76 (2.1)	9.48 (1.81)

Outcome	Manual cognitive rehabilitation using REHACOP (focused on attention, processing speed, learning and memory, language, executive functioning, and social cognition), Baseline, N = 21	Manual cognitive rehabilitation using REHACOP (focused on attention, processing speed, learning and memory, language, executive functioning, and social cognition), 3-month, N = 21	Waitlist control, Baseline, N = 21	Waitlist control, 3-month, N = 21
Mean (SD)				
Animals Mean (SD)	18.81 (4.39)	21.57 (6.28)	21.81 (6.88)	22.24 (6.79)
Supermarket Mean (SD)	16 (5.38)	18.81 (7.8)	19 (4.86)	21.1 (5.82)
P words Mean (SD)	24.52 (7.88)	27.62 (5.59)	28.67 (12.24)	30.57 (11.91)
Stroop Word-Colour Test Measured executive functioning Mean (SD)	34.86 (7.72)	42.57 (11.6)	41.48 (11.53)	43.62 (11.36)
Stroop interference Measured executive functioning Mean (SD)	-0.26 (7.63)	5.34 (8.52)	1.9 (6.12)	2.79 (5.47)

1 Brief Test of Attention - Polarity - Higher values are better

Backward Digits subtest of the Wechsler Adult Intelligence Scale III; - Polarity - Higher values are better
SDMT - Polarity - Higher values are better
Salthouse Perceptual Comparison Test - Polarity - Higher values are better
Trail-Making Test Part A - Polarity - Lower values are better
Hopkins Verbal Learning Test-Revised - learning - Polarity - Higher values are better
Hopkins Verbal Learning Test-Revised - recall - Polarity - Higher values are better
Calibrated Ideational Fluency Assessment - Polarity - Higher values are better
Stroop Word-Colour Test - Polarity - Higher values are better
Stroop interference - Polarity - Higher values are better
Final values for continuous outcomes
Note despite n=22 being randomised to each group, baseline values for outcomes only given for the n=21 per group that were analysed at end of intervention.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_Brief Test of Attention_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_backward digits_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Salthouse Perceptual Comparison Test_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Trail Making Test Part A_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Hopkins Verbal Learning Test - Learning_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Hopkins Verbal Learning Test - recall_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Calibrated Ideational Fluency Assessment - animals_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_Calibrated Ideational Fluency Assessment - supermarket_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Calibrated Ideational Fluency Assessment - P words_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Stroop Word-Colour Test_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Stroop Interference_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Rosti-Otajarvi, 2013

Bibliographic Reference	Rosti-Otajarvi, E.; Mantynen, A.; Koivisto, K.; Huhtala, H.; Hamalainen, P.; Patient-related factors may affect the outcome of neuropsychological rehabilitation in multiple sclerosis; Journal of the Neurological Sciences; 2013; vol. 334 (no. 12); 106-11

Study details

Secondary publication of another included study- see primary study for details	• Mantynen, A., Rosti-Otajarvi, E., Koivisto, K. et al. (2014) Neuropsychological rehabilitation does not improve cognitive performance but reduces perceived cognitive deficits in patients with multiple sclerosis: a randomised, controlled, multi-centre trial. Multiple Sclerosis 20(1): 99-107

Schirda, 2020

Bibliographic Reference	Schirda, B.; Duraney, E.; Lee, H. K.; Manglani, H. R.; Andridge, R. R.; Plate, A.; Nicholas, J. A.; Prakash, R. S.; Mindfulness training for emotion dysregulation in multiple sclerosis: A pilot randomized controlled trial; Rehabilitation Psychology; 2020; vol. 65 (no. 3); 206-218

Study details

Secondary publication of another included study- see primary study for details	• Manglani, H. R., Samimy, S., Schirda, B. et al. (2020) Effects of 4-week mindfulness training versus adaptive cognitive training on processing speed and working memory in multiple sclerosis. Neuropsychology 34(5): 591-604

Shahpouri, 2019

Bibliographic Reference	Shahpouri, M. M.; Barekatain, M.; Tavakoli, M.; Sanaei, S.; Shaygannejad, V.; Evaluation of cognitive rehabilitation on the cognitive performance in multiple sclerosis: A randomized controlled trial; Journal of Research in Medical Sciences; 2019; vol. 24; 110

Study details

Trial name / registration number	IRCT2016042227522N1
Study location	Iran
Study setting	Outpatient - those referred to an MS clinic
Study dates	Conducted from August 2016 to April 2017
Sources of funding	Supported by Isfahan University of Medical Sciences
Inclusion criteria	Ability to read and write; Extended Disability Severity Scale of ≤5.5; mild to moderate memorial impairment based on Everyday Memory Questionnaire; and mild to moderate depression status based on second version of Beck depression inventory.
Exclusion criteria	Those refusing to have primary psychological and cognitive assessment.
Recruitment / selection of participants	Recruited those referred to Kashani MS Clinic affiliated to Isfahan University of Medical Sciences

Intervention(s)	Tailored cognitive rehabilitation: 10 sessions of group cognitive rehabilitation (2 h per session, sessions every 7-10 days). Duration unclear but ~10-14 weeks based on spacing and number of sessions. General aim of therapist in each class was reinforcement and/or consolidation of previous cognitive abilities which have been impaired and reinforcing remaining abilities to compensate for those where there were impairments. Rehabilitation areas trained included attention, concentration, visual and auditory memory and autobiographical memory. Approaches were performed considering the severity of cognitive impairment and with the aim of optimisation of the residual functions. The mnemonic approach was utilised which includes visual imagery, theological organization, and relational strategies including mnemonics of fiction, the clues about the first word, chain connection, and the technique of Preview, Question, Read, Self-recitation and Test (PQRST). Memory and its disturbances in the daily life were explained for the participants; then, the autobiographical memory, its subtypes, and its disturbances were represented. The technique of recalling positive memories through autobiographical memory was trained, and then, the psychologist presented several samples and requested the participants to recall and then present their positive memories. Of n=33 randomised, n=3 said to have not received the allocated intervention (excluded from analysis).
Population subgroups	None
Comparator	Control - discussion of experiences and coping strategies only: attended similar classes with regard to the number and duration of sessions; however, the content of the sessions was different and was not supporting cognitive rehabilitation. In these sessions, patients were requested to present their experiences of cognitive impairments, and cases with successful coping with new conditions were admired. Duration unclear but ~10-14 weeks based on spacing and number of sessions.
Number of participants	66 randomised, 56 analysed at follow-up (3-months after start of intervention - intervention duration unclear but ~10-14 weeks based on spacing and number of sessions)
Duration of follow-up	3-months after the start of the intervention (intervention duration unclear but ~10-14 weeks based on spacing and number of sessions)
Indirectness	None
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (>65% both groups) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (score up to 5.5 was inclusion criterion)

	• Severity of cognitive impairment (mild/moderate/severe) - unclear (mild-moderate impairments included proportion with each unclear) • Disease modifying treatment status (currently using and not currently using) - using (all using one) • Mood disorders (presence or absence) - present (mild-moderate depression on BDI inclusion criterion) • Computerised vs clinician led - clinician led • Group vs individual - mixed/unclear (described as group despite saying treatment tailored to each individual) Analysis - per protocol (some excluded for not receiving intended intervention)

Study arms

Tailored cognitive rehabilitation (N = 33)

Control - discussion of experiences and coping strategies (N = 33)

Characteristics

Arm-level characteristics

Characteristic	Tailored cognitive rehabilitation (N = 33)	Control - discussion of experiences and coping strategies (N = 33)
% Female Sample size	n = 20 ; % = 71.4	n = 19 ; % = 67.8
Mean age (SD) Mean	32.21	30.46

Characteristic	Tailored cognitive rehabilitation (N = 33)	Control - discussion of experiences and coping strategies (N = 33)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
EDSS score Mean	2.28	7.07
Duration of disease (years) Mean	7.46	7.07
None Sample size	n = 18 ; % = 64.28	n = 19 ; % = 67.8
one Sample size	n = 7 ; % = 25	n = 6 ; % = 21.4
two Sample size	n = 3 ; % = 10.7	n = 3 ; % = 10.7
Relapsing-remitting Sample size	n = 19 ; % = 67.8	n = 20 ; % = 71.4

Characteristic	Tailored cognitive rehabilitation (N = 33)	Control - discussion of experiences and coping strategies (N = 33)
Primary progressive Sample size	n = 3 ; % = 10.7	n = 3 ; % = 10.7
Secondary progressive Sample size	n = 6 ; % = 21.4	n = 5 ; % = 17.8
Beta interferon Sample size	n = 19 ; % = 67.8	n = 21 ; % = 75
Fingolimod Sample size	n = 6 ; % = 21.4	n = 5 ; % = 17.8
Rituximab Sample size	n = 3 ; % = 10.7	n = 2 ; % = 7.1

Note that patient characteristics at baseline are given for the n=28 analysed in each group, not the n=33 per group randomised

Outcomes

Study timepoints

- Baseline
- 3 month (3-months - 3 months after start of intervention (intervention duration unclear but ~10-14 weeks based on spacing and number of sessions))

Results - raw data

Outcome	Tailored cognitive rehabilitation, Baseline, N = 28	Tailored cognitive rehabilitation, 3-month, N = 28	Control - discussion of experiences and coping strategies, Baseline, N = 28	Control - discussion of experiences and coping strategies, 3-month, N = 28
Everyday Memory Questionnaire Scale 0-140? Mean (SD)	126.86 (49.39)	92.93 (44.29)	109.07 (46.39)	112.57 (41.14)
Prospective and Retrospective Memory Questionnaire Scale 16-80? Mean (SD)	49.07 (9.11)	36.11 (9.76)	42.86 (9.7)	45.57 (7.73)
Digit Span test for attention assessment Mean (SD)	10.14 (3.54)	12 (2.95)	12 (2.62)	11.54 (2.41)
Physical health Mean (SD)	59.46 (15.92)	66.93 (15.59)	58.42 (12.4)	56.25 (12.09)
Mental health Mean (SD)	50.53 (17.09)	67.77 (15.12)	52.18 (12.7)	50.9 (15.32)

Outcome	Tailored cognitive rehabilitation, Baseline, N = 28	Tailored cognitive rehabilitation, 3-month, N = 28	Control - discussion of experiences and coping strategies, Baseline, N = 28	Control - discussion of experiences and coping strategies, 3-month, N = 28
Beck Depression Inventory-II Scale usually 0-63. Mean (SD)	20.8 (6.59)	11 (6.86)	20.89 (6.59)	20.64 (5.69)

Everyday Memory Questionnaire - Polarity - Lower values are better
Prospective and Retrospective Memory Questionnaire - Polarity - Lower values are better
Digit Span test for attention assessment - Polarity - Higher values are better
MSQoL-54 - Polarity - Higher values are better
Beck Depression Inventory-II - Polarity - Lower values are better
Final values for continuous outcomes
Despite n=33 being randomised to each group, data for baseline and 3-month follow-up only given for the n=28 analysed.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_EMQ_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Prospective and Retrospective Memory Questionnaire_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

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2 **Results_digit span for attention_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

1 **Results_MSQoL-54 physical_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_MSQoL-54 mental_3 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Beck Depression Inventory_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Sharifi, 2019

Bibliographic Reference	Sharifi, A.; Yazdanbakhsh, K.; Momeni, K.; The effectiveness of computer-based cognitive rehabilitation in executive functions in patients with multiple sclerosis; Journal of Kermanshah University of Medical Sciences; 2019; vol. 23 (no. 1)

Study details

Trial name / registration number	Not reported
Study location	Iran
Study setting	Outpatient - members of MS society in a single city in Iran
Study dates	Not reported
Sources of funding	Funded as part of a thesis - Cognitive Technologies and Sciences Development Headquarter
Inclusion criteria	MS diagnosis; age of 18 - 45 years; reading and writing literacy; and a willingness to participate in the study
Exclusion criteria	Dementia and severe psychiatric disorder recorded in medical or psychiatric files; participation in other rehabilitation programs; and severe motor disabilities interfering with the study process.

Recruitment / selection of participants	Convenience sampling was used to select people with MS that were members of MS Society in city of Kermanshah, Iran. Card sorting test performed on 60 patients and then the n=20 with lowest scores (perseverative error ≤20) were selected and randomly divided into two groups.
Intervention(s)	Computerised cognitive rehabilitation focused on executive function: 12 sessions (50 min per session) of computer-based cognitive rehabilitation, being held twice weekly. Captain's Log cognitive rehabilitation software used. Two programs focused on executive functions were selected and administered, which were stimulus reaction/inhibition (red light and green light) and scanning reaction/inhibition (mouse hunt), each comprising 15 different stages. Stages got more difficulty with increasing stage number and entering next stage required completion of the previous task. Therapist carefully reviewed how each assignment was performed and explained it for the experimental group in a simple and straightforward language. The program of each session was different from that of the previous session.
Population subgroups	None
Comparator	Control - no training: the control group received no training.
Number of participants	20 randomised, 20 assumed to be analysed as no missing data reported
Duration of follow-up	end of intervention - not explicitly stated but likely 6 weeks based on number of sessions and sessions per week.
Indirectness	Population - unclear if required cognitive impairment to be included Outcome - time-point <3-month minimum in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - unclear • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (suggests all had EDSS <3.5) • Severity of cognitive impairment (mild/moderate/severe) - unclear (presence of an impairment may not have been an inclusion criterion) • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (severe psychiatric disorder excluded) • Computerised vs clinician led - computerised

	• Group vs individual - individual Analysis - number analysed unclear but assumed intention to treat as no missing data mentioned

Study arms

Computerised cognitive rehabilitation focused on executive function (N = 10)

Control - no training (N = 10)

Characteristics

Arm-level characteristics

Characteristic	Computerised cognitive rehabilitation focused on executive function (N = 10)	Control - no training (N = 10)
% Female Sample size	n = 6 ; % = 60	n = 5 ; % = 50
Mean age (SD) Mean (SD)	38.1 (8.71)	36 (6.35)
Ethnicity Custom value	NR	NR
Comorbidities	NR	NR

Characteristic	Computerised cognitive rehabilitation focused on executive function (N = 10)	Control - no training (N = 10)
Custom value		

Outcomes

Study timepoints

- Baseline
- 6 week (6-weeks - end of intervention (6 weeks not explicitly stated but assumed based on total number of sessions and sessions per week))

Results - raw data

Outcome	Computerised cognitive rehabilitation focused on executive function, Baseline, N = 10	Computerised cognitive rehabilitation focused on executive function, 6-week, N = 10	Control - no training, Baseline, N = 10	Control - no training, 6-week, N = 10
Wisconsin Card Sorting Test - Number of categories Mean (SD)	2.2 (1.23)	4.8 (1.13)	3.5 (1.18)	3.5 (0.7)
Wisconsin Card Sorting Test - Total errors Mean (SD)	30.9 (8.77)	19 (4.39)	27.9 (2.45)	40.7 (2.45)

Wisconsin Card Sorting Test - Number of categories - Polarity - Higher values are better
Wisconsin Card Sorting Test - Total errors - Polarity - Lower values are better

Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_WCST number of categories_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol*

Section	Question	Answer
		and unclear if cognitive impairment an inclusion criterion)

Results_WCST total errors_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol*

Section	Question	Answer
		and unclear if cognitive impairment an inclusion criterion)

Stuifbergen, 2018

Bibliographic Reference	Stuifbergen, A. K.; Becker, H.; Perez, F.; Morrison, J.; Brown, A.; Kullberg, V.; Zhang, W.; Computer-assisted cognitive rehabilitation in persons with multiple sclerosis: Results of a multi-site randomized controlled trial with six-month follow-up; Disability & Health Journal; 2018; vol. 11 (no. 3); 427-434

Study details

Trial name / registration number	NCT 03200899
Study location	USA
Study setting	Outpatient - recruitment from community
Study dates	Not reported
Sources of funding	Supported by the National Institutes of Health, National Institute of Nursing Research 1R01NR014362
Inclusion criteria	18–60 years of age; able to understand and comply with the study protocol; visual acuity with correction sufficient to work on a computer screen; clinically definite MS for at least 6 months and exacerbation free for 90 days); and score at least 10 (indicating some problems in at least 5 areas) on Perceived Deficits Questionnaire.
Exclusion criteria	No further criteria reported

Recruitment / selection of participants	Participants were recruited from three large metropolitan communities in Texas: Houston, San Antonio and Dallas. Recruited via physician referral, targeted mailings to persons with MS on the mailing list of the National MS Society, contact with support groups, and notices in MS newsletters and web sites.
Intervention(s)	Computer-assisted cognitive rehabilitation (MAPSS-MS intervention): aims to help persons with MS acquire the highest level of cognitive functioning and functional independence. The intervention includes group sessions (2 h per week for 8 weeks) focused on building efficacy for use of cognitive strategies and a home-based computer training program (45 min three times per week). Programme's conceptual model proposes accurate knowledge of cognitive problems, lifestyle adjustments (sleep, stress management, physical activity) that support cognitive functioning, and self-efficacy to manage cognitive challenges will support persons with MS in the use of compensatory cognitive strategies and cognitive skills. Group component - first four sessions involved common cognitive problems experienced with MS (attention and processing speed, memory and language, visuospatial and executive functioning) and development of relevant compensatory strategies. The final four sessions focused on lifestyle behaviours to support cognitive functioning, including managing fatigue and stress and increasing physical activity. Computer component - Lumosity program from Lumos Labs used. Facilitator prescribed exercises from a study-specific protocol addressing the most common deficits experienced by persons with MS (attention, memory, flexibility, and problem solving). Arranged so that the most basic cognitive skills (attention) were addressed first. Each participant was asked to complete 3 sessions (45–60 min of training) a day three times a week, (approximately 45 games) and to keep a written log of practice time. To promote consistency in testing and intervention delivery, the researchers trained neuropsychological testers and facilitators at each site in the study procedures.
Population subgroups	None
Comparator	Control - usual care + freely available games: received their usual care and a referral to “MyBrainGames”, available for free at MultipleScerosis.com. Games challenge processing speed, working memory attention and task switching ability. Asked to keep a log of practice time. Also had weekly check-in calls with research staff during 8-week intervention period.
Number of participants	183 randomised, 183 appear to have been analysed at all time-points despite missing data (n=27 missing 5 months, 3 months after the end of the intervention; n=33 missing at 8 months, 6 months after the end of the intervention)
Duration of follow-up	Up to 6 months after the end of the 8-week intervention period (8 months). Extracted 8-week and
Indirectness	None

Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - majority relapsing-remitting (69% both groups) • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (mean EDSS ~5.0 in both groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear • Computerised vs clinician led - mixed (some computerised and some in-clinic components) • Group vs individual - mixed (some individual and some group components) Analysis -intention to treat with last observation carried forward imputation.

Study arms

Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills) (N = 93)

Control - usual care + freely available computer games (N = 90)

Characteristics

Arm-level characteristics

Characteristic	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills) (N = 93)	Control - usual care + freely available computer games (N = 90)
% Female	n = 80 ; % = 86	n = 80 ; % = 89
Sample size		

Characteristic	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills) (N = 93)	Control - usual care + freely available computer games (N = 90)
Mean age (SD) Mean (SD)	49.8 (7.5)	49.4 (8.5)
Non-Hispanic Sample size	n = 84 ; % = 90	n = 81 ; % = 90
Spanish/Hispanic Sample size	n = 9 ; % = 10	n = 9 ; % = 10
White Sample size	n = 73 ; % = 79	n = 64 ; % = 71
African American Sample size	n = 17 ; % = 18	n = 17 ; % = 19
Multiple categories Sample size	n = 0 ; % = 0	n = 1 ; % = 1
Other Sample size	n = 3 ; % = 3	n = 8 ; % = 9
Comorbidities Custom value	NR	NR

Characteristic	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills) (N = 93)	Control - usual care + freely available computer games (N = 90)
Years since diagnosis Mean (SD)	13.9 (8.05)	12.1 (8.07)
Benign sensory Sample size	n = 3 ; % = 3	n = 3 ; % = 3
Relapsing-remitting Sample size	n = 64 ; % = 69	n = 61 ; % = 69
Primary progressive Sample size	n = 3 ; % = 3	n = 5 ; % = 6
Secondary progressive Sample size	n = 14 ; % = 15	n = 10 ; % = 11
Progressive-relapsing Sample size	n = 1 ; % = 1	n = 1 ; % = 1
Unknown/could not classify Sample size	n = 8 ; % = 9	n = 9 ; % = 10
EDSS score	5.1 (1.63)	5.3 (1.5)

Characteristic	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills) (N = 93)	Control - usual care + freely available computer games (N = 90)
Mean (SD)		

Outcomes

Study timepoints

- Baseline
- 5 month (5-months - 3 months after the end of the 8-week intervention period)
- 8 month (8-months - 6 months after the end of the 8-week intervention period)

Results - raw data

Outcome	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), Baseline, N = 93	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), 5-month, N = 93	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), 8-month, N = 93	Control - usual care + freely available computer games, Baseline, N = 90	Control - usual care + freely available computer games, 5-month, N =	Control - usual care + freely available computer games, 8-month, N = 90
Total Mean (SD)	52.4 (12)	57.2 (12.3)	56.1 (12.9)	49.6 (10.3)	54.7 (12.3)	53.6 (12.9)
Delay Mean (SD)	11.6 (3.4)	12.4 (3.5)	12.4 (3.6)	11 (3.6)	11.9 (3.7)	11.6 (3.7)

Outcome	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), Baseline, N = 93	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), 5-month, N = 93	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), 8-month, N = 93	Control - usual care + freely available computer games, Baseline, N = 90	Control - usual care + freely available computer games, 5-month, N =	Control - usual care + freely available computer games, 8-month, N = 90
Total Mean (SD)	21.7 (6.4)	21.9 (6.8)	21.9 (7)	20.2 (6.9)	20.7 (6.1)	20.1 (6.7)
Delay Mean (SD)	8.4 (2.7)	8.2 (2.6)	8.2 (2.7)	8 (2.7)	7.7 (2.5)	7.5 (2.7)
3 seconds Mean (SD)	41 (14.4)	46.9 (11.6)	47.6 (11.9)	40.1 (13.2)	44.3 (12.4)	45.9 (11.8)
2 seconds Mean (SD)	29.3 (13.2)	35.1 (12.4)	34.8 (13.2)	28.5 (11.4)	31.6 (12.5)	33.4 (12.2)
SDMT Symbol Digit Modalities Test. Assesses complex scanning and visual tracking. Mean (SD)	49.8 (11.8)	52.8 (13)	54.6 (12.2)	49 (12.4)	50.7 (12.2)	52 (12.4)
COWAT Controlled Oral Word	36.4 (11.1)	40.2 (12.7)	39.5 (12.1)	36.2 (11.8)	38.1 (11.7)	36.9 (11.9)

Outcome	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), Baseline, N = 93	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), 5-month, N = 93	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), 8-month, N = 93	Control - usual care + freely available computer games, Baseline, N = 90	Control - usual care + freely available computer games, 5-month, N =	Control - usual care + freely available computer games, 8-month, N = 90
Association Test. Assesses verbal fluency and word finding. Mean (SD)						
Everyday Problems Test-Revised Performance on cognitive-related instrumental activities of daily living - cognitive ability to reason and solve problems encountered in daily living. 12-item version of original 30-item version. Scale possibly 0-12. Mean (SD)	22.9 (4.6)	23.8 (4.8)	24.2 (4.8)	22.8 (4.9)	23.1 (4.3)	23.5 (4.4)
General Self-Efficacy Scale Self-report measure of confidence in the ability to affect outcomes in various	61.5 (12.2)	64 (10.6)	63.7 (11.1)	60.3 (11)	62.5 (11.4)	61.1 (12)

Outcome	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), Baseline, N = 93	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), 5-month, N = 93	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), 8-month, N = 93	Control - usual care + freely available computer games, Baseline, N = 90	Control - usual care + freely available computer games, 5-month, N =	Control - usual care + freely available computer games, 8-month, N = 90
contexts and situations. Scale usually 17-85. Mean (SD)						
CES-D Depression Center for Epidemiologic Studies Depression Scale. Scale usually 0-60 Mean (SD)	11.4 (6.2)	9.9 (6.2)	10.1 (6.2)	11.4 (5.8)	11.5 (6.6)	10.5 (5.9)
Multi-Factorial Memory Questionnaire - Strategy subscale Measure of use of memory strategies (self-efficacy?). Scale 0-76 Mean (SD)	38.4 (13.4)	40.5 (11.4)	40.2 (11)	36.7 (11.8)	39.6 (11.3)	39.5 (11.2)
PROMIS - Applied Cognition-Abilities Short Form 8a	22.5 (7.2)	25.6 (7.7)	25.6 (7.4)	22.5 (7.8)	23.4 (7.3)	23 (7.8)

Outcome	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), Baseline, N = 93	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), 5-month, N = 93	Computer-assisted cognitive rehabilitation (memory, attention, problem-solving skills), 8-month, N = 93	Control - usual care + freely available computer games, Baseline, N = 90	Control - usual care + freely available computer games, 5-month, N =	Control - usual care + freely available computer games, 8-month, N = 90
Assess self-reported cognitive function. Scale 8-40. Mean (SD)						
Adherence - meeting or exceeding prescribed computer training time Custom value	68% met or exceeded total training time prescribed	NA	NA	41/90 spent time on the MyBrain game (range 10 min per week to 370 min). 50% 45 min or less per week	NA	NA
Adherence - mean number of group classes attended (out of possible 8) Custom value	mean (SD) classes attended was 6.4 (2.3, range 0-8)	NA	NA	NA	NA	NA

1 CVLT-II - Polarity - Higher values are better
2 BVMT-R - Polarity - Higher values are better
3 PASAT - Polarity - Higher values are better
4 SDMT - Polarity - Higher values are better

COWAT - Polarity - Higher values are better
Everyday Problems Test-Revised - Polarity - Higher values are better
General Self-Efficacy Scale - Polarity - Higher values are better
CES-D Depression - Polarity - Lower values are better
Multi-Factorial Memory Questionnaire - Strategy subscale - Polarity - Higher values are better
PROMIS - Applied Cognition-Abilities Short Form 8a - Polarity - Higher values are better
Adherence - mean number of group classes attended (out of possible 8) - Polarity - Higher values are better
Final values for continuous outcomes
Data missing but intention to treat with imputation using last observation carried forward method used.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_CVLT total_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT total_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT delay_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_CVLT delay_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_BVMT-R total_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_BVMT-R total_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_BVMT-R delay_5 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_BVMT-R delay_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1
2 **Results_PASAT 3 seconds_5 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3
4 **Results_PASAT 3 seconds_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT 2 seconds_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_PASAT 2 seconds_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_SDMT_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_COWAT_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_COWAT_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Everyday Problems Test-Revised_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Everyday Problems Test-Revised_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1
2 **Results_General Self-efficacy scale_5 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3
4 **Results_General Self-efficacy scale_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_CES-D depression_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results_CES-D depression_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Multifactorial memory questionnaire - strategy_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_Multifactorial memory questionnaire - strategy_8 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_PROMIS applied cognition abilities_5 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Results_PROMIS applied cognition abilities_8 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Results_adherence computer training_end of treatment**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results_adherence group classes attended_end of treatment

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Vilou, 2020

Bibliographic Reference	Vilou, I.; Bakirtzis, C.; Artemiadis, A.; Ioannidis, P.; Papadimitriou, M.; Konstantinopoulou, E.; Aretouli, E.; Messinis, L.; Nasios, G.; Dardiotis, E.; Kosmidis, M.; Grigoriadis, N.; Computerized cognitive rehabilitation for treatment of cognitive impairment in multiple sclerosis: an explorative study; Journal of Integrative Neuroscience; 2020; vol. 19 (no. 2); 341-347

Study details

Trial name / registration number	Not reported
Study location	Greece
Study setting	Outpatient - recruited from outpatient department
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	Adults diagnosed with relapsing-remitting MS; clinically and radiologically stable for at least 3 months before the inclusion; performed 1.5 Standard Deviation units below average on at least one of the neuropsychological measures administered; and were not diagnosed with a psychiatric condition
Exclusion criteria	No further criteria reported

Recruitment / selection of participants	Participants were recruited from outpatient clinic
Intervention(s)	Computerised cognitive rehabilitation (BrainHQ) - focus on memory, attention and processing speed: 6-week (twice weekly sessions for ~40 min) cognitive rehabilitation intervention using the web based BrainHQ platform (BrainHQ, Posit Sciences). Enables clinicians to design a custom-made rehabilitation programme using a variety of training modules. Following modules were used in this study: episodic memory (Memory Grid, Rhythm Recall, and To-Do List Training modules), attention (Divided Attention, Double Decision, Mixed Signals, and Freeze Frame modules) and processing speed (Eye for Detail, Hawk-Eye, Visual Sweeps and Sound Sweeps modules). Home-based programme and performed in native language. Trained individually for the use of the platform by a neuropsychologist. The activities were set in advance and were given to patients in printed form. Each session involved training on two scheduled activities (20 min per activity). Weekly contact with trained neuropsychologist and assistance available when needed. Scheduled visits were performed every 2 weeks, to review and optimize the levels of difficulty in each activity, according to patients' performance.
Population subgroups	None
Comparator	Control: no definition provided, assume received no additional intervention.
Number of participants	47 randomised, 47 appear to have been analysed at end of treatment (6 weeks)
Duration of follow-up	6-weeks - end of intervention period
Indirectness	Outcome - time-point <3 months minimum in protocol
Additional comments	• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - all relapsing-remitting • According to disability (EDSS <6 and EDSS ≥6) - <6.0 (mean <6.0 in both groups) • Severity of cognitive impairment (mild/moderate/severe) - unclear • Disease modifying treatment status (currently using and not currently using) - unclear • Mood disorders (presence or absence) - unclear (diagnosis of psychiatric condition excluded so possibly absent) • Computerised vs clinician led - computerised

	• Group vs individual - individual Analysis - presume intention to treat as no missing data mentioned

Study arms

Computerised cognitive rehabilitation (BrainHQ) - focus on memory, attention and processing speed (N = 23)

Control - no intervention? (N = 24)

Characteristics

Arm-level characteristics

Characteristic	Computerised cognitive rehabilitation (BrainHQ) - focus on memory, attention and processing speed (N = 23)	Control - no intervention? (N = 24)
% Female Sample size	n = 20 ; % = 87	n = 20 ; % = 83.3
Mean age (SD) Mean (SD)	33.5 (16)	37.8 (19)
Ethnicity Custom value	NR	NR

Characteristic	Computerised cognitive rehabilitation (BrainHQ) - focus on memory, attention and processing speed (N = 23)	Control - no intervention? (N = 24)
Comorbidities Custom value	NR	NR
Duration since diagnosis (years) Mean (SD)	8.3 (10.3)	10 (8.5)
Duration since onset (years) Mean (SD)	9.9 (10.5)	12.5 (6.8)
EDSS score Mean (SD)	2.9 (1.5)	3.5 (2.5)

Outcomes

Study timepoints

- Baseline
- 6 week (6-weeks - end of treatment)

1 **Results - raw data**

Outcome	Computerised cognitive rehabilitation (BrainHQ) - focus on memory, attention and processing speed, Baseline, N = 23	Computerised cognitive rehabilitation (BrainHQ) - focus on memory, attention and processing speed, 6-week, N = 23	Control - no intervention?, Baseline, N = 24	Control - no intervention?, 6-week, N = 24
SDMT Symbol Digit Modalities Test. Measures information processing speed Mean (SD)	49.1 (19)	50 (12)	46.1 (13)	44.5 (13)
Greek Verbal Learning Test Measures verbal learning Mean (SD)	54.2 (26)	63.7 (17)	56.5 (14)	54.4 (14)
BVMT-R Brief Visuospatial Memory Test-Revised. Measures visuospatial memory Mean (SD)	22.6 (14)	27.5 (10)	22.8 (11)	22.5 (9)

Outcome	Computerised cognitive rehabilitation (BrainHQ) - focus on memory, attention and processing speed, Baseline, N = 23	Computerised cognitive rehabilitation (BrainHQ) - focus on memory, attention and processing speed, 6-week, N = 23	Control - no intervention?, Baseline, N = 24	Control - no intervention?, 6-week, N = 24
Part A Measures visual attention Mean (SD)	51.5 (23)	38.2 (20)	46.5 (22)	43.4 (21)
Part B Measures task switching Mean (SD)	105.9 (62)	73.4 (27)	100.8 (54)	82.5 (24)
Colour Mean (SD)	58.7 (27)	65.2 (18)	56.9 (19)	57.5 (23)
Colour-Word Mean (SD)	38 (13)	44 (16)	36.7 (8)	38.8 (9)
Compliance with protocol Definition of compliance unclear No of events	n = NA ; % = NA	n = 12 ; % = 52.1	n = NA ; % = NA	n = NR ; % = NR

1 SDMT - Polarity - Higher values are better
2 Greek Verbal Learning Test - Polarity - Higher values are better

BVMT-R - Polarity - Higher values are better
Trail Making Test - Polarity - Lower values are better
Stroop Test - Polarity - Higher values are better
Final values for continuous outcomes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Results_SDMT_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_Greek Verbal Learning Test_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_BVMT-R_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_Trail Making Test Part A_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_Trail Making Test Part B_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_Stroop Test Colour_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_Stroop Test Colour-Word_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum in protocol)*

Results_compliance with protocol_6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

D.2 Studies extracted in previous review version – bold text indicates outcomes relevant to the new protocol that have been added in the updated review

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Cerasa A, Gioia MC, Valentino P, Nistico R,	RCT, Italy	N=26 randomised	Patients with relapsing remitting MS. Inclusion: No	Intervention	Control	6 wks	Selective reminding test long term	Intervention (N=12	Fondazione Italiana Sclerosi	Allocation concealme

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Chiriaco C, Pirritano D et al. Computer-assisted cognitive rehabilitation of attention deficits for multiple sclerosis: a randomized trial with FMRI correlates. Neurorehabilitation and Neural Repair. 2013; 27(4):284-295. (Guideline Ref ID CERASA2013)		Intervention N=12 analysed Control N=11 analysed	evidence of a severe cognitive impairment; predominant deficits in either attention and/or information processing speed, working memory and/or executive function; no clinical relapses and steroid treatment for at least one month prior to study entry; no concomitant therapy with antidepressant or psychoactive drugs; EDSS ranging 0 to 4; no history of psychiatric problems; and optimal visual acuity	Twice weekly for one-hour sessions for six weeks. Training consisted of the Rehacom software.	Twice weekly for one-hour sessions for six weeks. Visuomotor coordination task		storage 6 wks mean (SD)	throughout) 36.9 (SD 12.46) Control (N=11 throughout) 29.9 (9.8)	Multiplaonlus and Ministero Universita' e Ricerca	nt: Inadequate Randomisation: computer generated Triple blind fMRI study
							Selective reminding test consistent long-term retrieval	Intervention 24.86 (11.05) Control 17.1 (7.3)		
							Selective reminding test delayed	Intervention 7.11 (2.93) Control 6.2 (3.02)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			Patient population: Intervention M/F 3/9, age 31.7 (SD 9.2), education 11 (5-13) yrs, disease duration 52.1 (35.6) mths, EDSS 3 (1-4), Fatigue Severity Scale 2.6 (SD 1.7), MMSE 28.7 (SD 1.5) Control M/F 3/8, age 33.7 (SD 10.3) yrs, education 12 (5-17) yrs, disease duration 61,6 (62.1) mths, EDSS 2 (2-4), FSS 3.1 (SD 1.8), MMSE 28.5 (1.6) No statistically significant differences were reported				Spatial recall test immediate	Intervention 18.42 (6.22) Control 24.3 (3.99)		
							Spatial recall test delayed	Intervention 5.58 (2.47) Control 8.30 (1.89)		
							Word list generation	Intervention 20.8 (5.96) Control 20.6 (5.59)		
							Symbol digit modalities test	Intervention 38.69 (9.9) Contr		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								ol 37.3 (8.45)		
							Stroop test	Intervention 19.41 (5.14) Control 16.5 (5.22)		
							Paced auditory serial addition test – 3	Intervention 41.23 (12.7) Control 41 8.79)		
							Trail making			
							Trail making test A	Intervention 44.83 (13.1) Control		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								40.9 (13.94)		
							Trail making test B	Intervention 120.9 (37.9) Control 121.1 (37.4)		
							Trail making test B-A	Intervention 76.08 (34.1) Control 76.9 (30.7)		
							State trait anxiety inventory Y1	Intervention 36.6 (8.9) Control 41 (11.1)		
							State trait anxiety inventory Y2	Intervention 35.5		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								(8.6) Control 46 (11.1)		
							Beck II	Intervention 4.33 (3.17) Control 12.8 (13.5)		
							Fatigue Severity Scale	Intervention 2.83 (1.63) Control 4.22 (1.77)		
							EDSS			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								Intervention 3 (1-4) Control 2 (2-4)		

1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Chiaravalloti ND, Moore NB, Nikelshpur OM, DeLuca J. An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial. Neurology. 2013; 81(24):2066-2072. (Guideline Ref ID CHIARAVALLOTI2013)	RCT Computerised random number generation Treatment allocation was concealed. Participant and outcome assessor blinded	N=88 randomised N=46 modified Story Memory Technique Intervention N=45 immediate follow up Long term follow up N=40 Control N=41 and N=38 respectively	Patients with clinically definite MS and 1) new learning impairment, 2) aged 30-70 yrs, 3) free of exacerbations and steroid use for 1 mth or more 4) no major mental health problem Intervention: mean (SD) age 48.13 (10.17), 76% female, months since diagnosis 170.87 (120.51), N=33 relapsing remitting Control: age 49.32 (8,47), 76% female,	Modified Story Memory Technique 2 sessions every week for five weeks N=19 Booster sessions 1 per month N=21 Placebo booster sessions	Placebo Met with therapist for same time as intervention. Engaged in non-training specific tasks No contact after 5 wks	5 wks and 6 mths post end of intervention	California Verbal Learning Test (CVLT) immediate follow up learning slope, adjusted for baseline	Intervention 95%CI 1.67 to 2.10 Placebo 1.26 to 1.72 (p=0.0075). Treatment effect maintained at follow up	NIH	
							CVLT slope 10% improvement immediate follow-up	Intervention 62% Control 37%		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			months since diagnosis 173.37 (103.44), N=22 relapsing remitting No significant differences reported at baseline					(p=0.009)		
							CVLT total learning T-score, mean (SD) immediate follow-up	**Intervention 50.13 (11.99) Placebo 45.24 (13.44), P=0.078**		
							Objective everyday memory (Rivermead Behavioural Memory Test Story Memory) immediate follow up, adjusted for baseline	Intervention 95%CI 1.382 to 1.763 Placebo 1.050 to 1.450 (p<0.0115).		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							Subjective everyday cognition and emotional functioning (FAMS - Functional Assessment of Multiple Sclerosis) immediate follow-up, adjusted for baseline	**Intervention 95%CI 16.400 to 23.361 Placebo 11.953 to 18.914 (p<0.05).**		
							Frontal Systems Behavior Scale (FrSBe) – reported by relatives/significant others – <u>apathy</u> immediate follow-up,	**Intervention 95%CI 30.559 to 37.729 Placebo 27.013 to**		•

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							adjusted for baseline	33.237 (p<0.05).		
							FrSBe – reported by relatives/significant others – executive dysfunction immediate follow-up, adjusted for baseline	Intervention 95%CI 38.319 to 46.165 Placebo 34.690 to 41.528 (p<0.06).		
							Attention - Digit Span Scaled score, mean (SD) immediate follow-up	Intervention 10.51 (2.36) Placebo 10.27 (2.86)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								, P=0.667		
							Working memory – Letter Number Sequencing Scaled score, mean (SD) immediate follow-up	Intervention 11.22 (3.21) Placebo 10.49 (3.21), P=0.292		
							Processing speed – SDMT z-score, mean (SD) immediate follow-up	Intervention -1.15 (1.33) Placebo -1.00 (1.42), P=0.616		
							State Anxiety T-	Interventio		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							score, mean (SD) immediate follow-up	n 51.23 (15.97) Placebo 54.24 (15.47), P=0.407		
							Trait Anxiety T-score, mean (SD) immediate follow-up	Intervention 54.77 (16.59) Placebo 59.06 (14.49), P=0.235		
							Chicago Multidimensional Depression Inventory T-score, mean	l intervention 55.05 (15.7		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							(SD) immediate follow-up	0) Placebo 56.39 (12.92), P=0.686		
							Attention - Digit Span Scaled score, mean (SD) 6-month follow-up (post end of intervention)	Intervention 10.63 (2.71) Placebo 10.40 (2.85), P=0.723		
							Working memory – Letter Number Sequencing Scaled score, mean (SD) 6-month follow-up	Intervention 10.37 (3.04) Placebo 10.37 (3.05),		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							(post end of intervention)	P=0.997		
							Processing speed – SDMT z-score, mean (SD) 6-month follow-up (post end of intervention)	Intervention - 1.00 (1.34) Placebo - 0.97 (1.40), P=0.0.923		
							CVLT Total Learning T-score, mean (SD) 6-month follow-up (post end of intervention)	Intervention 42.79 (15.75) Placebo 35.94 (16.47), P=0.074		
							CVLT Learning	Intervention		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							Slope z-score, mean (SD) 6-month follow-up (post end of intervention)	n 1.11 (0.61) Placebo 1.00 (0.56), P=0.422		
							Rivermead Behavioural Memory Test – Story Memory Immediate Profile Score, mean (SD) 6-month follow-up (post end of intervention)	Intervention 1.34 (0.88) Placebo 1.43 (0.85), P=0.671		
							Rivermead Behavioural Memory Test – Story Memory Delayed Profile Score, mean	Intervention 1.51 (0.76) Placebo 1.48		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							(SD) 6-month follow-up (post end of intervention)	(0.70), P=0.814		
							FrSBe Apathy after illness (family) T-score, mean (SD) 6-month follow-up (post end of intervention)	Intervention 67.81 (24.31) Placebo 63.88 (20.96), P=0.627		
							FrSBe Executive Dysfunction after illness (family) T-score, mean (SD) 6-month follow-up (post end of intervention)	Intervention 59.69 (16.04) Placebo 60.75 (17.12), P=0.857		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							FAMS General Contentment, mean (SD) 6-month follow-up (post end of intervention)	Intervention 17.17 (6.82) Placebo 14.48 (6.31), P=0.108		
							State Anxiety T-score, mean (SD) 6-month follow-up (post end of intervention)	Intervention 49.83 (12.75) Placebo 53.44 (13.87), P=0.0.268		
							Trait Anxiety T-score, mean (SD) 6-month follow-up	Intervention 54.72 (13.5		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							(post end of intervention)	**2) Placebo 56.22 (16.18), P=0.679**		
							Chicago Multidimensional Depression Inventory T-score, mean (SD) 6-month follow-up (post end of intervention)	**Intervention 54.44 (15.62) Placebo 56.48 (11.46), P=0.487**		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Chiaravalloti ND, DeLuca		N=29	Patients with clinically definite	Rehabilitation	Control	11 wks	Hopkins Verbal	Rehabilitati		Inadequate randomisati

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
J, Moore NB, Ricker JH. Treating learning impairments improves memory performance in multiple sclerosis: a randomized clinical trial. Multiple Sclerosis. 2005; 11(1):58-68. (Guideline Ref ID CHIARAVALLOTI2005)	RCT, USA	Rehabilitation N=15 Week 6 and 11 N=14 Control N=14 Week 6 and 11 N=14	MS (Poser criteria). Exclusion criteria: age over 69, reported history of neurological disorders, alcohol or drug abuse, bipolar disorder, psychotic disorder, schizophrenia or head injury resulting in more than 30 mins loss of consciousness. All patients were one month post most recent exacerbation and/or steroid treatment. 17 patients had a relapsing-remitting course, 4 primary-	Eight therapeutic sessions (2 x 4 wks). Participant learns the selective memory trial (SMT). Within the SMT, the participant was taught two interrelated skills: 1) to use visualisation i.e., imagery to facilitate new learning (sessions 1-4) and 2) to utilize context to learn new information e.g., a story even if information is seemingly unrelated (sessions 5-8). Each session latest	Met with the same therapist as did the rehabilitation gp. Sessions were held at the same frequency as the rehabilitation gp but the control gp engaged in non-training orientated tasks to control for professional contact. Training sessions for the two gps were matched for stimulus presentation, content, examiner		Learning Test-Revised(HVLT)week 6 – new learning abilities	on N=14 throughout mean 2.57 Control N=14 throughout -0.79 p=0.08	None reported	on, unclear allocation concealment, assessor and patient blinding
							HVLT week 6 % improved – new learning abilities	Rehabilitation 8/14 Control 5/14		
							HVLT week 6 to week 11	p=0.496		
							HVLT week 0 to week 11	P=0.21		
							HVLT week 0 to 11 mean change	Rehabilitation 3.07		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			progressive and 7 secondary-progressive. Duration of MS 12 to 432 mths, mean 135.72 (SD 87.53) All patients were determined to have impaired verbal new learning, as documented by performance at least one standard deviation below the mean for a healthy control sample on an adaptation of the Buschke Selective Reminding Test	approximately 45 mins	contact, and session duration.			(5.88) control 0.57 (4.20)		
							Memory functioning questionnaire week 0 to week 11	P=0.055		
							Remember things in everyday life week 0 to 6	Rehabilitation 2.00 Control -1.29 p<0.01		
							Remember things in everyday life week 0 to 11	Rehabilitation 3.07 control -1.86 p<0.001		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			Rehabilitation: Age 45.14 (SD13.78), Education yrs 14.64 (SD2.71), female 64%, right-handed 93%, ambulation index 3.21 (SD2.81), duration of MS diagnosis 168.07 (SD101.24) mths, WAIS-R vocabulary scale 10.64 (SD2.79) Control: Age 46 (SD9.28), Education yrs 15.04 (SD2.82), female 57%, right-handed 86%, ambulation index 2.43 (SD2.62), duration of MS				Subjective assessment of overall memory functioning	P=0.055		
							Subjective assessment of ability to remember things in everyday life week 0 to 6	P<0.01 in favour of rehabilitation		
							Subjective assessment of ability to remember things in everyday life week 0 to 11	P<0.001 in favour of rehabilitation		
							Depressive symptomatology week 0 to 6	P=3.04		
							Depressive symptomatology week 6 to 11	P=0.17		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			diagnosis 100.21 (SD60.12)* mths, WAIS-R vocabulary scale 10.64 (SD2.56) * P<0.05 Neuropsychological test scores mean (SD): Rehabilitation Animal naming 18.42 (3.86), block design 18.07 (10.06), COWAT 36.57 (12.33), Digit span forward 8.79 (1.97), Digit span backward 6.93 (2.73), HVLT total learning 24 (5.60), HVLT delayed recall 7.50 (3.80), HVLT recognition hits 11.29 (0.91),				Trait anxiety week 0 to 6 Trait anxiety week 0 to 11	P=0.56 P=0.06		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			Letter-number sequencing 10.43 (2.98), PASAT total score 98.79 (41.01), Symbol Digit Modalities Test 44.21 (13.07), Oral Trail Making Test A: time 10.57 (3.62), Test B 31.26 (17.37) Control Animal naming 19.79 (4.82), block design 22.08 (9.34), COWAT 35.64 (10.92), Digit span forward 8.14 (1.70), Digit span backward 6.71 (2.20), HVLT total learning 27.07 (3.52), HVLT delayed recall							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			8.14 (2.82), HVLT recognition hits 11.36 (1.01), Letter-number sequencing 9.93 (3.47), PASAT total score 105.79 (39.35), Symbol Digit Modalities Test 43.14 (13.20), Oral Trail Making Test A: time 7.82 (1.88)*, Test B 22.33 (6.10) * P<0.05							

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Fink F, Rischkau E, Butt M, Klein J, Eling P, Hildebrandt H. Efficacy of an executive function intervention programme in MS: a placebo-controlled and pseudo-randomized trial. Multiple Sclerosis. 2010; 16(9):1148-1151. (Guideline Ref ID FINK2010)	Described as pseudo random, Germany	N=50 Results Cognitive intervention (N=14), placebo group (N=17), and untrained group (N=19) 6 weeks Cognitive N=11 placebo N=14 untrained group N=15 One-year Cognitive N=6	Patients with relapsing remitting MS (41 women and nine men, mean age 44.8 (SD8.2), mean disease duration 92.4 (SD92), not using corticosteroids during the last four weeks before enrolment, with an EDSS score ≤ 7 and no neuropsychiatric disorder or dementia. Cognitive mean (SD): preference shifting (PS) (trials to criterion (TTC) 49.8 (26.8), PS	Cognitive intervention 6-week programme. Participants spent 25-30 minutes per day, four times per week, on textbook exercises for executive functioning and they met with a psychologist for 1.5 hrs to receive feedback and to discuss the exercises	Placebo Trained 5 days per week for 40 minutes. Patients had to respond fast and accurately to visual stimuli. They had to call the psychologist once a week to report on time having spent training. The amount of time invested in completing the exercises was comparable	1 yr	Preference Shifting trials to criterion mean (SD)	Post – treatment Cognitive N=11 throughout 33.0 (19.0) Placebo N=14 throughout 38.8 (18.7) Untrained group N=15 throughout 40.8 (22.7) 1 yr	Sanofi-Aventis Inc., Bayer HealthCare Inc., Merck-Serono Inc and the Villigst foundation	• Randomisation and allocation concealment unclear • Patients experiencing a relapse were exclude from analysis • Assessor and patient blind

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
		placebo N=8 untrained group N=6	reaction time (RT) ms 667 (150), response shifting (RS) TTC 55.0 (24.4), RS RT ms 698 (191), 2 back com 3.4 (4.6), 2 back om 3.2 (2.0), 2-back RT ms 668 (195), California Verbal Learning Test (CVLT) 11.0 (2.0) Placebo mean (SD): preference shifting (PS) (trials to criterion (TTC) 42.3 (22.1), PS reaction time (RT) ms 610 (140), response shifting (RS) TTC 43.2 (20.6), RS RT ms 648 (191), 2 back com 2.6 (1.8), 2		in cognitive and placebo gps Untrained group No cognitive intervention during the intervention period			Cognitive N=6 throughout 59.2 (22.5) Placebo N=8 throughout o 45.7 (20.1) Untrained group N=6 throughout 37.8 (24.2)		
							Preference shifting RT (ms) mean (SD)	Post-treatment Cognitive 638 (185)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			back om 2.6 (2.4), 2-back RT ms 619 (150), California Verbal Learning Test (CVLT) 11.6 (1.6) Untrained group mean (SD): preference shifting (PS) (trials to criterion (TTC) 44.7 (25.0), PS reaction time (RT) ms 590 (90), response shifting (RS) TTC 40.0 (23.9), RS RT ms 650 (148), 2 back com 3.4 (4.2), 2 back om 2.3 (1.2), 2-back RT ms 582 (175), California Verbal Learning Test					Placebo 598 (124) Untrained group 697 (144) 1 yr Cognitive 685 (142) Placebo 734 (196) Untrained group 600 (204)			
							Response shifting trials to criterion mean (SD)	Post-treatment Cognitive		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			(CVLT) 12.4 (1.9)					49.3 (23.7) Placebo 49.9 (27.0) Untrained group 39.8 (25.1) 1 yr Cognitive 40.4 (31.6) Placebo 49.9 (25.2) Untrained group 51.9 (26.2)		
							Response shifting RT (ms) mean (SD)	Post-treatment Cogni		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								tive 656 (219) Placebo 676 (170) Untrained group 727 (173) 1-yr Cognitive 684 (230) Placebo 747 (230) Untrained group 675 (235)		
							2-back commissions mean (SD)	Post-treatment		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								Cognitive 4.2 (6.5) placebo 3.1 (1.6) Untrained group 3.0 (5.7) 1 yr Cognitive 4.2 (5.2) Placebo 2.2 (1.5) Untrained group 4.3 (2.6)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							2-back omissions mean (SD)	Post-treatment Cognitive 1.5 (0.7) Placebo 1.4 (1.2) Untrained group 2.5 (2.3) 1 yr Cognitive 1.6 (1.1) Placebo 3.5 (1.5) Untrained group		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								1.7 (1.1)		
							2-back RT (ms) mean (SD)	Post-treatment Cognitive 589 (146) Placebo 680 (241) Untrained group 604 (189) 1 yr 685 (184) placebo 587 (202) Untrained group 582 (185)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							California Verbal Learning Test learning mean (SD)	Post treatment Cognitive 12.1 (2.1) Placebo 11.5 (1.2) Untrained group 11.5 (2.1) 1 yr Cognitive 12.5 (2.1) Placebo 11.5 (1.1) Untrained group 12.3 (1.8)		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Flavia M, Stampatori C, Zanotti D, Parrinello G, Capra R. Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis. Journal of the Neurological Sciences. 2010; 288(1-2):101-105. (Guideline Ref ID FLAVIA2010)	Pseudo-randomised control, Italy	N=20 N=10 Rehabilitation N=10 Control	Patients with relapsing remitting MS (Poser and Brinar criteria). All had an EDSS score of ≤ 4. Information processing, working memory and attention were assessed by the Paced Auditory Serial Addition Test 2" and 3" (PASAT) and executive function by the Wisconsin Card Sorting Test (WCST). Patients were included in the study if their scores in both tests fell below	Rehabilitation 3-month duration. Individual sessions last for 1 hr with a frequency of three sessions per week. Sessions consisted of computer-assisted training of attention, information processing and planning exercises for executive functions. The software used, Plan a Day and Divided	Control No treatment	3 mths	Paced Auditory Serial Addition Test (PASAT) 2" change score median (lower quartile upper quartile)	Control 0.00 (0.00 12.75) Rehabilitation 22.00 (17.00 27.00) p=0.004 in favour of rehabilitation	None reported	• Randomisation inadequate • Allocation concealment adequate • Double blind
							PASAT 3" change score median (lower quartile upper quartile)	Control 7.00 (0.00		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			z=-1.5 for PASAT (either 2" or 3" interval) and T=35 for WCST in any of the following measures: total errors (WCSTte), number of perseverative errors (WCSTpe) and number of perseverative response (WCSTpr). Exclusion criteria were the following: one or more clinical exacerbations in the previous year, loss of visual acuity, ongoing major psychiatric disorder, substance abuse and a MINI Mental State Examination	Attention, were part of the RehCom package (www. Schohfried.at), a software package with a special keyboard with large buttons, which limits the interference of motor and coordination impairments and expertise on computer use. The Plan a Day procedure trains the patient's ability to organise, plan and develop solution strategies employing realistic simulations of a set of scheduled dates and duties				26.50) Rehabilitation 36.00 (24.50 44.75) p=0.023 in favour of rehabilitation		
							Wisconsin Care Sorting Test total error (WCSTte) change score median (lower quartile upper quartile)	Control 45.00 (21.50 62.75) Rehabilitation 20.00 (15.25		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			(MMSE) score < 24. Rebilitation: median age yrs 44.0, education 9 yrs, illness duration 18.5 yrs, EDSS 1.5 Control: median age yrs 42, education yrs 8, illness duration yrs 16.5, EDSS 2.5 no significant differences reported Groups matched at baseline on Paced Auditory Serial Additions Test (PASAT) 2" and 3", Wisconsin Card Sorting Test, controlled oral word	to be organised at specific places in a small city map. Times for planning and schedules were registered for each patient at each session and only improvement and acquisition of sufficient planning abilities for fulfilling all of the appointments required let the level to be ameliorated in the following treatment session. This was considered a strategic behaviour acquisition. In Divided Attention, the patient is required to				27.50) p=0.037 in favour of rehabilitation		
							WCST perseverative responses (pr) change score median (lower quartile upper quartile)	Control 37.9 (21.50 59.5) Rehabilitation 17.5 (16.0 27.5) p=0.08		
							WCST perseverative errors (pe) change score median (lower	Control 28.50 (14.25 42.50		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			association, Test of Everyday Attention, Selective Reminding Test, Symbol Digit Modalities Test, Montgomery-Asberg Depression Rating Scale and Multiple Sclerosis Quality of Life	simulate a train driver, carefully observing the control panel of a train and the countryside. Several distractions, such a crossing animals, and train speed must be taken into account with increasing levels of difficulty. Specific speed information training, which has been shown to be effective in patients with brain injuries, was combined with each Divided Attention session, consisting of a modified PASAT task with numbers, words			quartile upper quartile)	) Rehabilitation 14.50 (11.25 18.75) p=0.051		
							Controlled Oral Word Association (COWA/P)	Control 27.50 (17.75 39.75) Rehabilitation 36.00 (27.50 44.50) p=0.236		
							COWA/S change score	Control		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
				and months of the year			median (lower quartile upper quartile)	35.50 (29.00 42.00) Rehabilitation 44.50 (27.25 47.00) p=0.398		
							Test of Everyday Attention auditory stimulus) TEAam change score median (lower quartile upper quartile)	Control 580.00 (551.75 670.75) Rehabilitation 724.00 (596.50		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								848.75 p=0.097) p=0.097		
							TEA visual stimulus (vm) change score median (lower quartile upper quartile)	Control 1040 (829.75 1105.50) Rehabilitation 902.00 (857.25 1040.00) p0.771		
							TEA total omitted (to) change score median (lower quartile upper quartile)	Control 6.00 (3.00 6.75) Reha		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								bilitation 3.00 (2.00 4.75) p=0.141		
							TEA total errors (te) change score median (lower quartile upper quartile)	Control 6.5 (4.00 8.00) Rehabilitation 3.00 (2.00 4.75) p=0.104		
							Selective Reminding Test consistent long-term retrieval (SRT/CLTR) change score median (lower quartile upper quartile)	Control 16.00 (7.00 29.000 Rehabilitation 19.00 (14.0		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								0 29.50) p=0.559		
							SRT delayed recall (DR) change score median (lower quartile upper quartile)	Control 5.50 (4.25 7.75) Rehabilitation 6.50 (4.50 8.75) p=0.607		
							10/36 SRT visuo-spatial learning – long term retrieval (LTR) change score median (lower quartile upper quartile)	Control 14.00 (11.25 17.50) Rehabilitation 17.50 (14.5		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								0 19.50) p=0.204		
							10/36 SRT delayed recall (DR) change score median (lower quartile upper quartile)	Control 4.00 (3.25 5.75) Rehabilitation 6.00 (4.25 6.75) p=0.353		
							Symbol Digit Modalities Test (SDMT) change score median (lower quartile upper quartile)	Control 38.00 (28.5 0 45.75) Rehabilitation 34.50 (31.0		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								0 44.75) p=0.942		
							Montomery-Asberg Depression Rating Scale (MADRS) change score median (lower quartile upper quartile)	Control 14.00 (8.75 22.50) Rehabilitation 4.50 (3.00 6.50) p=0.01 in favour of rehabilitation		
							Multiple Sclerosis Quality of Life (MSQoL) change score median (lower	Control 155.00 (142.50		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							quartile upper quartile)	184.50) Rehabilitation 189.00 (165.75 208.75) p=0.285		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Hildebrandt H, Lanz M, Hahn HK, Hoffmann E, Schwarze B, Schwendemann G et al. Cognitive training in MS: effects and relation to brain atrophy. Restorative Neurology and Neuroscience. 2007; 25(1):33-43. (Guideline Ref ID HILDEBRANDT2007)	RCT Germany	N=42 N=17 Cognitive retraining N=25 control	Patients with relapsing remitting MS diagnosed according to the McDonald criteria. All patients were formerly in-patients and treated for acute relapse. Enrolment was started at least 4 weeks after stopping methylprednisolone treatment. Exclusion criteria: EDSS score higher than 7.0, s current or past psychiatric disorder and substance	Cognitive training Compact disc with memory and working memory rehabilitation tasks (VILAT-G 1.o (Hildenbrandt, 2002). Patients were requested to train for 6 week, at least 5 days a week, for 30 minutes a day The subject was presented with a word list which had to be memorised. Subsequently, a series of calculations was presented.	Control No training	6 weeks	Expanded Disability Status Scale mean (SD) 6 weeks	Rehabilitation N=17 throughout 2.7 (2.06) Control N=25 throughout 2.6 (1.80) ns	Biogen Idec Germany, Sanofi-Aventis Inc, and Serono Inc	• Randomisation inadequate • Allocation concealment unclear • Assessor blinded • ITT analysis
							Time Walk Test (Multiple Sclerosis Functional Composite Scale MSFC) mean (SD) 6 weeks	Rehabilitation -2.128 (5.52) Control -0.175 (2.88) ns		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			abuse. Patients received treatment with either interferon beta or glatirameracetate Group performance as baseline. Depending on the specific task a performance below one standard deviation or above one standard deviation of the published norms were defined as impaired. According to this criterion 28% of the control group and 41% of the treatment group showed	Subjects had to judge whether the result of the new calculation was larger, smaller or equal to the previous result. After a series of calculations, the program asked to type the word list that had been memorised at the beginning of the trial. Typing the memorised words in a sequence that was structured by a common semantic category was rewarded by a special feedback sentence. Initially retrieval cues were presented.			Nine Hole Peg Test (MSFC)	Rehabilitation -0.134 (0.81) Control -0.083 (0.94) p=0.032		
							Learning trials (California Verbal Learning Test (CVLT)) mean (SD) 6 weeks	Rehabilitation 12.29 (2.12) Control 11.30 (1.94) p=0.030		
							Short delay free recall (CVLT) mean (SD) 6 weeks	Rehabilitation 13.18 (3.05)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			impairments on the PASAT, 24% vs 23.4% in CVLT learning or recall, 20% vs 12% in cognitive speed, 36% vs 17% in object alteration. Taking the results of all neuropsychological tests together 48% of control group and 47% of the treatment group showed some impairment					Control 11.32 (3.45) p=0.067		
							Short delay cued recall mean (SD) 6 weeks	Rehabilitation 13.47 (3.0) Control 12.48 (2.95) p=0.056		
							Long delay free recall (CVLT) mean (SD) 6 weeks	Rehabilitation 13.24 (3.35) Control 12.16 (3.22) p=0.025		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							Long delay cued recall (CVLT) mean (SD) 6 weeks	Rehabilitation 13.31 (3.16) Control 12.96 (2.69) ns		
							PASAT (MSFC) mean (SD) 6 weeks	Rehabilitation 0.017 (0.83) Control 0.010 (1.09) p=0.049		
							Object alternation RTs mean (SD) 6 weeks	Rehabilitation 820 (323) Control 744		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								(233) ns		
							Object alteration errors mean (SD) 6 weeks	Rehabilitation 1.18 (1.70) Control 2.16 (3.04) p=0.085		
							Alertness without cueing mean (SD) 6 weeks	Rehabilitation 248 (85) Control 233 (45) ns		
							Alertness with cueing mean (SD) 6 weeks	Rehabilitation 234 (80) Control 223		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								(46) ns		
							SF12 Bodily Score mean (SD) 6 weeks	Rehabilitation 38.6 (12.1) Control 41.1 (11.9) ns		
							SF12 Mental Score	Rehabilitation 48.5 (13.3) Control 47.8 (9.7) ns		
							Beck Depression Inventory mean (SD) 6 weeks	Rehabilitation 10.3 (8.5) Control		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								11.0 (7.9) ns		
							Fatigue Severity Scale mean (SD) 6 weeks	Rehabilitation 37.5 (15.0) Control 36.8 (14.5) ns		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Jonsson A, Korfitzen EM, Heltberg A, Ravnborg MH, Byskov-Ottosen E. Effects of neuropsychological	RCT, Denmark	N=40 (N=130 potential subject, N=11 refused to participate, N=71 excluded) Cognitive	Patients fulfilling Schumacher's diagnostic criteria of MS. Hospitalised patients. Exclusion criteria:	Cognitive training and neuropsychotherapy. Direct training of concentration was done using compiled text, inverted text, mirror-written	Control (non-specific mental stimulation) Patient and therapist saw and discussed different kinds of films,	6 mths	**Change from baseline values**		Danish Health Ministry, Danish Multiple Sclerosis Association	• Randomisation unclear • Allocation concealment unclear
							Memory span Difference in t score units mean 45.6 days	Cognitive N=16 (not stated if ITT) throughout		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
treatment in patients with multiple sclerosis. Acta Neurologica Scandinavica. 1993; 88(6):394-400. (Guideline Ref ID JONSSON1993)		training N=20 N=16 completers Control N=20 N=16 completers	symptoms or signs of neurological or cerebral disease, psychiatric illness, age over 60 yrs, severe visual or motor dysfunction, very severe cognitive impairment, history of drug or alcohol abuse, no cognitive impairment Mean (SD) Cognitive: age 46.1 (7.3) yrs, education 10.9 (2.0) yrs, disease duration 15.0 (11.2) yrs, disease severity EDSS 5.6 (1.7), days of hospitalisation 47.2 (8.9), neuropsychologi	text, “two-in-one” pictures, labyrinths etc. Memory was trained both directly and by learning compensator strategies such as visualisation using pictures of increasing complexity, shopping list and appointments, or a calendar. The calendar was also used for planning daily activities. Stories of different lengths and complexity were read aloud, and the patient was encouraged to visualise and then retell the stories in order to learn how to	read and discussed newspaper articles and played games without and relation to the training of a specific cognitive dysfunction. No corrections or explanations were given. Personal problems and problems concerning disease acceptance were also discussed			2.2 Control N=16 throughout 2.0 p=0.94		• Patient blind
							Verbal learning Difference in t score units mean 45.6 days	Cognitive 2.3 Control 1.2 p=0.55		
							Visuo-spatial memory Difference in t score units mean 45.6 days	Cognitive 2.8 control 0.4 p=0.08		
							Visuo-motor speed Difference in t score units mean 45.6 days	Cognitive 0.4 Control 2.4		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			cal testing 6.0 (1.3) hrs, no. of treatment hrs 17.3 (3.9) female:male 9:11 Control: age 43.0 (9.0) yrs, education 12.2 (2.9) yrs, disease duration 15.1 (8.5) yrs, disease severity EDSS 5.6 (1.8), days of hospitalisation 44.2 (7.8), neuropsychological testing 5.5 (1.3) hrs, no. of treatment hrs 6.2 (17.2) female:male 10:10 Six had relapsing	structure text. Patients with visuo-spatial and orientation difficulties were trained partly with mosaic games, being correct and urged to work slowly and systematically, and practical with practical exercises such as walking or wheelchair driving in and outside of the hospital. Along with the cognitive training the patients took part in neuropsychotherapy to realise and accept their present cognitive				p=0.07		
							Visual perception Difference in t score units mean 45.6 days	Cognitive 2.0 Control 0.6 p=0.04 in favour of the treatment group		
							Sum of 11 tests Difference in t score units mean 45.6 days	Cognitive 1.8 Control 1.1 p=0.53		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			remitting disease course, 25 secondary chronic progressive disease and 9 had primary chronic progressive disease Occupational status: 1 under training, 1 was unemployed, 8 had sick leave, and 30 had disablement pension Neuropsychological findings: Equal impairment in the two treatment gps except for two cognitive factors, visuo-spatial	and behavioural level of functioning, learning how best to use available resources. The therapist issued a goal-directed treatment program based on the patient's individual neuropsychological test profile and personal problems Both group were treated for 1 to 1.5 hrs 3 times a week, always on an individual basis. When possible, the closest relative was involved in			WAIS similarities Difference in t score units mean 45.6 days	Cognitive 1.0 Control 0.77 p=0.91		
							WAIS picture arrangement Difference in t score units mean 45.6 days	Cognitive 5.2 Control 7.3 p=0.42		
							Beck depression inventory Difference in raw scores, converted to positive values mean 45.6 days	Cognitive 2.4 Control 0.0 p=0.04 in favour of the treatment group		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			memory and visual perception, which were significantly more impaired in the cognitive gp. Compared with a normal Danish sample all cognitive factors but one (visual perception) were significantly impaired in both treatment gps. There were no significant different on the Beck Depression Inventory and the State Trait Anxiety Inventory	treatment. In addition, all patients underwent daily individual physiotherapy and other activities			State Trait Anxiety Inventory 1 Difference in raw scores, converted to positive values mean 45.6 days	Cognitive 5.6 Control 2.7 p=0.17		
							State Trait Anxiety Inventory 2 Difference in raw scores, converted to positive values mean 45.6 days	Cognitive 3.8 Control 3.5 p=0.92		
							Memory span Difference in t score units 6 mths	Cognitive 1.8 Control 2.4 p=0.76		
							Verbal learning Difference in t	Cognitive 2.2 Contr		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							score units 6 mths	ol 0.6 p=0.40		
							Visuo-spatial memory Difference in t score units 6 mths	Cognitive 2.7 control 0.2 p=0.05 in favour of the treatment group		
							Visuo-motor speed Difference in t score units 6 mths	Cognitive 0.5 Control -1.0 p=0.44		
							Visual perception Difference in t score units 6 mths	Cognitive 2.2 Control 1.0		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								p=0.09		
							Sum of 11 tests Difference in t score units 6 mths	Cognitive 1.6 Control -0.5 p=0.09		
							WAIS similarities Difference in t score units 6 mths	Cognitive 1.5 control 2.1 p=0.81		
							WAIS picture arrangement Difference in t score units 6 mths	Cognitive 3.7 control 4.2 p=0.87		
							Beck depression inventory Difference in raw scores,	Cognitive 1.1 Control -		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							converted to positive values 6 mths	2.7 p=0.03 in favour of treatment		
							State Trait Anxiety Inventory 1Difference in raw scores, converted to positive values 6 mths	Cognitive 1.1 Control -1.6 p=0.42		
							State Trait Anxiety Inventory 2Difference in raw scores, converted to positive values 6 mths	Cognitive 1.5 Control 0.6 p=0.75		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Lincoln NB, Dent A, Harding J, Weyman N, Nicholl C, Blumhardt LD et al. Evaluation of cognitive assessment and cognitive intervention for people with multiple sclerosis. Journal of Neurology, Neurosurgery, and Psychiatry. 2002; 72(1):93-98. *(Guideline Ref ID LINCOLN2002)*	RCT	N=240 (total) Intervention gp n=79 (n=5 withdrawn 4 months and n=6 at 8 months) Assessment gp n=79 (n=7 withdrawn at 4 months and n=8 at 8 months) Control gp n=82 (n=5 withdrawn at 4 and 8 months)	Patients with either clinically definite, clinically probable, or laboratory supported multiple sclerosis. Inclusion criteria included being able to cooperate with assessment for 30 mins at a time. Selection criteria were based on the assumption that patients might benefit as much from being told that they had no cognitive deficit as from being identified. Therefore, patients were not excluded on the basis of a	Rehabilitation Detailed cognitive assessment as above. Included various techniques such as diaries, lists, visual mnemonics. Maximum 6 mth duration	Screening Shortened version of the National adult reading test (NART) as a measure of premorbid intelligence and the brief repeatable battery (BRB-N) to evaluate verbal reasoning, visual memory, attention and speed of information processing. In addition, the ambulation index was administered	8 mths	General Health Questionnaire (GHQ) 4 mths	Control N=77 Median 21.0 IQR13-34 Assessment N=72 21.0 13-31 Intervention N=74 22.0 15-34 P=0.73	NHS Executive Research and Development Programme in Physical and Complex Disabilities	• P values relate to 3 arm comparison • Patients thought to be representative of those seen in clinical practice • High levels of variance due to heterogeneity of patients • Some patients receiving assessments did not
							GHQ 8 mths	Control N=77 18.0 13-35 Assessment N=71		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			cognitive screening assessment. Control: Men 25, women 52, type of MS: secondary progressive (SP) 35, relapsing remitting (RR) 37, primary progressive (PP) 6, unknown 4, working 28, not working 49, age median 40.5, age left education median 16.0, NART 101 Assessment: Men 16, women 56, type of MS: secondary progressive (SP) 33, relapsing		as a measure of physical mobility, the Guy's neurological disability scale (GNDS) as a measure of effects of multiple sclerosis and mood was assessed on the general health questionnaire-28 (GHQ-28). The occupational, educational history and the disease duration and course were established Assessment			18.5 13-35 Intervention N=73 21.0 15-36 P=0.59		see a health professional. Psychological assessment may need to be provided in the context of multi-disciplinary treatment • The significant results in favour of the control gp could imply that
							SF36 4 mths	**Physical health component** Control N=77 25.6 21-45 Assessment N=72 27.1 20-47 Intervention N=74 31.4		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			remitting (RR) 35, primary progressive (PP) 6, unknown 5, working 33, not working 39, age median 43.0, age left education median 16.0, NART 106 Assessment: Men 26, women 48, type of MS: secondary progressive (SP) 26, relapsing remitting (RR) 35, primary progressive (PP) 7, unknown 12, working 28, not working 46, age median 43.0, age left education median 16.0, NART 103		Patients received detailed cognitive assessment taking about 3 hrs. Patients were assessed on measures of memory, attention and executive functioning using the Wechsler memory scale revised, Stroop neuropsychological screening test, and modified card sorting test and were asked to complete an everyday			24-41 p=0.45 **Mental health component** Control N=77 44.7 36-55 Assessment N=72 44.7 35-57 Intervention N=74 46.9 39-55 p=0.55		cognitive assessment may have detrimental effects on quality of life, particularly if it is not carried out in conjunction with an intervention programme
							Overall Quality of Life	Control N=77		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
					memory questionnaire (EMQ). Further assessment were selected on the basis of patients' performance and included the test of everyday attention (TEA), behavioural assessment of the dysexecutive syndrome (BADS), "doors and people" recognition memory test (RMT), and the verbal and spatial		(OQoL) 4 mths	7.0 5-8 Assessment N=72 6.0 5-7 Intervention N=74 6.0 -8 p=0.15		
							Satisfaction with Quality of Life (SQoL) 4 mths	Control N=77 4.0 4-5 Assessment N=72 4.0 4-5 Intervention N=74 4.0 4-5		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
					reasoning task (VESPAR). The assessments were selected according to the nature of the patients' problems so that they were representative of cognitive assessments used in clinical practice. An assistant psychologist under the supervision of a chartered clinical psychologist conducted the assessments.			p=0.32		
							SF36 8 mths	**Physical health component** Control N=77 30.0 25-38 Assessment N=71 32.1 25-42 Intervention N=73 30.7 24-38 p=0.55 **Mental health comp**		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
					Formal psychological reports were sent to the patients' general practitioners and hospital staff involved in the patients' care. The information obtained was summarised for patients and when the patients agreed, their relatives Control – no assessment Received no further assessment following screening tests and results of		**onent** Control N=77 47.3 36-57 Assessment N=71 49.3 33-58 Intervention N=73 46.9 36-54 p=0.76			
							OQoL 8 mths	Control N=77 6.5 5-8 Assessment N=71 6.0 4-7 Intervention		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
					screening assessment were not given to the medical and rehabilitation staff or patients and their relatives			N=73 6.0 4-8 p=0.04 In favour of control vs assessment gp		
							SQoL 8 mths	Control N=77 5.0 4-8 Assessment N=71 4.0 3-5 Intervention N=73 4.0 3-5 p=0.04 in favou		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								r of control vs assessment gp		
							Extended activities of daily living (EADL) 4 mths	Control N=77 48.0 37-60 Assessment N=72 43.0 37-60 Intervention N=74 45.0 25-56 p=0.23		
							EADL 8 mths	Control N=77 47.5 37-59 Assessment		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								N=71 44.5 26-61 Intervention N=73 42.0 27-55 p=0.21		
							Everyday memory questionnaire (EMQ) 4 mths	Control N=77 16.5 7-42 Assessment N=72 18.5 5-31 Intervention N=74 17.0 7-35 p=0.69		
							EMQ 8 mths	Control N=77		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								14.07-37 Assessment N=71 15.05-31 Intervention N=73 15.06-32 p=0.76		
							Dysexecutive syndrome questionnaire (DEX) 4 mths	Control N=77 17.09-32 Assessment N=72 16.07-31 Intervention N=74 20.013-27		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								p=0.000.77		
							Dysexecutive syndrome questionnaire (DEX) 8 mths	Control N=77 median 16.5 9-32 Assessment N=71 18.0 (7-31) Intervention N=73 18.0 10-29 p=0.98		
							Memory aids questionnaire (MAQ) 4 mths	Control N=77 10.0 7-15 Assessment N=72 11.0		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								7-14 Intervention N=74 10.0 5-16 p=0.92		
							MAQ 8 mths	Control N=77 10.0 7-14 Assessment N=71 9.0 6-15 Intervention N=73 10.0 5-14 p=0.80		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							CARER OUTCOMES GHQ 4 mths	Control median 22.0 IQR 14-31 Assessment 24.0 16-35 Intervention 22.0 13-29 p=0.35		
							GHQ 8 mths	Control 18.0 13-30 Assessment 18.5 13-32 Intervention 21.0 12-32		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								p=0.59		
							EMQ 4 mths	Control 14.03-35 Assessment 11.54-28 Intervention 21.05-34 p=0.90		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							EMQ 8 mths	Control 10.03-31 Assessment 10.03-25 Intervention 13.03-29 p=0.88		
							DEX 4 mths	Control 17.09-33 Assessment 11.57-31 Intervention 11.58-32 p=0.80		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							DEX 8 mths	Control 10.09-32 Assessment 10.07-28 Intervention 13.08-31 p=0.72		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures		Effect sizes	Source of funding	Comments
Mantynen A, Rosti-Otajarvi E, Koivisto K, Lilja A,	RCT Computer gener	N=102 randomised N=60 intervention	Patients with clinically definite relapsing remitting MS, EDSS < 6,	Neuropsychological rehabilitation Computer-based attention and	Control	6 mths and 1 yr	**End of intervention**			Social Insurance Institutio	
							Compliance with intervention	**said to be 94.1% (n=1 terminate**			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Huhtala H, Hamalainen P. Neuropsychological rehabilitation does not improve cognitive performance but reduces perceived cognitive deficits in patients with multiple sclerosis: A randomised, controlled, multi-centre trial. Multiple Sclerosis. 2014; 20(1):99-107. (Guideline Ref ID MANTYNEN 2014)	ated random number table, independent allocation of subjects, neuropsychological assessment blinded	N=56 at 6 mths N=50 at one year N=42 control N=40 at 6 mths N=28 at one year	subjective (total score of questions 1, 2 and 11 in the Multiple Sclerosis Neuropsychological Questionnaire ≥ 6) and objective Symbol Digit Modalities Test total score ≤ 50) deficits in attention and processing speed and age 18-59 Exclusions: Included overall cognitive impairment (performance on all tests of the Brief Repeatable Battery of Neuropsychological Tests under -1.5 SD	working memory retraining used for increasing awareness of attentional problems, learning strategies, psychoeducation and homework assignment connected with rehabilitation goals as well as psychological support to promote coping with cognitive impairments Once a week for 13 weeks				**d due to difficult life situation)**	n in Finland	
							Achievement of personal goals (Goal attainment score, range of scale used unclear)	**Intervention – 56.2 (8.5), range 41.0-75.0**		
							6 months - N=58 and N=40 throughout			
							Brutscke Selective Reminding Test (BSRT)/long term storage 6 mths	Intervention mean (SD) 56.7 (14.7) Control 53.9 (11.1)		
							BSRT consistent	Intervention		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Rosti-Otajarvi E, Mantynen A, Koivisto K, Huhtala H, Hamalainen P. Neuropsychological rehabilitation has beneficial effects on perceived cognitive deficits in multiple sclerosis during nine-month follow-up. Journal of the Neurological Sciences. 2013; 334(1-2):154-160. (Guideline			compared to healthy controls) Intervention: Mean age 43.5 (SD 8.7), female:male 45:13, duration of MS 9.2 (SD 6.6) Control Mean age 44.1 (SD 8.8), female:male 31:9, duration of MS 10.1 (SD7.1 yrs)				long-term retrieval	50.2 (18.2) control 45.7 (15.2)		
							BSRT delayed recall	Intervention 10.4 (2.2) Control 10.0 (1.7)		
							10/36 (total correct)	Intervention 23.8 (4.5) Control 20.9 (4.8)		
							10/36 delayed recall	Intervention 8.5 (SD 1.9) Contr		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Ref ID ROSTI2013)								ol 7.4 (1.9)		
							3 PASAT total correct	Intervention 46.7 (11.8) Control 43.5 (11.0)		
							2 PASAT total correct	Intervention 32.9 (12.1) Control 30.8 (19.3)		
							COWAT	Intervention 25.5 (7.1) Control 24.2 (7.9)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							Stroop colour naming time	Intervention 73.7 (17.7) Control 77.0 (17.8)		
							Stroop colour/word interference – time	Intervention 116.2 (36.2) Control 116.0 (30.3)		
							Trail Making A (time)	Intervention 32.1 (12.4) Control 31.0 (9.2)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							Trail Making B time	Intervention 79.1 (36.4) Control 75.4 (35.6)		
							SDMT	**Intervention 50.6 (12.1) Control 48.2 (8.2)**		
							Perceived Deficits Questionnaire, total score Intervention	**Intervention 27.9 (11.7) Control 36.8 (12.6)**		
							BDI-II, total score	**Intervention 9.8**		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								(7.5) Control 10.0 (6.2)		
							Multiple Sclerosis Impact Scale-29, physical total score	Intervention 22.6 (16.4) Control 26.7 (17.7)		
							MSIS-29, psychological score	Intervention 24.9 (18.2) Control 27.1 (17.3)		
							Multiple Sclerosis Neuropsychological Questionnair	Intervention 24.0 (8.1) Contr		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							e-Patient, total score	ol 28.5 (10.5)		
							Multiple Sclerosis Neuropsychological Questionnaire-Informant, total score	Intervention 19.3 (10.4) Control 20.7 (11.1)		
							Brief version of the World Health Organisation Quality of life, S1 physical health total score	Intervention 14.2 (2.5) Control 13.6 (2.2)		
							WHO-BREF S2 psychological total score	Intervention 14.0 (2.9) Control		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								13.7 (2.2)		
							WHOQOL-BREF S3 (social relationship total score)	Intervention 14.5 (3.2) Control 14.6 (2.6)		
							WHOQOL-BREF S4 (environment total score)	Intervention 15.2 (2.6) Control 14.7 (2.2)		
							Fatigue – FSMC (Fatigue Scale for Motor and Cognitive Fatigue) – cognitive total score	Intervention 31.0 (9.7) Control 33.6 (9.2)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							1 year – N=50 and N=28 throughout			
							Perceived Deficits Questionnaire, total score Intervention	Intervention mean (SD) 27.9 (11.8) Control 35.2 (13.0)		
							Multiple Sclerosis Neuropsychological Questionnaire-Patient, total score	Intervention 22.3 (9.2) Control 28.3 (11.6)		
							Multiple Sclerosis Neuropsychological	Intervention 18.6 (8.8)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							Questionnaire-Informant, total score	Control 19.8 (11.0)		
							BDI-II, total score	Intervention 10.8 (7.7) Control 9.7 (7.0)		
							Multiple Sclerosis Impact Scale-29, physical total score	Intervention 22.9 (15.5) Control 24.2 (14.0)		
							MSIS-29, psychological score	Intervention 23.6 (16.8) Control 22.5 (16.9)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							Brief version of the World Health Organisation Quality of life, S1 physical health total score	Intervention 14.4 (2.6) Control 13.7 (2.4)		
							WHO-BREF S2 psychological total score	Intervention 14.1 (2.7) Control 13.6 (2.5)		
							WHOQOL-BREF S3 (social relationship total score)	Intervention 14.5 (3.7) Control 14.4 (2.7)		
							WHOQOL-BREF S4 (environment total score)	Intervention 15.3 (2.5) Contr		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								ol 14.4 (2.2)		
							Fatigue – FSMC (Fatigue Scale for Motor and Cognitive Fatigue) – cognitive total score	**Intervention 29.6 (8.9) Control 32.2 (9.0)**		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Mattioli F, Stampatori C, Scarpazza C, Parrinello G, Capra R. Persistence of the effects of attention and executive functions intensive rehabilitation in relapsing remitting multiple sclerosis. Multiple Sclerosis and Related Disorders. 2012; 1(4):168-173. (Guideline Ref ID		N=24 N=11 Control N=13 Intervention	Patients with relapsing remitting MS. June 2007 to December 2008. Inclusion: "Stable" course (no relapses in the previous year), EDSS < 4 and if their scores fell below Z= -1.5 for the PASAT and T=35 for WCST. Exclusion criteria: One or more clinical exacerbations in the previous year, loss of visual acuity, ongoing psychiatric disorders, substance abuse and a mini mental state	Intensive neuropsychological training 3 mths duration (1 hr session for three times per week) Attention, information processing and planning exercises for executive functions. Plan a day and divided attention components of the RehaCom package.	No rehabilitation	9 mths (6 months after end of intervention)	PASAT 2" Lower quartile, median, upper quartile.	3 mths Contr (N=11 throughout) ol 0, 0, 11 Intervention (N=13 throughout) 3, 14, 46 p<0.05 in favour of rehab 9 mths Control 0, 0, 21 Interv		Randomisation: alternate number Allocation concealment: unclear Outcome assessor blinded

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
MATTIOLI2012)			examination of <24. Population: Control age 46.90 (SD 10.24) yrs, education 10.63 (4.80) yrs, illness 20.00 (8.91) yrs, EDSS 2.40 (1.20) Intervention age 45.46 (10.48) yrs, education 8.80 (3.70) yrs, illness 16.69 (7.76) yrs, EDSS 2.34 (1.19) No statistically significant differences were noted No relapses occurred. Immunomodulating therapy was					ention 7, 11, 46 ns		
							PASAT 3”	3 mths Control -8, 0, 20 Intervention 8, 17, 41 p<0.05 in favour of rehab 9 mths Control 0, 3, 21 Intervention 14, 20, 30 p<0.05 in favou		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			taken by 5/11 patients in the control group 6/13 intervention group					r of rehab		
							WCSTcat	3 mths Control 1, 1, 5 Intervention 0, 3, 6 ns 9 mths Control 0, 2, 4 Intervention 0, 3, 6 ns		
							WCSTte	**3 mths Control -31, -20, 3 Intervention -53, -42, 0 P<0.0**		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								5 9 mths Control -27, -17, 35 Intervention -54, -40.31, 4 ns		
							WCSTpr	3 mths Control -27.5, -3, 5 Intervention -44, -26, 1 ns 9 ths Control -30, -14, 30,		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								Intervention -45, -31.5, 8 ns		
							WCSTpe	3 mths Control -23.5, -6, 0 Intervention -41, -28, -13 p<0.05 in favour of rehab 9 mths Control -20.7, -15, 21 Intervention		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								-45, -27, 19 p<0.05 in favour of rehab		
							COWA/P	3 mths Control -6, -3, 10 Intervention 3, 7, 17 p<0.05 in favour of rehab 9 mths Control -0.5, 2, 9 Intervention		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								1, 8, 12 ns		
							COWA/S	3 mths Control - 1.5, 2, 13 Intervention 3, 5, 16 ns 9 mths Control - 3.5, 0, 7 Intervention 0, 8, 21 p<0.05 in favour of rehab		
							TEAam	3 mths Contr		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								ol -55, -15, 143 Intervention -14, 119, 255 ns 9 mths Control -126.5, -13, 129 Intervention -10, 16, 309 ns		
							TEAvm	3 mths Control -67, 5, 427 Intervention		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								-260, -51, 541 ns 9 mths Control -136, -55, 148 Intervention -119, -98, 395 ns		
							TEAto	3 mths Control -2.5, -2, 5 Intervention -4, -2, 3 ns 9 mths Control -4, -1, 3		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								Intervention -5, -1, 2 ns		
							TEAte	3 mths Control -2, 0, 5 Intervention -8, -4, 3 ns 9 mths Control -4.5, -3, 1 Intervention -6, -3, 4 ns		
							SRT/CTRL	3 mths Control -9, -3, 12 Intervention -7, -4,		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								28 ns 9 mths Control 0, 2, 34 Intervention -3, 0, 16 ns		
							SRT/DR	3 mths Control 0, 0, 2 Intervention -1, 0, 3 ns 9 mths Control 0.5, 1, 3 Intervention 0, 2, 3 ns		
							10/36 SRT LTR	3 mths Contr		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								ol -3.5, -2, 5 Intervention -4, 2, 10 ns 9 mths Control -3, -1, 7 Intervention -1, 0, 4 ns		
							10/36 SRT DR	3 mths Control -1.5, 0, 2 Intervention -1, 0, 28 ns 9 mths -1.5, -1, 4		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								Intervention 0, 1, 5 ns		
							SDMT	3 mths Control -4, 0, 7 Intervention -2, 0, 28 ns 9 mths Control -3, 2, 11 Intervention 0, 3, 29 ns		
							MADRAS	3 mths Control -1.5, 1, -24.5 Interv		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								ention -9, -4, 1 p<0.05 in favour of rehab 9 mths -2.5, 3, 28 Control -15, -8, 6 p<0.05 in favour of rehab		
							MNSQoL	3 mths Control 17, -7, 25 Intervention -8, -14,		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								49 ns 9 mths Control -22.5, -13, 46 Intervention -17, 33, 104 p<0.05 in favour of rehab		

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	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Mendozzi L, Pugnetti L, Motta A, Barbieri E, Gambini A,	Pseudorandom	N=60 N=20 specific cognitive	Patients with a relapsing-remitting course or secondary chronic	Specific cognitive retraining programme (SCRP)	Non-specific cognitive retraining	40 days after completion of cognitiv	Spatial span (Corsi) % change mean (SD) 40 days	SCRP 25.4 (21.5) N=20	Gruppo Volontari per la Ricerca	Randomisation inadequate

	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Cazzullo CL. Computer-assisted memory retraining of patients with multiple sclerosis. Italian Journal of Neurological Sciences.: Springer-Verlag. 1998; 19(6):S431-S438. (Guideline Ref ID MENDOZZI 1998)		programme (SCRP) N=20 non-specific cognitive retraining programme (NCRP) N=20 control	progressive course were eligible Inclusion criteria: Stable clinical condition for at least the 2 months prior to the first cognitive retraining session, at least 5 yrs formal education, and sufficient visual function and manual dexterity to perform the neuropsychological tests. Exclusion criteria: Patients with a history or current clinical evidence of mental disorders, those who suffered a neurological relapse during	15 bi-weekly sessions lasting 45 min each average 8 weeks duration The programmes employed were part of Rehacom. Sessions consisted of two consecutive training periods of about 20 min each, one spent on a memory task and the other on an attention task. In the encoding phase of the memory training programme a varying number of pictures of objects or geometric figures was displayed, as cards, on the	programme (NCRP) Two periods of similar duration to SCRP, one spent on a visual tracking task and the other on a reaction-time task. Control group No training received during intervention period	e retraining	post completion	throughout NCRP N=20 throughout 14.7 (23.1) Control - 1.1 (15.5) N=20 throughout	sulla Multipla	Allocation concealment unclear Single blind
							Digit span (forward) % change mean (SD) 40 days post completion	SCRP 17.8 (22.9) NCRP 0.0 (17.5) Control - 6.35 (21.1)		
							Digit span (backwards) % change	SCRP 10.8		

	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			the trial were retired from the study and replaced by a new entry. Psychotherapeutic interventions and counselling were intentionally avoided SCRP M:F 9:11, age mean SD 47.92 (9.4) yrs, education mean (SD) 12.69 (4.8), EDSS score mean (SD) 3.65 (2.2), illness duration mean (SD) 12.00 (7.7) yrs, Raven PM-38 score mean (SD) 111.00 (9.0)	screen in a regular array. The patient had to memorise the location of the figures. After pressing a button, the figures were hidden. At the edge of the screen a figure was displayed exactly matching one of the hidden figures. The patient then had to indicate the location of the hidden figures corresponding to that displayed. There were 12 levels of difficulty A similar task was used for training attention, except that the "cards"			mean (SD) 40 days post completion	(29.4) NCRP - 1.25 (20.0) Control - 5.75 (28.2)		
							Paired associates (easy) % change mean (SD) 40 days post completion	SCRP 10.3 (20.5) NCRP 1.9 (11.1) Control 1.1 (10.4)		
							Paired associates (hard) % change mean (SD) 40 days post completion	SCRP 59.0 (87.0) NCRP 21.6 (46.5) Control		

	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			NCRP M:F 8:12, age mean SD 45.92 (12.1) yrs, education mean (SD) 13.00 (3.5), EDSS score mean (SD) 4.00 (2.1), illness duration mean (SD) 10.70 (7.6) yrs, Raven PM-38 score mean (SD) 110.55 (11.9) Control M:F 10:10, age mean SD 45.38 (6.8) yrs, education mean (SD) 11.71 (3.6), EDSS score mean (SD) 3.30 (2.0), illness duration mean (SD) 10.15 (6.9)	containing the figures were never hidden: the task was to locate the figures exactly corresponding to the one displayed on the edge of the screen. At each response the patient received positive or negative feedback				2.21 (64.8)		
							Short story recall % change mean (SD) 40 days post completion	SCRP 37.6 (33.0) NCRP 1.55 (23.6) Control 22.9 (40.4)		
							Visual reproduction % change mean (SD) 40 days post completion	SCRP 49.1 (48.8) NCRP 46.9 (77.1) Control -0.7 (21.0)		
							Luria-Nebraska neuropsychol	SCRP 2.5 (3.0)		

	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			yrs, Raven PM-38 score mean (SD) 109.00 (10.6)				ogical battery memory scale % change mean (SD) 40 days post completion	NCRP 0.4 (2.8) Control -0.6 (2.2)		
							Recognition memory % change mean (SD) 40 days post completion	SCRP 5.5 (5.4) NCRP 6.8 (13.3) Control -0.4 (9.8)		
							Signal detection hits % change mean (SD) 40 days post completion	SCRP 8.5 (17.9) NCRP 3.8 (12.5) Control 6.4 (14.8)		
							Signal detection	SCRP 9.4		

	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							reaction time (s) % change mean (SD)	(10.3) NCRP 4.5 (8.8) Control 1.7 (9.7)		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Shatil E, Metzer A, Horvitz O, Miller A. Home-based personalized cognitive training in MS patients: a study of adherence and cognitive performance.	Controlled trial, Israel	N=97 N=59 cognitive training N=22 completers N=48 control N=24 completers	Outpatients with multiple sclerosis. Inclusion criteria: Diagnosis of relapsing remitting or relapsing progressive MS, had health dominant hand functioning, Hebrew speakers, owned and were able to use a home	Cognitive training CogniFit Personal Coach (CPC), a home-based, computerised, individualised cognitive training program. Three times a week	Control No training	12 wks	Auditory working memory mean SD 12 weeks	Cognitive N=22 throughout 0.69 (0.78) Control N=24 throughout 0.62 (0.87) p=0.436		• Randomisation inadequate • Allocation concealment inadequate • Partially assessor

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Neurorehabilitation. 2010; 26(2):143-153. (Guideline Ref ID SHATIL2010)			personal computer and expressed an interest in taking part in the study. Exclusion criteria: any neurological disease, drug or alcohol abuse or dependence, as well as major depression and/or known conditions which required the use of psychotropic medication. Primary progressive MS. Training gp: female 77%, age mean SD 49.9 (1.9) yrs, university 71%, high school 29%, Zung				Awareness mean SD 12 weeks	Cognitive - 0.09 (1.04) Control - 0.13 (1.39) p=0.990		• blinded (computer assessment) • P values ANCOVA controlling for baseline score and age
							Divided attention mean SD 12 weeks	Cognitive 2.37 (0.78) Control 2.41 (0.72) p=0.698		
							Avoiding distraction mean SD 12 weeks	Cognitive - 0.70 (0.47) Control - 0.67 (0.69)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			Depression Scale mean SD 62.84 (9.74), Fatigue Severity Scale mean SD 40.91 (14.78), EDSS mean SD 2.56 (2.09) Control: female 75%, age mean SD 42.3 (10.7)*, university 71%, high school 29%, Zung Depression Scale mean SD 58.44 (7.43), Fatigue Severity Scale mean SD 40.76 (17.26), EDSS mean SD 2.53 (1.66)					p=0.940		
							Hand-eye co-ordination mean SD 12 weeks	Cognitive 0.26 (1.20) Control 0.562 (0.140) p=0.140		
							General memory mean SD 12 weeks	Cognitive 1.13 (0.82) Control 0.56 (1.10) p=0.002		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			* significant difference At baseline 15/22 completers in the training gp were classified by the program as having low or intermediate scores on general memory, visual working memory or verbal working memory				Inhibition mean SD 12 weeks	Cognitive - 0.16 (0.62) control - 0.30 (0.59) p=0.830		
							Naming mean SD 12 weeks	Cognitive 0.68 (0.56) Control 0.54 (0.85) p=0.851		
							Planning mean SD 12 weeks	Cognitive 0.07 (0.77) Control 0.00 (0.90)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								p=0.513		
							Response time mean SD 12 weeks	Cognitive - 0.39 (0.74) Control - 0.51 (0.67) p=0.252		
							Shifting Attention mean SD 12 weeks	Cognitive 0.37 (0.91) Control 0.48 (0.62) p=0.529		
							Spatial perception mean SD 12 weeks	Cognitive 0.46 (0.69) Control 0.54		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								(0.64) p=507		
							Time estimation mean SD 12 weeks	Cognitive 0.62 (0.61) Control 0.34 (1.00) p=0.249		
							Visual working memory mean SD 12 weeks	Cognitive 1.15 (0.84) Control 0.65 (1.03) p=0.003		
							Visual perception mean SD 12 weeks	Cognitive 0.54 (0.58) Control		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								0.45 (0.64 _ p=0.077		
							Visual scanning mean SD 12 weeks	Cognitive - 0.53 (0.74) Control - 0.57 (0.94) p=0.710		
							Verbal auditory working memory	Cognitive 1.09 (0.81) Control 0.53 (1.02) p=0.003		
							Adherence – unprompted adherence to the training	**Intervention – 22/59**		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							in the intervention group (completed entire training regimen of 24 sessions)	**(37.3 %)**		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Solari A, Motta A, Mendozzi L, Pucci E, Forni M, Mancardi G et al. Computer-aided retraining of memory and attention in people with multiple	RCT, Italy	N=82 randomised Treatment: received treatment n=40, followed up to week 8 n=38, followed up to week 16 n=38, included in	Patients meeting the diagnostic criteria of Posner and who complained of poor attention or memory, confirmed by a score below the 80th percentile in at least two components of the Brief Repeatable	Cognitive training Individual treatment as outpatients for 45 mins, twice a week, for 8 consecutive weeks. The training program was Rehacom. The study treatment consisted of the	Control As for cognitive training except the treatment consisted of the Rehacom visuo-constructional and visuo-motor coordination	16 weeks	Improvement greater than 20% in at least two of the five BRBNT 8 weeks	Cognitive 18/40 Control 16/37	National MS Society	• Double blind • Randomisation adequate • Allocation concealment adequate
							Improvement greater than 20% in at least two of the five BRBNT 16 weeks	Cognitive 19/40 Control 20/37		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
sclerosis: a randomized, double-blind controlled trial. Journal of the Neurological Sciences. 2004; 222(1-2):99-104. (Guideline Ref ID SOLARI2004)		analysis n=40 Control: Received control treatment N=37, followed up to week 8 n=37, followed up to week 16 n=37, included in analysis n=37	Battery of Neuropsychological Tests (BRBNT). Exclusion criteria: less than 18, ongoing major psychiatric disorder, one or more exacerbations in 3 mths prior to enrolment, immunomodulant or immunosuppressant treatment initiated in 4 mths prior to enrolment, and cognitive rehabilitation in the 6 mths prior to enrolment. Psychotropic drugs and drugs for spasticity, tremor, bladder disturbances and fatigue	Rehacom memory and attention retraining procedures	retraining procedures.		Buschke selecting reminding: consistent long-term retrieval change score 8 weeks mean 95%CI	Cognitive N=40 throughout 138.4 (40.2 to 236.5) Control N=37 throughout 92.1 (17.2 to 160.7)		• N=2 in cognitive retraining discontinued due to exacerbations
							Buschke selective reminding delayed recall change score 8 wks mean 95%CI	Cognitive 159.9 (59.6 to 260.4) Control		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			could not be initiated. If already prescribed, doses and schedules had to be held constant over the study period Mean age 44 yrs (range 22-65), 64% women, mean age of disease onset was 29 yrs (range 19 to 53) and median Expanded Disability Status Scale (EDSS) 3.5 (range 1.5 to 7.0) Disease course Cognitive training relapsing remitting 42.5%,					24.5 (2.1 to 46.9)		
							Symbol digit modalities change score 8 weeks mean 95%CI	Cognitive 13.3 (5.4 to 21.1) Control 9.4 (0.0 to 19.0)		
							PASAT 2 change score 8 weeks mean 95%CI	Cognitive 24.1 (6.4 to 41.9) Control 32.7 (4.7 to 60.7)		
							Word list generation	Cognitive		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			relapsing progressive 50.0%, chronic progressing 7.5% Control: relapsing remitting 59.5%, relapsing progressive 40.5% The groups were matched at baseline except that study arm participants were older, had lower scores on the				change score 8 weeks mean 95%CI	5.9 (-8.3 to -20.0) Control -17.2 (-26.0 to -8.3)		
							10/36 Spatial recall: Immediate recall change score 8 weeks mean 95%CI	Cognitive 23.8 (8.8 to 38.8) Control 27.6 (4.9 to 50.3)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			word list generation test and a higher score on 10.36 spatial recall (delayed recall)				10/36 Spatial recall: Delayed recall change score 8 weeks mean 95%CI	Cognitive 19.6 (4.4 to 34.9) Control 80.6 (32.5 to 128.8)		
							Buschke selective reminding consistent long-term retrieval week 16 change score mean 95%CI	Cognitive 160.0 (59.6 to 260.4) Control 143.2 (48.5 to 237.8)		
							Buschke delayed recall week 16	Cognitive 9.8 (-		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							change score mean 95%CI	2.9 to -22.5) Control 44.3 (11.6 to 76.9)		
							Symbol digit modalities week 16 change score mean 95%CI	Cognitive 15.4 (6.8 to 24.0) Control 16.9 (4.9 to 28.9)		
							PASAT 2-week 16 change score mean 95%CI	Cognitive 16.4 (0.6 to 32.2) Control 38.5 (4.8		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								to 72.2)		
							Word list generation week 16 change score mean 95%CI	Cognitive 31.7 (15.9 to 45.4) Control 0.0 (-9.8 to -9.8)		
							10/36 spatial recall: immediate recall week 16 change score mean 95%CI	Cognitive 17.4 (0.4 to 34.3) Control 26.6 (4.1 to 48.9)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							10/36 spatial recall: Delayed recall week 16 change score mean 95%CI	Cognitive 12.0 (-8.1 to -32.1) Control 77.1 (27.1-127.0)		
							MSQOL-54 mental health 8 weeks mean (se) change score higher score better	Cognitive 26.9 (11.6) Control 9.3 (6.8)		
							MSQOL-54 mental health 16 weeks mean (se) change score	Cognitive 15.6 (7.4) Control 22.7 (11.4)		
							MSQOL-54 cognitive	Cognitive		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							function 8 weeks mean (se) change score	36.0 (13.6) Control 43.0 (20.3)		
							MSQOL-54 cognitive function 16 weeks mean (se) change score	Cognitive 42.7 (20.0) Control 55.9 (23.0)		
							Chicago Mood Depression Inventory (negative scores better, % change) week 8	Cognitive -1.6 (3.0) Control 0.0 (3.3)		
							Chicago Mood Depression Inventory (negative scores better,	Cognitive -5.6 (3.0) Control -		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							% change) week 16	5.3 (3.4)		
							Compliance – median (range) sessions attended (out of scheduled 16 sessions)	**Cognitive – 16.0 (7.0-16.0) Control – 16.0 (12.0-17.0)**		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Stuifbergen AK, Becker H, Perez F, Morison J, Kullberg V, Todd A. A randomized	RCT	N=63 randomised N=36 intervention N=34 analysed	Clinically definite MS for at least six mths that was documented by a physician and stable	Memory and Problem-Solving Skills for people with Multiple Sclerosis (MAPSS-MS)	Waiting list	5 mths	CVLT Total mean (SD)	2 mths Control N=27 throughout 50.2 (12.1) Intervention N=34	National Institutes of Health, National	Randomisation: unclear Allocation concealment: unclear

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
controlled trial of a cognitive rehabilitation intervention for persons with multiple sclerosis. Clinical Rehabilitation. 2012; 26(10):882-893. (Guideline Ref ID STUIFBERGEN2012)		N=27 waiting list N=27 analysed	disease status at the time of study entry. Aged 18-60 yrs. Responded 'sometimes' or more often to at least five problems on the Perceived Deficits Questionnaire Intervention: 85% female, 20-35 yrs 9%, 36-50 yrs 41%, 51-60 yrs 50%, high school grad 38%, Associate degree 9%, Bachelor's degree 24%, Graduate degree 29%, White 85%,	Teaches the use of compensatory skills, retraining skills (the computer component) and environmental/lifestyle support for cognitive functioning. a) Eight weekly 2-hr group sessions focused on building efficacy for use of cognitive compensatory strategies (b) a computer-assisted cognitive training program. Enabled the participants to engage in				throughout 52.2 (12.3) 5 mths control 53.8 (14.3) intervention 58.4 (13.6)	Institute of Nursing Research	
							CVLT Delay	2 mths Control 10.7 (4.1) Intervention 12.3 (3.6) 5 mths control 12.5 (4.1) Intervention 12.5 (4.1)		
							BVMT Total	2 mths Control 24.1 (7.8) Intervention 23.8 (7.6) 5 mths Control 24.6 (6.9) Intervention 24.9 (6.0)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			unemployed 65% Waiting list: 93%, female, 20-35 yrs 11%, 36-50 yrs 48%, 51-60 yrs 41%, high school grad 26%, Associate degree 7%, Bachelor's degree 41%, Graduate degree 26%, White 93%, unemployed 48%	practice sessions (minimum of 45 minutes three times per week). Translation of skills practiced to everyday issues was a focus of the group sessions.			BVMT Delay	2 mths Control 9.1 (3.1) Intervention 9.3 (3.0) 5 mths Control 8.8 (2.8) Intervention 9.3 (2.1)		
							JLO	2 mths Control 27.4 (4.2) Intervention 27.8 (3.9) 5 mths Control 27.4 (4.2) Intervention 27.8 (3.9)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							SDMT	2 mths Control 48.1 (14.0) Intervention 49.6 (11.1) 5 mths Control 50.6 (13.1) Intervention 49.7 (12.7)		
							PASAT-3 second	2 mths Control 46.7 (11.2) Intervention 45.2 (11.2) 5 mths Control 47.2 (10.7) Intervention 47.4 (9.6)		
							PASAT-2 second	2 mths Control 34.9 (11.5) Intervention 34.0 (9.3) 5 mths Control 38.1 (9.8)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								Intervention 34.2 (9.8)		
							COWAT	2 mths Control 35.3 (11.7) Intervention 35.8 (10.6) 5 mths Control 36.4 (12.0) Intervention 36.1 (10.7)		
							DKFES-Descriptive	2 mths Control 38.8 (12.3) Intervention 34.9 (11.1) 5 mths Control 41.7 (10.5) Intervention 39.6 (8.7)		
							DKEFS sort	2 mths 10.1 (3.2) Intervention 9.2 (2.7) 5 mths Control 10.9 (2.7)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								Intervention 10.2 (2.1)		
							Self-efficacy	2 mths Control 540.19 (203.25) Intervention 553.24 (167.58) 5 mths Control 534.26 (201.06) Intervention 557.72 (157.84)		
							Memory strategy	2 mths Control 40.43 (9.34) Intervention 43.63 (9.34) 5 mths Control 41.15 (10.65) Intervention 43.12 (11.93)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							MSNQ	2 mths Control 27.92 (11.11) Intervention 29.68 (10.74) 5 mths Control 26.15 (11.56) Intervention 28.41 (11.13)		
							Adherence – participation in intervention	**Meeting or exceeding minimum times of practice sessions per week: 79-82% each week** **Meeting or exceeding minimum number of minutes of required**		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								practice per week: 67-82% each week		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Tesar N, Bandion K, Baumhackl U. Efficacy of a neuropsychological training programme for patients with multiple sclerosis -- a randomised controlled trial. Wiener Klinische Wochenschrift. 2005; 117(21-22):747-754. (Guideline Ref ID TESAR2005)	RCT	N=20 N=10 Rehabilitation N=9 Control (N=1 drop out)	Patients with MS meeting the criteria of Posner plus a positive MRI scan. Inclusion criteria: mild to moderate cognitive deficit, adequate vision, no previous psychiatric history, no drug or alcohol abuse, no additional medical diagnosis, no acute exacerbation in the past 30 days and therefore no corticosteroid therapy, no IQs below 85 and age no more than 60 yrs. In the Beck	Rehabilitation Rehacom computer training. Direct functional training of the two cognitive areas which were most severely affected and then teaching of compensation strategies to everyday life. 12 sessions each last one hour. Total duration 4 wks	Control No treatment	3 mths	Beck Depression Inventory mean (SD)	Immediate Rehabilitation 8.6 (4.1) Control 7.7 (3.2) 3 mths Rehabilitation 8.3 (5.8) Control 8.3 (3.4)	None reported	• Randomisation unclear • Allocation concealment adequate • Patient unblinded assessor unclear
							Fatigue Impact Scale (MFIS) mean (SD)	Immediate Rehabilitation		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			Depression Inventory, the participants were to be within the non-clinical range Rehabilitation: Age mean SD 45.3 (9.2), 70% female, retired early 60%, EDSS mean (SD) 4.5 (1.7), relapsing remitting 70%, chronic progressive 30%, Interferon beta-1b 50%, IQ mean (SD) 104.10 (12.08) Control: Age mean SD 46.9 (11.2), 55.6% female, retired early 55.6%,					41.2 (13.2) Control 33.3 (16.5) 3 mths Rehabilitation 41.8 (15.5) Control 31.7 (18.8)		
							Computer-aided card-sorting correct procedure mean (SD)	Immediate Rehabilitation 47.1 (19.9) Control 47.5 (18.6)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			EDSS mean (SD) 4.4 (1.9), relapsing remitting 33.3%, chronic progressive 30%, Interferon beta-1b 22.2%, IQ mean (SD) 106.22 (10.86)					3 mths Rehabilitation 42.1 (12.6) Control 53.9 (21.5)		
							Computer-aided card-sorting incorrect mean (SD)	Immediate Rehabilitation 15 (6) Control 16.1 (3) 3 mths Rehabilitation 14.1 (4.1)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								Control 16.8 (2.2)		
							Sustained attention correct mean (SD)	Immediate Rehabilitation 47.1 (19.9) Control 47.5 (18.6) mths Rehabilitation 42.1 (12.6) Control 53.9 (21.5)		
							Sustained attention	Immediate		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							incorrect mean SD	Rehabilitation 45.7 (17.6) Control 48.4 (13) 3 mths Rehabilitation 46.2 (16.1) Control 51.2 (14.2)		
							Sustained attention reaction time mean SD	Immediate Rehabilitation 40.2 (6.7)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								Control 43.5 (7.8) 3 mths Rehabilitation 42.7 (9.7) Control 46.8 (7.5)		
							Sustained attention variation reaction time mean SD	Immediate Rehabilitation 52 (8.2) Control 44.4 (10.6) 3 mths		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								Rehabilitation 44.8 (11.7) Control 50.7 (7.7)		
							Verbal learning test	Immediate Rehabilitation 52 (8.2) Control 48.2 (13.1) 3 mths Rehabilitation 56.9 (13.1) Control		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								50.4 (13.6)		
							Non-verbal learning test	Immediate Rehabilitation 42.3 (8) Control 42.5 (8.9) 3 mths Rehabilitation 49 (14.9) Control 48.3 (12.2)		
							Spatial construction	Immediate Rehabilitati		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								on 11.2 (2.9) Control 9 (2.4) 3 mths Rehabilitation 10.6 (2.9) Control 10.4 (2.1)		
							Satisfaction – overall rating of programme in terms of coping with existing cognitive impairments (rated on scale of 1-5	**Intervention – 3/10 (30%) said programme was average**		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							with 5 indicating very good in helping to cope with impairments and 1 indicating not at all helpful)	**and 7/10 (70%) said programme was above-average**		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Vogt A, Kappos L, Calabrese P, Stocklin M, Gschwind L, Opwis K et al. Working memory training in patients with multiple	Controlled trial, Switzerland	N=45 N=15 high intensity training N=15 distributed training N=15 control	Outpatients with clinically definite multiple sclerosis according to the McDonald criteria. 36/45 female, 36/45 relapsing remitting , 8/45 secondary progressive, 1/45 chronic	High intensity 45 mins training 4 times per week for 4 weeks BrainStim (Penner et al., 2006). City Map trains spatial orientation by	Distributed training 45 mins training 2 times per week for 8 weeks Control	High intensity and control 4 weeks Distributed 8 weeks	Corsi blocks backward mean SD high intensity and control 4 wks distributed 8 wks	High intensity N=15 throughout 8.87 (2.03) Distributed 9.33 (1.58)	Swiss Multiple Sclerosis Society	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
sclerosis - comparison of two different training schedules. Restorative Neurology and Neuroscience. 2009; 27(3):225-235. (Guideline Ref ID VOGT2009)			progressive. Mean EDSS 2.9 (SD1.6), mean disease duration 10.2 yrs (6.9). Inclusion criteria: Patients with stable disease (no relapse), no change in symptomatic medication over the last 3 mths, no treatment with steroids over the last month and no other neurological or mental illness. High intensity: age mean (SD) 43.20 (8.8), education mean (SD) 1.6* (0.51), EDSS mean (SD) 3.23 (1.80), disease duration mean (SD) yrs	either visual stimulus or verbal instructions to be remembered and finding the path using given arrows along a virtual city map. Find pairs trains visual object memory and the updating function of working memory. Memorize numbers: trains people to remember numbers whilst performing a mental arithmetic distraction task The program adapts level of difficulty to participants performance	No training			N=15 throughout Control 8.13 (1.76)		
							Digit span backward mean SD high intensity and control 4 wks distributed 8 wks	High intensity 7.87 (2.38) Distributed 7.41 (1.72) Control 6.40 (1.99)		
							2-back, numbers correct mean SD high intensity and control 4 wks distributed 8 wks	High intensity 55.07 (4.02) Distributed 57.33 (4.06)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			9.13 (5.42) * 0=secondary school 1=college 2=university Distributed: age mean (SD) 43.40 (12.33), education mean (SD) 1.47* (0.52), EDSS mean (SD) 2.30 (1.09), disease duration mean (SD) yrs 8.13 (6.34) Control: age mean (SD) 46.27 (10.53), education mean (SD) 1.53* (0.52), EDSS mean (SD) 3.20 (1.63), disease duration mean (SD) yrs 12.06 (8.99)					Control 55.27 (3.92)		
							2-back, omissions mean SD high intensity and control 4 wks distributed 8 wks	High intensity 0.40 (0.73) Distributed 0.06 (0.26) Control 0.53 (1.12)		
							2-back, reaction time mean SD high intensity and control 4 wks distributed 8 wks	High intensity 767.66 (272.31) Distributed 666.4 (191.57) Contr		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			There were no significant differences between the groups Patients performing lower than 1SD below the published population norms was described as impaired: Corsi blocks forward 3 impaired high intensity, 7 distributed and 5 control. Corsi blocks backward 4 high intensity, 6 distributed and 5 control. Digit span forward 5 high intensity, 5 distributed and 10 control. Digit span backward 5 high intensity, 4 distributed and					ol 762.07 (257.49)		
							PASAT mean SD high intensity and control 4 wks distributed 8 wks	High intensity 50.41 (7.91) Distributed 53.61 (5.69) Control 48.53 (11.10)		
							Corsi blocks forward mean SD high intensity and control 4 wks distributed 8 wks	High intensity 9.21 (1.93) Distributed 8.40 (1.24) Control		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			10 control. PASAT 6 high intensity, 3 distributed and 6 control. Faces symbol test 6 high intensity, 5 distributed and 6 control. Fatigue Scale for Motor and Cognitive Functions (FSMC) 14 high intensity, 15 distributed and 15 control. Modified Fatigue Impact Scale (MFIS) 8 high intensity, 10 distributed and 9 control. Depression 3 high intensity, 1 distributed and 2 control					8.80 (1.52)		
							Digit Span forward mean SD high intensity and control 4 wks distributed 8 wks	High intensity 7.20 (2.01) Distributed 7.73 (1.94) Control 6.73 (1.62)		
							Faces Symbol Test mean SD high intensity and control 4 wks distributed 8 wks	High intensity 2.54 (0.73) Distributed 2.13 (0.73) Control 2.49 (0.91)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							Symbol Digit Modalities Test mean SD high intensity and control 4 wks distributed 8 wks	High intensity 53.87 (14.78) Distributed 62.22 (16.22) Control 58.67 (19.19)		
							Fatigue Scale for Motor and Cognitive Functions mean SD high intensity and control 4 wks distributed 8 wks	High intensity 61.73 (19.08) Distributed 58.00 (22.08) Control 65.06		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								(16.68)		
							Modified Fatigue Impact Scale mean SD high intensity and control 4 wks distributed 8 wks	High intensity 34.13 (17.34) Distributed 34.23 (19.66) Control 37.53 (7.29)		
							Allgemeine Depressionsskala mean SD high intensity and control 4 wks distributed 8 wks	High intensity 12.21 (12.20) Distributed 10.26 (7.32) Control 12.86		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								(10.98)		
							Functional Assessment of MS mean SD high intensity and control 4 wks distributed 8 wks	High intensity 118.61 (34.08) Distributed 134.20 (18.57) Control 122.93 (32.77)		

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Appendix E – Forest plots

E.1 General cognitive rehabilitation (multi-component and multi-domain) vs. control, 1-6 months

Figure 2: Selective Reminding Test – Long-term Storage and Consistent Long-term Retrieval (higher better)

	Multi-domain cogn. rehab			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
1.1.1 Long-term storage									
Manglani 2020	43.3	13.9	17	44.2	19.7	17	16.6%	-0.90 [-12.36, 10.56]	
Mantynen 2014	56.7	14.7	58	53.9	11.1	40	83.4%	2.80 [-2.31, 7.91]	
Subtotal (95% CI)			**75**			**57**	**100.0%**	**2.19 [-2.48, 6.86]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.56); I² = 0%									
Test for overall effect: Z = 0.92 (P = 0.36)									
1.1.2 Consistent long-term retrieval									
Manglani 2020	33.3	16.6	17	36.3	23.3	17	19.3%	-3.00 [-16.60, 10.60]	
Mantynen 2014	50.2	18.2	58	45.7	15.2	40	80.7%	4.50 [-2.14, 11.14]	
Subtotal (95% CI)			**75**			**57**	**100.0%**	**3.06 [-2.91, 9.02]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 1 (P = 0.33); I² = 0%									
Test for overall effect: Z = 1.00 (P = 0.32)									
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%									

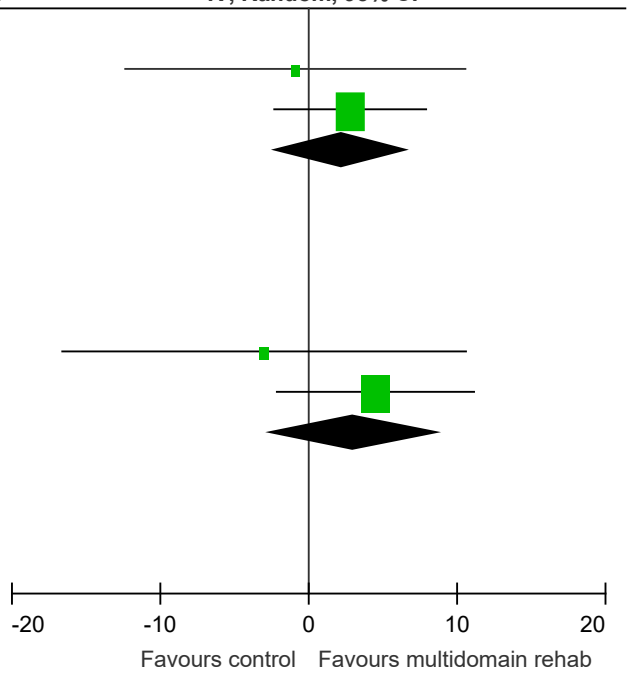

Figure 3: Selective Reminding Test – Delayed recall (higher better)

	Multi-domain cogn. rehab			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
1.2.3 Delayed recall								
Brissart 2020	12.1	3.3	52	11.6	3.1	49	25.6%	0.50 [-0.75, 1.75]
Manglani 2020	7.59	2.94	17	7.53	3.84	17	7.6%	0.06 [-2.24, 2.36]
Mantynen 2014	10.4	2.2	58	10	1.7	40	66.8%	0.40 [-0.37, 1.17]
Subtotal (95% CI)			**127**			**106**	**100.0%**	**0.40 [-0.23, 1.03]**
Heterogeneity: Chi² = 0.11, df = 2 (P = 0.95); I² = 0%								
Test for overall effect: Z = 1.24 (P = 0.21)								
Total (95% CI)			**127**			**106**	**100.0%**	**0.40 [-0.23, 1.03]**
Heterogeneity: Chi² = 0.11, df = 2 (P = 0.95); I² = 0%								
Test for overall effect: Z = 1.24 (P = 0.21)								
Test for subgroup differences: Not applicable								

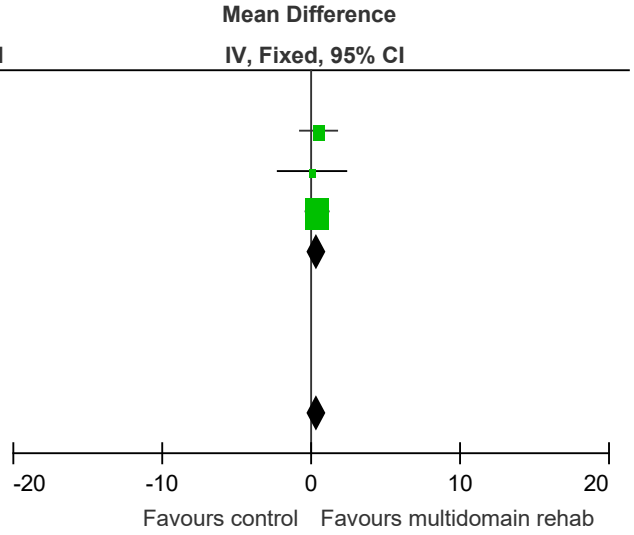

Figure 4: Selective Reminding Test – Mean free recall and learning index (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
1.3.1 Mean free recall							
Brissart 2020	10.6	2	52	10.6	1.8	49	0.00 [-0.74, 0.74]
1.3.2 Learning index							
Brissart 2020	60.7	23.8	52	54	20.3	49	6.70 [-1.91, 15.31]

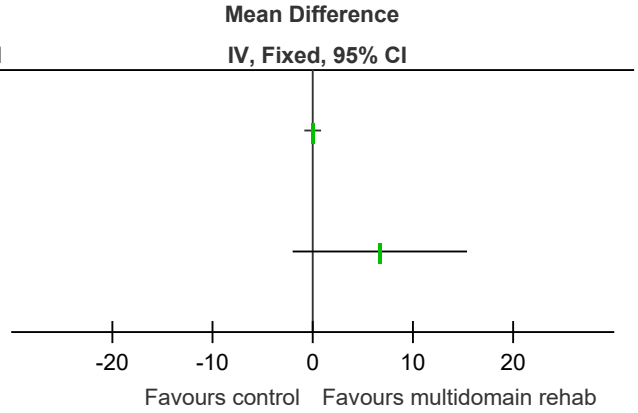

Figure 5: Spatial Recall Test – Total score and Delayed recall (higher better)

	Multi-domain cogn. rehab			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
1.4.1 Total score									
Brissart 2020	18.6	5	52	17.1	4.6	49	39.6%	1.50 [-0.37, 3.37]	
Manglani 2020	20.3	7.03	17	23.1	5.01	17	21.0%	-2.80 [-6.90, 1.30]	
Mantynen 2014	23.8	4.5	58	20.9	4.8	40	39.4%	2.90 [1.01, 4.79]	
Subtotal (95% CI)			**127**			**106**	**100.0%**	**1.15 [-1.30, 3.59]**	
Heterogeneity: Tau² = 3.02; Chi² = 6.22, df = 2 (P = 0.04); I² = 68%									
Test for overall effect: Z = 0.92 (P = 0.36)									
1.4.2 Delayed recall									
Brissart 2020	6.1	2.3	52	6.2	2.4	49	36.0%	-0.10 [-1.02, 0.82]	
Manglani 2020	6.88	2.91	17	8.24	2.02	17	24.8%	-1.36 [-3.04, 0.32]	
Mantynen 2014	8.5	1.5	58	7.4	1.9	40	39.1%	1.10 [0.40, 1.80]	
Subtotal (95% CI)			**127**			**106**	**100.0%**	**0.06 [-1.21, 1.32]**	
Heterogeneity: Tau² = 0.93; Chi² = 9.09, df = 2 (P = 0.01); I² = 78%									
Test for overall effect: Z = 0.09 (P = 0.93)									
Test for subgroup differences: Chi² = 0.61, df = 1 (P = 0.44), I² = 0%									

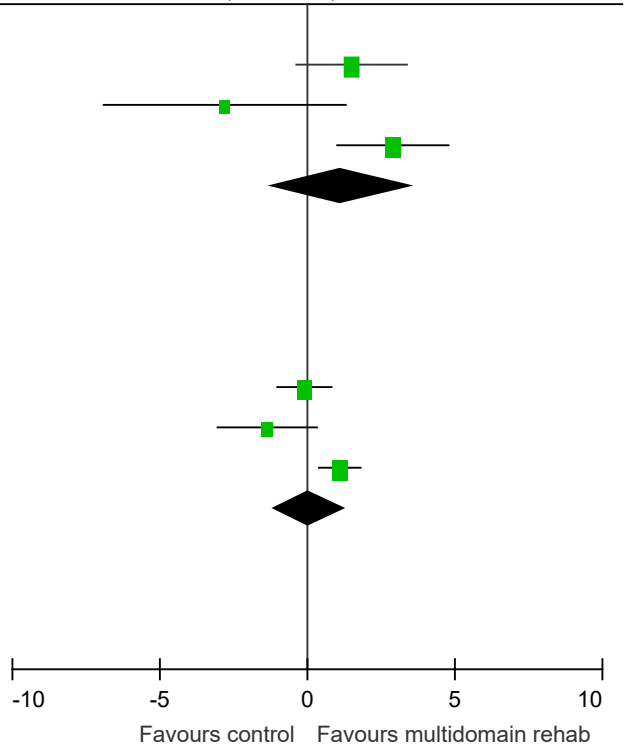

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Figure 6: SDMT (higher better)

Study or Subgroup	Multi-domain cogn. rehab Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 Similar at baseline								
Manglani 2020	53.2	13.5	17	53.5	15.2	17	6.3%	-0.30 [-9.96, 9.36]
Mantynen 2014	50.6	12.1	58	48.2	8.2	40	36.2%	2.40 [-1.62, 6.42]
Stuifbergen 2012	49.7	12.7	34	50.6	13.1	27	13.7%	-0.90 [-7.43, 5.63]
Stuifbergen 2018	52.8	13	93	50.7	12.2	90	43.8%	2.10 [-1.55, 5.75]
Subtotal (95% CI)			**202**			**174**	**100.0%**	**1.65 [-0.77, 4.06]**
Heterogeneity: Chi² = 0.93, df = 3 (P = 0.82); I² = 0%								
Test for overall effect: Z = 1.34 (P = 0.18)								
1.5.2 Larger difference at baseline (lower in intervention)								
Rilo 2018	42.62	12.46	21	47.52	13	21	100.0%	-4.90 [-12.60, 2.80]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**-4.90 [-12.60, 2.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.25 (P = 0.21)								
Test for subgroup differences: Chi² = 2.53, df = 1 (P = 0.11), I² = 60.4%								

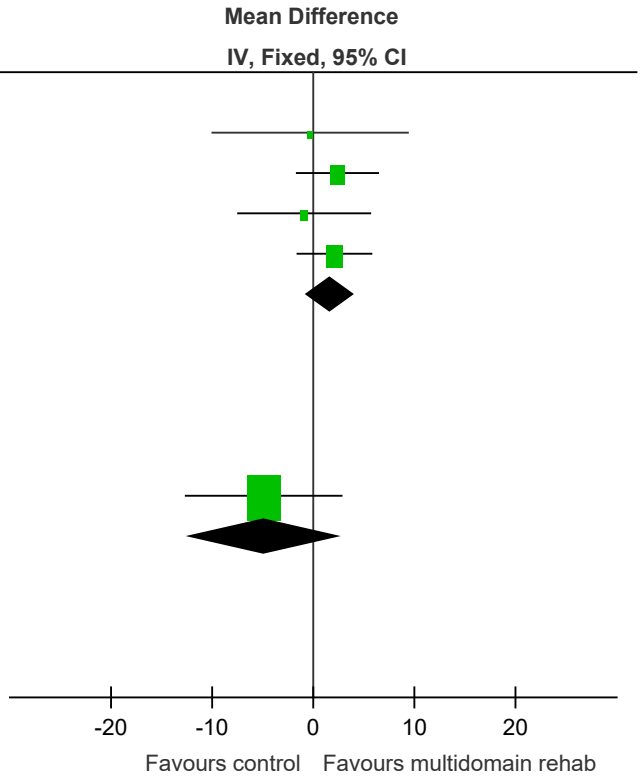

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Figure 7: PASAT – 2 seconds (higher better)

	Multi-domain cogn. rehab			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Manglani 2020	38.9	8.61	17	42.1	9.87	17	23.6%	-3.20 [-9.43, 3.03]
Mantynen 2014	32.9	12.1	58	20.8	19.3	40	22.7%	12.10 [5.36, 18.84]
Stuifbergen 2012	34.2	9.8	34	38.1	9.8	27	25.8%	-3.90 [-8.85, 1.05]
Stuifbergen 2018	35.1	12.4	93	31.6	12.5	90	27.9%	3.50 [-0.11, 7.11]
Total (95% CI)			**202**			**174**	**100.0%**	**1.96 [-4.31, 8.23]**

Heterogeneity: Tau² = 33.22; Chi² = 17.38, df = 3 (P = 0.0006); I² = 83%

Test for overall effect: Z = 0.61 (P = 0.54)

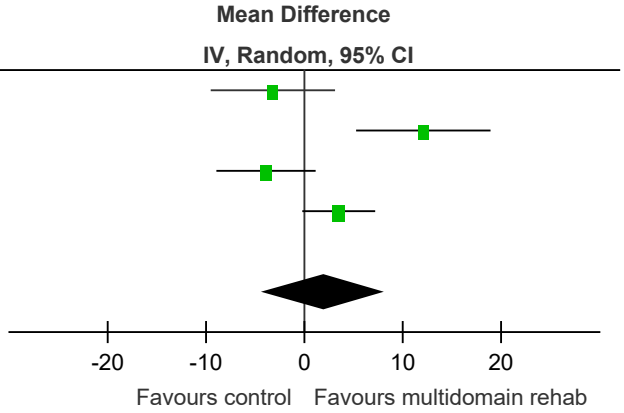


Figure 8: PASAT – 3 seconds (higher better)

	Multi-domain cogn. rehab			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
1.7.2 3 seconds								
Manglani 2020	51.1	8.52	17	52.7	6.73	17	6.5%	-1.60 [-6.76, 3.56]
Mantynen 2014	46.7	11.8	58	43.5	11	40	8.4%	3.20 [-1.37, 7.77]
Rahmani 2020	22.89	3.08	36	19.56	3.26	24	64.2%	3.33 [1.68, 4.98]
Stuifbergen 2012	47.4	9.6	34	47.2	10.7	27	6.5%	0.20 [-4.97, 5.37]
Stuifbergen 2018	46.9	11.6	93	44.3	12.4	90	14.4%	2.60 [-0.88, 6.08]
Subtotal (95% CI)			**238**			**198**	**100.0%**	**2.69 [1.37, 4.01]**

Heterogeneity: Chi² = 4.18, df = 4 (P = 0.38); I² = 4%

Test for overall effect: Z = 3.99 (P < 0.0001)

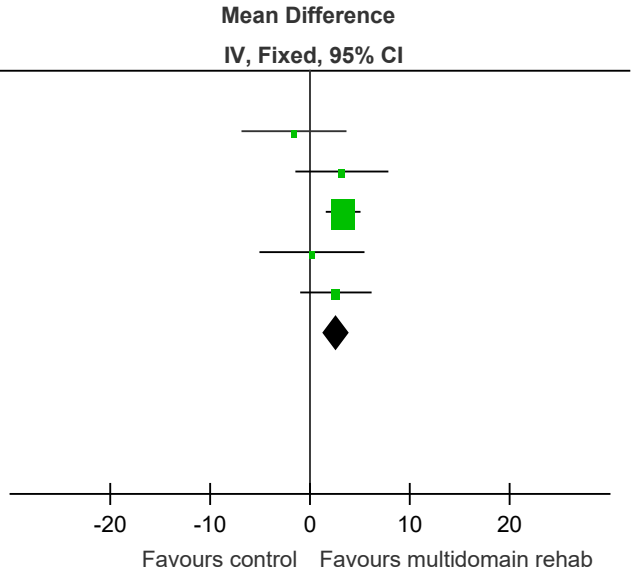


Figure 9: COWAT – Controlled Oral Word Association Test (higher better)

	Multi-domain cogn. rehab			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Mantynen 2014	25.5	7.1	58	24.2	7.9	40	49.4%	1.30 [-1.75, 4.35]
Stuifbergen 2012	36.1	10.7	34	36.4	12	27	13.8%	-0.30 [-6.08, 5.48]
Stuifbergen 2018	40.2	12.7	93	38.1	11.7	90	36.8%	2.10 [-1.44, 5.64]
Total (95% CI)			**185**			**157**	**100.0%**	**1.37 [-0.77, 3.52]**

Heterogeneity: Chi² = 0.49, df = 2 (P = 0.78); I² = 0%

Test for overall effect: Z = 1.25 (P = 0.21)

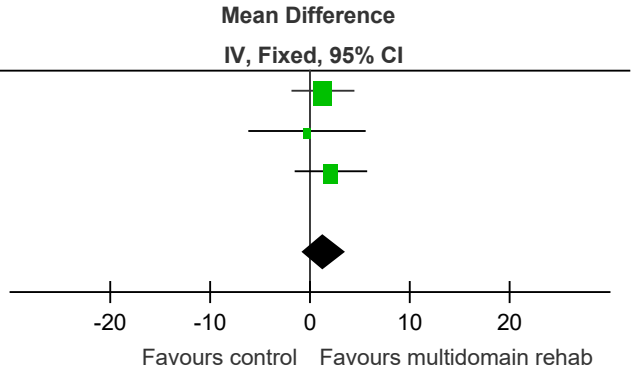


Figure 10: Stroop test time (lower better)

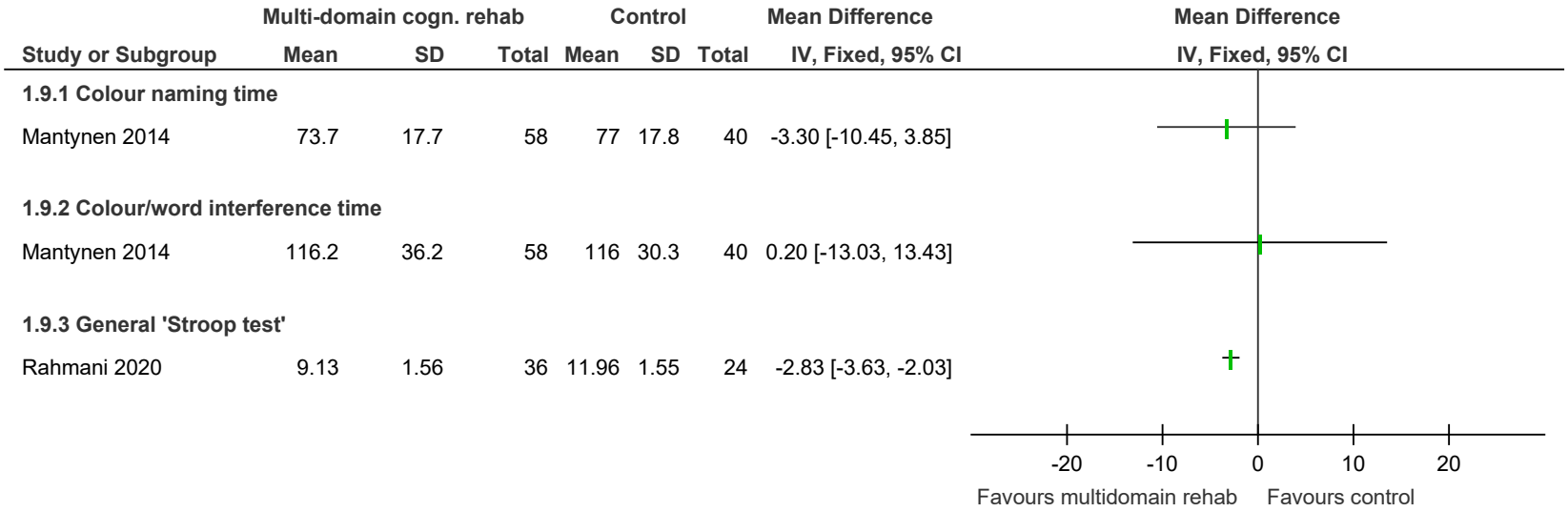


Figure 11: Stroop test (higher better)

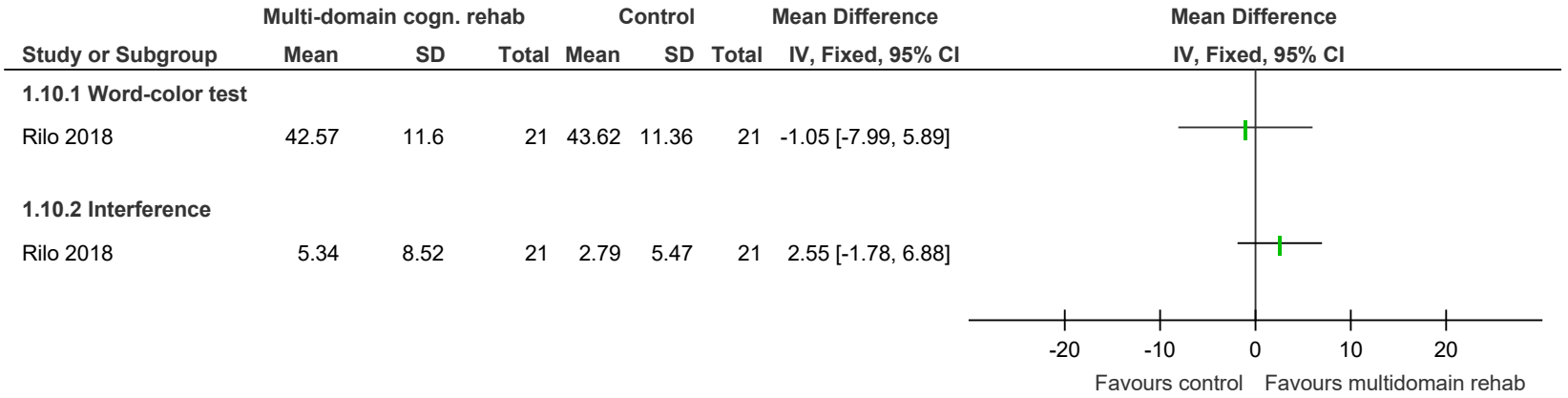


Figure 12: Trail Making Test Time – Parts A and B (lower better)

	Multi-domain cogn. rehab			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
1.11.1 Part A								
Mantynen 2014	32.1	12.4	58	31	9.2	40	85.9%	1.10 [-3.18, 5.38]
Rilo 2018	45.24	16.63	21	40.43	18.23	21	14.1%	4.81 [-5.74, 15.36]
Subtotal (95% CI)			**79**			**61**	**100.0%**	**1.62 [-2.34, 5.59]**
Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%								
Test for overall effect: Z = 0.80 (P = 0.42)								
1.11.2 Part B								
Mantynen 2014	79.1	36.4	58	75.4	35.6	40	100.0%	3.70 [-10.77, 18.17]
Subtotal (95% CI)			**58**			**40**	**100.0%**	**3.70 [-10.77, 18.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.50 (P = 0.62)								

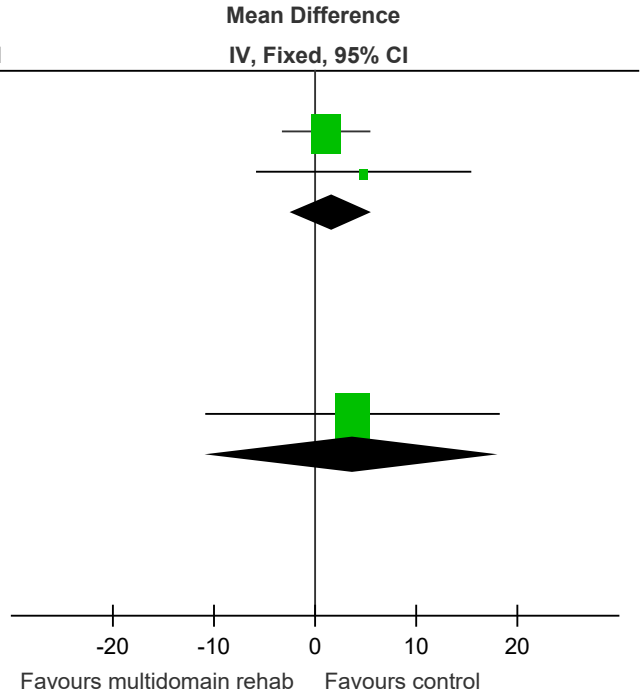


Figure 13: California Verbal Learning Test (higher better)

	Multi-domain cogn. rehab			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
1.12.1 Total								
Stuifbergen 2012	58.4	13.6	34	53.8	14.3	27	20.3%	4.60 [-2.47, 11.67]
Stuifbergen 2018	57.2	12.3	93	54.7	12.3	90	79.7%	2.50 [-1.06, 6.06]
Subtotal (95% CI)			**127**			**117**	**100.0%**	**2.93 [-0.26, 6.11]**
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.60); I² = 0%								
Test for overall effect: Z = 1.80 (P = 0.07)								
1.12.2 Delayed								
Stuifbergen 2012	12.5	4.1	34	12.5	4.1	27	20.3%	0.00 [-2.07, 2.07]
Stuifbergen 2018	12.4	3.5	93	11.9	3.7	90	79.7%	0.50 [-0.54, 1.54]
Subtotal (95% CI)			**127**			**117**	**100.0%**	**0.40 [-0.53, 1.33]**
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%								
Test for overall effect: Z = 0.84 (P = 0.40)								

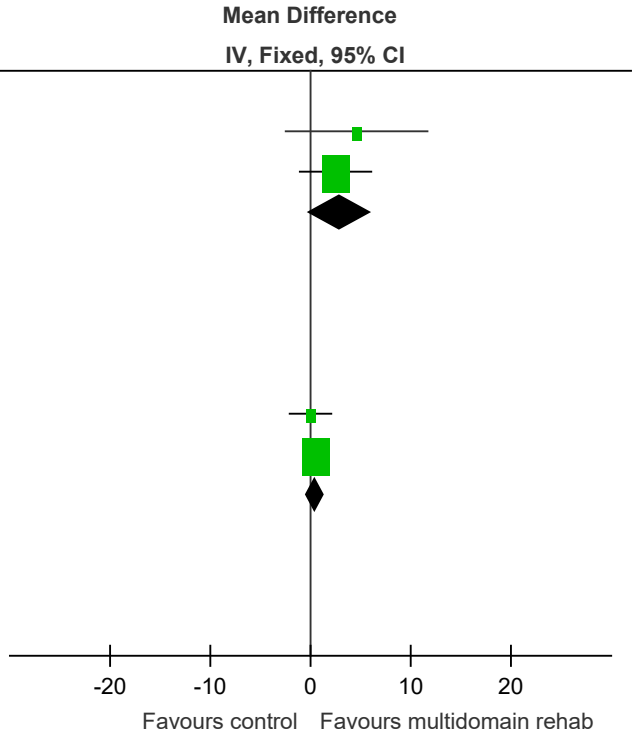


Figure 14: Hopkins Verbal Learning Test (higher better)

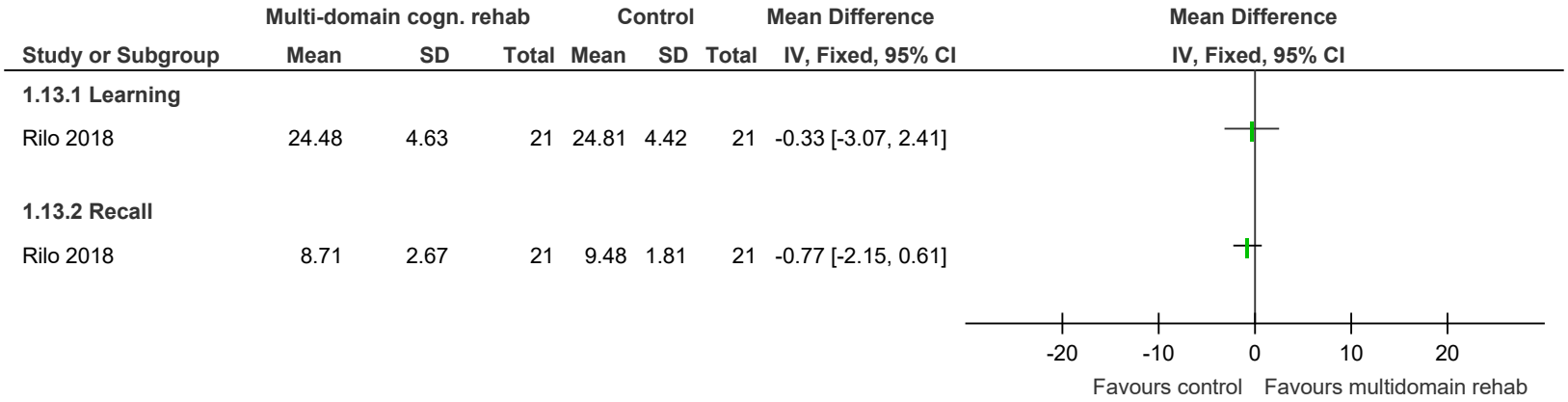


Figure 15: Brief Visuospatial Memory Test (higher better)

Study or Subgroup	Multi-domain cogn. rehab Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.14.1 Total								
Stuifbergen 2012	24.9	6	34	24.6	6.9	27	24.4%	0.30 [-2.99, 3.59]
Stuifbergen 2018	21.9	6.8	93	20.7	6.1	90	75.6%	1.20 [-0.67, 3.07]
Subtotal (95% CI)			**127**			**117**	**100.0%**	**0.98 [-0.65, 2.61]**
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%								
Test for overall effect: Z = 1.18 (P = 0.24)								
1.14.2 Delayed								
Stuifbergen 2012	9.3	2.1	34	8.8	2.8	27	25.3%	0.50 [-0.77, 1.77]
Stuifbergen 2018	8.2	2.6	93	7.7	2.5	90	74.7%	0.50 [-0.24, 1.24]
Subtotal (95% CI)			**127**			**117**	**100.0%**	**0.50 [-0.14, 1.14]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 1.53 (P = 0.12)								

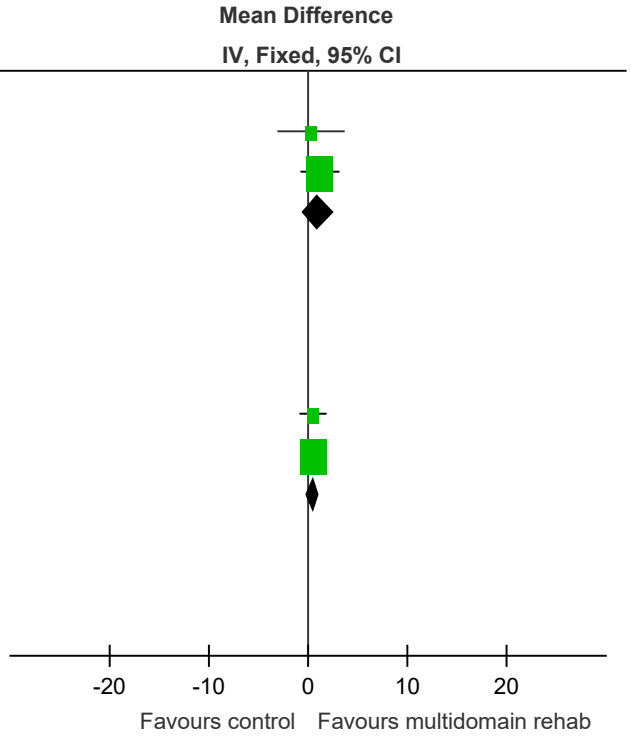


Figure 16: Digit Span Test (higher better)

Study or Subgroup	Multi-domain cogn. rehab Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.15.1 Forward								
Brissart 2020	5.8	1.2	52	5.7	1.1	49	100.0%	0.10 [-0.35, 0.55]
Subtotal (95% CI)			**52**			**49**	**100.0%**	**0.10 [-0.35, 0.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.44 (P = 0.66)								
1.15.2 Backward								
Brissart 2020	4.8	1.4	52	4.5	1.4	49	78.8%	0.30 [-0.25, 0.85]
Rilo 2018	6.43	1.75	21	6.24	1.73	21	21.2%	0.19 [-0.86, 1.24]
Subtotal (95% CI)			**73**			**70**	**100.0%**	**0.28 [-0.21, 0.76]**
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%								
Test for overall effect: Z = 1.12 (P = 0.26)								

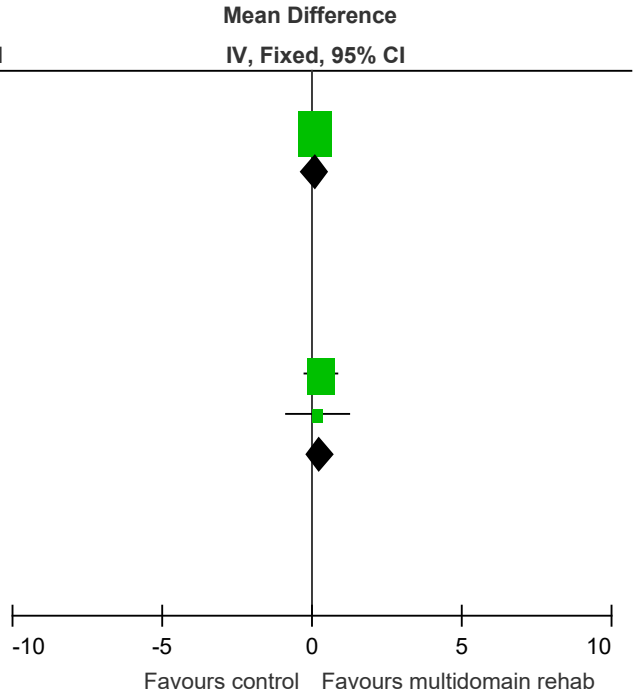
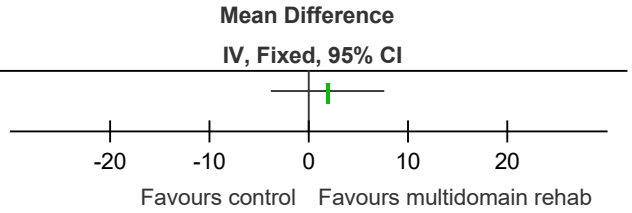


Figure 17: Word List Generation Test (higher better)

Study or Subgroup	Multi-domain cogn. rehab Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Manglani 2020	33.9	8.58	17	32	8.12	17	1.90 [-3.72, 7.52]



1

Figure 18: Wisconsin Card Sorting Test time (lower better)

Study or Subgroup	Multi-domain cogn. rehab Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Rahmani 2020	10.19	1.62	36	13.29	2.08	24	-3.10 [-4.09, -2.11]

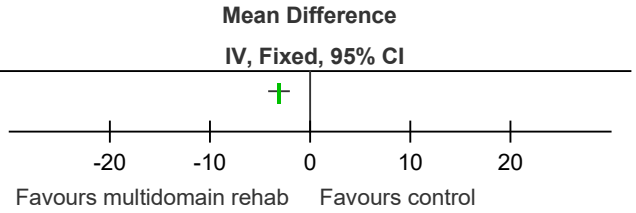


Figure 19: Test of Attentional Performances (TAP) – Working memory domain omissions (lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Brissart 2020	2.8	2.8	52	2.9	2.3	49	-0.10 [-1.10, 0.90]	

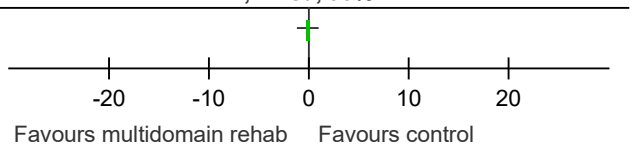


Figure 20: TAP – Flexibility domain correct answers (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Brissart 2020	91.4	14.6	52	96	4.9	49	-4.60 [-8.80, -0.40]	

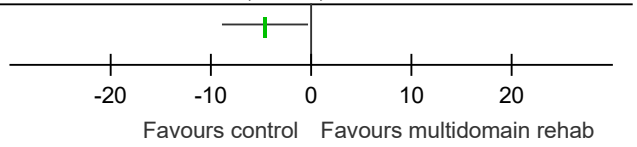


Figure 21: TAP – Incompatibility domain correct answers (higher better)

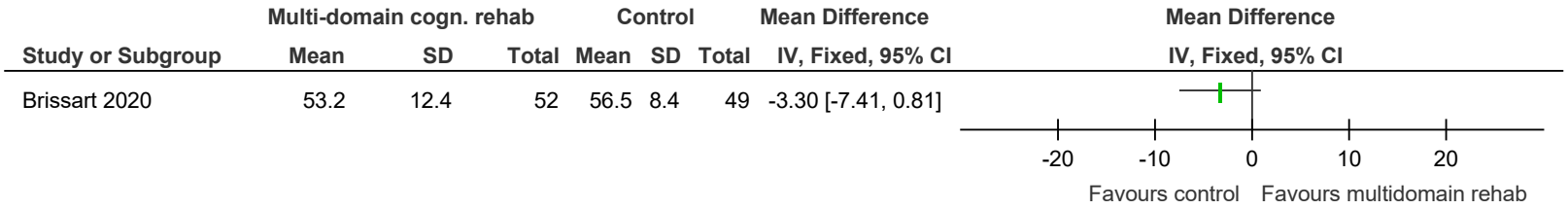


Figure 22: TAP – Reaction time across various domains (lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
1.21.1 Alertness - simple								
Pusswald 2014	250.6	29	20	269.8	20	20	-19.20 [-34.64, -3.76]	
1.21.2 Alertness - cued								
Pusswald 2014	242.8	29.2	20	264.3	19.3	20	-21.50 [-36.84, -6.16]	
1.21.3 Divided Attention - acoustic								
Pusswald 2014	575.5	105.2	20	605.1	119.8	20	-29.60 [-99.47, 40.27]	
1.21.4 Divided Attention - visual								
Pusswald 2014	806	91.7	20	865.5	48.7	20	-59.50 [-105.00, -14.00]	

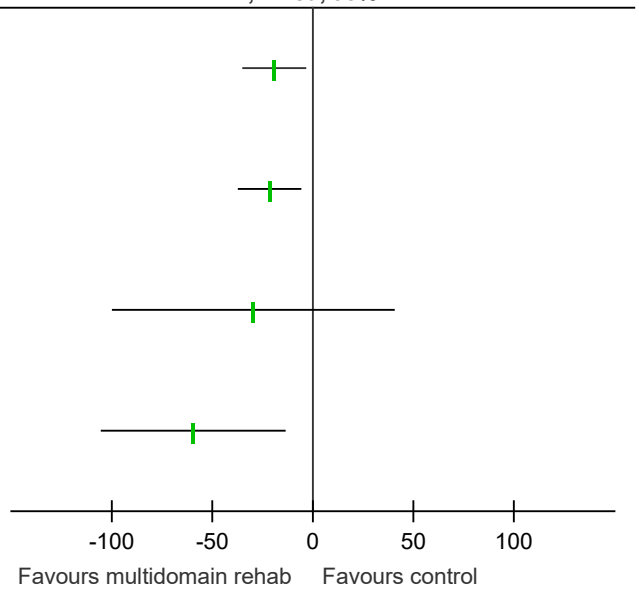


Figure 23: Brief Test of Attention (higher better)

Study or Subgroup	Multi-domain cogn. rehab Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Rilo 2018	12.81	4.2	21	15.1	3.71	21	-2.29 [-4.69, 0.11]

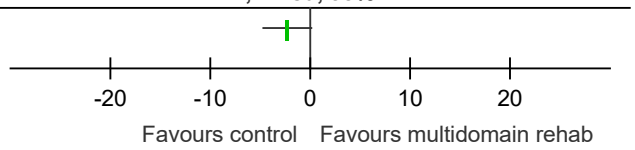


Figure 24: Delis-Kaplan Executive Function System (D-KEFS) (higher better)

Study or Subgroup	Multi-domain cogn. rehab Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.23.1 Descriptive							
Stuifbergen 2012	39.6	8.7	34	41.7	10.5	27	-2.10 [-7.02, 2.82]
1.23.2 Sort							
Stuifbergen 2012	10.2	2.1	34	10.9	2.7	27	-0.70 [-1.94, 0.54]

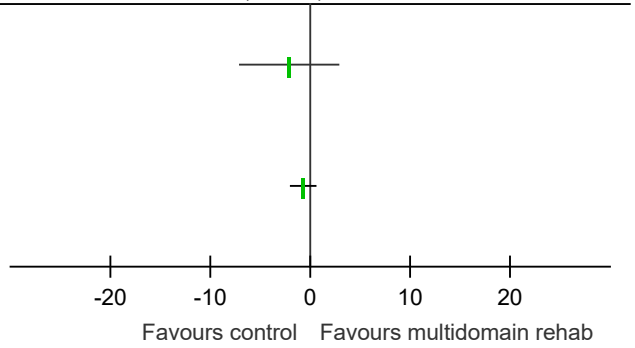


Figure 25: Verbal Fluency test (higher better)

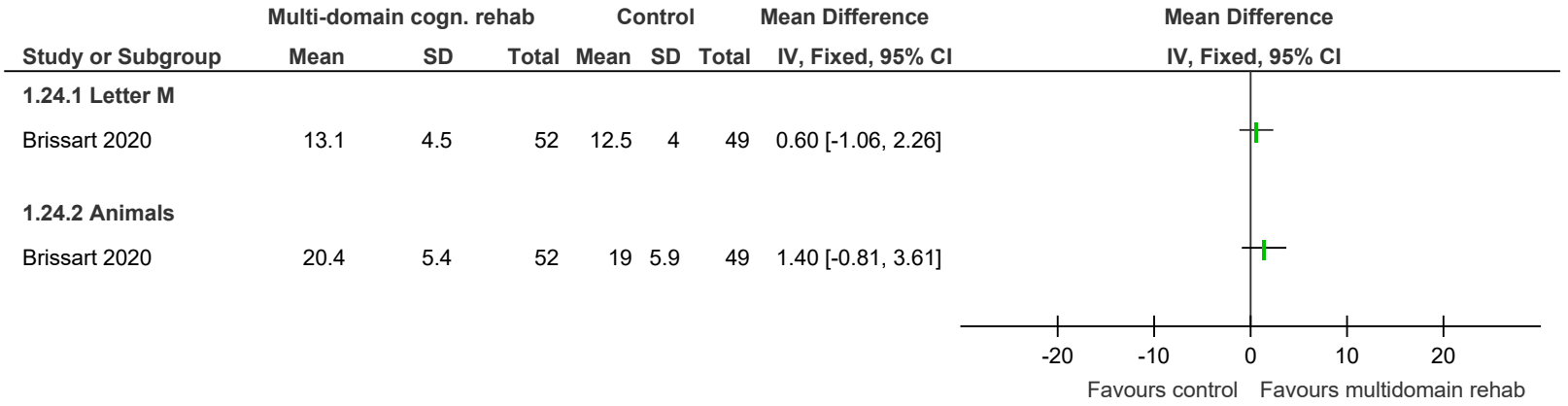


Figure 26: Calibrated Ideational Fluency Assessment (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
1.25.1 Animals								
Rilo 2018	21.57	6.28	21	22.24	6.79	21	-0.67 [-4.63, 3.29]	
1.25.2 Supermarket								
Rilo 2018	18.81	7.8	21	21.1	5.82	21	-2.29 [-6.45, 1.87]	
1.25.3 P-words								
Rilo 2018	27.62	5.59	21	30.57	11.91	21	-2.95 [-8.58, 2.68]	

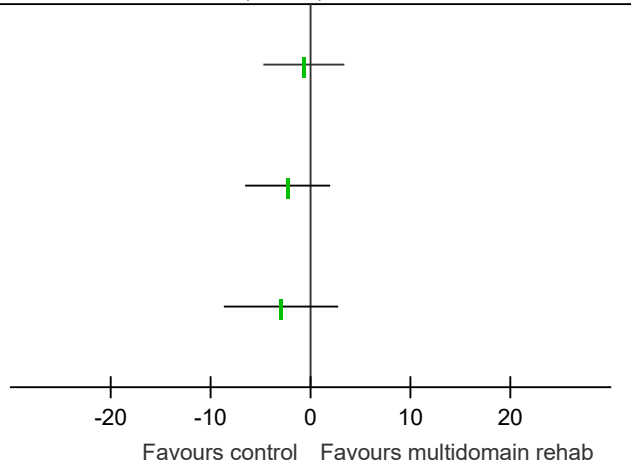


Figure 27: MUSIC – unclear which outcome set/measure this is referring to (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
1.26.1 Verbal memory								
Pusswald 2014	14.5	3.3	20	14.38	3.5	20	0.12 [-1.99, 2.23]	
1.26.2 Verbal retrieval								
Pusswald 2014	6.11	1.7	20	5.88	1.24	20	0.23 [-0.69, 1.15]	
1.26.3 Verbal fluency								
Pusswald 2014	14.72	3.9	20	14.88	2.9	20	-0.16 [-2.29, 1.97]	
1.26.4 Interferences								
Pusswald 2014	9.19	6.2	20	12.01	6.42	20	-2.82 [-6.73, 1.09]	

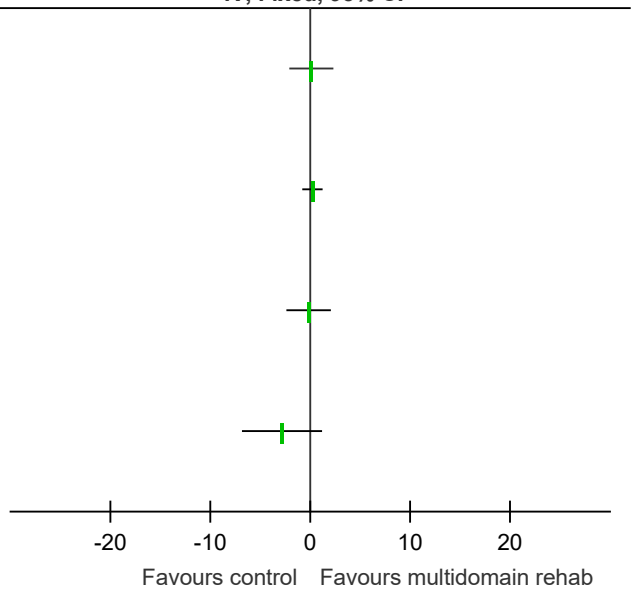


Figure 28: Judgement of Line Orientation test (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Stuifbergen 2012	27.8	3.9	34	27.4	4.2	27	0.40 [-1.66, 2.46]	

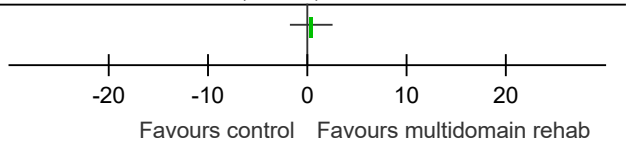


Figure 29: Salthouse Perceptual Comparison Test (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Rilo 2018	25.38	7.21	21	27.38	9.29	21	-2.00 [-7.03, 3.03]	

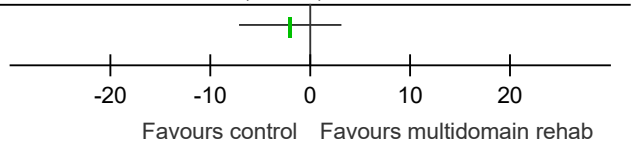


Figure 30: Code (assessing processing speed) (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Brissart 2020	47.3	9.6	52	49.2	12.8	49	-1.90 [-6.33, 2.53]	

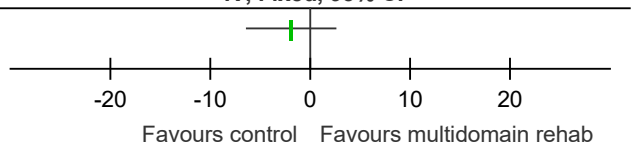


Figure 31: DO80 (assesses language) – Total score (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Brissart 2020	77.9	2.2	52	77.5	2.5	49	0.40 [-0.52, 1.32]	

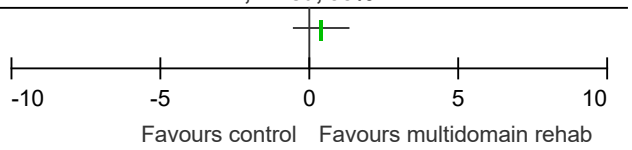


Figure 32: DO80 (assesses language) – Time (lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Brissart 2020	133.1	49.1	52	143.3	57.2	49	-10.20 [-31.05, 10.65]	

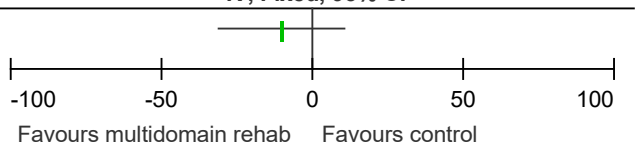


Figure 33: Perceived Deficits Questionnaire (scale usually 0-80; lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mantynen 2014	27.9	11.7	58	36.8	12.6	40	-8.90 [-13.83, -3.97]	

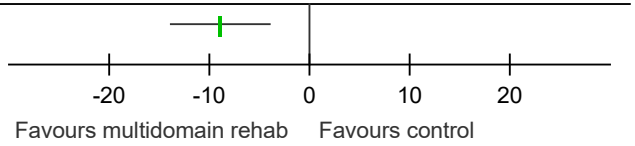


Figure 34: MS Neuropsychological Questionnaire (scale usually 0-60; lower better)

	Multi-domain cogn. rehab			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
1.33.1 Patient-reported								
Mantynen 2014	24	8.1	58	28.5	10.5	40	55.1%	-4.50 [-8.36, -0.64]
Stuifbergen 2012	28.41	11.13	34	26.15	11.56	27	44.9%	2.26 [-3.49, 8.01]
Subtotal (95% CI)			**92**			**67**	**100.0%**	**-1.47 [-8.06, 5.12]**
Heterogeneity: Tau² = 16.61; Chi² = 3.66, df = 1 (P = 0.06); I² = 73%								
Test for overall effect: Z = 0.44 (P = 0.66)								
1.33.2 Informant-reported								
Mantynen 2014	19.3	10.4	58	20.7	11.1	40	100.0%	-1.40 [-5.76, 2.96]
Subtotal (95% CI)			**58**			**40**	**100.0%**	**-1.40 [-5.76, 2.96]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.63 (P = 0.53)								

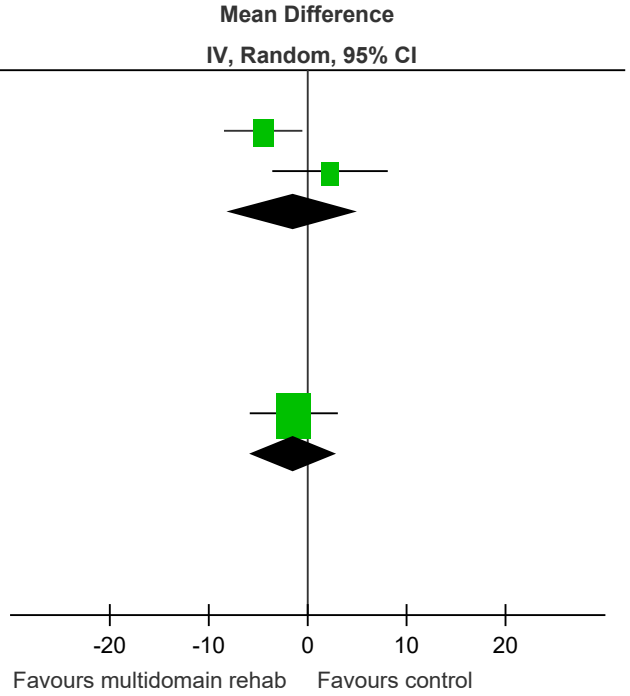


Figure 35: PROMIS – Applied Cognition Abilities Short Form 8a (scale 8-40; higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Stuifbergen 2018	25.6	7.7	93	23.4	7.3	90	2.20 [0.03, 4.37]	

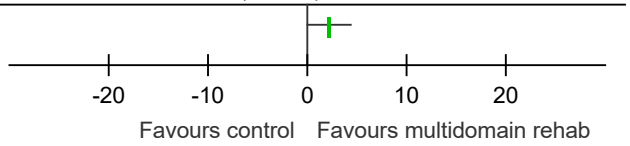


Figure 36: MSIS-29 (scale usually 0-100; lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.35.1 Physical								
Mantynen 2014	22.6	16.4	58	26.7	17.7	40	-4.10 [-11.02, 2.82]	
1.35.2 Psychological								
Mantynen 2014	24.9	18.2	58	27.1	17.3	40	-2.20 [-9.32, 4.92]	

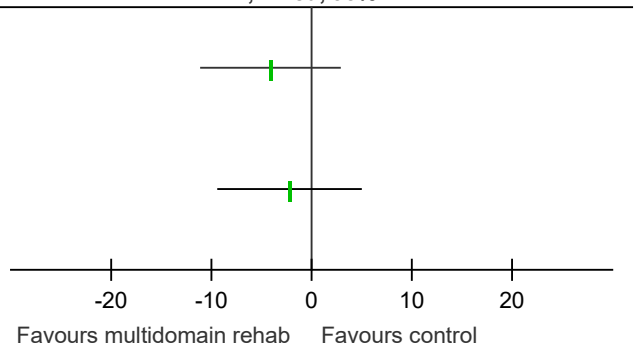


Figure 37: MS International Quality of Life Questionnaire - Index (scale 0-100; higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Brissart 2020	59.5	12.3	52	58.4	16.6	49	1.10 [-4.63, 6.83]	

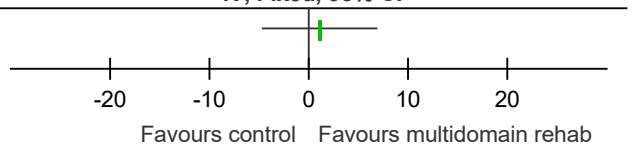


Figure 38: WHO-BREF Quality of Life (scale unclear; higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
1.37.1 S1 Physical health								
Mantynen 2014	14.2	2.5	58	13.6	2.2	40	0.60 [-0.34, 1.54]	
1.37.2 S2 Psychological								
Mantynen 2014	14	2.9	58	13.7	2.2	40	0.30 [-0.71, 1.31]	
1.37.3 S3 Social relationship								
Mantynen 2014	14.5	3.2	58	14.6	2.6	40	-0.10 [-1.25, 1.05]	
1.37.4 S4 environment								
Mantynen 2014	15.2	2.6	58	14.7	2.2	40	0.50 [-0.46, 1.46]	

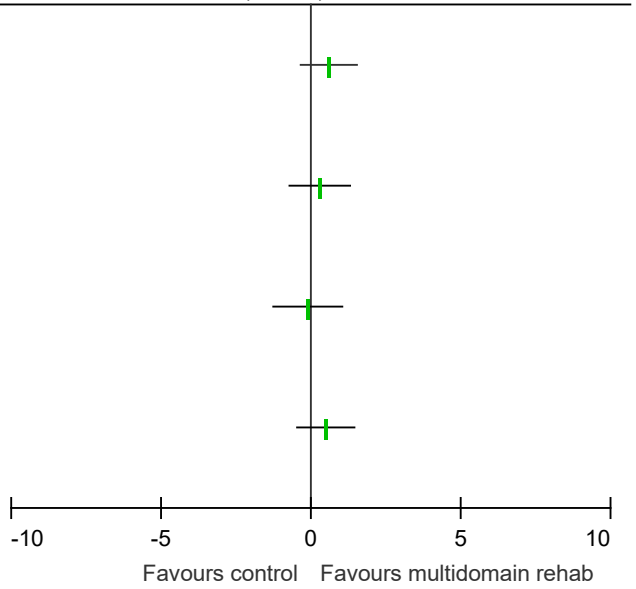


Figure 39: WHO Quality of Life and Satisfaction with life composite, z-score (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Manglani 2020	0.056	0.8285	17	0.16	0.8169	17	-0.10 [-0.66, 0.45]	

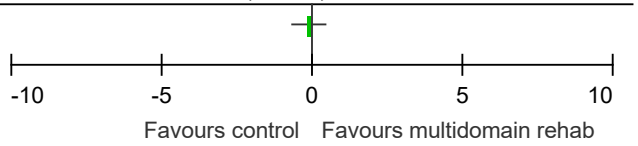


Figure 40: Memory span, t-score of various tests (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Jonsson 1993	1.8	5.5049	16	2.4	5.5049	16	-0.60 [-4.41, 3.21]	

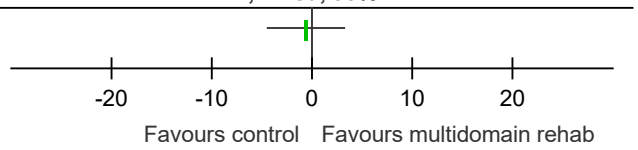


Figure 41: Verbal learning, t-score of various tests (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Jonsson 1993	2.2	5.3006	16	0.6	5.3006	16	1.60 [-2.07, 5.27]	

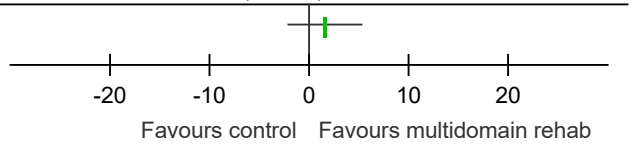


Figure 42: Visuospatial memory, t-score of various tests (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Jonsson 1993	2.7	3.4624	16	0.2	3.4624	16	2.50 [0.10, 4.90]	

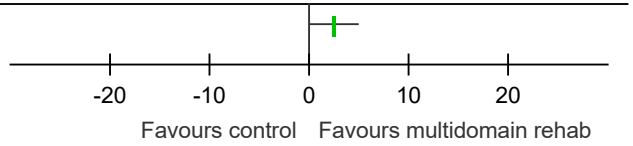


Figure 43: Visuo-motor speed, t-score of various tests (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Jonsson 1993	0.5	5.4213	16	-1	5.4213	16	1.50 [-2.26, 5.26]	

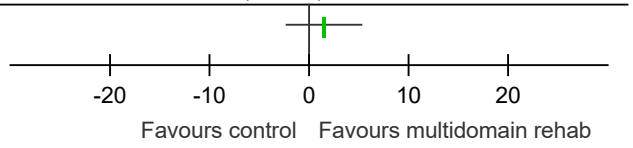


Figure 44: Visual perception, t-score of various tests (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Jonsson 1993	2.2	1.9373	16	1	1.9373	16	1.20 [-0.14, 2.54]

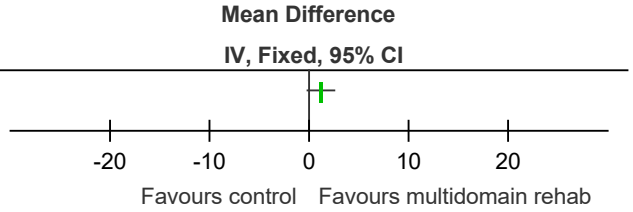


Figure 45: Sum of 11 cognitive tests, t-score of various tests (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Jonsson 1993	1.6	3.3903	16	-0.5	3.3903	16	2.10 [-0.25, 4.45]

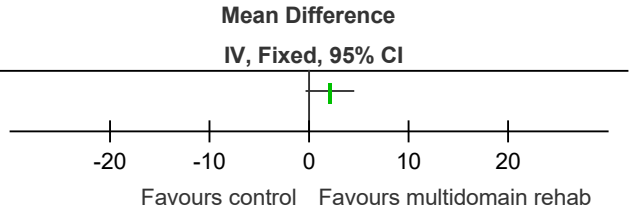


Figure 46: Information processing speed (unclear how measured) (lower better)

	Multi-domain cogn. rehab			Control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Rahmani 2020	1,041.4	53.69	36	1,122.5	81.28	24	-81.10 [-118.05, -44.15]

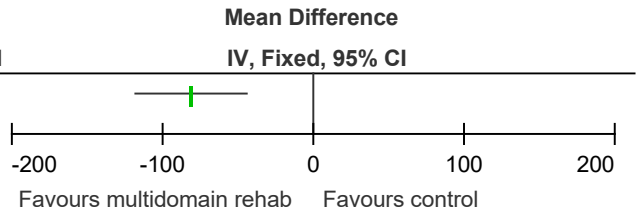


Figure 47: Wechsler Adult Intelligence Scale – Similarities test, t-score (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Jonsson 1993	1.5	6.9966	16	2.1	6.9966	16	-0.60 [-5.45, 4.25]	

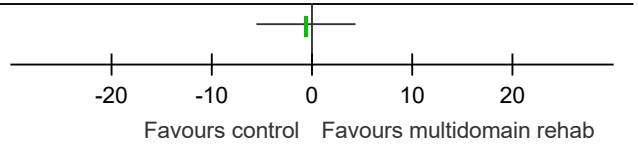


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Figure 48: Wechsler Adult Intelligence Scale – Picture Arrangement, t-score (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Jonsson 1993	3.7	8.5676	16	4.2	8.5676	16	-0.50 [-6.44, 5.44]	

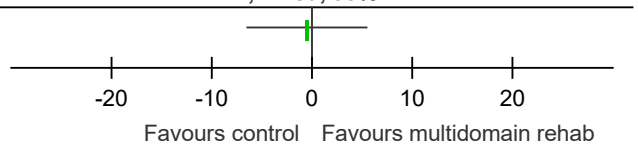

Figure 49: Fatigue – FSMC cognitive subscale (scale usually 10-50; lower better)

	Multi-domain cogn. rehab			Control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Mantynen 2014	31	9.7	58	33.6	9.2	40	-2.60 [-6.39, 1.19]

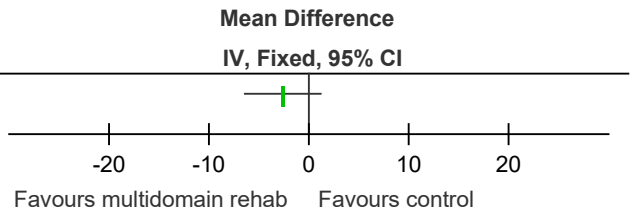

Figure 50: Beck Depression Inventory (scale usually 0-63; lower better)

	Multi-domain cogn. rehab			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Jonsson 1993	-1.1	4.7176	16	2.7	4.7176	16	38.7%	-3.80 [-7.07, -0.53]
Manglani 2020	11.4	9.28	17	10.2	10.1	17	15.3%	1.20 [-5.32, 7.72]
Mantynen 2014	9.8	7.5	58	10	6.2	40	46.0%	-0.20 [-2.92, 2.52]
Total (95% CI)			**91**			**73**	**100.0%**	**-1.38 [-4.21, 1.45]**

Heterogeneity: Tau² = 2.60; Chi² = 3.43, df = 2 (P = 0.18); I² = 42%

Test for overall effect: Z = 0.96 (P = 0.34)

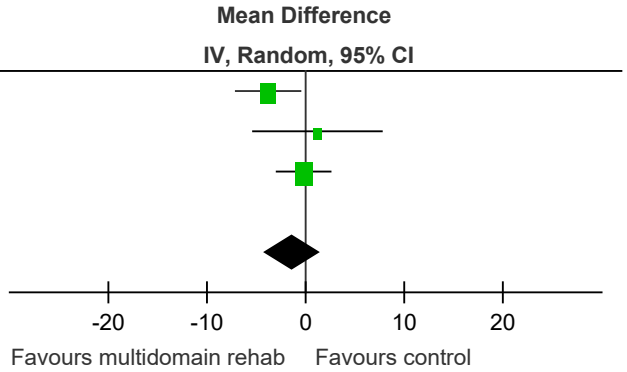

Figure 51: CES-D depression (scale usually 0-60; lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Stuifbergen 2018	9.9	6.2	93	11.5	6.6	90	-1.60 [-3.46, 0.26]	

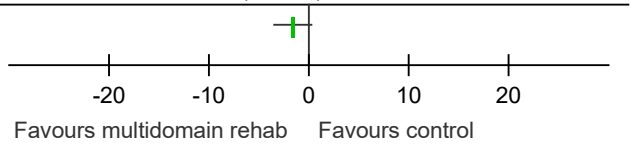

Figure 52: State-Trait Anxiety Inventory - State (scale usually 20-80; lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Jonsson 1993	-1.1	9.3398	16	1.6	9.3398	16	-2.70 [-9.17, 3.77]	

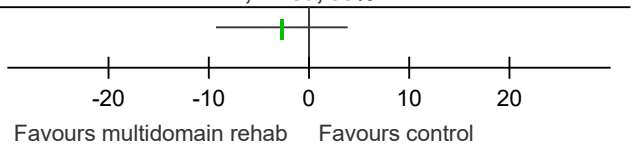

Figure 53: State-Trait Anxiety Inventory - Trait (scale usually 20-80; lower better)

	Multi-domain cogn. rehab			Control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Jonsson 1993	-1.5	7.9158	16	-0.6	7.9158	16	-0.90 [-6.39, 4.59]

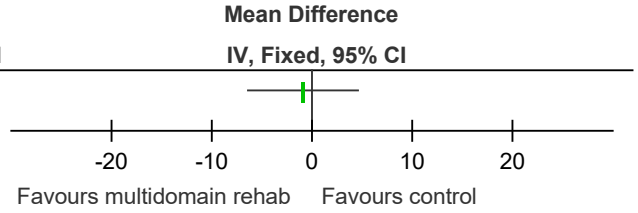

Figure 54: Penn State Worry Questionnaire (scale usually 16-80; lower better)

	Multi-domain cogn. rehab			Control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Manglani 2020	48.5	11.8	17	42.6	17.5	17	5.90 [-4.13, 15.93]

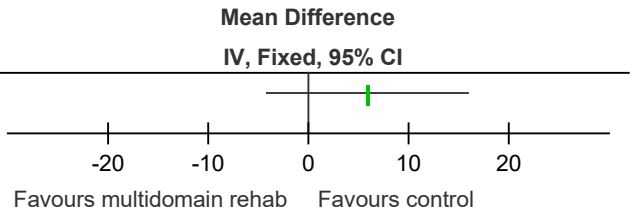

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Figure 55: Difficulties in Emotional Regulation Scale (DERS) (scale unclear; lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Manglani 2020	74.5	19.0605	17	75	18.866	17	-0.50 [-13.25, 12.25]	

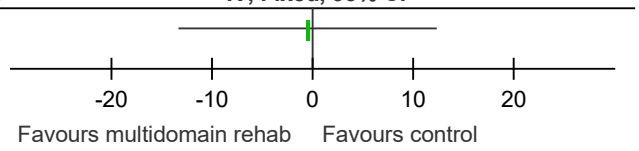

Figure 56: MS Self-Efficacy Scale – Control subscale (scale possibly 17-85; higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Stuifbergen 2012	557.72	157.84	34	534.26	201.06	27	23.46 [-69.09, 116.01]	

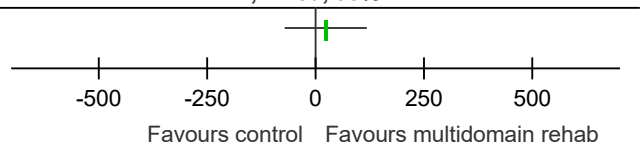

Figure 57: General Self-Efficacy Scale (scale possibly 17-85; higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Stuifbergen 2018	64	10.6	93	62.5	11.4	90	1.50 [-1.69, 4.69]	

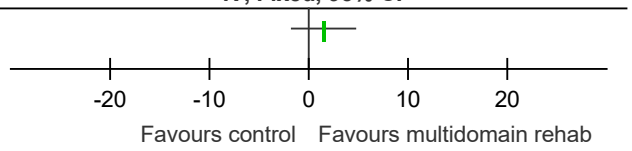

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Figure 58: Multi-factorial Memory Questionnaire (scale 0-76; higher better)

	Multi-domain cogn. rehab			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Stuifbergen 2012	43.12	11.93	34	41.15	10.65	27	25.1%	1.97 [-3.71, 7.65]
Stuifbergen 2018	40.5	11.4	93	39.6	11.3	90	74.9%	0.90 [-2.39, 4.19]
Total (95% CI)			**127**			**117**	**100.0%**	**1.17 [-1.68, 4.01]**

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%

Test for overall effect: Z = 0.81 (P = 0.42)

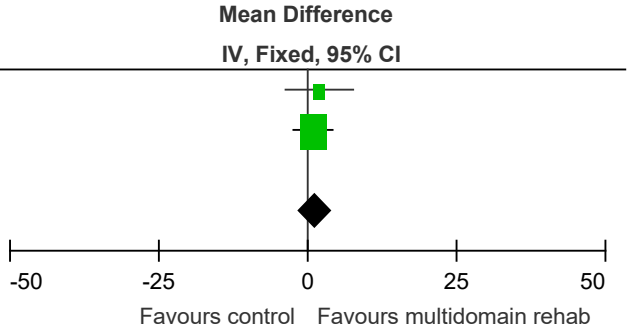


Figure 59: Everyday Problems Test-Revised (measure of activities of daily living performance) (scale unclear; higher better)

	Multi-domain cogn. rehab			Control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Stuifbergen 2018	23.8	4.8	93	23.1	4.3	90	0.70 [-0.62, 2.02]

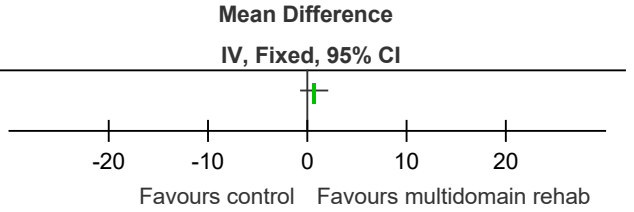
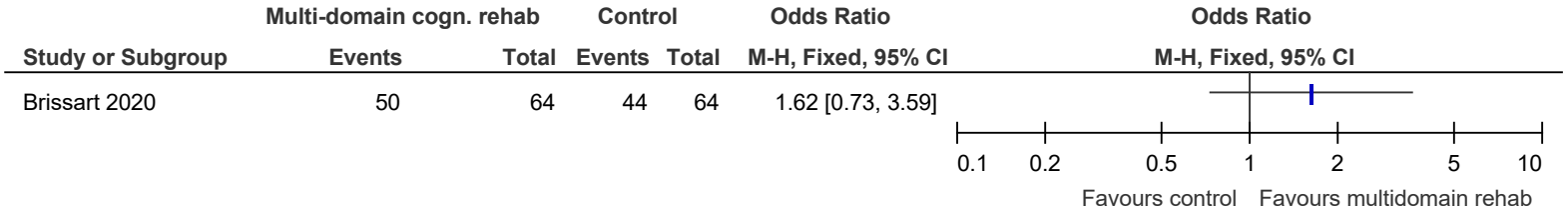


Figure 60: Adherence



E.2 General cognitive rehabilitation (multi-component and multi-domain) vs. control, >6 months – 1 year

Figure 61: SDMT (higher better)

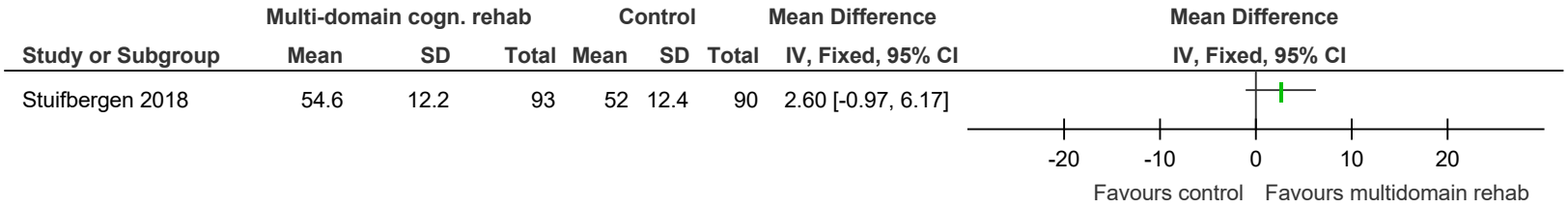


Figure 62: PASAT (higher better)

Study or Subgroup	Multi-domain cogn. rehab Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.5.1 2 seconds								
Stuifbergen 2018	34.8	13.2	93	33.4	12.2	90	100.0%	1.40 [-2.28, 5.08]
Subtotal (95% CI)			**93**			**90**	**100.0%**	**1.40 [-2.28, 5.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.75 (P = 0.46)								
2.5.2 3 seconds								
Rahmani 2020	21.89	3.06	36	19.46	3.41	24	80.5%	2.43 [0.74, 4.12]
Stuifbergen 2018	47.6	11.9	93	45.9	11.8	90	19.5%	1.70 [-1.73, 5.13]
Subtotal (95% CI)			**129**			**114**	**100.0%**	**2.29 [0.77, 3.80]**
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%								
Test for overall effect: Z = 2.95 (P = 0.003)								

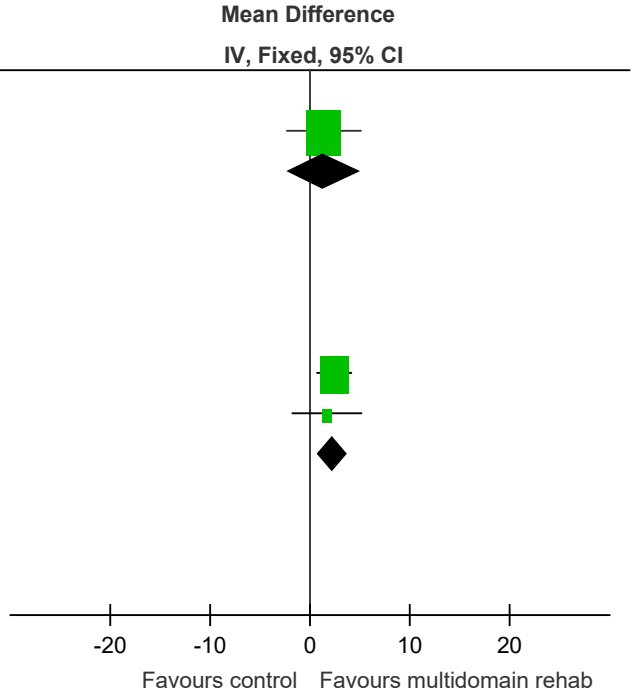


Figure 63: COWAT (higher better)

Study or Subgroup	Multi-domain cogn. rehab Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Stuifbergen 2018	39.5	12.1	93	36.9	11.9	90	2.60 [-0.88, 6.08]

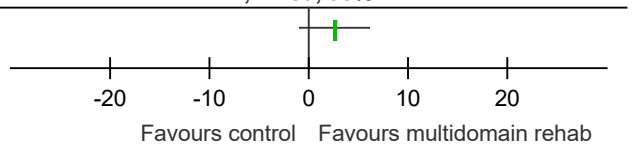


Figure 64: Stroop test time (lower better)

Study or Subgroup	Multi-domain cogn. rehab Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.7.3 General 'Stroop test'							
Rahmani 2020	9.77	1.54	36	11.96	1.33	24	-2.19 [-2.92, -1.46]

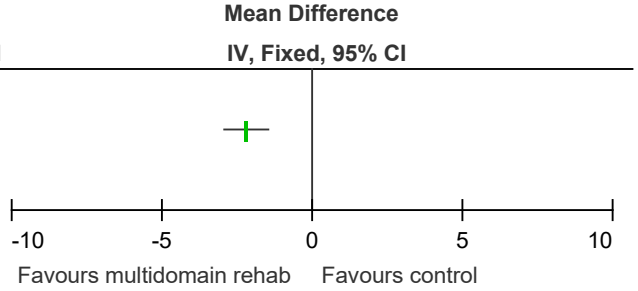


Figure 65: California Verbal Learning Test (higher better)

	Multi-domain cogn. rehab			Control			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
2.9.1 Total							
Stuifbergen 2018	56.1	12.9	93	53.6	12.9	90	2.50 [-1.24, 6.24]
2.9.2 Delayed							
Stuifbergen 2018	12.4	3.6	93	11.6	3.7	90	0.80 [-0.26, 1.86]

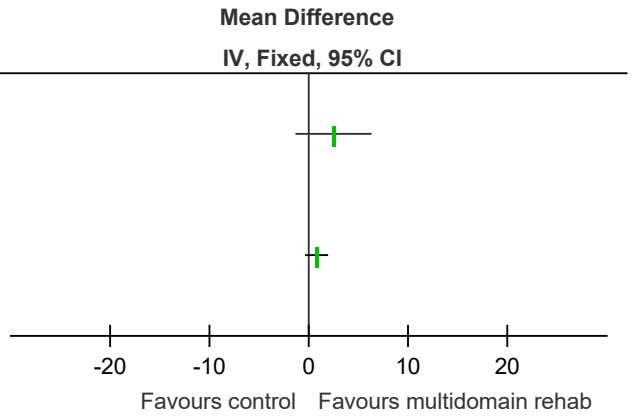


Figure 66: Brief Visuospatial Memory Test (higher better)

Study or Subgroup	Multi-domain cogn. rehab Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.10.1 Total							
Stuifbergen 2018	21.9	7	93	20.1	6.7	90	1.80 [-0.18, 3.78]
2.10.2 Delayed							
Stuifbergen 2018	8.2	2.7	93	7.5	2.7	90	0.70 [-0.08, 1.48]

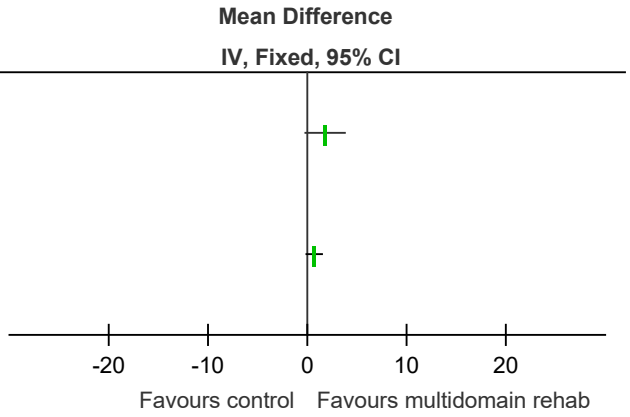


Figure 67: Wisconsin Card Sorting Test - Time (lower better)

Study or Subgroup	Multi-domain cogn. rehab Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Rahmani 2020	10.91	1.48	36	13.33	2.41	24	-2.42 [-3.50, -1.34]

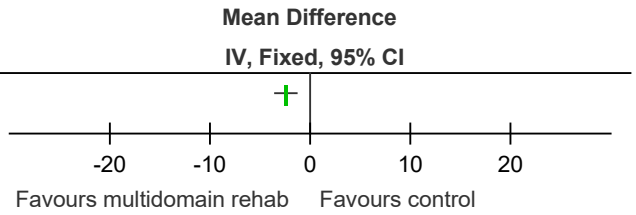


Figure 68: Information processing speed (unclear how measured) (lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Rahmani 2020	1,071.8	60.6	36	1,122.8	81.26	24	-51.00 [-89.06, -12.94]	

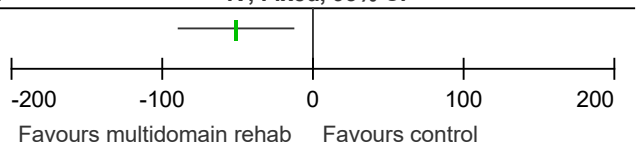


Figure 69: Perceived Deficits Questionnaire (scale usually 0-80; lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mantynen 2014	27.9	11.8	50	35.2	13	28	-7.30 [-13.12, -1.48]	

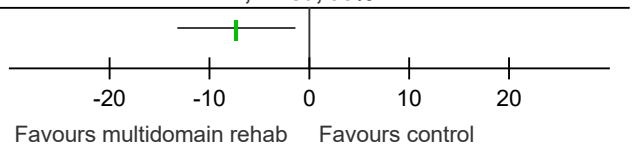


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Figure 70: MS Neuropsychological Questionnaire (scale usually 0-60; lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
2.20.1 Patient-reported								
Mantynen 2014	22.3	9.2	50	28.3	11.6	28	-6.00 [-11.00, -1.00]	
2.20.2 Informant-reported								
Mantynen 2014	18.6	8.8	50	19.8	11	28	-1.20 [-5.95, 3.55]	

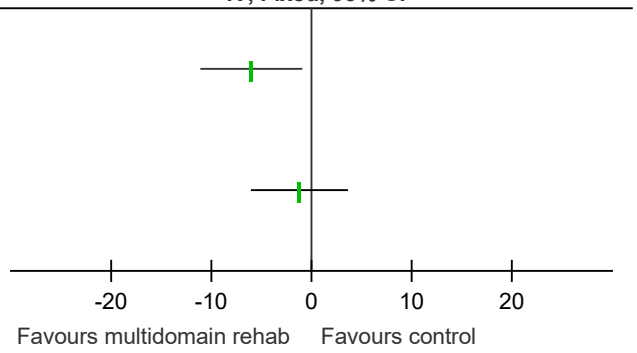

Figure 71: MSIS-29 (scale usually 0-100; lower better)

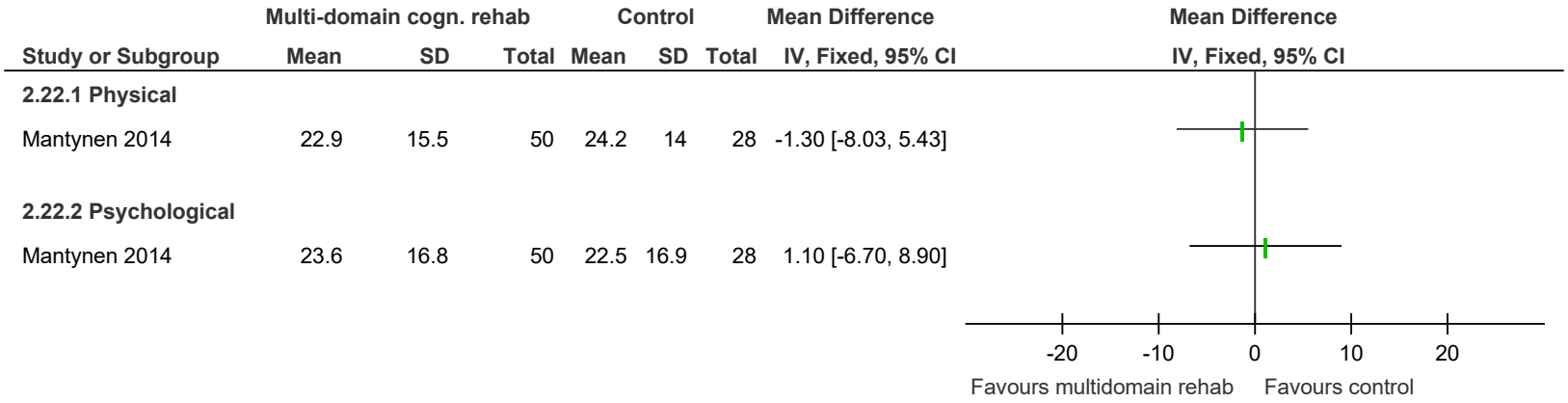

Figure 72: WHO-BREF Quality of Life (scale unclear; higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
2.24.1 S1 Physical health								
Mantynen 2014	14.4	2.6	50	13.7	2.4	28	0.70 [-0.44, 1.84]	
2.24.2 S2 Psychological								
Mantynen 2014	14.1	2.7	50	13.6	2.5	28	0.50 [-0.69, 1.69]	
2.24.3 S3 Social relationship								
Mantynen 2014	14.5	3.7	50	14.4	2.7	28	0.10 [-1.33, 1.53]	
2.24.4 S4 environment								
Mantynen 2014	15.3	2.5	50	14.4	2.2	28	0.90 [-0.17, 1.97]	

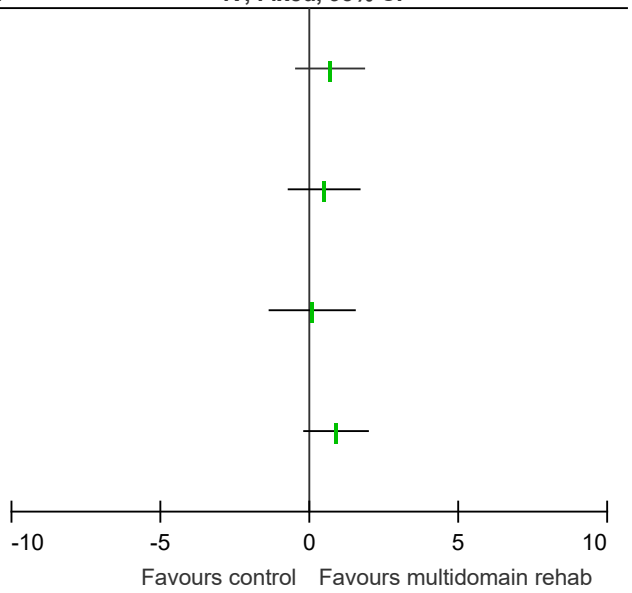

Figure 73: PROMIS – Applied Cognition Abilities Short Form 8a (scale 8-40; higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Stuifbergen 2018	25.6	7.4	93	23	7.8	90	2.60 [0.40, 4.80]	

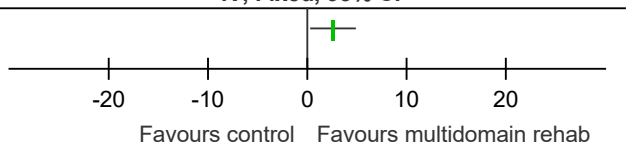

Figure 74: Fatigue – FSMC cognitive subscale (scale usually 10-50; lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mantynen 2014	29.6	8.9	50	32.2	9	28	-2.60 [-6.75, 1.55]	

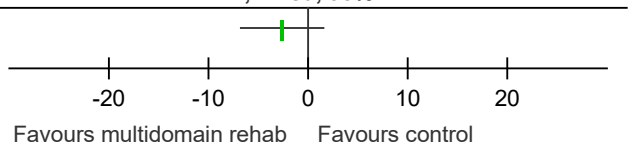

Figure 75: Beck Depression Inventory (scale usually 0-63; lower better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mantynen 2014	10.8	7.7	50	9.7	7	28	1.10 [-2.26, 4.46]	

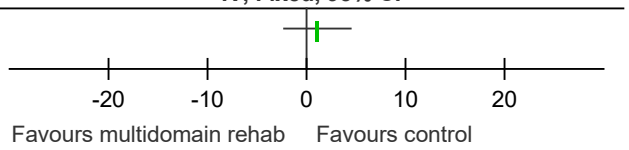

Figure 76: CES-D depression (scale usually 0-60; lower better)

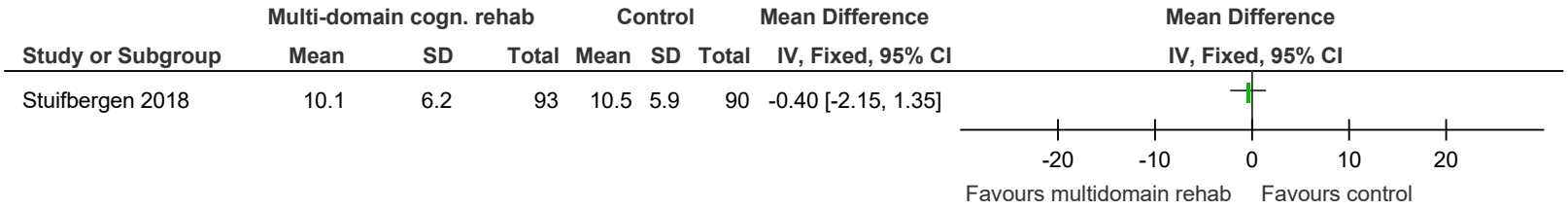

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Figure 77: General Self-Efficacy Scale (scale possibly 17-85; higher better)

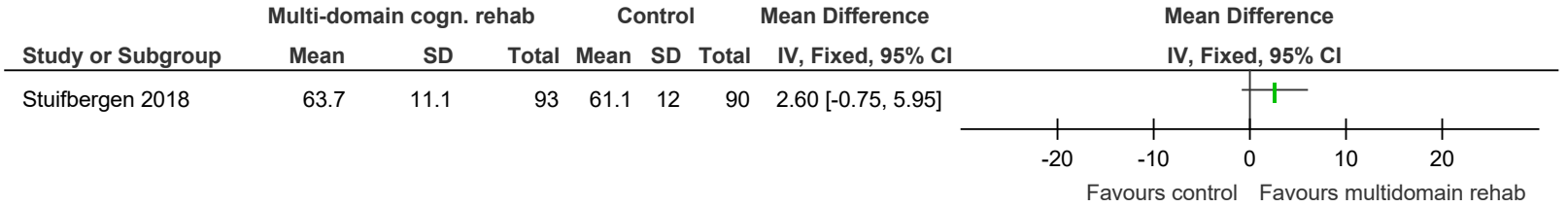


Figure 78: Multi-factorial Memory Questionnaire – Strategy subscale, indicates use of memory strategies (scale 0-76; higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Stuifbergen 2018	40.2	11	93	39.5	11.2	90	0.70 [-2.52, 3.92]	

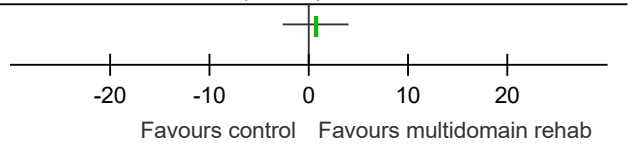
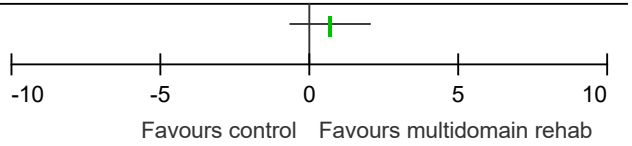


Figure 79: Everyday Problems Test-Revised (measure of activities of daily living performance) (scale unclear; higher better)

	Multi-domain cogn. rehab			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Stuifbergen 2018	24.2	4.8	93	23.5	4.4	90	0.70 [-0.63, 2.03]	



E.3 General cognitive rehabilitation (multi-component and multi-domain) vs. psychoeducation + information-sharing, 3 months

Figure 80: Addenbrooke's Cognitive Examination (scale 0-100; higher better)

	Multi-domain cogn. rehab			Psychoed + inform			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Mani 2018	93.3	5.03	15	86.4	6.49	15	6.90 [2.74, 11.06]

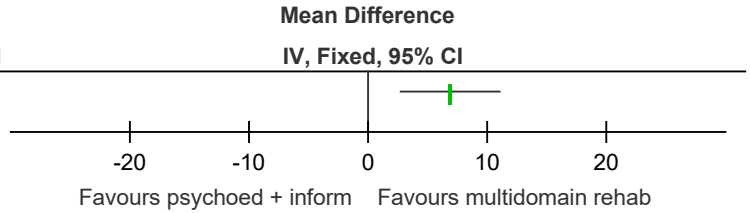


Figure 81: Wisconsin Card Sorting Test – Categories completed (higher better)

	Multi-domain cogn. rehab			Psychoed + inform			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Mani 2018	4.25	2	15	2.4	1.3	15	1.85 [0.64, 3.06]

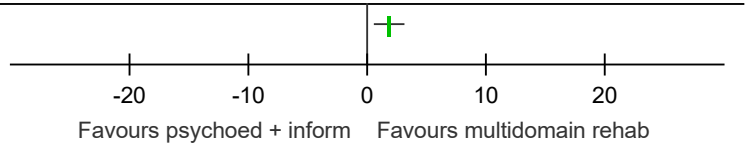


Figure 82: Wisconsin Card Sorting Test – Errors (lower better)

	Multi-domain cogn. rehab			Psychoed + inform			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
3.3.1 Perseverative errors							
Mani 2018	4.16	3.85	15	12.2	4.33	15	-8.04 [-10.97, -5.11]
3.3.2 Non-perseverative errors							
Mani 2018	15.08	5.61	15	19.8	6	15	-4.72 [-8.88, -0.56]

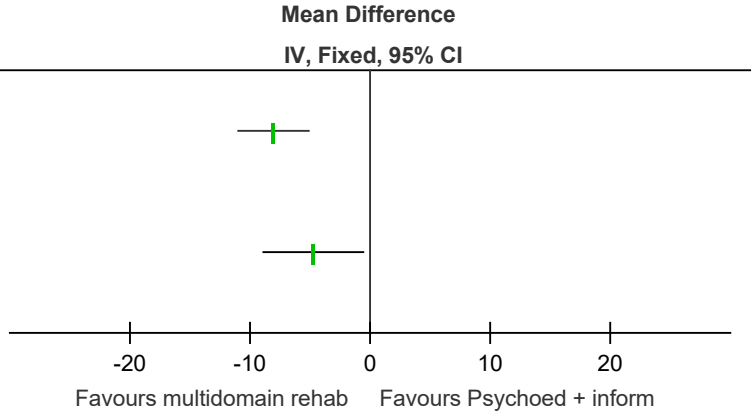


Figure 83: Wisconsin Card Sorting Test – Time (lower better)

	Multi-domain cogn. rehab			Psychoed + inform			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
Mani 2018	308.1	100.44	15	340.8	77.93	15	-32.70 [-97.03, 31.63]

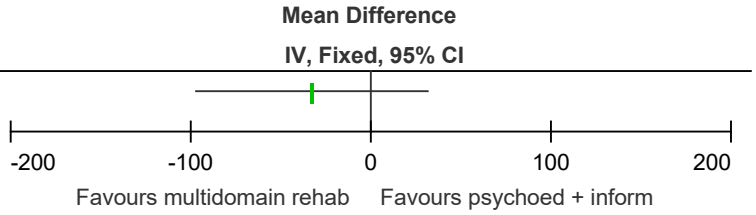


Figure 84: Behavior Rating Inventory of Executive Function-Adult (BRIEF-A) – Global Executive Function (scale 0-150; lower better)

	Multi-domain cogn. rehab			Psychoed + inform			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mani 2018	97.41	6.61	15	125.99	18.22	15	-28.58 [-38.39, -18.77]	

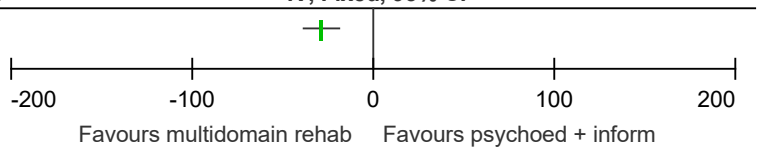


Figure 85: Memory Functioning Questionnaire – General rating (scale unclear; higher better)

	Multi-domain cogn. rehab			Psychoed + inform			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mani 2018	51.28	4.31	15	44.41	8.01	15	6.87 [2.27, 11.47]	

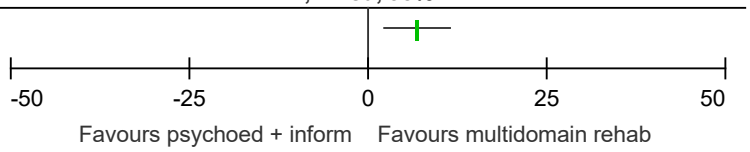
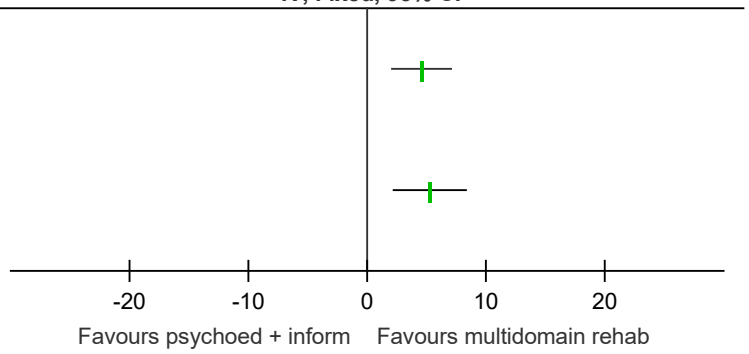


Figure 86: Weschler Memory Scale-Revised (scale unclear; higher better)

	Multi-domain cogn. rehab			Psychoed + inform			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.7.1 Visual memory								
Mani 2018	16.58	2.93	15	12	3.94	15	4.58 [2.10, 7.06]	
3.7.2 Verbal memory								
Mani 2018	19.32	3.18	15	14.05	5.1	15	5.27 [2.23, 8.31]	



E.4 General cognitive rehabilitation (multi-component and multi-domain) vs. non-specific cognitive rehabilitation programme, 4 months

Figure 87: SDMT (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lamargue 2020	57.8	10.2	18	57.2	9.1	17	0.60 [-5.80, 7.00]	

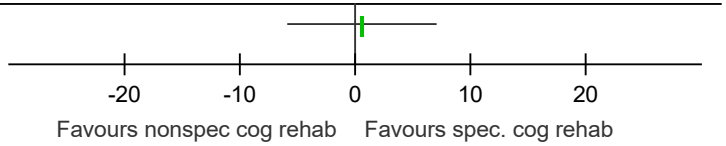


Figure 88: Stroop test time (lower better)

Study or Subgroup	Specific cogn. rehab Mean	SD	Total	Non-specific cogn. rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.2.1 Colour naming							
Lamargue 2020	61.6	9.4	18	66.5	9.9	17	-4.90 [-11.30, 1.50]
4.2.2 Word reading							
Lamargue 2020	50.3	14.4	18	48.5	7.5	17	1.80 [-5.75, 9.35]
4.2.3 Interference							
Lamargue 2020	44.6	26.3	18	38.2	15.8	17	6.40 [-7.88, 20.68]

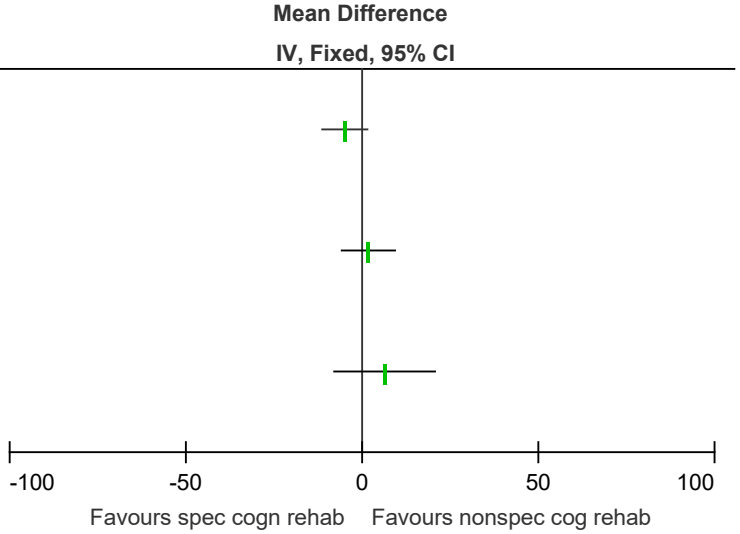


Figure 89: Trail Making Test time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
4.3.1 Part A							
Lamargue 2020	34.9	11.5	18	30.2	9.9	17	4.70 [-2.40, 11.80]
4.3.2 Part B							
Lamargue 2020	69.6	19.2	18	63.5	16.5	17	6.10 [-5.74, 17.94]

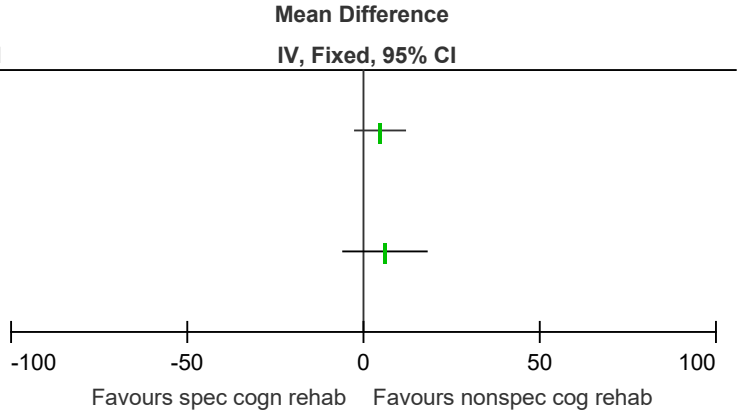


Figure 90: California Verbal Learning Test – correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
4.4.1 Learning trials - List A							
Lamargue 2020	63.7	6	18	65.7	10.2	17	-2.00 [-7.59, 3.59]
4.4.2 Learning trials - List B							
Lamargue 2020	7.9	2.2	18	8.3	2.3	17	-0.40 [-1.89, 1.09]
4.4.3 Immediate recall							
Lamargue 2020	13.7	2	18	13.5	2.4	17	0.20 [-1.27, 1.67]
4.4.4 Delayed recall							
Lamargue 2020	14.2	1.7	18	14.1	1.8	17	0.10 [-1.06, 1.26]
4.4.5 Immediate cued recall							
Lamargue 2020	14.3	1.7	18	13.8	1.8	17	0.50 [-0.66, 1.66]
4.4.6 Delayed cued recall							
Lamargue 2020	14	1.9	18	14.2	1.8	17	-0.20 [-1.43, 1.03]
4.4.7 Recognition							
Lamargue 2020	15.4	1	18	15.7	0.6	17	-0.30 [-0.84, 0.24]

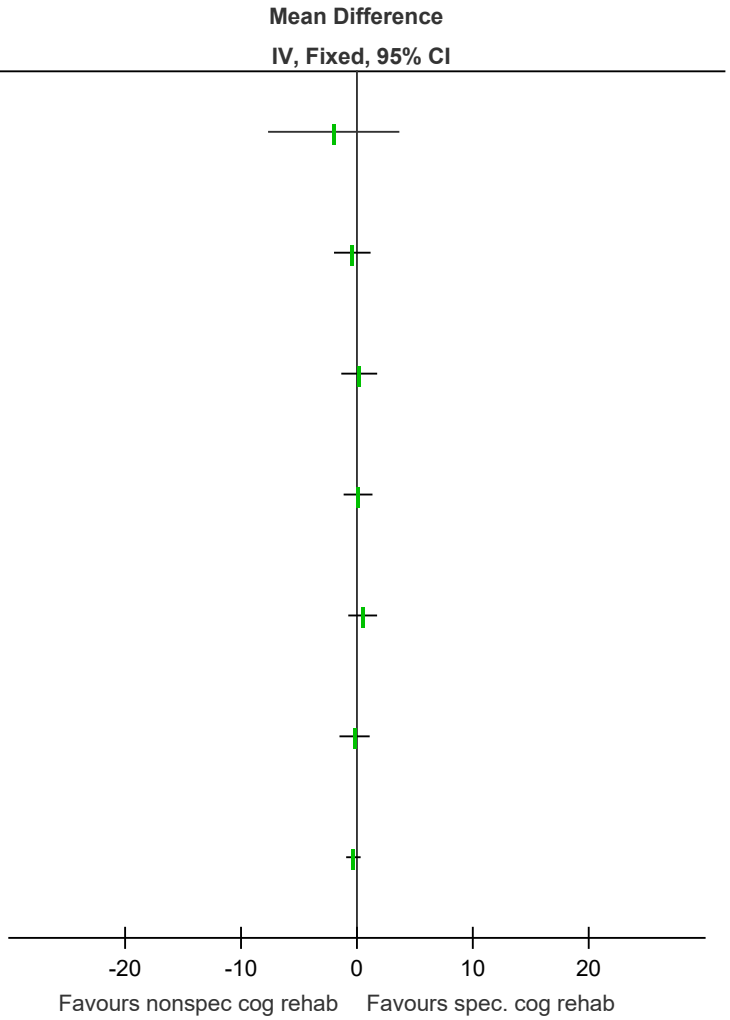


Figure 91: Test of Attentional Performances (TAP) – Alertness reaction time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
4.6.1 Without warning							
Lamargue 2020	250.1	45.1	18	273.3	38.6	17	-23.20 [-50.96, 4.56]
4.6.2 With warning							
Lamargue 2020	248.2	45.5	18	261.9	41.2	17	-13.70 [-42.43, 15.03]

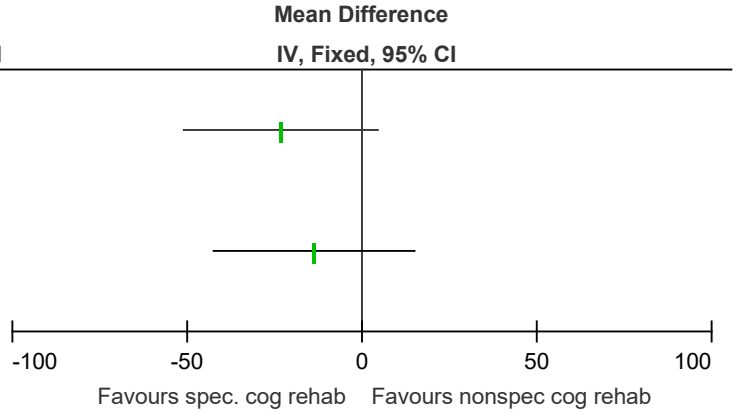


Figure 92: TAP – Visual Scanning correct answers (higher better)

Study or Subgroup	Specific cogn. rehab Mean	SD	Total	Non-specific cogn. rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.7.1 With a target							
Lamargue 2020	43.6	4.4	18	40.3	7.8	17	3.30 [-0.93, 7.53]

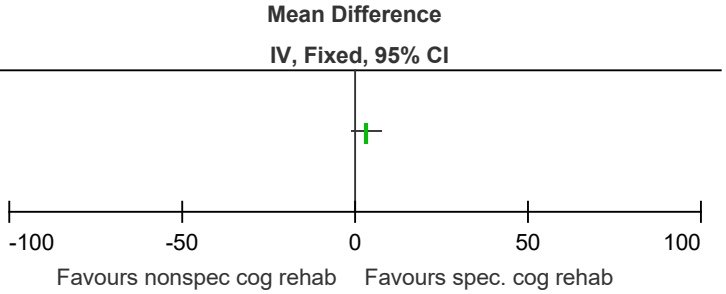


Figure 93: TAP – Visual Scanning reaction time (lower better)

Study or Subgroup	Specific cogn. rehab Mean	SD	Total	Non-specific cogn. rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.8.1 Without target							
Lamargue 2020	6,460.1	2,882.9	18	5,723.4	1,837.3	17	736.70 [-855.94, 2329.34]
4.8.2 With target							
Lamargue 2020	3,325.3	1,291.4	18	3,023.5	786	17	301.80 [-402.13, 1005.73]

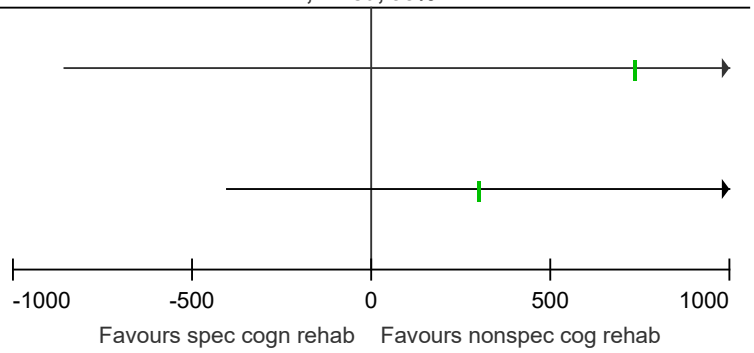


Figure 94: TAP – Divided attention (visual attention) correct answers (higher better)

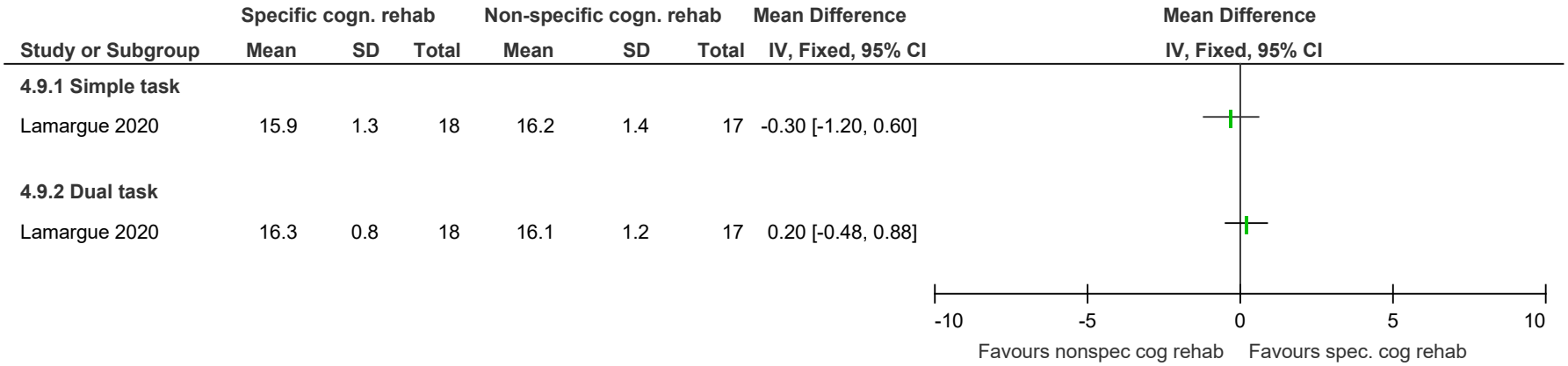


Figure 95: TAP – Divided attention (visual attention) reaction time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
4.10.1 Simple task							
Lamargue 2020	803.6	97.3	18	856.9	120.7	17	-53.30 [-126.19, 19.59]
4.10.2 Dual task							
Lamargue 2020	824.8	115.5	18	800.5	91.8	17	24.30 [-44.63, 93.23]

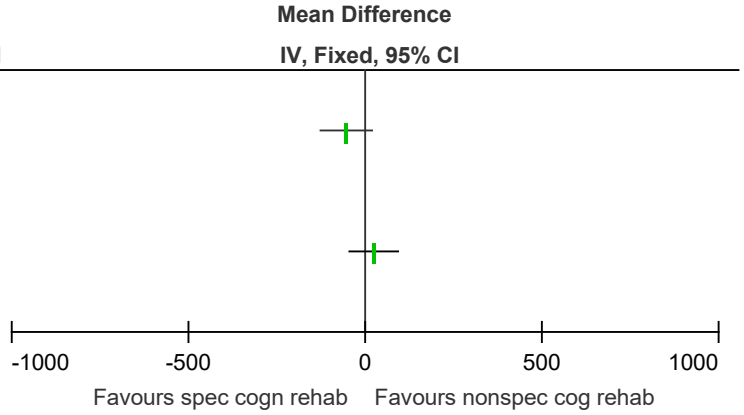


Figure 96: TAP – Divided attention (auditory attention) correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
4.11.2 Dual task							
Lamargue 2020	15.7	0.6	18	15.3	1.5	17	0.40 [-0.37, 1.17]

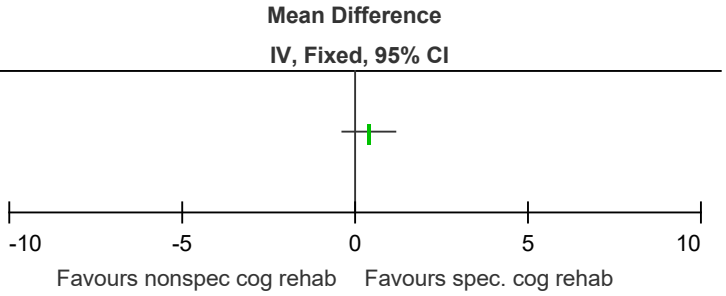


Figure 97: TAP – Divided attention (auditory attention) reaction time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
4.12.1 Simple task							
Lamargue 2020	525.4	90.6	18	560.1	119.8	17	-34.70 [-105.37, 35.97]
4.12.2 Dual task							
Lamargue 2020	574.4	102.3	18	583.6	98.6	17	-9.20 [-75.76, 57.36]

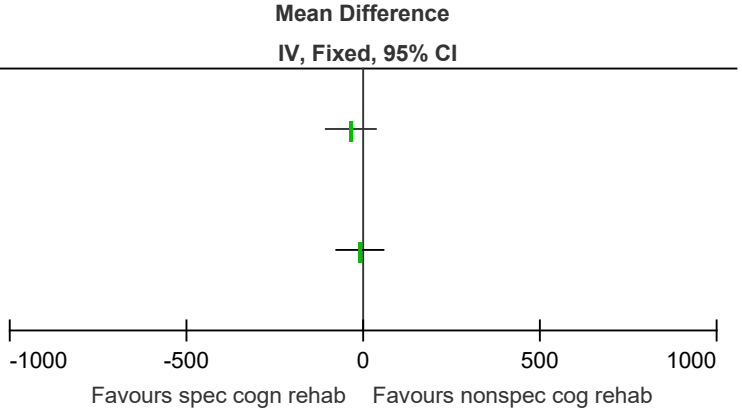


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Figure 98: TAP – N-back reaction time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
Lamargue 2020	703.3	120.8	18	753.1	209.8	17	-49.80 [-164.08, 64.48]

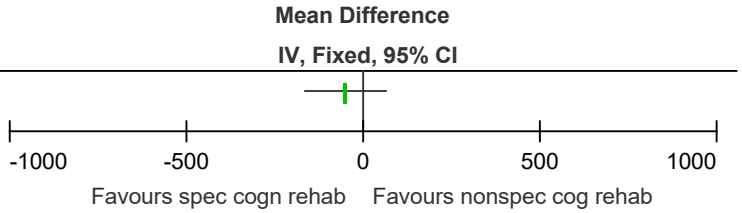


Figure 99: TAP – N-back correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lamargue 2020	13.7	1	18	13.2	1.6	17	0.50 [-0.39, 1.39]	

Figure 100: Baddeley's Dual Task forward span (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lamargue 2020	5.8	0.9	18	5.5	1.1	17	0.30 [-0.37, 0.97]	

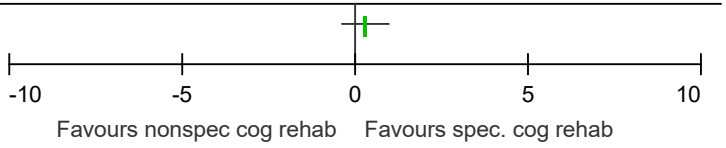


Figure 101: Backward span – correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Lamargue 2020	4.1	1.1	18	3.7	0.9	17	0.40 [-0.26, 1.06]

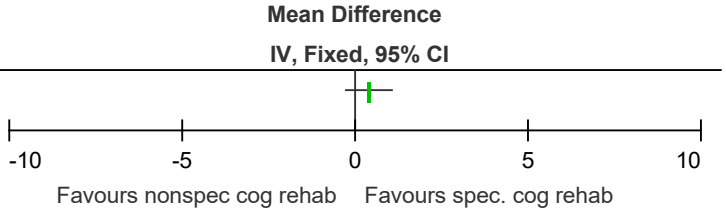


Figure 102: Fluency – correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
4.17.1 Semantic							
Lamargue 2020	29.6	7.6	18	30.8	7.8	17	-1.20 [-6.31, 3.91]
4.17.2 Phonemic							
Lamargue 2020	20.6	5.8	18	21.2	4.3	17	-0.60 [-3.97, 2.77]

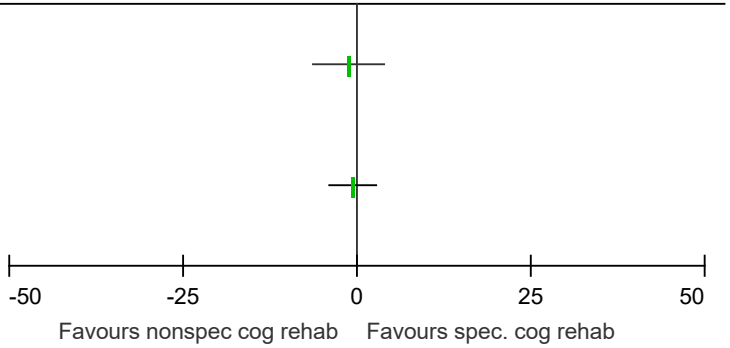


Figure 103: Rey Complex Figure (visuo-construction and episodic memory) – correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lamargue 2020	34.5	1.5	18	33.9	2	17	0.60 [-0.58, 1.78]	

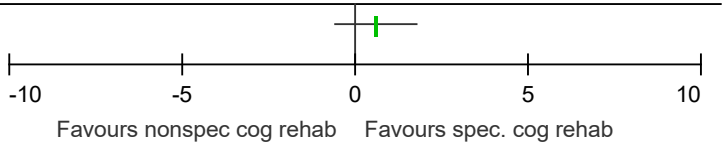


Figure 104: Rey Complex Figure (visuo-construction and episodic memory) – time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lamargue 2020	192.2	67.1	18	162.7	73	17	29.50 [-17.03, 76.03]	

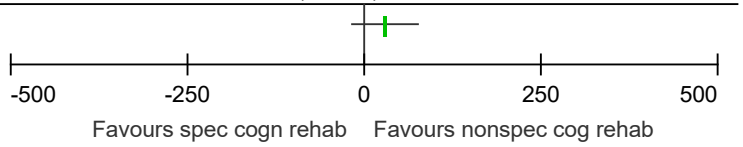


Figure 105: DO80 naming task – correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lamargue 2020	78.2	1.5	18	78.1	1.9	17	0.10 [-1.04, 1.24]	

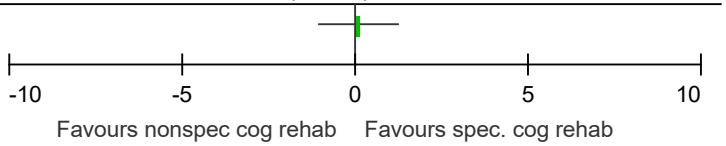


Figure 106: Daily Cognitive Activities Questionnaire (scale 0-60; higher better)

Study or Subgroup	Specific cogn. rehab Mean	SD	Total	Non-specific cogn. rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Lamargue 2020	55.9	14.1	18	49.2	16.9	17	6.70 [-3.64, 17.04]

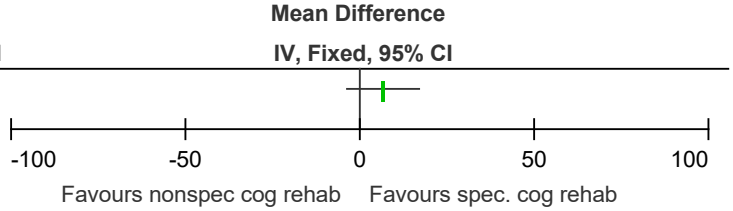


Figure 107: Beck Depression Inventory (scale usually 0-63; lower better)

Study or Subgroup	Specific cogn. rehab Mean	SD	Total	Non-specific cogn. rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Lamargue 2020	10.5	7.3	18	9.5	6.7	17	1.00 [-3.64, 5.64]

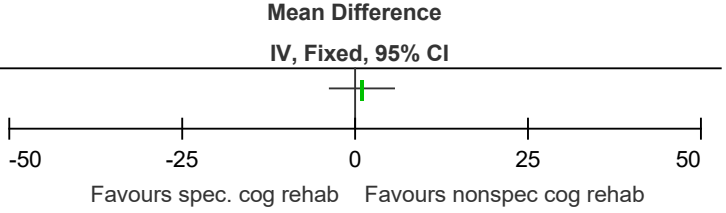


Figure 108: State-Trait Anxiety Inventory (scale usually 20-80; lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
4.23.1 STAI-A (state?)							
Lamargue 2020	36.9	16.1	18	32.2	8.4	17	4.70 [-3.74, 13.14]
4.23.2 STAI-B (trait?)							
Lamargue 2020	42.5	12.1	18	39.4	9.2	17	3.10 [-4.00, 10.20]

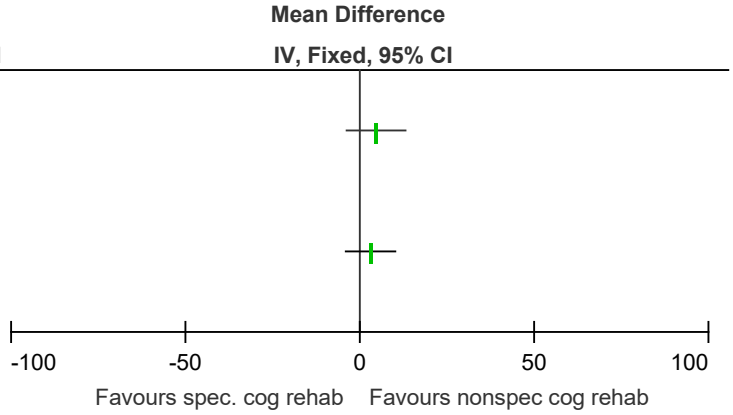


Figure 109: Modified Fatigue Impact Scale – Cognitive subscale (scale usually 0-40; lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
Lamargue 2020	17.2	7.9	18	17.5	9.9	17	-0.30 [-6.26, 5.66]

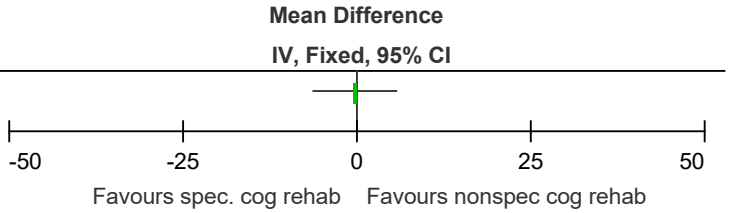
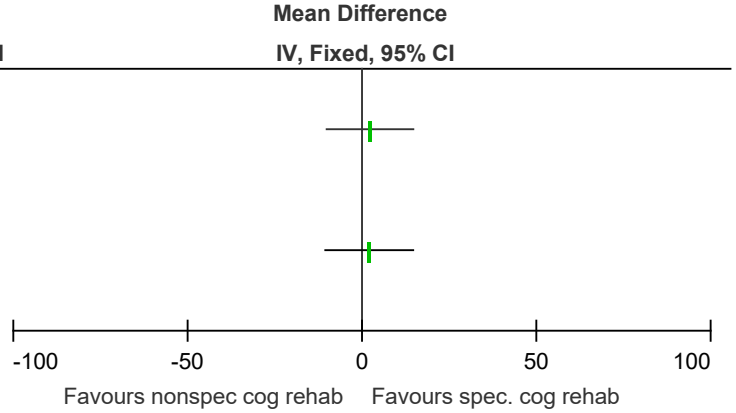


Figure 110: SF-36 quality of life (scale usually 0-100; higher better)

Study or Subgroup	Specific cogn. rehab Mean	SD	Total	Non-specific cogn. rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.25.1 Physical							
Lamargue 2020	58.1	16.7	18	55.8	20.5	17	2.30 [-10.13, 14.73]
4.25.2 Psychological							
Lamargue 2020	59.9	17.7	18	57.8	20.2	17	2.10 [-10.51, 14.71]



E.5 General cognitive rehabilitation (multi-component and multi-domain) vs. non-specific cognitive rehabilitation programme, 8 months

Figure 111: SDMT (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Lamargue 2020	58.7	10.3	18	59.4	10	17	-0.70 [-7.43, 6.03]

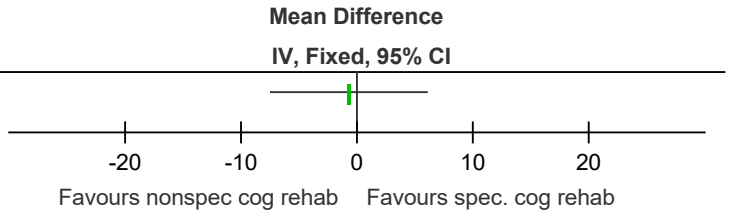


Figure 112: Stroop test time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
5.2.1 Colour naming							
Lamargue 2020	60.8	9.3	18	64.1	11.2	17	-3.30 [-10.14, 3.54]
5.2.2 Word reading							
Lamargue 2020	46.8	7.3	18	48.4	8.4	17	-1.60 [-6.83, 3.63]
5.2.3 Interference							
Lamargue 2020	38.4	14.2	18	40.2	16.5	17	-1.80 [-12.03, 8.43]

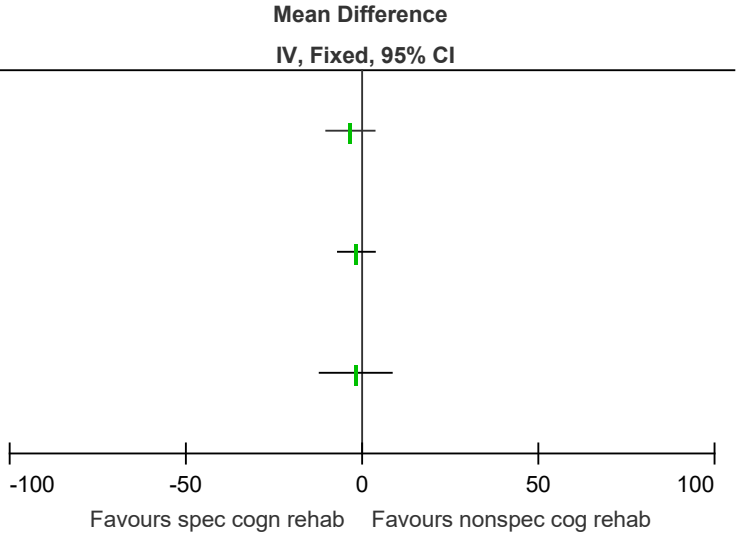


Figure 113: Trail Making Test time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
5.3.1 Part A							
Lamargue 2020	31	8.3	18	28.3	10.6	17	2.70 [-3.63, 9.03]
5.3.2 Part B							
Lamargue 2020	67.1	24.4	18	57.2	17.9	17	9.90 [-4.22, 24.02]

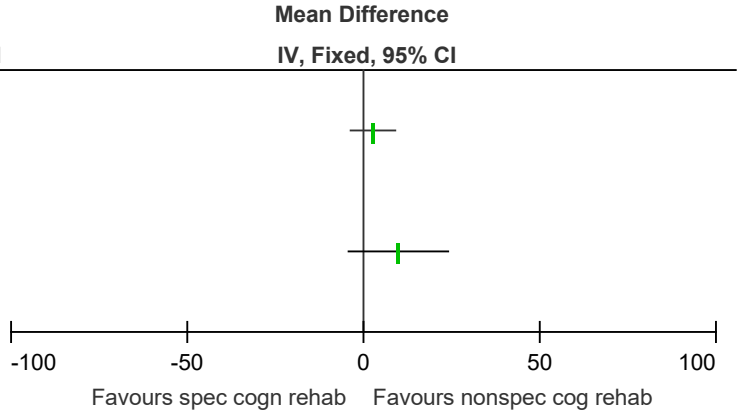


Figure 114: California Verbal Learning Test (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
5.4.1 Learning trials - List A							
Lamargue 2020	67.8	6.4	18	66.1	7.8	17	1.70 [-3.04, 6.44]
5.4.2 Learning trials - List B							
Lamargue 2020	8	2.4	18	8	2.9	17	0.00 [-1.77, 1.77]
5.4.3 Immediate recall							
Lamargue 2020	13.5	2.4	18	14.1	2	17	-0.60 [-2.06, 0.86]
5.4.4 Delayed recall							
Lamargue 2020	14.4	2	18	14.4	1.8	17	0.00 [-1.26, 1.26]
5.4.5 Immediate cued recall							
Lamargue 2020	14.6	1.9	18	14.2	1.9	17	0.40 [-0.86, 1.66]
5.4.6 Delayed cued recall							
Lamargue 2020	14.8	1.6	18	14.6	1.5	17	0.20 [-0.83, 1.23]
5.4.7 Recognition							
Lamargue 2020	15.7	0.7	18	15.8	0.4	17	-0.10 [-0.48, 0.28]

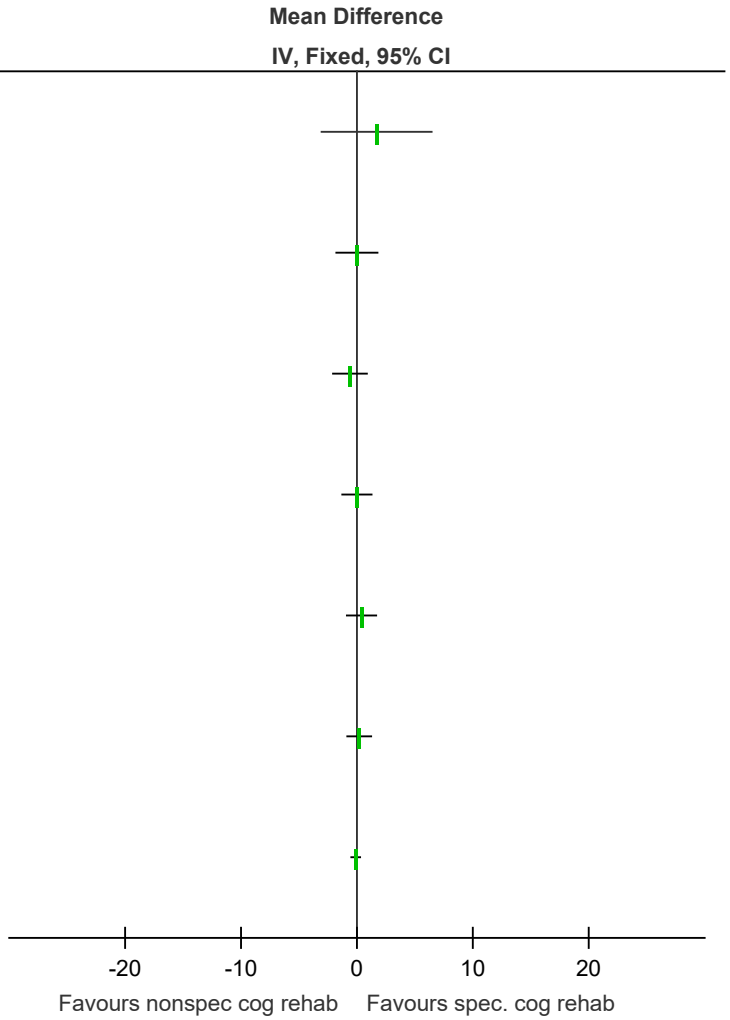


Figure 115: Test of Attentional Performances (TAP) – Alertness reaction time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
5.6.1 Without warning							
Lamargue 2020	251.1	38.9	18	267.2	38.4	17	-16.10 [-41.72, 9.52]
5.6.2 With warning							
Lamargue 2020	262.5	75.1	18	250	31	17	12.50 [-25.19, 50.19]

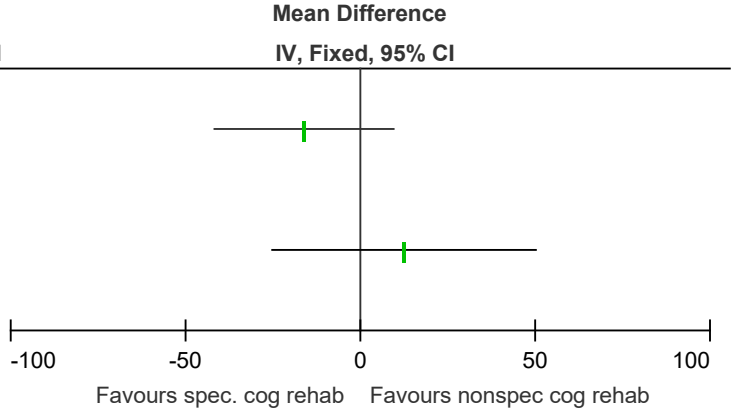


Figure 116: TAP – Visual Scanning correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
5.7.1 Without target							
Lamargue 2020	49.8	0.5	18	49.8	0.4	17	0.00 [-0.30, 0.30]
5.7.2 With target							
Lamargue 2020	40.8	6	18	43.1	4.4	17	-2.30 [-5.77, 1.17]

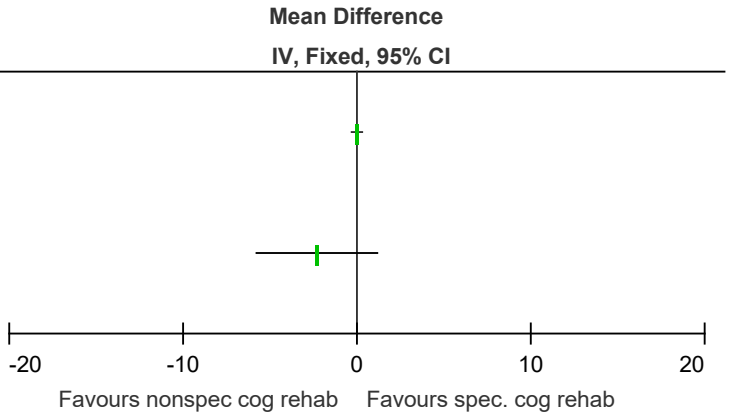


Figure 117: TAP – Visual Scanning reaction time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
5.8.1 Without target								
Lamargue 2020	5,596.6	1,995.7	18	5,456.7	1,467.1	17	139.90 [-1016.11, 1295.91]	
5.8.2 With target								
Lamargue 2020	2,860.2	906.8	18	2,789.2	628.7	17	71.00 [-443.59, 585.59]	

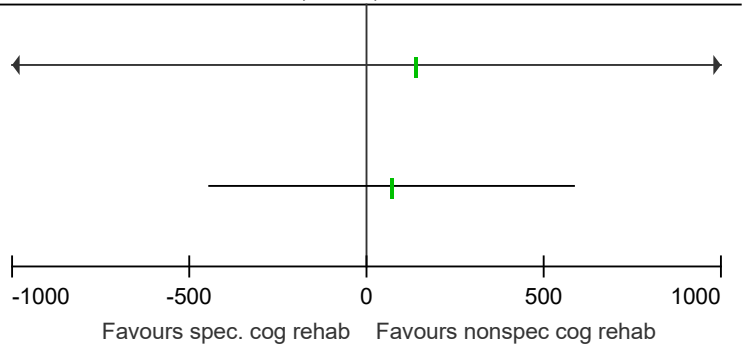


Figure 118: TAP – Divided Attention (visual attention) correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
5.9.1 Simple task							
Lamargue 2020	15.7	2.2	18	15.8	1.4	17	-0.10 [-1.31, 1.11]
5.9.2 Dual task							
Lamargue 2020	16	1	18	15.8	1.1	17	0.20 [-0.50, 0.90]

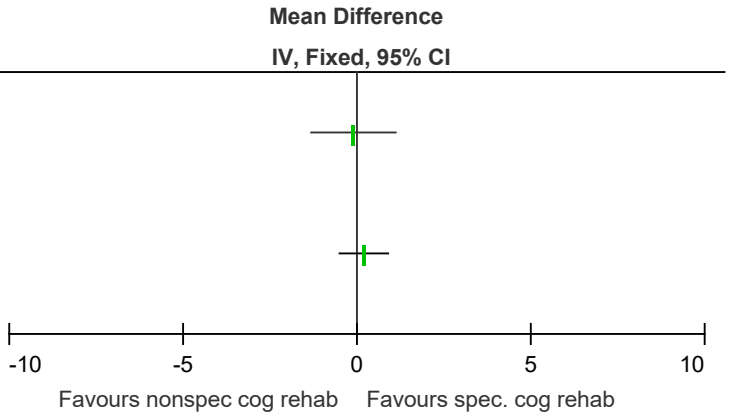


Figure 119: TAP – Divided Attention (visual attention) reaction time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
5.10.1 Simple task							
Lamargue 2020	809.3	145.2	18	829.2	91.8	17	-19.90 [-99.92, 60.12]
5.10.2 Dual task							
Lamargue 2020	782.9	116.7	18	811.2	79.7	17	-28.30 [-94.19, 37.59]

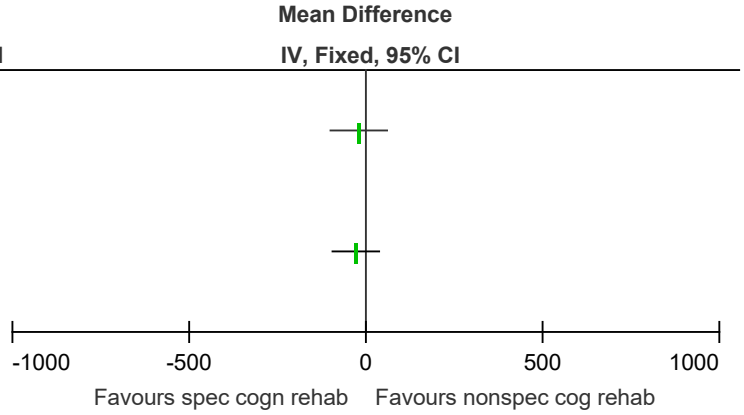


Figure 120: TAP – Divided Attention (auditory attention) correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
5.11.1 Simple task							
Lamargue 2020	15.8	0.4	18	15.8	0.4	17	0.00 [-0.27, 0.27]
5.11.2 Dual task							
Lamargue 2020	15.7	0.8	18	15.3	1.7	17	0.40 [-0.49, 1.29]

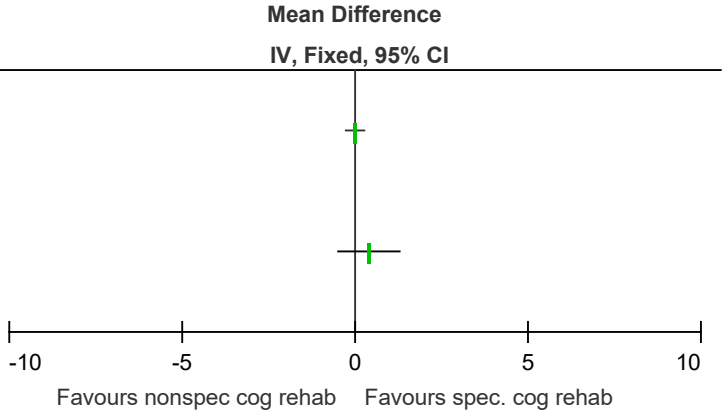


Figure 121: TAP – Divided Attention (auditory attention) reaction time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
5.12.1 Simple task							
Lamargue 2020	558.4	64.2	18	561.5	124.4	17	-3.10 [-69.26, 63.06]
5.12.2 Dual task							
Lamargue 2020	596.9	106.5	18	588.4	101.4	17	8.50 [-60.38, 77.38]

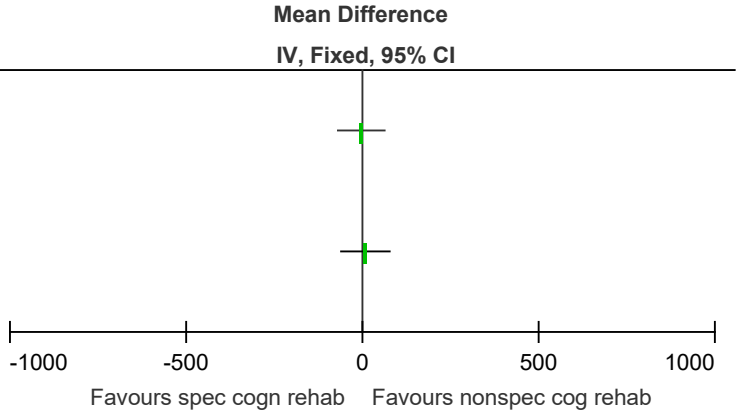


Figure 122: TAP – N-back reaction time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
Lamargue 2020	648.3	103.5	18	698.5	214.7	17	-50.20 [-162.90, 62.50]

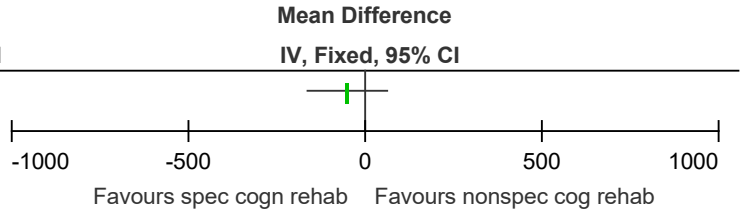
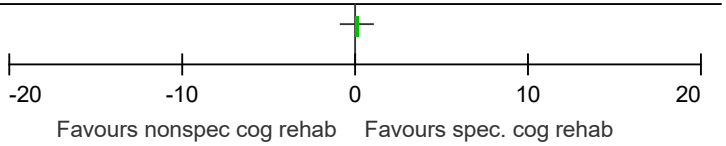


Figure 123: TAP – N-back correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lamargue 2020	13.7	1.4	18	13.6	1.4	17	0.10 [-0.83, 1.03]	



1

Figure 124: Baddeley's Dual Task forward span correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lamargue 2020	5.7	1	18	5.4	1.1	17	0.30 [-0.40, 1.00]	

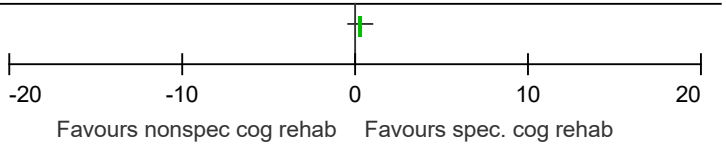


Figure 125: Backward Span correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lamargue 2020	4.7	1	18	4.2	1	17	0.50 [-0.16, 1.16]	

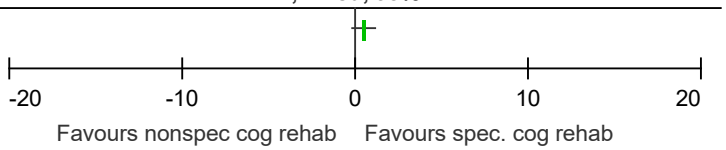


Figure 126: Fluency correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.17.1 Semantic								
Lamargue 2020	5.8	0.9	18	5.5	1.1	17	0.30 [-0.37, 0.97]	
5.17.2 Phonemic								
Lamargue 2020	5.8	0.9	18	5.5	1.1	17	0.30 [-0.37, 0.97]	

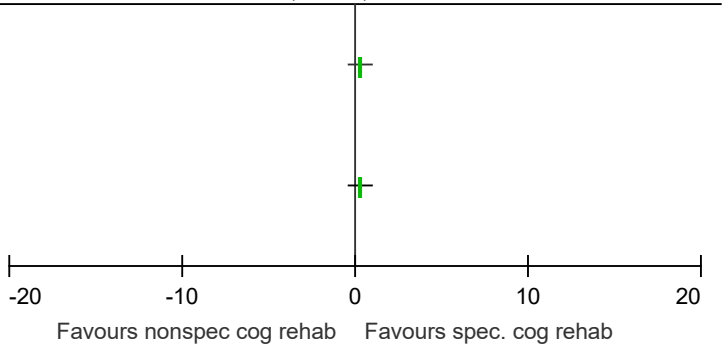


Figure 127: Rey Complex Figure (visuo-construction and episodic memory) correct answers (higher better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lamargue 2020	34.7	1.1	18	33.7	1.4	17	1.00 [0.16, 1.84]	

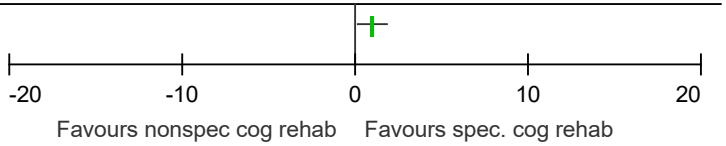


Figure 128: Rey Complex Figure (visuo-construction and episodic memory) reaction time (lower better)

	Specific cogn. rehab			Non-specific cogn. rehab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lamargue 2020	173	55.2	18	158.9	69.5	17	14.10 [-27.63, 55.83]	

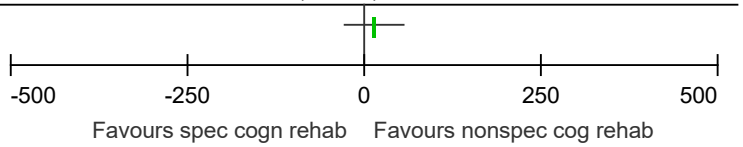
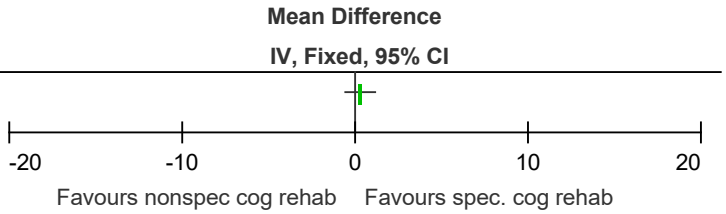


Figure 129: DO80 naming task correct answers (higher better)

Study or Subgroup	Specific cogn. rehab Mean	SD	Total	Non-specific cogn. rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Lamargue 2020	79	1.3	18	78.7	1.3	17	0.30 [-0.56, 1.16]



E.6 General cognitive rehabilitation (multi-component and multi-domain) tailored to individual + outpatient rehabilitation vs. outpatient rehabilitation only, 3 months

Figure 130: Computer-aided card sorting – correct (higher better)

Study or Subgroup	Cogn. + outpatient rehab Mean	SD	Total	Outpatient rehab only Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Tesar 2005	42.1	12.6	10	53.9	21.5	9	-11.80 [-27.87, 4.27]

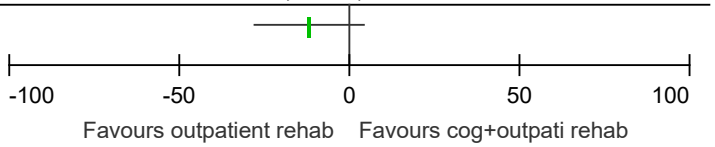


Figure 131: Computer-aided card sorting – incorrect (lower better)

	Cogn. + outpatient rehab			Outpatient rehab only			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Tesar 2005	14.1	4.1	10	16.8	2.2	9	-2.70 [-5.62, 0.22]

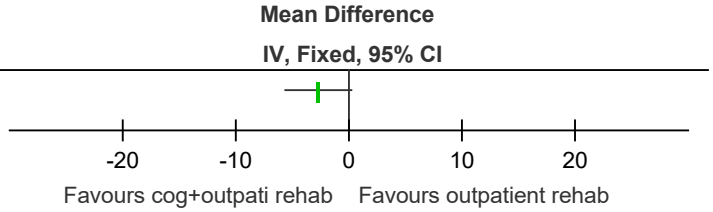


Figure 132: Sustained Attention – correct (higher better)

	Cogn. + outpatient rehab			Outpatient rehab only			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Tesar 2005	42.1	12.6	10	53.9	21.5	9	-11.80 [-27.87, 4.27]

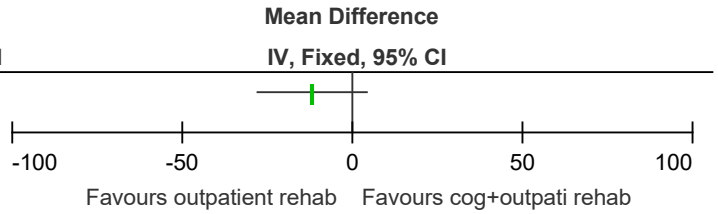
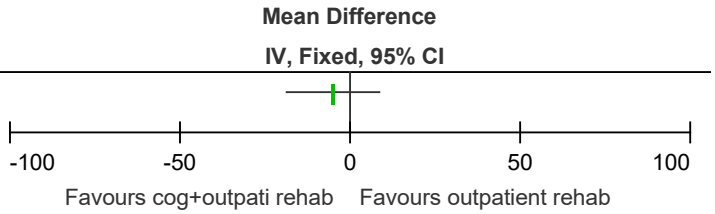


Figure 133: Sustained Attention – incorrect (lower better)

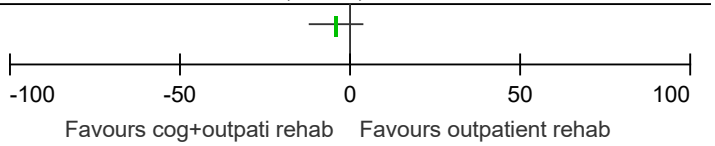
Study or Subgroup	Cogn. + outpatient rehab Mean	SD	Total	Outpatient rehab only Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Tesar 2005	46.2	16.1	10	51.2	14.2	9	-5.00 [-18.62, 8.62]



1

Figure 134: Sustained Attention – reaction time (lower better)

Study or Subgroup	Cogn. + outpatient rehab Mean	SD	Total	Outpatient rehab only Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Tesar 2005	42.7	9.7	10	46.8	7.5	9	-4.10 [-11.86, 3.66]



2

Figure 135: Sustained Attention – variation reaction time (lower better)

	Cogn. + outpatient rehab			Outpatient rehab only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tesar 2005	44.8	11.7	10	50.7	7.7	9	-5.90 [-14.73, 2.93]	

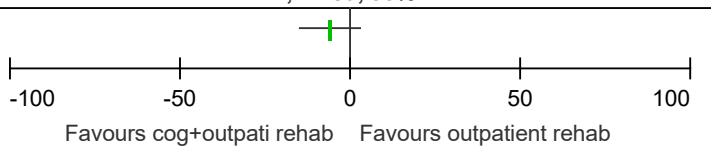


Figure 136: Verbal Learning Test (higher better)

	Cogn. + outpatient rehab			Outpatient rehab only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tesar 2005	56.9	13.1	10	50.4	13.6	9	6.50 [-5.54, 18.54]	

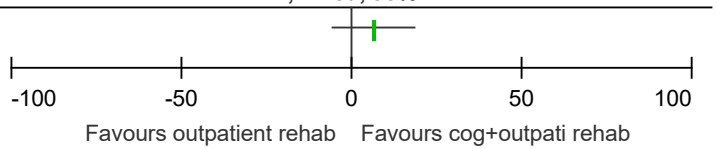
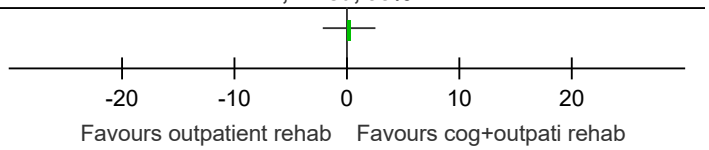


Figure 137: Spatial Construction (higher better)

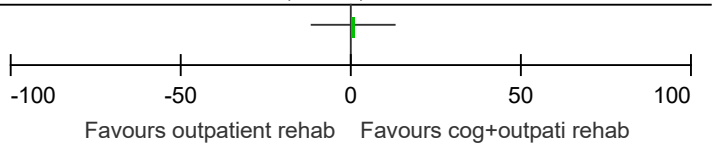
	Cogn. + outpatient rehab			Outpatient rehab only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tesar 2005	10.6	2.9	10	10.4	2.1	9	0.20 [-2.06, 2.46]	



1

Figure 138: Non-verbal Learning Test

	Cogn. + outpatient rehab			Outpatient rehab only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tesar 2005	49	14.9	10	48.3	12.2	9	0.70 [-11.50, 12.90]	



2

Figure 139: Beck Depression Inventory (scale usually 0-63; lower better)

	Cogn. + outpatient rehab			Outpatient rehab only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tesar 2005	8.3	5.8	10	8.3	3.4	9	0.00 [-4.23, 4.23]	

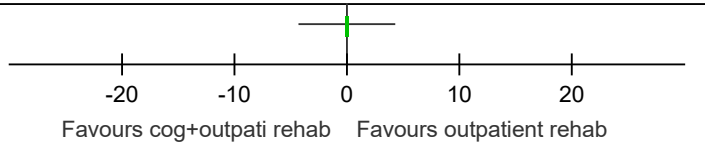
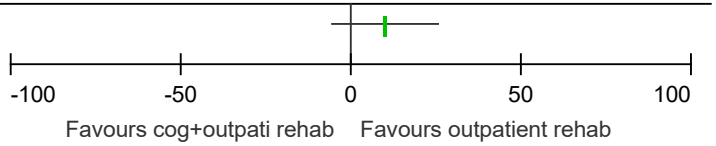


Figure 140: Modified Fatigue Impact Scale (scale usually 0-84; lower better)

	Cogn. + outpatient rehab			Outpatient rehab only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tesar 2005	41.8	15.5	10	31.7	18.8	9	10.10 [-5.49, 25.69]	



E.7 Goal Attainment Scaling (GAS) goals (multi-component cognitive rehabilitation tailored to individual) + usual rehabilitation vs. usual rehabilitation only, 4 months

Figure 141: BRIEF-A – General Executive composite (T-score; lower better)

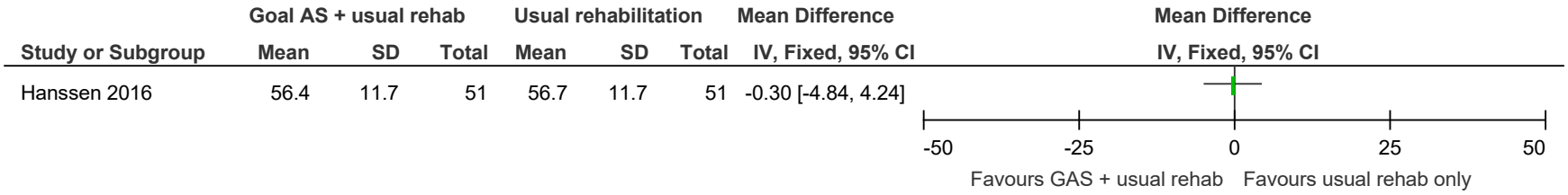


Figure 142: BRIEF-A – Meta-cognition Index (T-score; lower better)

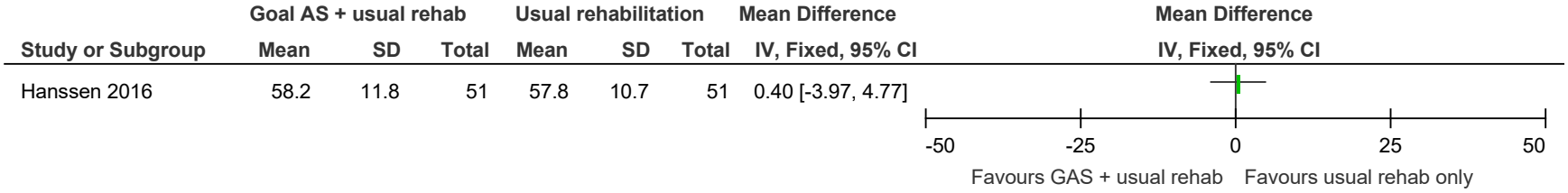


Figure 143: MSIS-29 psychological subscale (Norwegian version, scale 9-45; lower better)

	Goal AS + usual rehab			Usual rehabilitation			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Hanssen 2016	18.3	6.9	51	19.9	7.7	51	-1.60 [-4.44, 1.24]

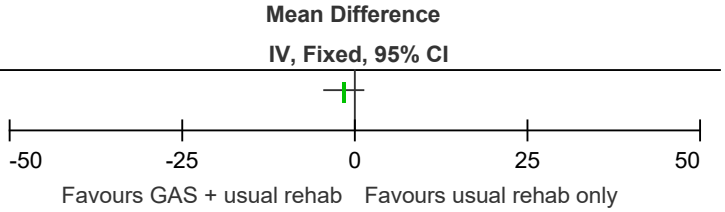
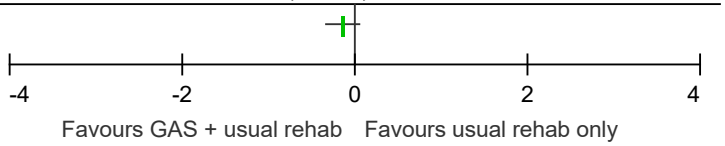


Figure 144: Hopkins Symptom Checklist-25 (measure of psychological health; scale 1-4; lower better)

	Goal AS + usual rehab			Usual rehabilitation			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Hanssen 2016	1.6	0.49	51	1.74	0.5	51	-0.14 [-0.33, 0.05]



E.8 Goal Attainment Scaling (GAS) goals (multi-component cognitive rehabilitation tailored to individual) + usual rehabilitation vs. usual rehabilitation only, 7 months

Figure 145: BRIEF-A – General Executive composite (T-score; lower better)

	Goal AS + usual rehab			Usual rehabilitation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hanssen 2016	56.3	11.8	54	55.2	11.5	48	1.10 [-3.43, 5.63]	

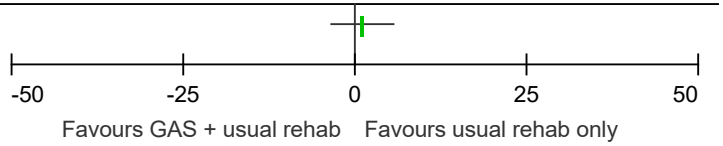


Figure 146: BRIEF-A – Meta-cognition Index (T-score; lower better)

	Goal AS + usual rehab			Usual rehabilitation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hanssen 2016	57.7	11.9	54	56.7	10.9	48	1.00 [-3.43, 5.43]	

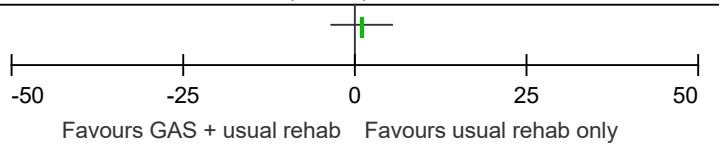
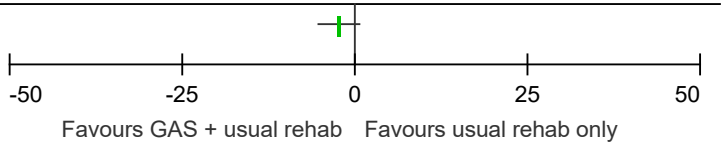


Figure 147: MSIS-29 psychological subscale (Norwegian version, scale 9-45; lower better)

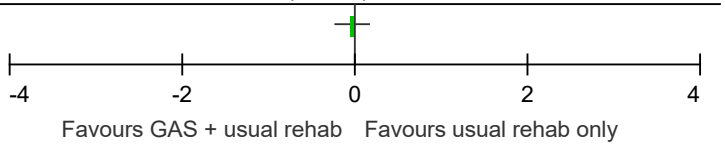
	Goal AS + usual rehab			Usual rehabilitation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hanssen 2016	18.3	7.2	54	20.6	8	48	-2.30 [-5.27, 0.67]	



1

Figure 148: Hopkins Symptom Checklist-25 (measure of psychological health; scale 1-4; lower better)

	Goal AS + usual rehab			Usual rehabilitation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hanssen 2016	1.62	0.47	54	1.65	0.53	48	-0.03 [-0.23, 0.17]	



E.9 Multi-domain cognitive rehabilitation (pen/paper or computer tasks with no additional teaching strategies) vs. control, 2-6 months

Figure 149: SDMT (higher better)

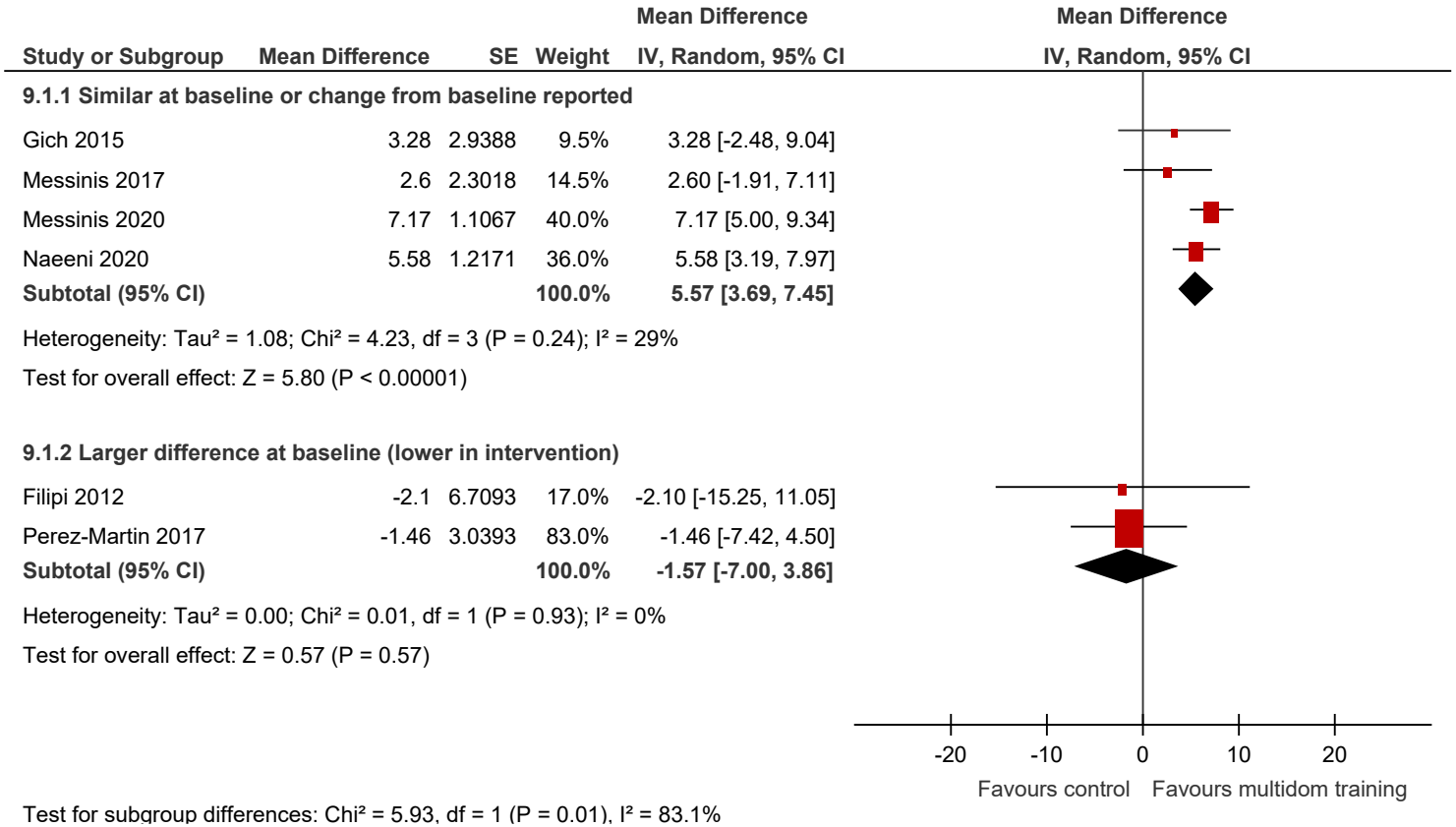
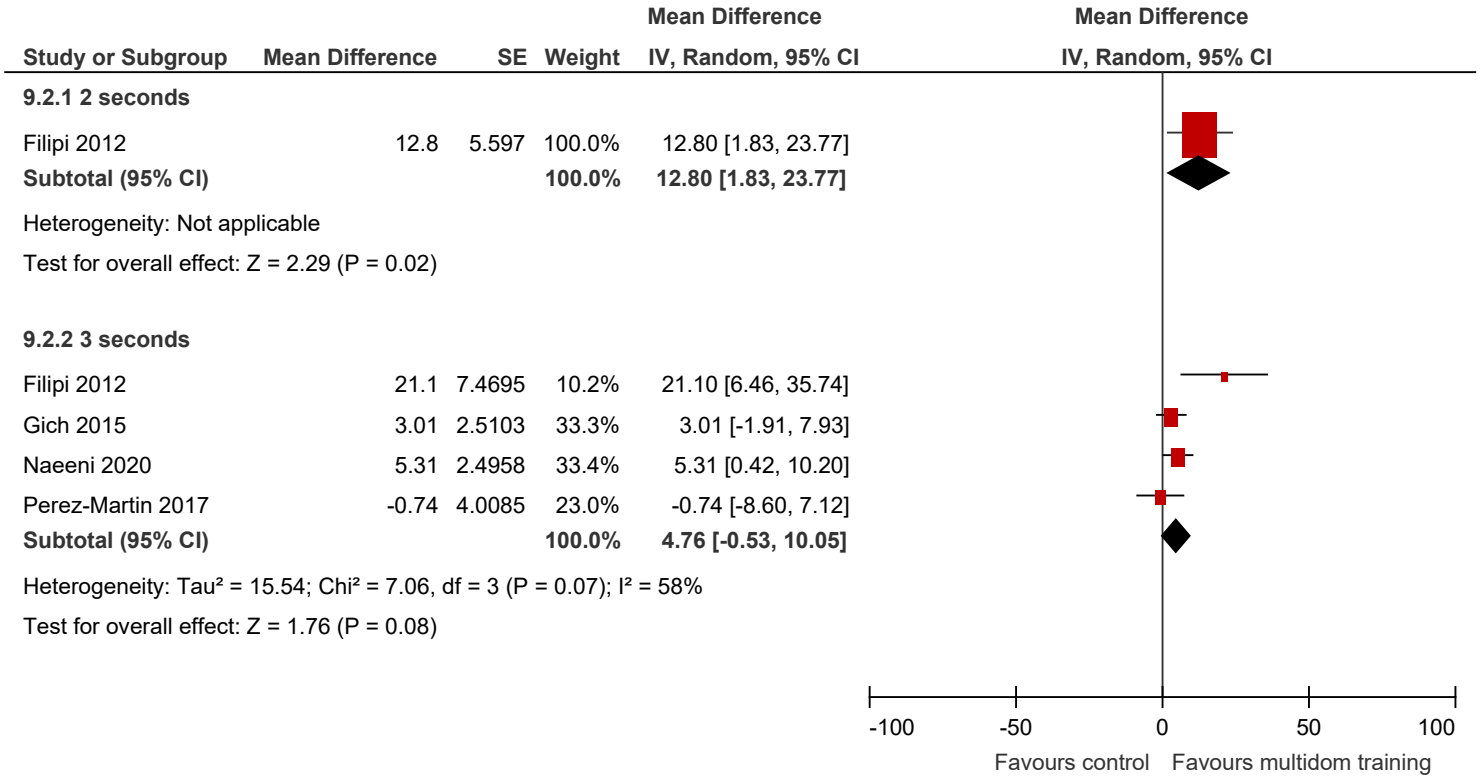


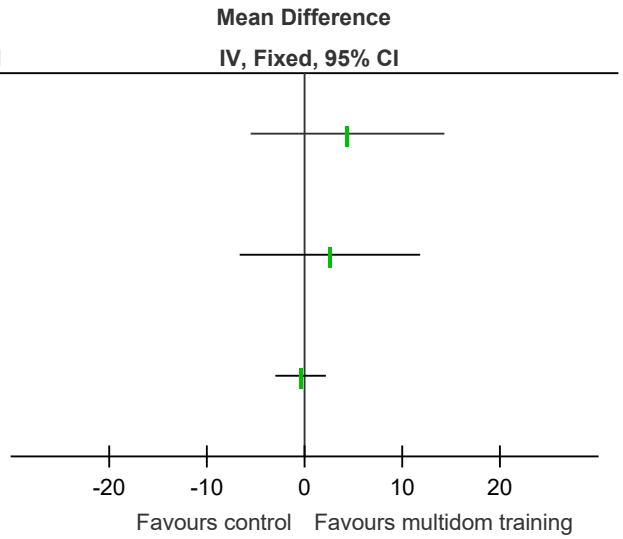
Figure 150: PASAT (higher better)



1

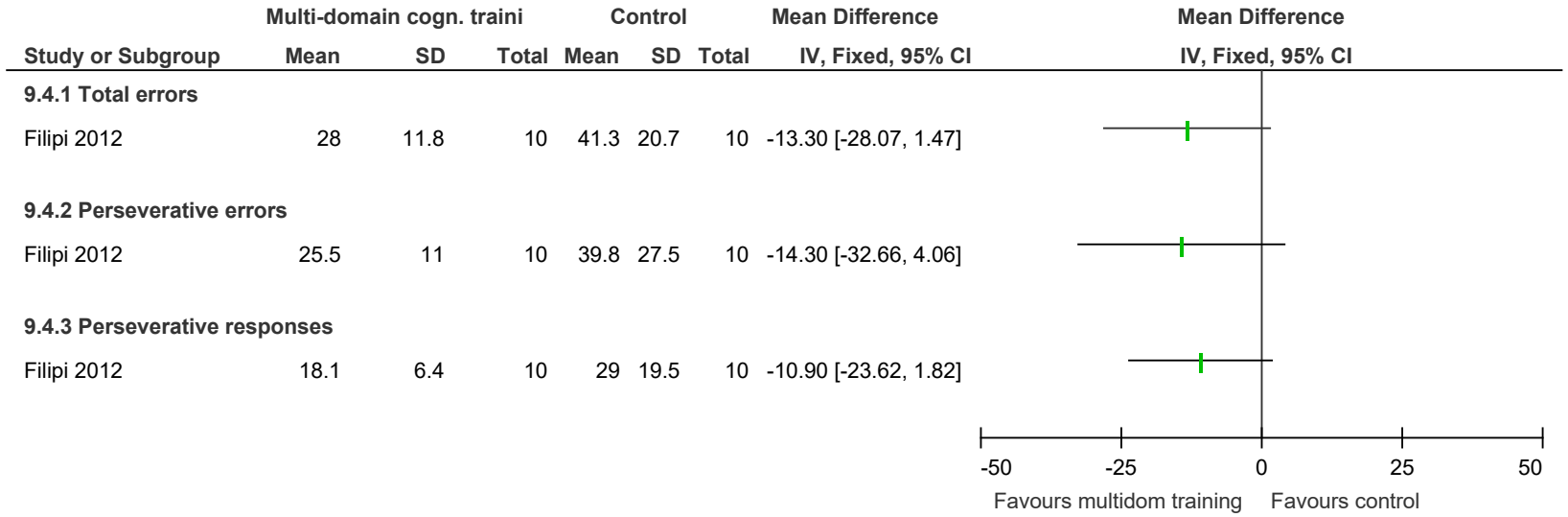
Figure 151: COWAT (higher better)

Study or Subgroup	Multi-domain cogn. traini Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
9.3.1 Phonemic cues							
Filipi 2012	34.4	11.2	10	30	11.2	10	4.40 [-5.42, 14.22]
9.3.2 Semantic cues							
Filipi 2012	37.6	12.4	10	35	8	10	2.60 [-6.55, 11.75]
9.3.3 Animals							
Perez-Martin 2017	19.23	4.45	30	19.63	5.51	32	-0.40 [-2.89, 2.09]



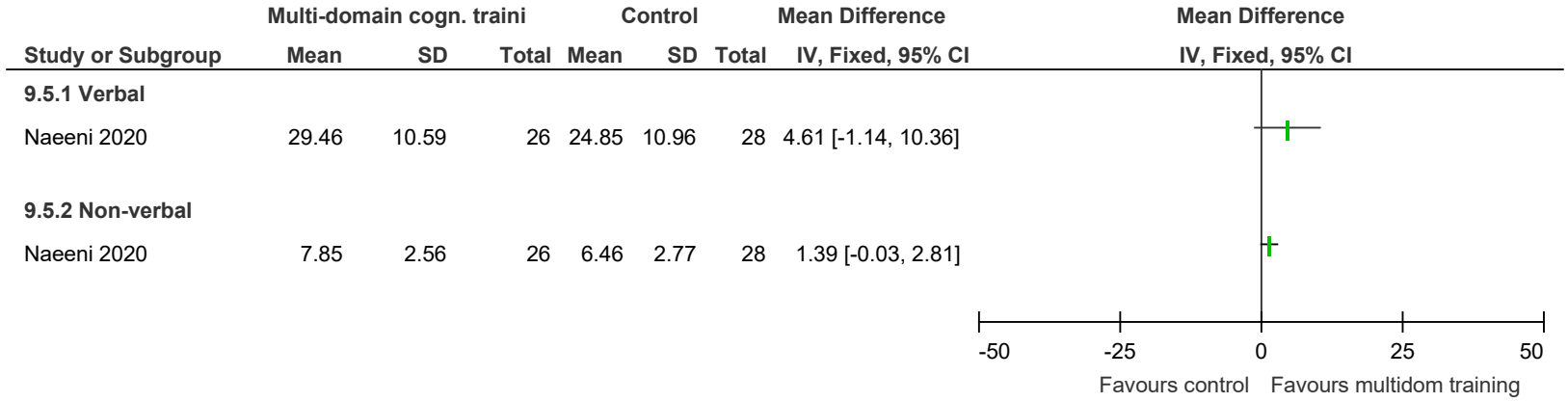
1

Figure 152: Wisconsin Card Sorting Test – errors/perseverative responses (lower better)



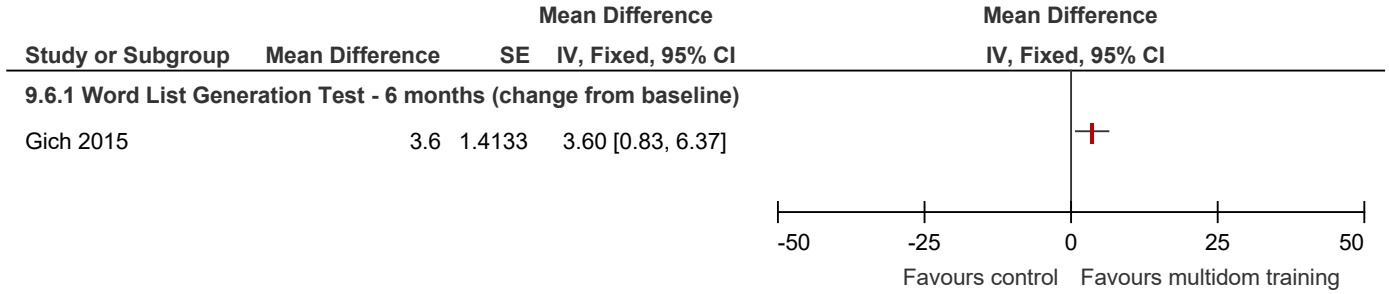
1

Figure 153: Card Sorting Test – Delis-Kaplan Executive Function System (D-KEFS) (higher better)



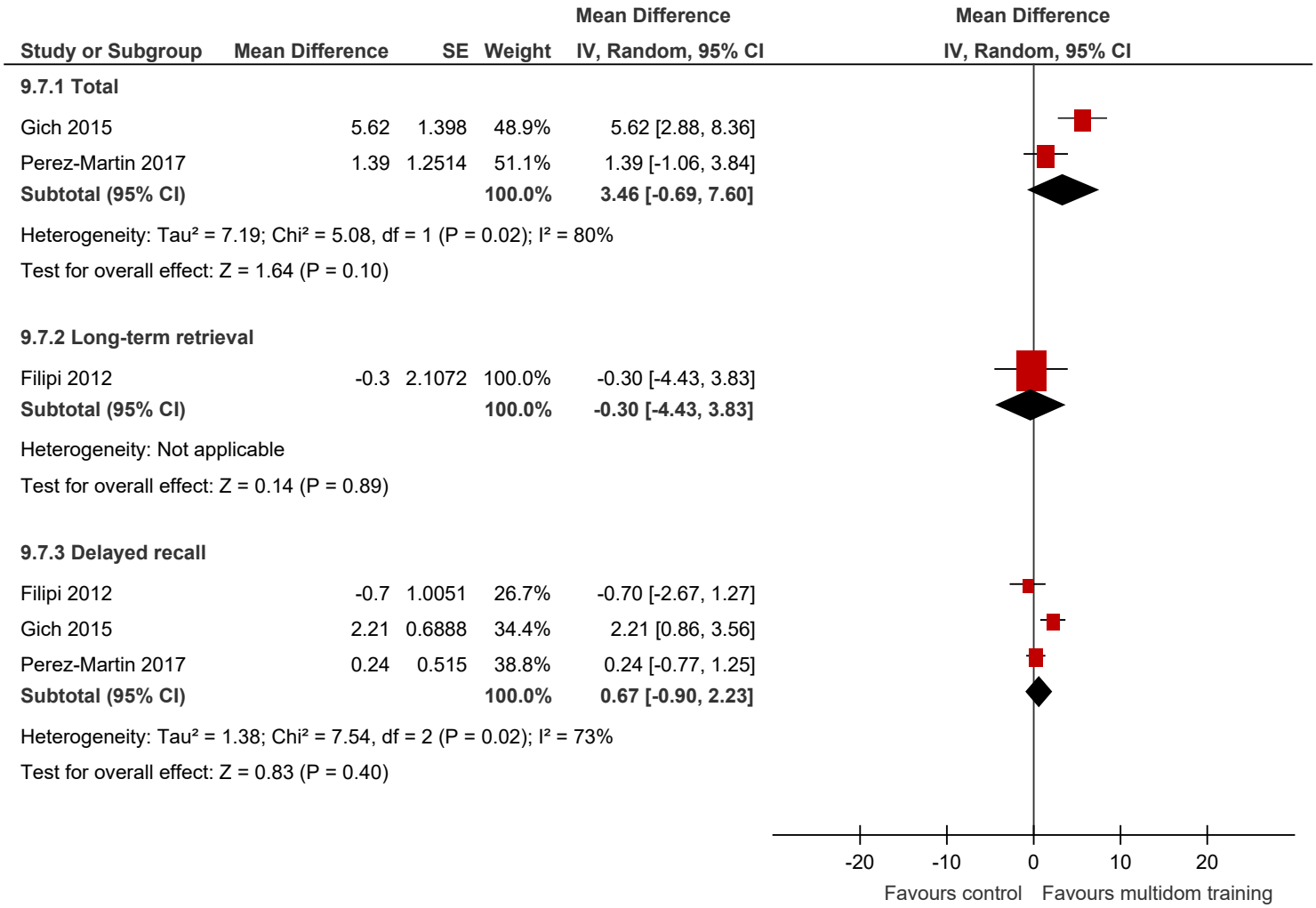
1

Figure 154: Word List Generation Test (higher better)



1

Figure 155: Spatial Recall Test (10/36 SPART; higher better)


Mean Difference
Mean Difference
Study or Subgroup
Mean Difference
SE
Weight
IV, Random, 95% CI
IV, Random, 95% CI
9.7.1 Total
Gich 2015 5.62 1.398 48.9% 5.62 [2.88, 8.36]
Perez-Martin 2017 1.39 1.2514 51.1% 1.39 [-1.06, 3.84]
Subtotal (95% CI) 100.0% 3.46 [-0.69, 7.60]
Heterogeneity: Tau² = 7.19; Chi² = 5.08, df = 1 (P = 0.02); I² = 80%
Test for overall effect: Z = 1.64 (P = 0.10)
9.7.2 Long-term retrieval
Filipi 2012 -0.3 2.1072 100.0% -0.30 [-4.43, 3.83]
Subtotal (95% CI) 100.0% -0.30 [-4.43, 3.83]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)
9.7.3 Delayed recall
Filipi 2012 -0.7 1.0051 26.7% -0.70 [-2.67, 1.27]
Gich 2015 2.21 0.6888 34.4% 2.21 [0.86, 3.56]
Perez-Martin 2017 0.24 0.515 38.8% 0.24 [-0.77, 1.25]
Subtotal (95% CI) 100.0% 0.67 [-0.90, 2.23]
Heterogeneity: Tau² = 1.38; Chi² = 7.54, df = 2 (P = 0.02); I² = 73%
Test for overall effect: Z = 0.83 (P = 0.40)
-20
-10
0
10
20
Favours control
Favours multidom training

1

Figure 156: Selective Reminding Test (higher better)

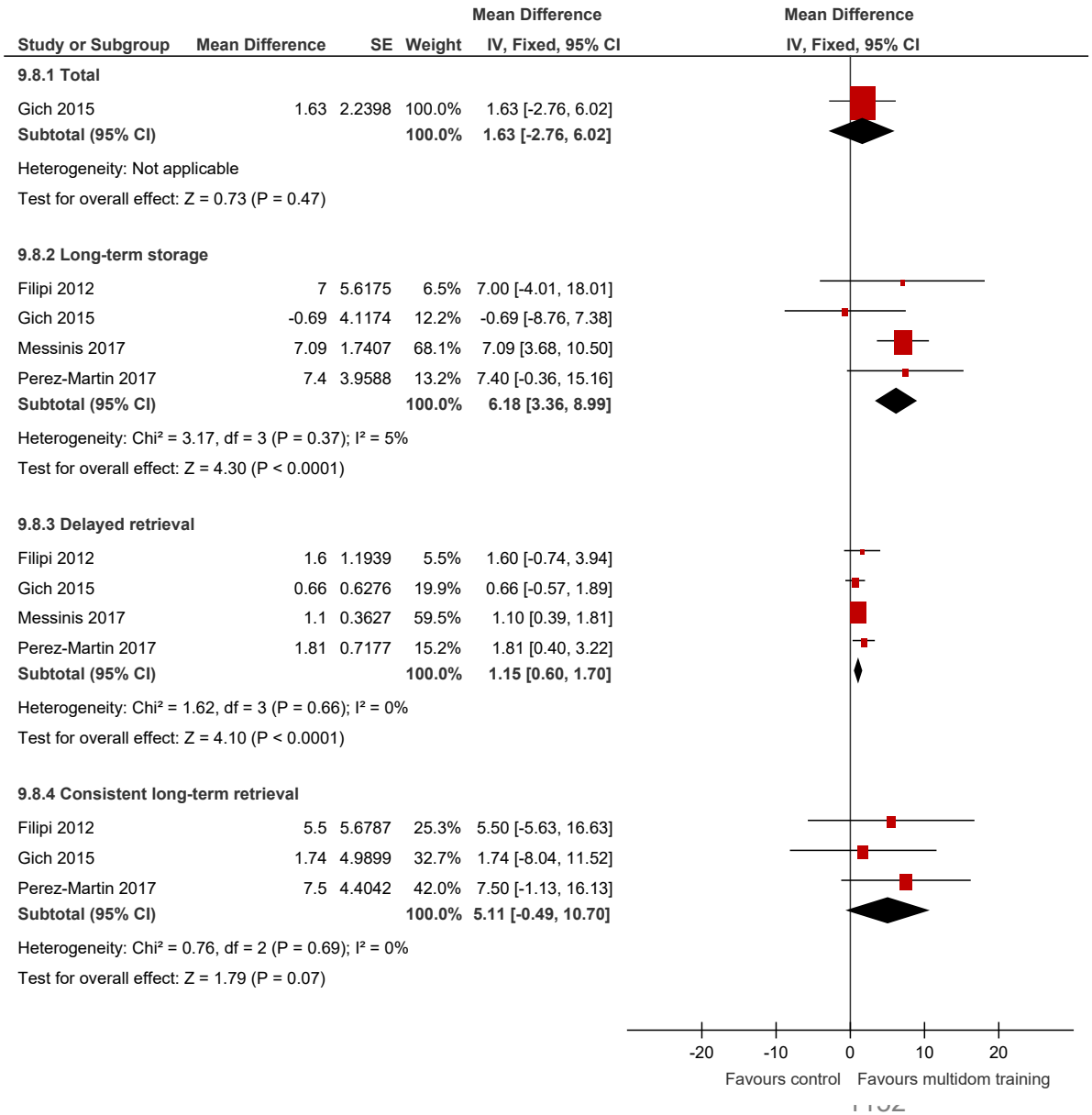

Mean Difference
Mean Difference
Study or Subgroup Mean Difference SE Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
9.8.1 Total
Gich 2015 1.63 2.2398 100.0% 1.63 [-2.76, 6.02]
Subtotal (95% CI) 100.0% 1.63 [-2.76, 6.02]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)
9.8.2 Long-term storage
Filipi 2012 7 5.6175 6.5% 7.00 [-4.01, 18.01]
Gich 2015 -0.69 4.1174 12.2% -0.69 [-8.76, 7.38]
Messinis 2017 7.09 1.7407 68.1% 7.09 [3.68, 10.50]
Perez-Martin 2017 7.4 3.9588 13.2% 7.40 [-0.36, 15.16]
Subtotal (95% CI) 100.0% 6.18 [3.36, 8.99]
Heterogeneity: Chi² = 3.17, df = 3 (P = 0.37); I² = 5%
Test for overall effect: Z = 4.30 (P < 0.0001)
9.8.3 Delayed retrieval
Filipi 2012 1.6 1.1939 5.5% 1.60 [-0.74, 3.94]
Gich 2015 0.66 0.6276 19.9% 0.66 [-0.57, 1.89]
Messinis 2017 1.1 0.3627 59.5% 1.10 [0.39, 1.81]
Perez-Martin 2017 1.81 0.7177 15.2% 1.81 [0.40, 3.22]
Subtotal (95% CI) 100.0% 1.15 [0.60, 1.70]
Heterogeneity: Chi² = 1.62, df = 3 (P = 0.66); I² = 0%
Test for overall effect: Z = 4.10 (P < 0.0001)
9.8.4 Consistent long-term retrieval
Filipi 2012 5.5 5.6787 25.3% 5.50 [-5.63, 16.63]
Gich 2015 1.74 4.9899 32.7% 1.74 [-8.04, 11.52]
Perez-Martin 2017 7.5 4.4042 42.0% 7.50 [-1.13, 16.13]
Subtotal (95% CI) 100.0% 5.11 [-0.49, 10.70]
Heterogeneity: Chi² = 0.76, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.79 (P = 0.07)
-20
-10
0
10
20
Favours control
Favours multidom training

Figure 157: Brief Visuospatial Memory Test-Revised (higher better)

Study or Subgroup	Multi-domain cogn. traini Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Messinis 2017	24.5	6.02	32	20.8	6.85	26	14.1%	3.70 [0.34, 7.06]
Messinis 2020	3.78	1.87	19	0.29	2.25	17	85.9%	3.49 [2.13, 4.85]
Total (95% CI)			**51**			**43**	**100.0%**	**3.52 [2.26, 4.78]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%

Test for overall effect: Z = 5.47 (P < 0.00001)

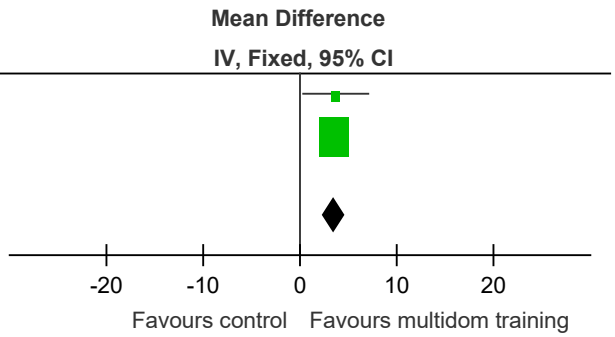
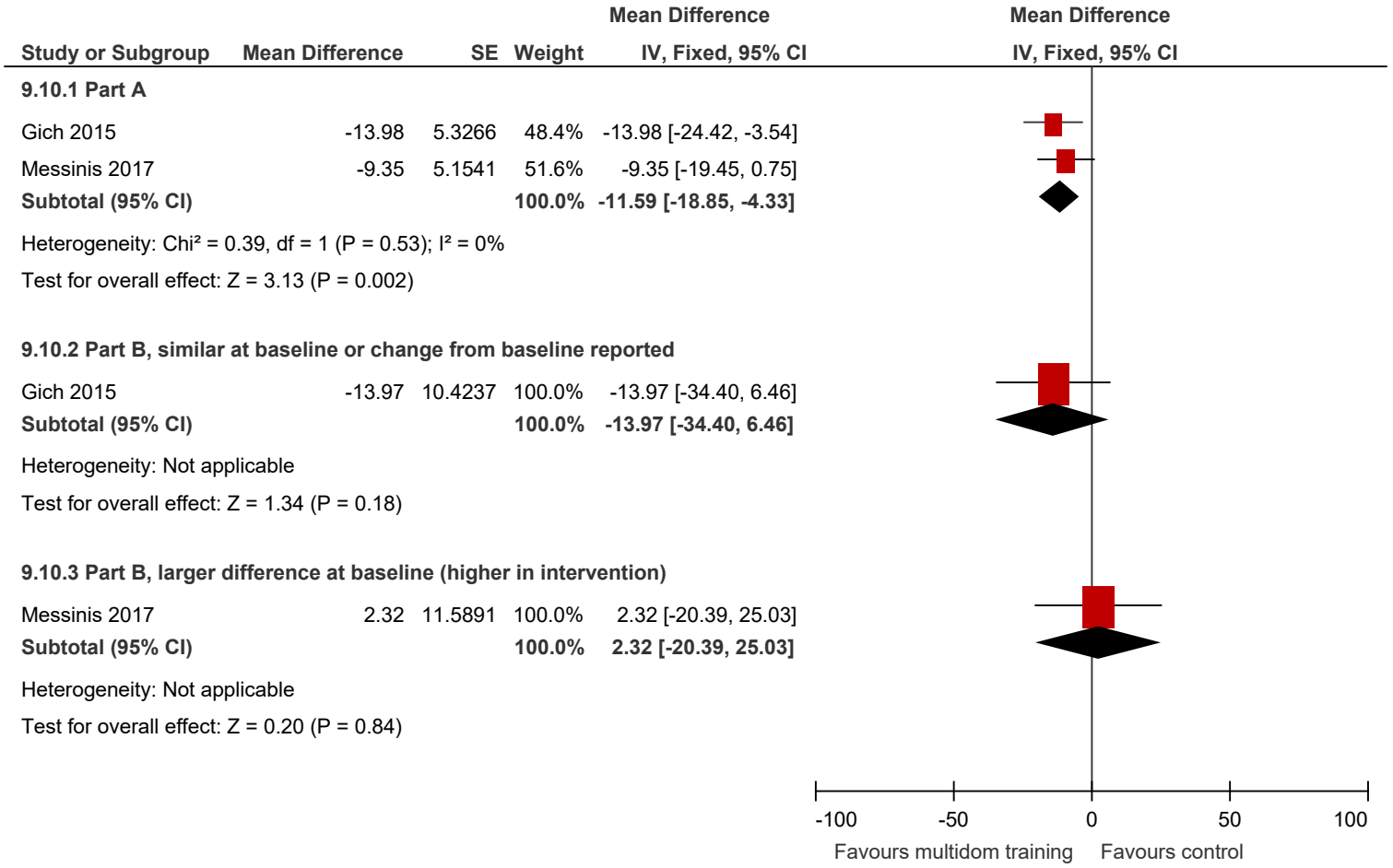


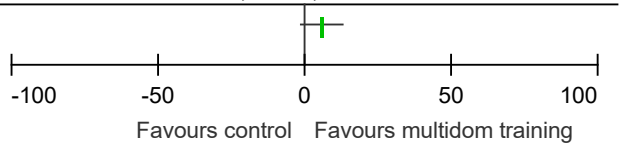
Figure 158: Trail Making Test (lower better)



1

Figure 159: Stroop Neuropsychological Screening Test (higher better)

	Multi-domain cogn. traini			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Messinis 2017	63.5	13.25	32	57.6	14.2	26	5.90 [-1.23, 13.03]	



2

Figure 160: Test of Everyday Attention median (higher better)

	Multi-domain cogn. traini			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
9.12.1 Auditory stimulus								
Filipi 2012	750.3	171.4	10	612.8	117.2	10	137.50 [8.81, 266.19]	
9.12.2 Visual stimulus								
Filipi 2012	959.1	132.4	10	1,048.7	193.4	10	-89.60 [-234.87, 55.67]	

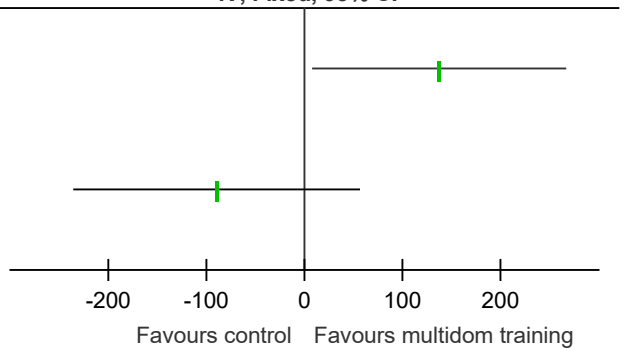


Figure 161: Test of Everyday Attention – errors/omissions (lower better)

Study or Subgroup	Multi-domain cogn. traini Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
9.13.1 Total omitted stimuli							
Filipi 2012	4.5	1.8	10	4.6	3	10	-0.10 [-2.27, 2.07]
9.13.2 Total errors							
Filipi 2012	4.8	4.3	10	6.1	6.1	10	-1.30 [-5.93, 3.33]

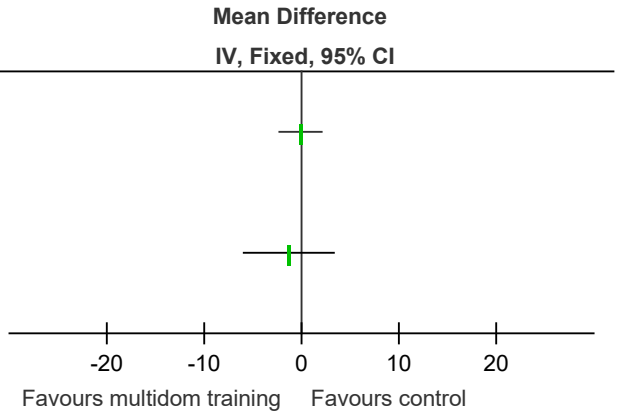


Figure 162: Integrated Auditory Visual-2 (IVA-2; higher better)

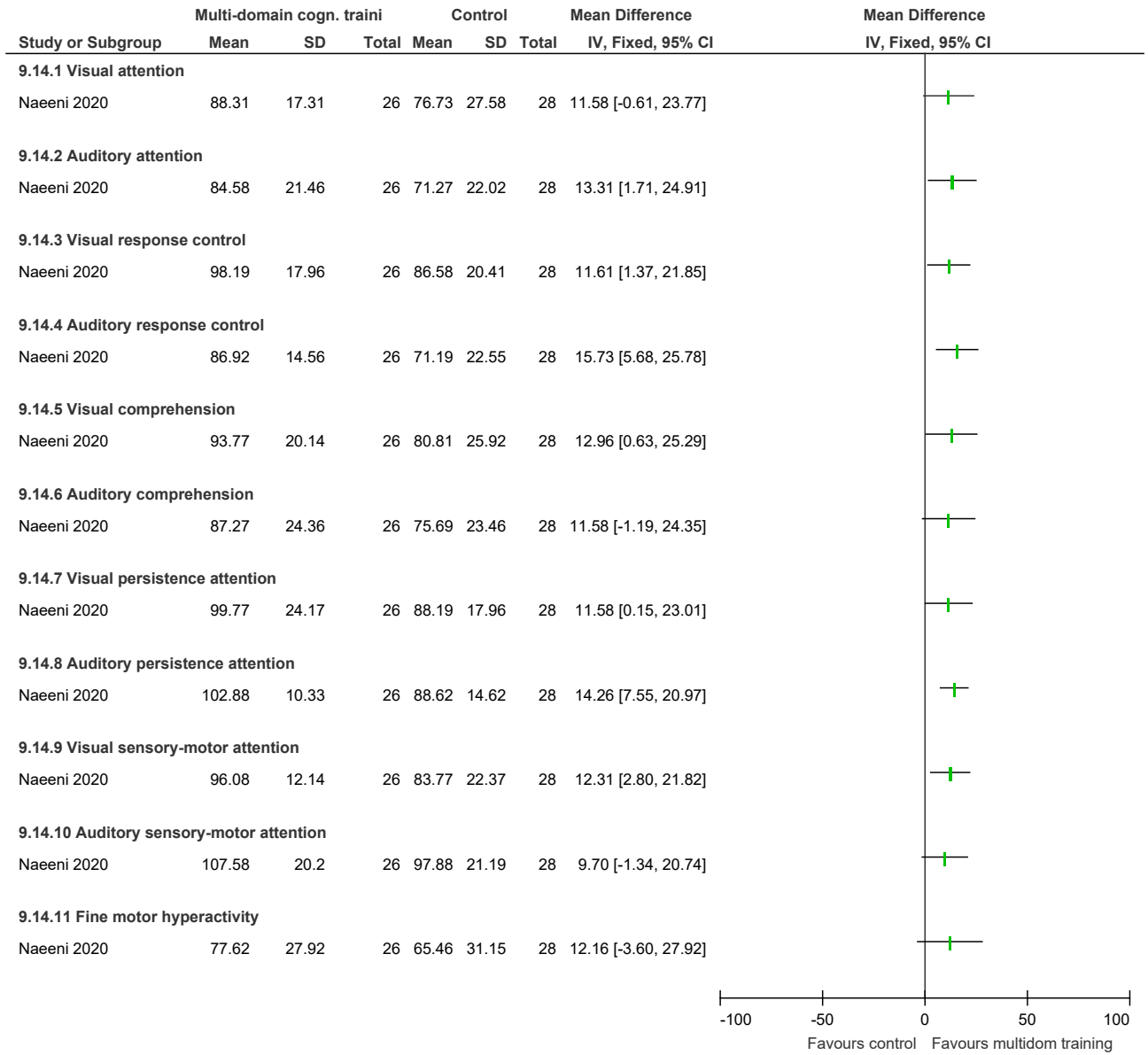

Multi-domain cogn. traini
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total IV, Fixed, 95% CI
IV, Fixed, 95% CI
9.14.1 Visual attention
Naeeni 2020 88.31 17.31 26 76.73 27.58 28 11.58 [-0.61, 23.77]
9.14.2 Auditory attention
Naeeni 2020 84.58 21.46 26 71.27 22.02 28 13.31 [1.71, 24.91]
9.14.3 Visual response control
Naeeni 2020 98.19 17.96 26 86.58 20.41 28 11.61 [1.37, 21.85]
9.14.4 Auditory response control
Naeeni 2020 86.92 14.56 26 71.19 22.55 28 15.73 [5.68, 25.78]
9.14.5 Visual comprehension
Naeeni 2020 93.77 20.14 26 80.81 25.92 28 12.96 [0.63, 25.29]
9.14.6 Auditory comprehension
Naeeni 2020 87.27 24.36 26 75.69 23.46 28 11.58 [-1.19, 24.35]
9.14.7 Visual persistence attention
Naeeni 2020 99.77 24.17 26 88.19 17.96 28 11.58 [0.15, 23.01]
9.14.8 Auditory persistence attention
Naeeni 2020 102.88 10.33 26 88.62 14.62 28 14.26 [7.55, 20.97]
9.14.9 Visual sensory-motor attention
Naeeni 2020 96.08 12.14 26 83.77 22.37 28 12.31 [2.80, 21.82]
9.14.10 Auditory sensory-motor attention
Naeeni 2020 107.58 20.2 26 97.88 21.19 28 9.70 [-1.34, 20.74]
9.14.11 Fine motor hyperactivity
Naeeni 2020 77.62 27.92 26 65.46 31.15 28 12.16 [-3.60, 27.92]
-100
-50
0
50
100
Favours control
Favours multidom training

Figure 163: Digit Span (Weschler Adult Intelligence Scale III; higher better)

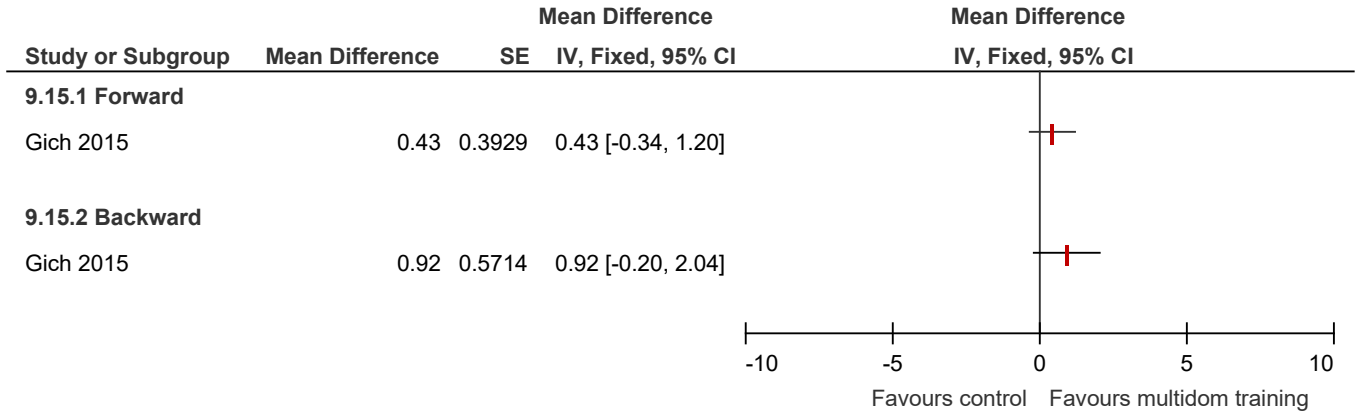
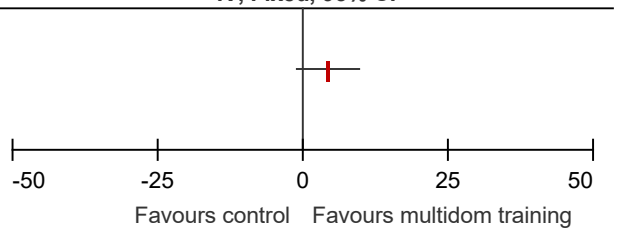


Figure 164: Block Design (Weschler Adult Intelligence Scale III; higher better)

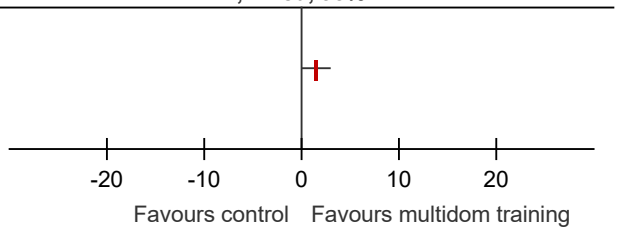
Study or Subgroup	Mean Difference	SE	IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
9.16.1 Block design (Weschler Adult Intelligence Scale III) - 6 months (change from baseline)				
Gich 2015	4.35	2.7347	4.35 [-1.01, 9.71]	



1

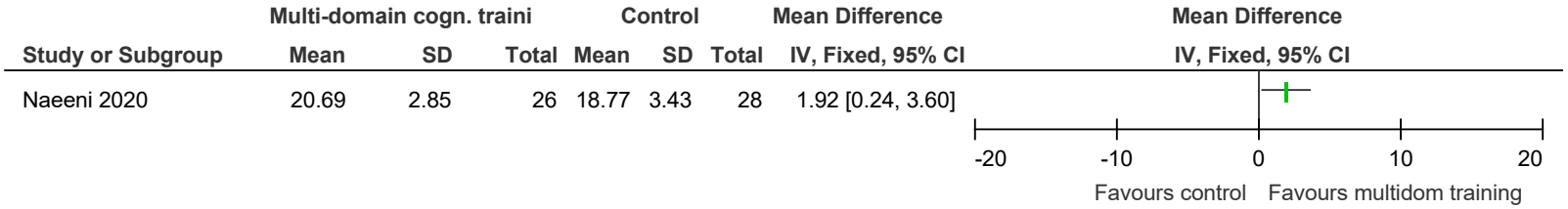
Figure 165: Letter-Number Sequencing (Weschler Adult Intelligence Scale III; higher better)

Study or Subgroup	Mean Difference	SE	IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
9.17.1 Letter-number sequencing (Weschler Adult Intelligence Scale III) - 6 months (change from baseline)				
Gich 2015	1.48	0.7245	1.48 [0.06, 2.90]	



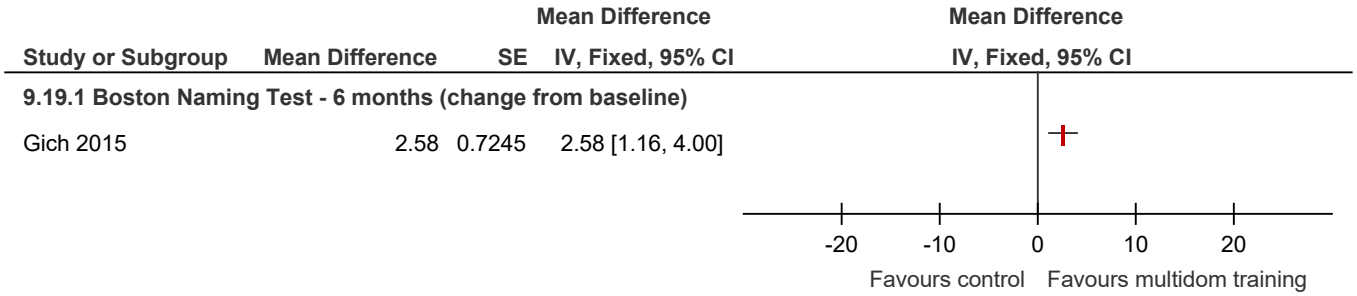
2

Figure 166: Judgement of Line Orientation (higher better)



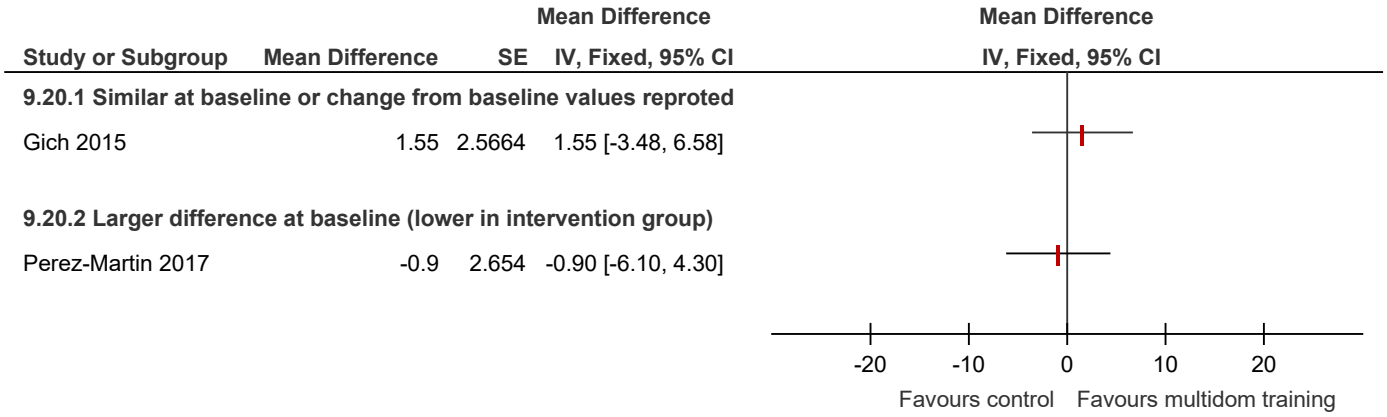
1

Figure 167: Boston Naming Test (higher better)



2

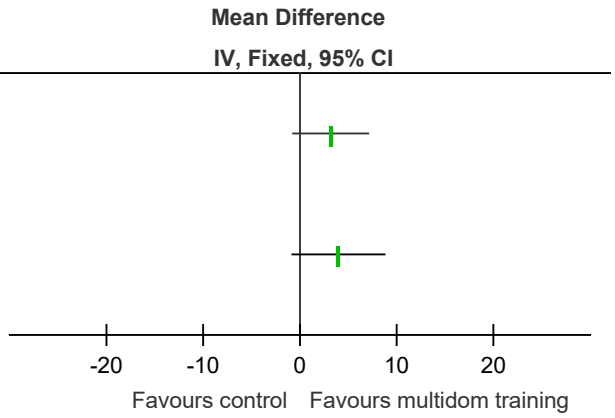
Figure 168: FAS test (verbal fluency; higher better)



1

Figure 169: Verbal Fluency Test (higher better)

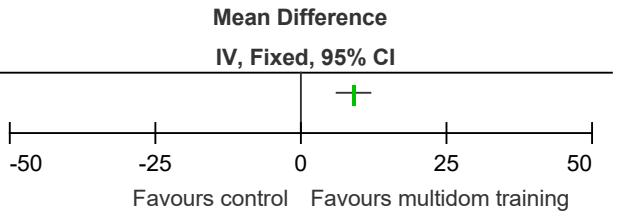
Study or Subgroup	Multi-domain cogn. traini Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
9.21.1 Phonemic							
Messinis 2017	33.13	7.01	32	29.95	7.88	26	3.18 [-0.70, 7.06]
9.21.2 Semantic							
Messinis 2017	43.56	8.34	32	39.58	9.83	26	3.98 [-0.78, 8.74]



1

Figure 170: Greek Verbal Learning Test (higher better)

Study or Subgroup	Multi-domain cogn. traini Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Messinis 2020	8.1	5.76	19	-0.94	2.72	17	9.04 [6.15, 11.93]



2

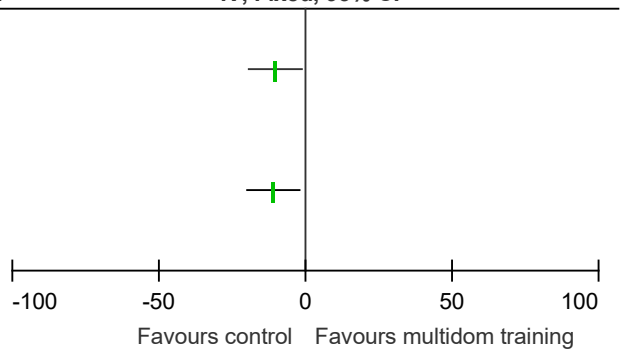
Figure 171: MS Neuropsychological Questionnaire (scale usually 0-60; lower better)

	Multi-domain cogn. traini			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Perez-Martin 2017	23.87	11.83	30	25.63	11.83	32	-1.76 [-7.65, 4.13]	

1

Figure 172: MS-QoL-54 (scale usually 0-100; higher better)

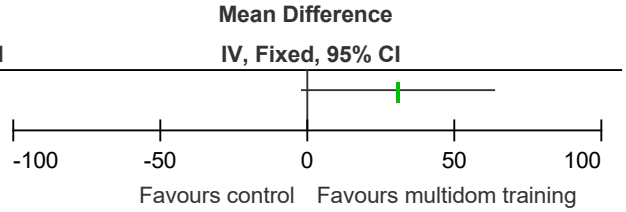
	Multi-domain cogn. traini			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
9.24.1 Physical composite								
Perez-Martin 2017	52.99	19.2	30	63.24	16.98	32	-10.25 [-19.30, -1.20]	
9.24.2 Mental composite								
Perez-Martin 2017	56.39	18.7	30	67.32	17.06	32	-10.93 [-19.86, -2.00]	



2

Figure 173: MS Quality of Life (scale unclear; higher better)

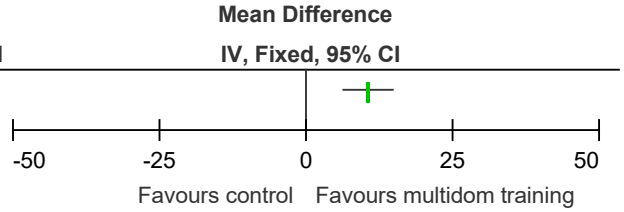
Study or Subgroup	Multi-domain cogn. traini Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Filipi 2012	188.44	47.92	10	157.56	22.1	10	30.88 [-1.83, 63.59]



1

Figure 174: EQ-5D visual analogue (scale 0-100; higher better)

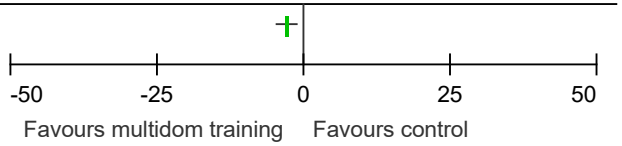
Study or Subgroup	Multi-domain cogn. traini Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Messinis 2020	9.42	4.79	19	-1.17	7.6	17	10.59 [6.38, 14.80]



2

Figure 175: Beck Depression Inventory-Fast Screen (scale usually 0-21; lower better)

	Multi-domain cogn. traini			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Messinis 2020	-2.57	2.36	19	0.29	2.82	17	-2.86 [-4.57, -1.15]	



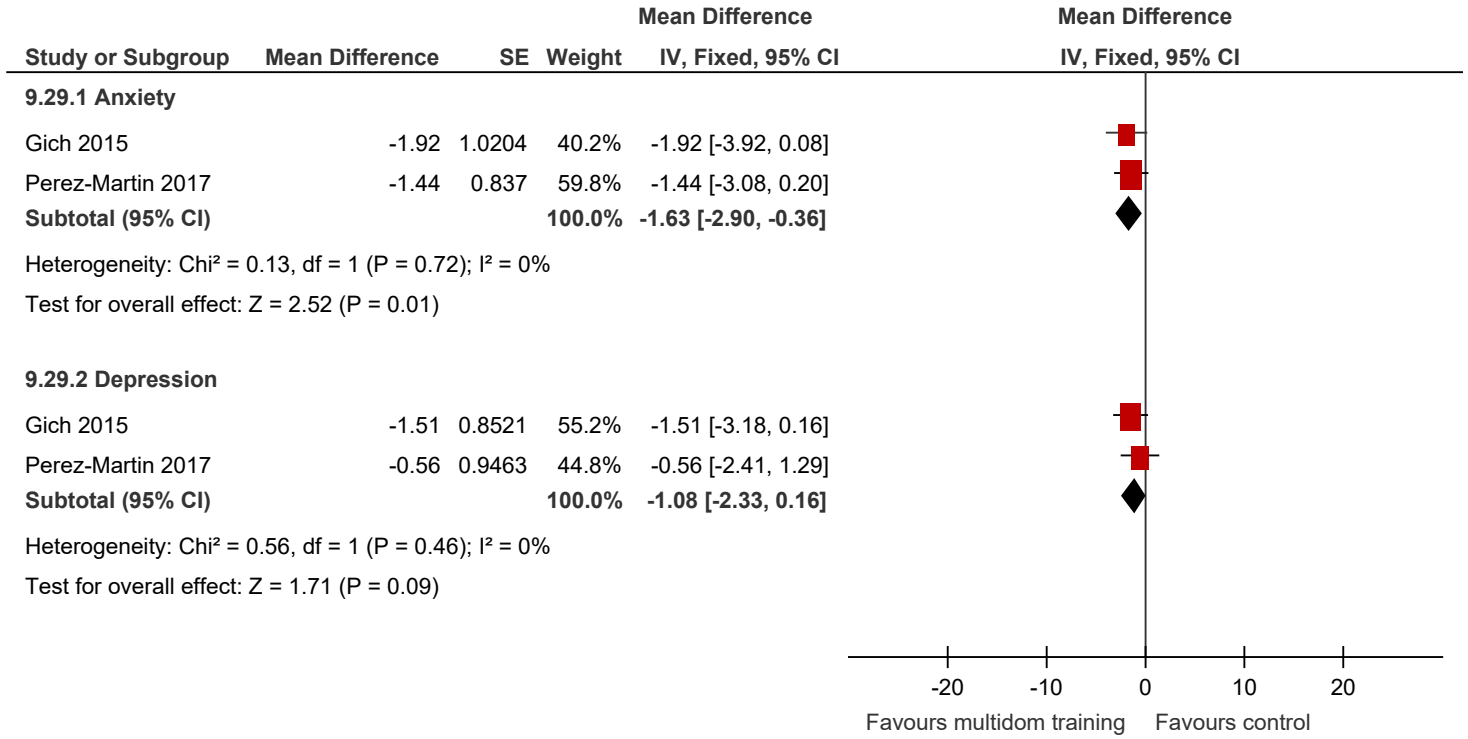
1

Figure 176: Montgomery-Asberg Depression Scale (scale usually 0-60; lower better)

	Multi-domain cogn. traini			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Filipi 2012	5.9	5.7	10	14.7	8.9	10	-8.80 [-15.35, -2.25]	

2

Figure 177: Hospital Anxiety and Depression Scale (HADS; scale usually 0-21; lower better)



1

Figure 178: Modified Fatigue Impact Scale – Cognitive subscale (scale usually 0-40; lower better)

	Multi-domain cogn. traini			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Messinis 2020	-5.68	3	19	-0.88	2.26	17	-4.80 [-6.52, -3.08]	

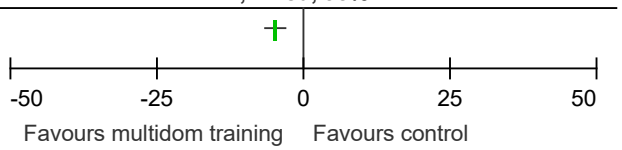
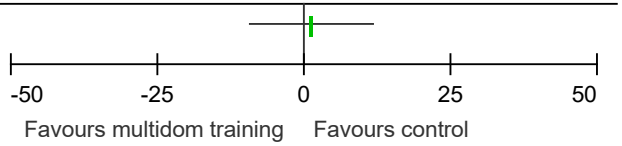


Figure 179: Fatigue Severity Scale (scale usually 9-63; lower better)

	Multi-domain cogn. traini			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Perez-Martin 2017	30.51	20.22	30	29.21	21.94	32	1.30 [-9.19, 11.79]	



E.10 Multi-domain cognitive rehabilitation (pen/paper or computer tasks with no additional teaching strategies) vs. control, 9 months

Figure 180: PASAT (higher better)

Study or Subgroup	Multi-domain cogn. traini Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
10.1.1 2 seconds							
Filipi 2012	18	13.5	9	6.8	10.6	9	11.20 [-0.01, 22.41]
10.1.2 3 seconds							
Filipi 2012	29.5	14.5	9	15.2	18.5	9	14.30 [-1.06, 29.66]

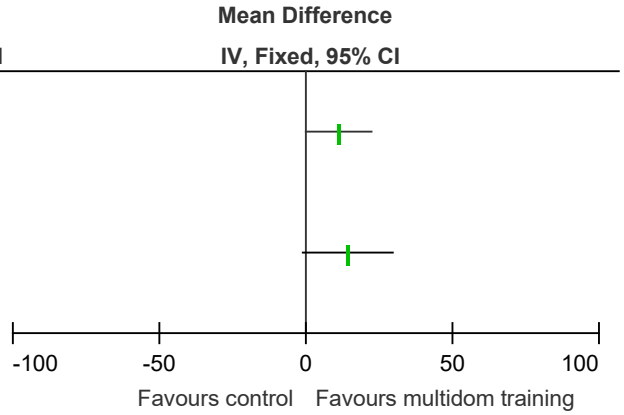


Figure 181: SDMT (higher better)

Study or Subgroup	Multi-domain cogn. traini Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Filipi 2012	35	12	9	34.7	16.3	9	0.30 [-12.92, 13.52]

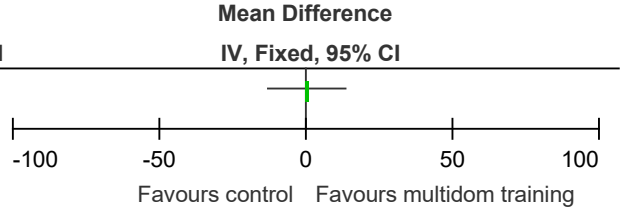


Figure 182: COWAT (higher better)

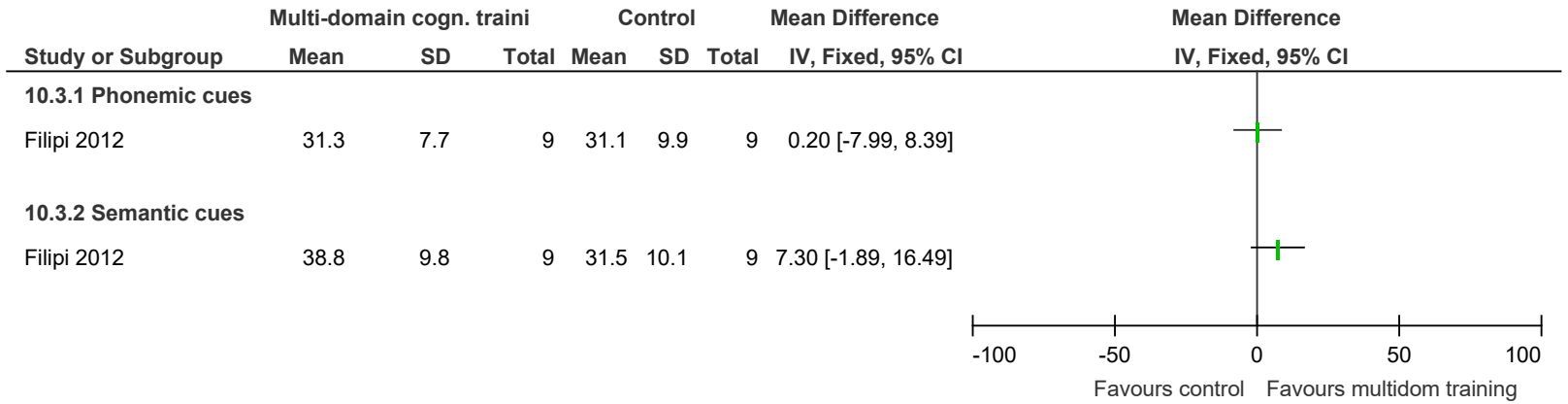
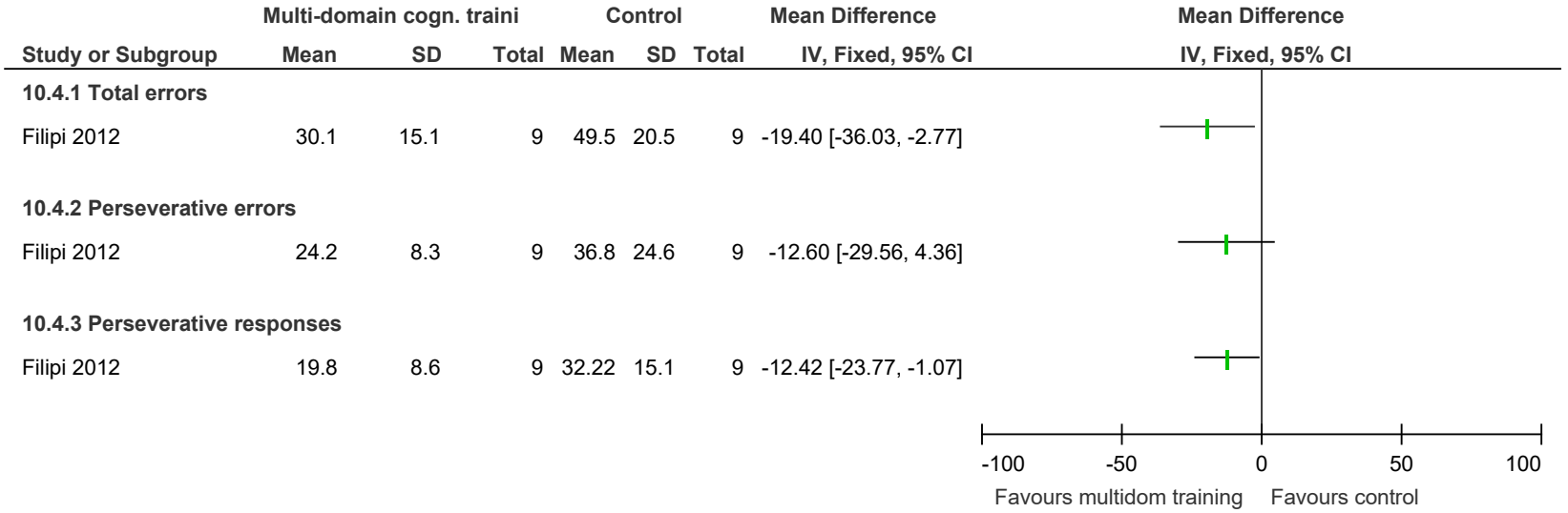
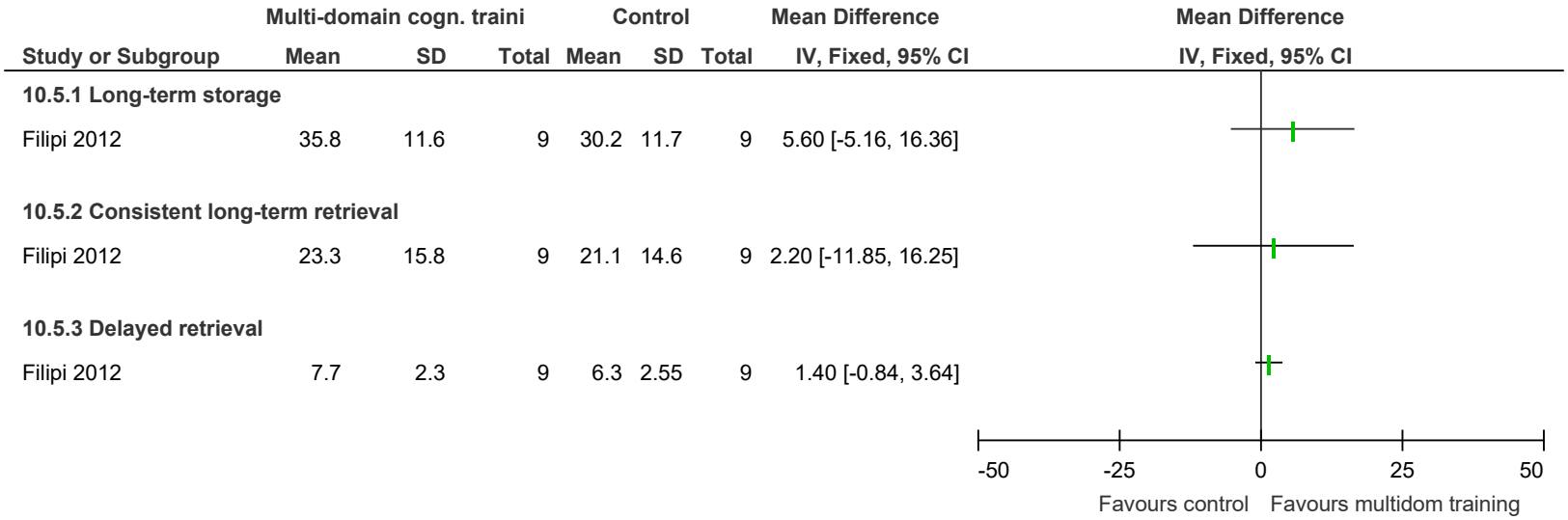


Figure 183: Wisconsin Card Sorting Test – errors/perseverative responses (lower better)



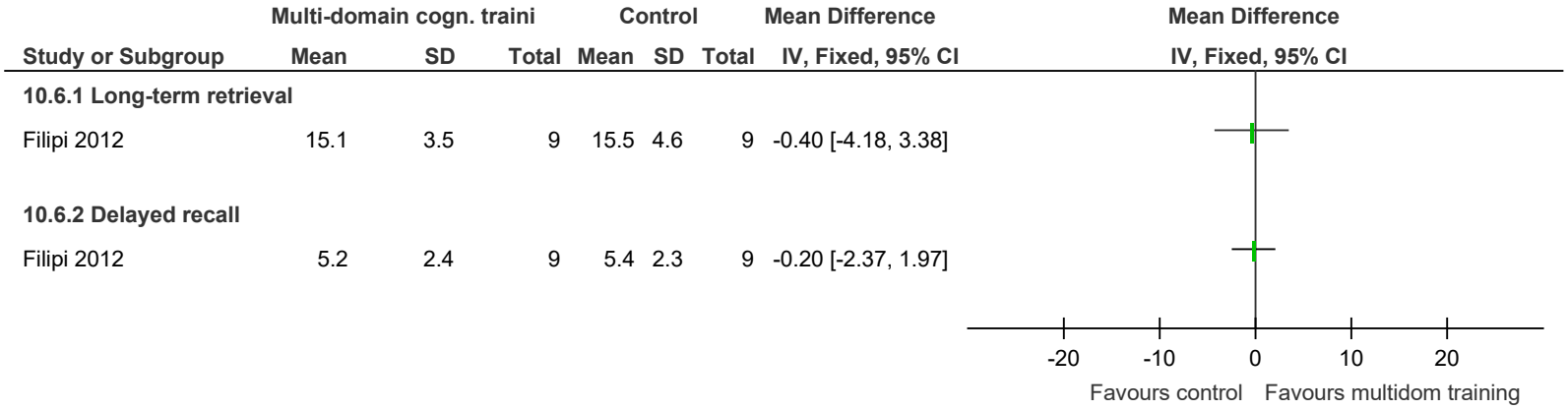
1

Figure 184: Selective Reminding Test (higher better)



1

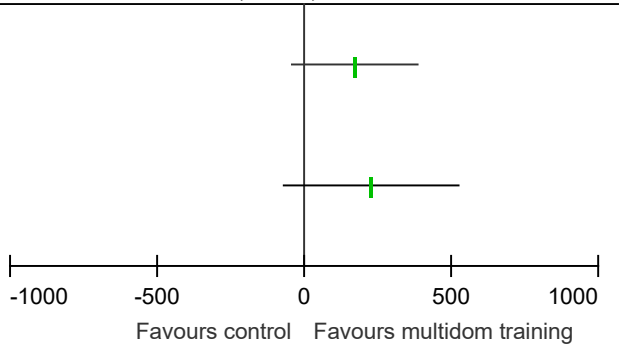
Figure 185: Spatial Recall Test (10/36 SPART; higher better)



1

Figure 186: Test of Everyday Attention – median (higher better)

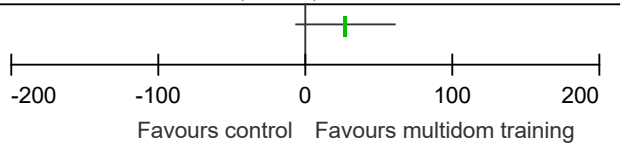
	Multi-domain cogn. traini			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
10.7.1 Auditory stimulus								
Filipi 2012	672.7	123.7	9	500.1	302.4	9	172.60 [-40.85, 386.05]	
10.7.2 Visual stimulus								
Filipi 2012	962.7	133.5	9	734.5	434.7	9	228.20 [-68.89, 525.29]	



1

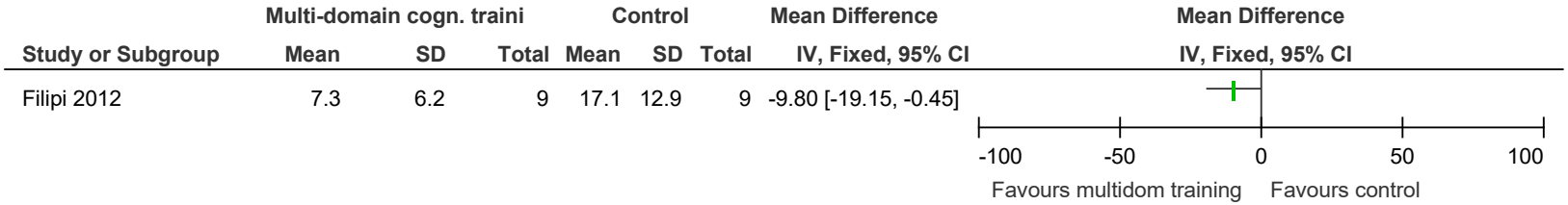
Figure 187: MS quality of life (scale unclear; higher better)

	Multi-domain cogn. traini			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Filipi 2012	198.5	40.36	9	171.13	33.4	10	27.37 [-6.15, 60.89]	



2

Figure 188: Montgomery-Asberg Depression Scale (scale usually 0-60; lower better)



E.11 Multi-domain cognitive rehabilitation tailored to individual (CogniFit – computer tasks, with no additional teaching strategies) vs. control, 3 months

Figure 189: Divided Attention (higher better)

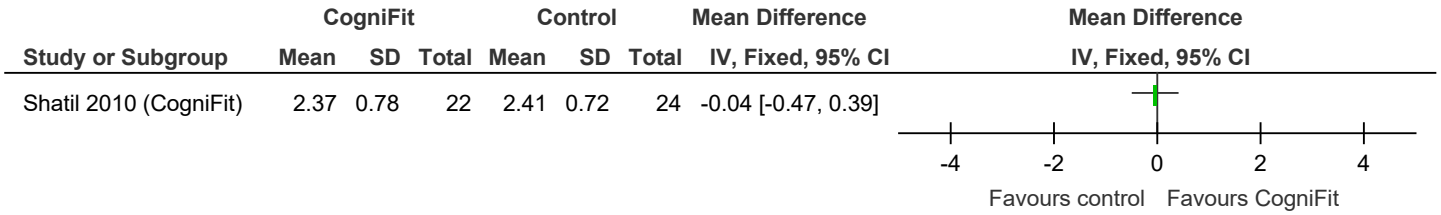
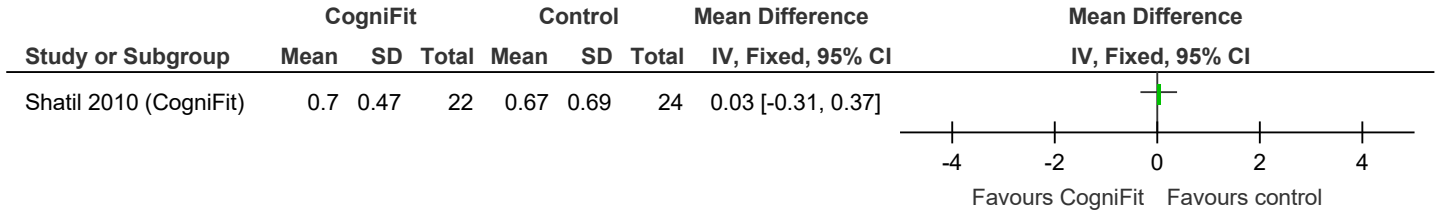
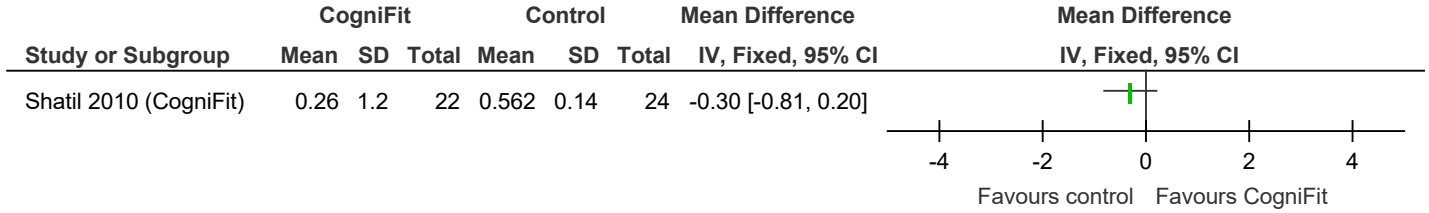


Figure 190: Avoiding Distractions (lower better)



1

Figure 191: Hand-eye Coordination (higher better)



2

Figure 192: General Memory (higher better)

Study or Subgroup	CogniFit Mean	CogniFit SD	CogniFit Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Shatil 2010 (CogniFit)	1.13	0.82	22	0.56	1.1	24	0.57 [0.01, 1.13]

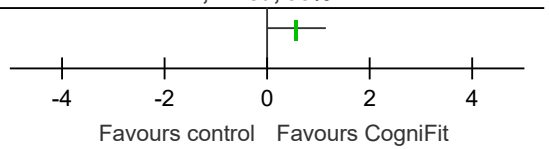


Figure 193: Naming (higher better)

Study or Subgroup	CogniFit Mean	CogniFit SD	CogniFit Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Shatil 2010 (CogniFit)	0.68	0.56	22	0.54	0.85	24	0.14 [-0.27, 0.55]

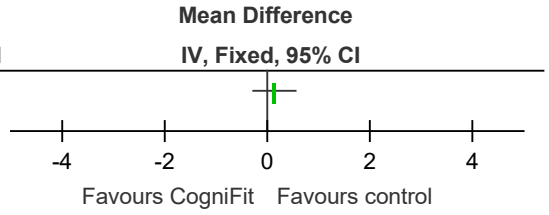
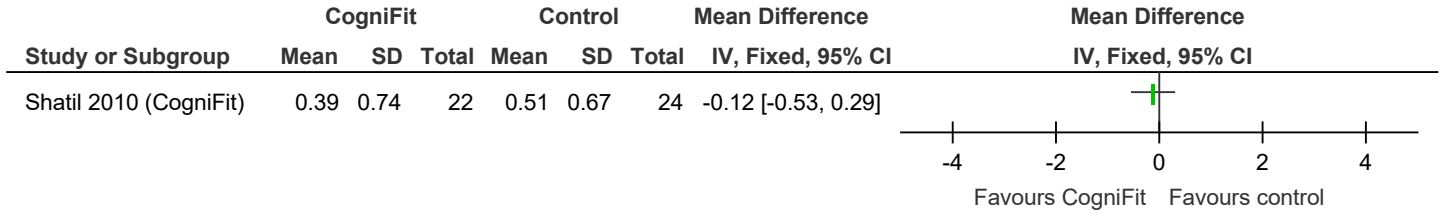
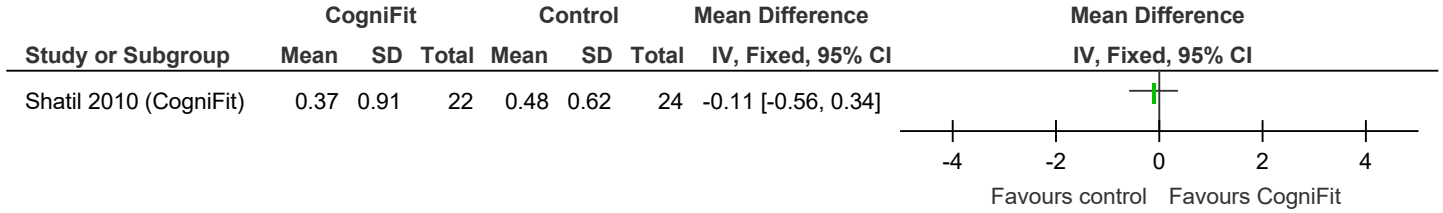


Figure 194: Response time (lower better)



1

Figure 195: Shifting Attention (higher better)



2

Figure 196: Spatial Perception (higher better)

	CogniFit			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shatil 2010 (CogniFit)	0.46	0.69	22	0.54	0.64	24	-0.08 [-0.47, 0.31]	

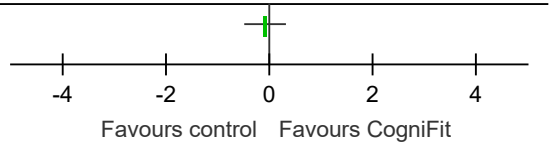


Figure 197: Time Estimation (lower better)

	CogniFit			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shatil 2010 (CogniFit)	0.62	0.61	22	0.34	1	24	0.28 [-0.19, 0.75]	

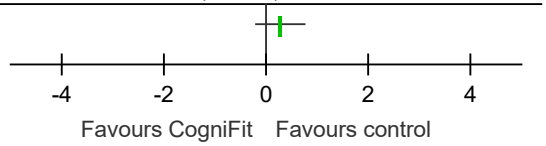
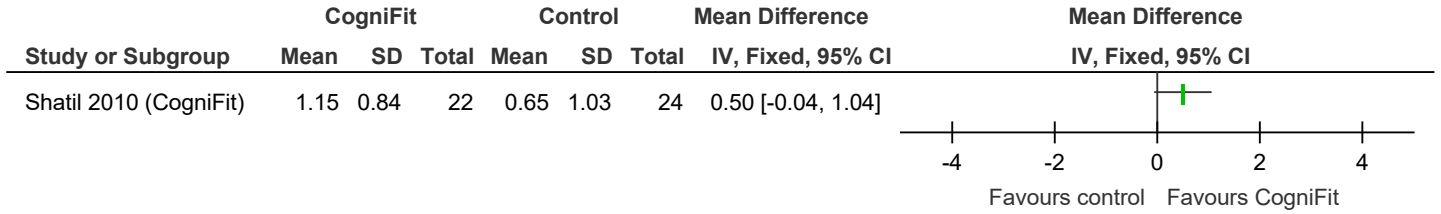
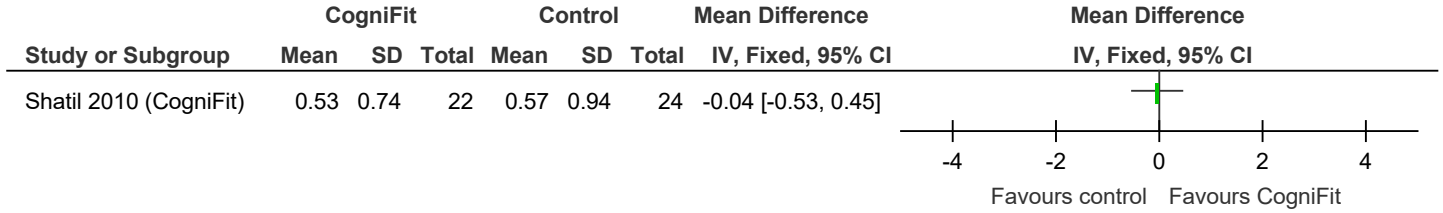


Figure 198: Visual Working Memory (higher better)



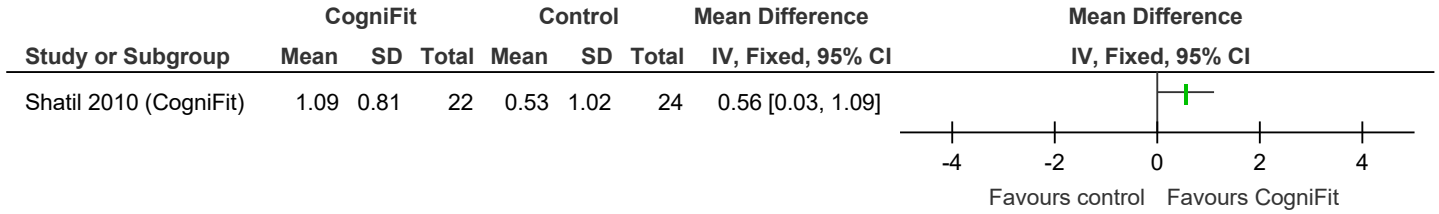
1

Figure 199: Visual Scanning (higher better)



2

Figure 200: Verbal Auditory Working Memory (higher better)



1

E.12 Brain training apps/games (targeting general cognitive function/multiple domains) vs. control, 1.5-3 months

Figure 201: Trail Making Test (lower better)

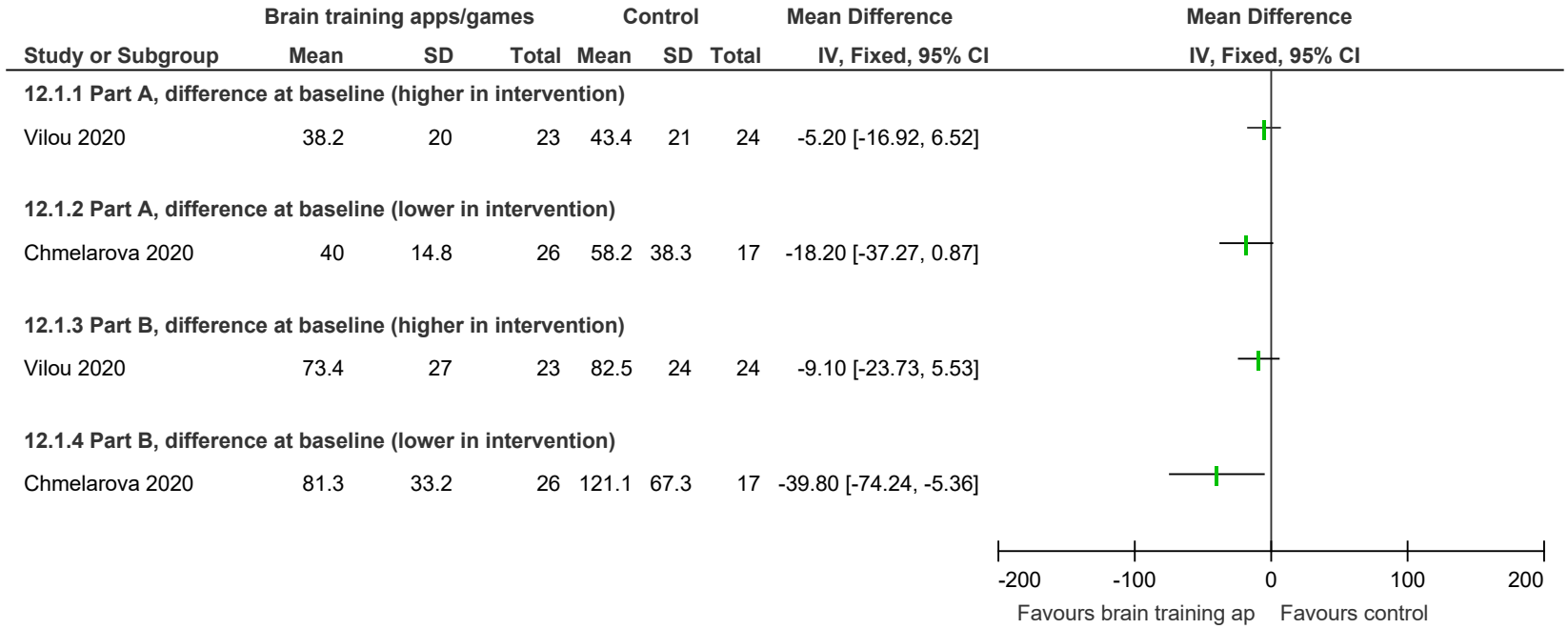


Figure 202: Stroop Test (higher better)

Study or Subgroup	Brain training apps/games Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
12.2.1 General 'Stroop Test'								
de Giglio 2015	27.54	7.44	18	23.38	8.64	16	49.1%	4.16 [-1.29, 9.61]
de Giglio 2016	28.8	4.9	12	24.9	8.1	12	50.9%	3.90 [-1.46, 9.26]
Subtotal (95% CI)			**30**			**28**	**100.0%**	**4.03 [0.21, 7.85]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%								
Test for overall effect: Z = 2.07 (P = 0.04)								
12.2.2 Color								
Vilou 2020	65.2	18	23	57.5	23	24	100.0%	7.70 [-4.08, 19.48]
Subtotal (95% CI)			**23**			**24**	**100.0%**	**7.70 [-4.08, 19.48]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.28 (P = 0.20)								
12.2.3 Color-Word								
Vilou 2020	44	16	23	38.8	9	24	100.0%	5.20 [-2.26, 12.66]
Subtotal (95% CI)			**23**			**24**	**100.0%**	**5.20 [-2.26, 12.66]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.37 (P = 0.17)								

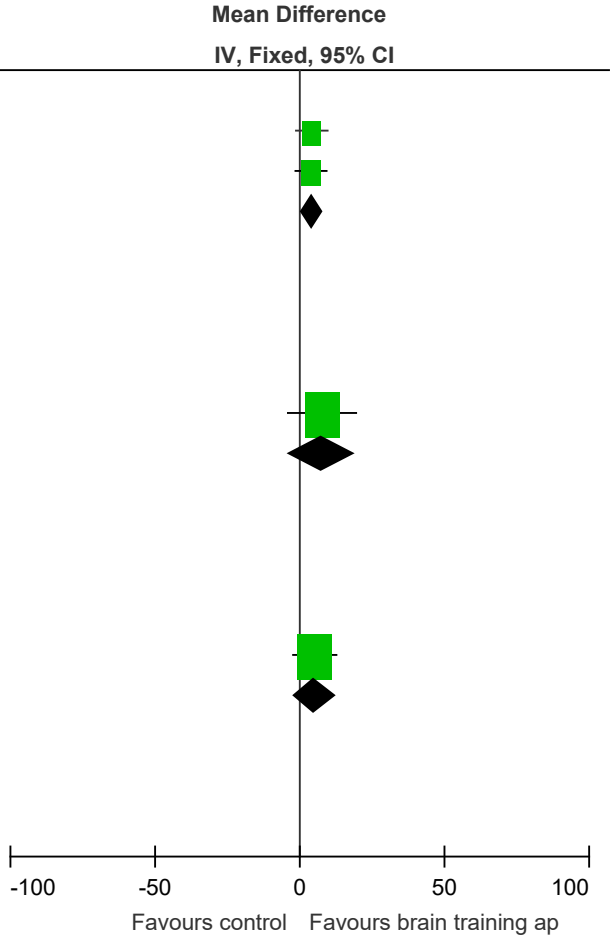


Figure 203: PASAT (higher better)

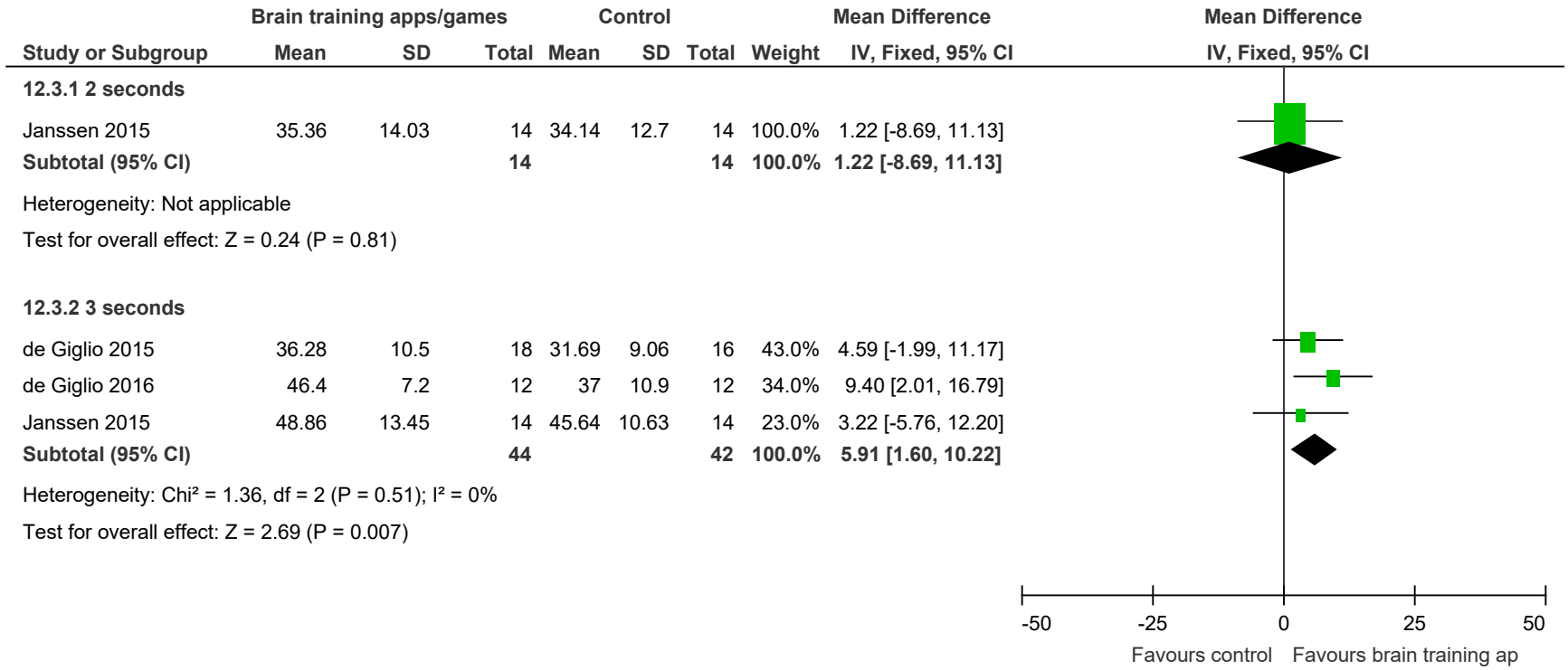
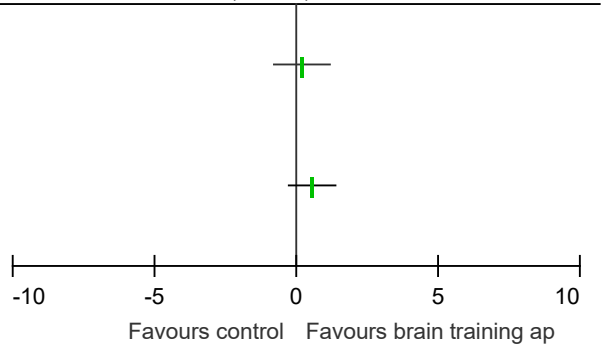


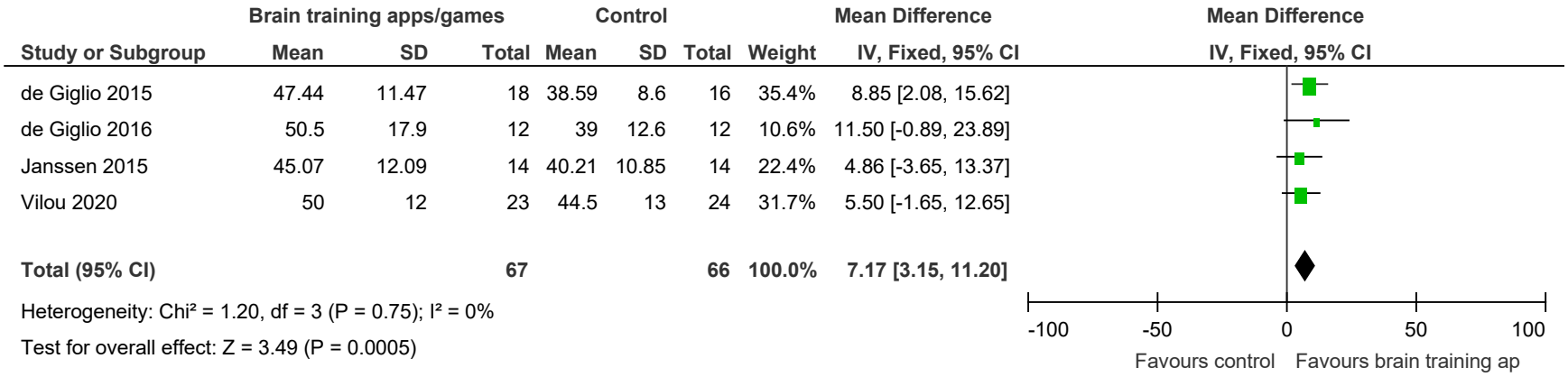
Figure 204: PASAT (z-score; higher better)

	Brain training apps/games			Control			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
12.4.1 2 second								
Charvet 2015	-0.28	1.05	11	-0.48	1.17	9	0.20 [-0.78, 1.18]	
12.4.2 3 second								
Charvet 2015	0.24	0.99	11	-0.32	0.88	9	0.56 [-0.26, 1.38]	



1

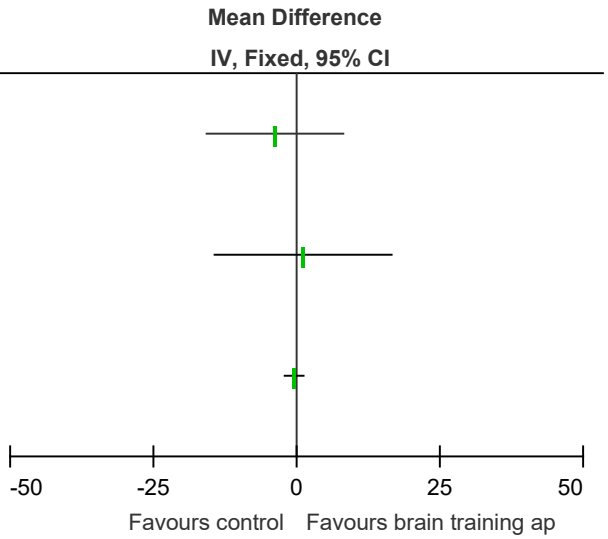
Figure 205: SDMT (higher better)



1

Figure 206: Selective Reminding Test (higher better)

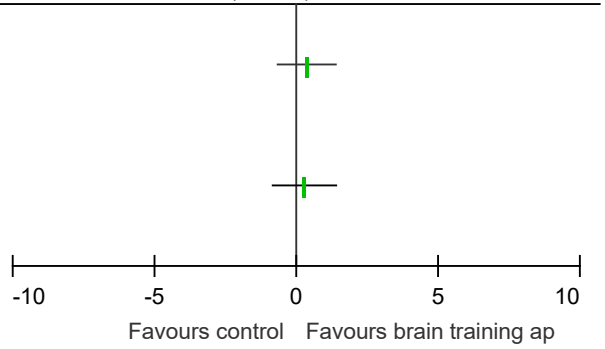
Study or Subgroup	Brain training apps/games Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
12.6.1 Long-term storage							
Janssen 2015	47.36	19.77	14	51.14	11.29	14	-3.78 [-15.71, 8.15]
12.6.2 Consecutive long-term retrieval							
Janssen 2015	39.43	21.14	14	38.29	20.53	14	1.14 [-14.30, 16.58]
12.6.3 Delayed recall							
Janssen 2015	8.86	2.41	14	9.29	2.02	14	-0.43 [-2.08, 1.22]



1

Figure 207: Selective Remining Test (z-score; higher better)

	Brain training apps/games			Control			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
12.7.1 Learning trials								
Charvet 2015	0.13	1.45	11	-0.24	0.86	9	0.37 [-0.65, 1.39]	
12.7.2 Delay								
Charvet 2015	0.59	1.39	11	0.3	1.16	9	0.29 [-0.83, 1.41]	



1

Figure 208: Spatial Recall Test (10/36 SPART; higher better)

	Brain training apps/games			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
12.8.1 Correct								
Janssen 2015	22	6.15	14	19.43	6.78	14	2.57 [-2.22, 7.36]	
12.8.2 Delayed								
Janssen 2015	7.57	3.01	14	6.5	3.57	14	1.07 [-1.38, 3.52]	

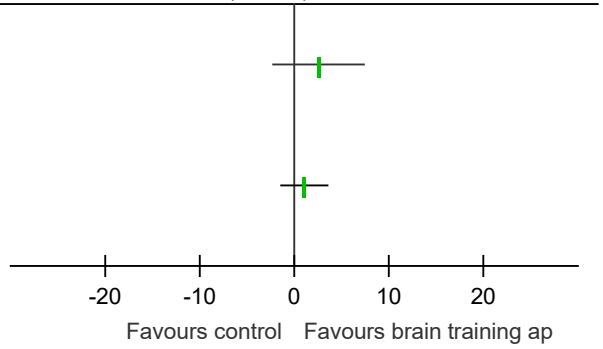


Figure 209: Word List Generation Test (higher better)

	Brain training apps/games			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Janssen 2015	27.79	9.25	14	28.07	6.12	14	-0.28 [-6.09, 5.53]	

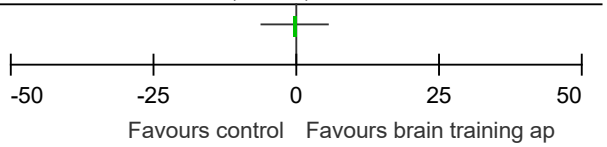


Figure 210: Brief Visuospatial Memory Test-Revised (higher better)

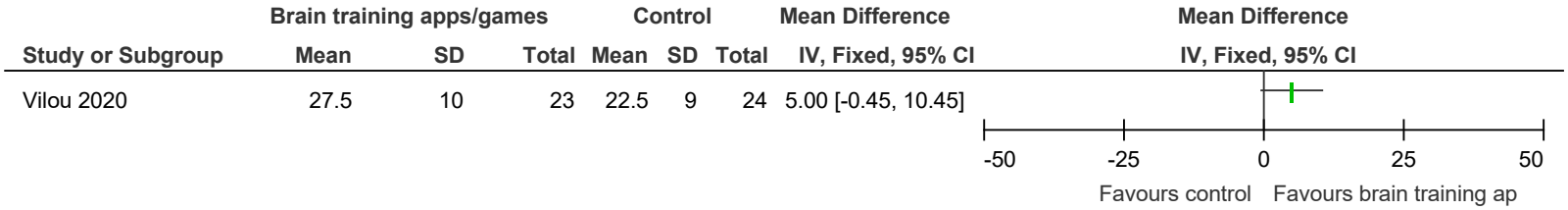


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Figure 211: Brief Visuospatial Memory Test-Revised (z-score; higher better)

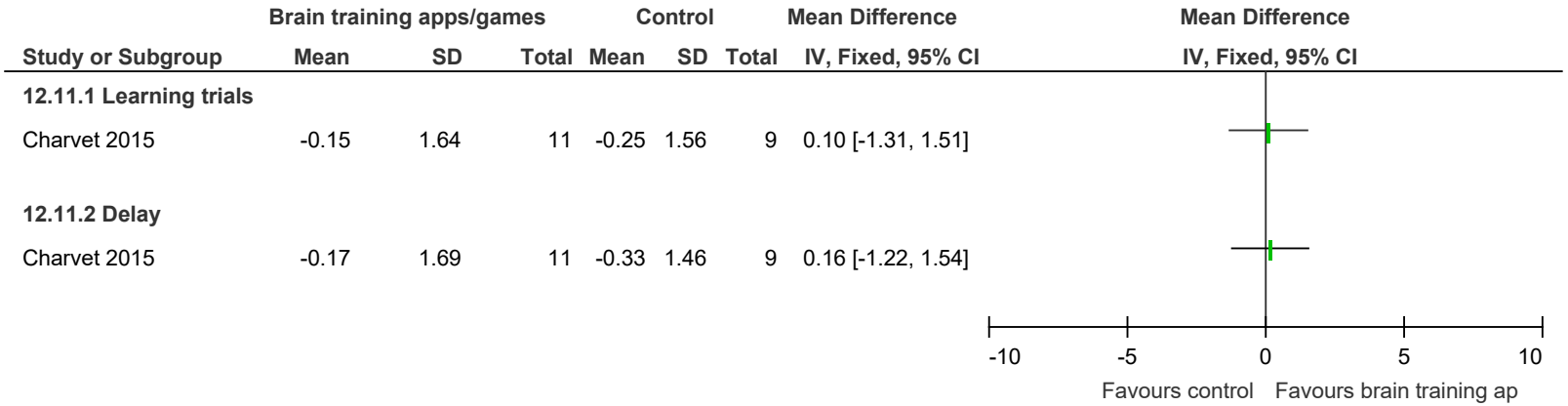

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Figure 212: Greek Verbal Learning Test (higher better)

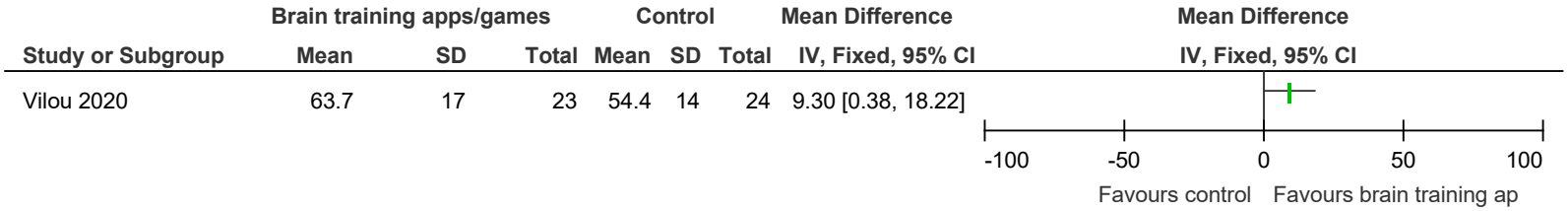

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Figure 213: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; higher better)

	Brain training apps/games			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
12.13.1 Immediate memory (scale 40-152?)								
Chmelarova 2020	107.8	16.9	26	97.7	17.5	17	10.10 [-0.45, 20.65]	
12.13.2 Visuospatial/constructional (scale 50-131?)								
Chmelarova 2020	106.9	10.9	26	101.9	15.3	17	5.00 [-3.39, 13.39]	
12.13.3 Language (scale 40-134?)								
Chmelarova 2020	107.7	10.7	26	100.4	14.2	17	7.30 [-0.60, 15.20]	
12.13.4 Attention (scale 40-150?)								
Chmelarova 2020	94.8	15.8	26	81.4	15.4	17	13.40 [3.89, 22.91]	
12.13.5 Delayed memory (scale 40-133?)								
Chmelarova 2020	108.4	16.1	26	98.8	15	17	9.60 [0.16, 19.04]	
12.13.6 Total score (scale 40-160?)								
Chmelarova 2020	107.3	15.2	26	94.9	17.2	17	12.40 [2.35, 22.45]	

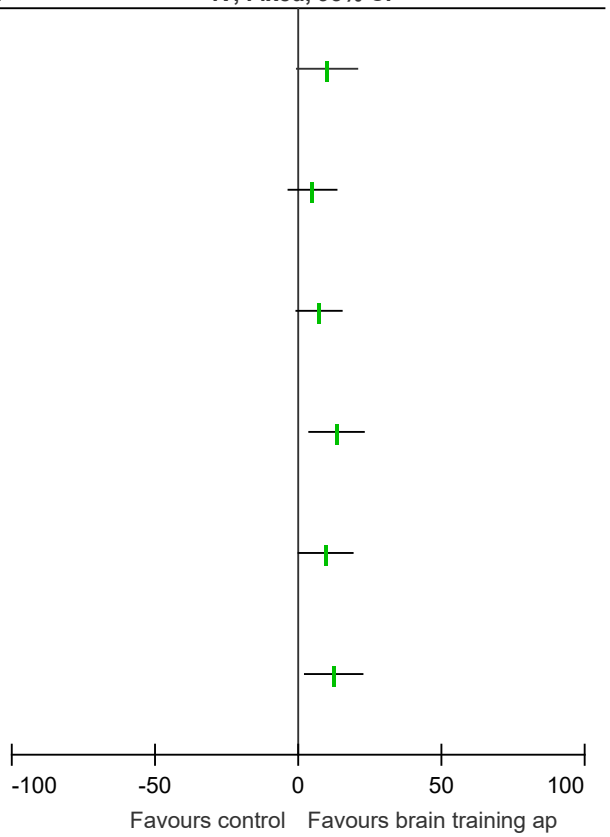

Figure 214: Weschler Adult Intelligence Scale IV – Letter-Number Sequencing (higher better)

Study or Subgroup	Brain training apps/games Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Charvet 2015	-0.04	0.73	11	-0.04	0.72	9	0.00 [-0.64, 0.64]

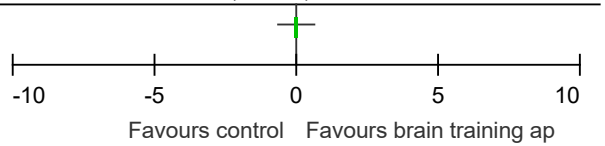

Figure 215: Corsi Block Tapping Test – Visual Span (z-score; higher better)

Study or Subgroup	Brain training apps/games Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Charvet 2015	-0.26	0.68	11	-0.52	0.67	9	0.26 [-0.33, 0.85]

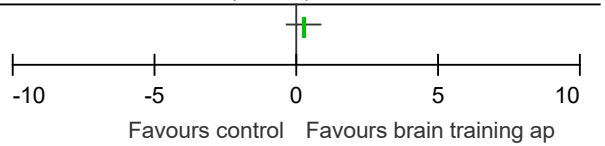

Figure 216: Delis-Kaplan Executive Function System (D-KEFS; z-score; higher better)

	Brain training apps/games			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
12.16.1 Trail 5								
Charvet 2015	0.64	0.43	11	0.63	0.26	9	0.01 [-0.30, 0.32]	
12.16.2 Trails 2/3 combo								
Charvet 2015	0.27	0.77	11	0	1.08	9	0.27 [-0.57, 1.11]	

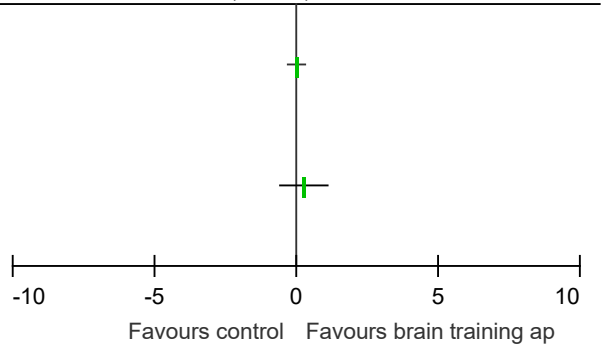

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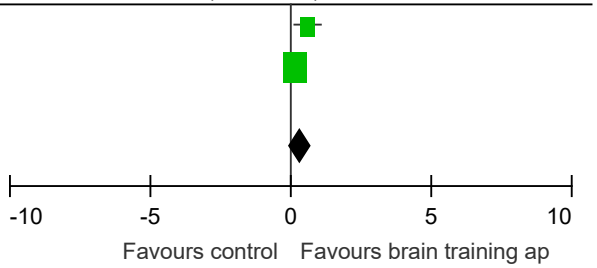
Figure 217: General Cognitive Composite (average of multiple cognitive tests; higher better)

	Brain training apps/games			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Charvet 2015	0.46	0.59	11	-0.14	0.48	9	36.5%	0.60 [0.13, 1.07]	
Charvet 2017	0.25	0.45	74	0.09	0.37	61	63.5%	0.16 [0.02, 0.30]	
Total (95% CI)			**85**			**70**	**100.0%**	**0.32 [-0.09, 0.74]**	

Heterogeneity: Tau² = 0.07; Chi² = 3.11, df = 1 (P = 0.08); I² = 68%

Test for overall effect: Z = 1.51 (P = 0.13)



1

Figure 218: Self-reported improvement in cognition

Study or Subgroup	Brain training apps/games Events	Total	Control Events	Total	Odds Ratio M-H, Fixed, 95% CI
Charvet 2017	42	74	19	61	2.90 [1.43, 5.91]

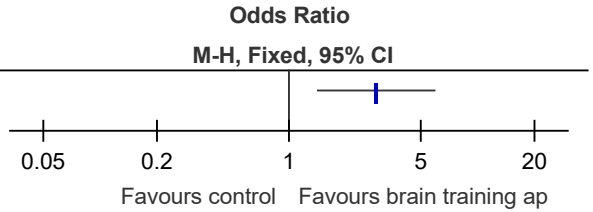


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Figure 219: MSQoL-54 (scale usually 0-100; higher better)

Study or Subgroup	Brain training apps/games Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
12.19.1 Physical composite							
de Giglio 2015	62.7	11.84	18	62.72	14.84	16	-0.02 [-9.12, 9.08]
12.19.2 Mental health composite							
de Giglio 2015	61.5	12.9	18	54.03	16	16	7.47 [-2.38, 17.32]

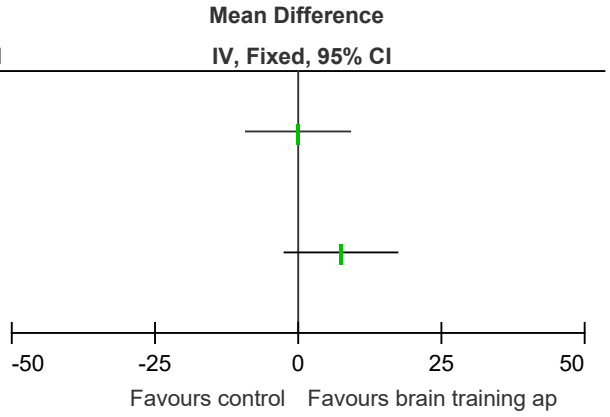


Figure 220: Modified Fatigue Impact Scale – Cognitive subscale (scale usually 0-40; lower better)

	Brain training apps/games			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
de Giglio 2015	11.06	7.17	26	18.06	8.86	17	-7.00 [-12.03, -1.97]	

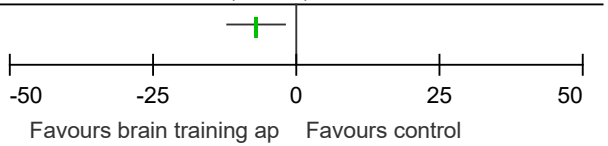
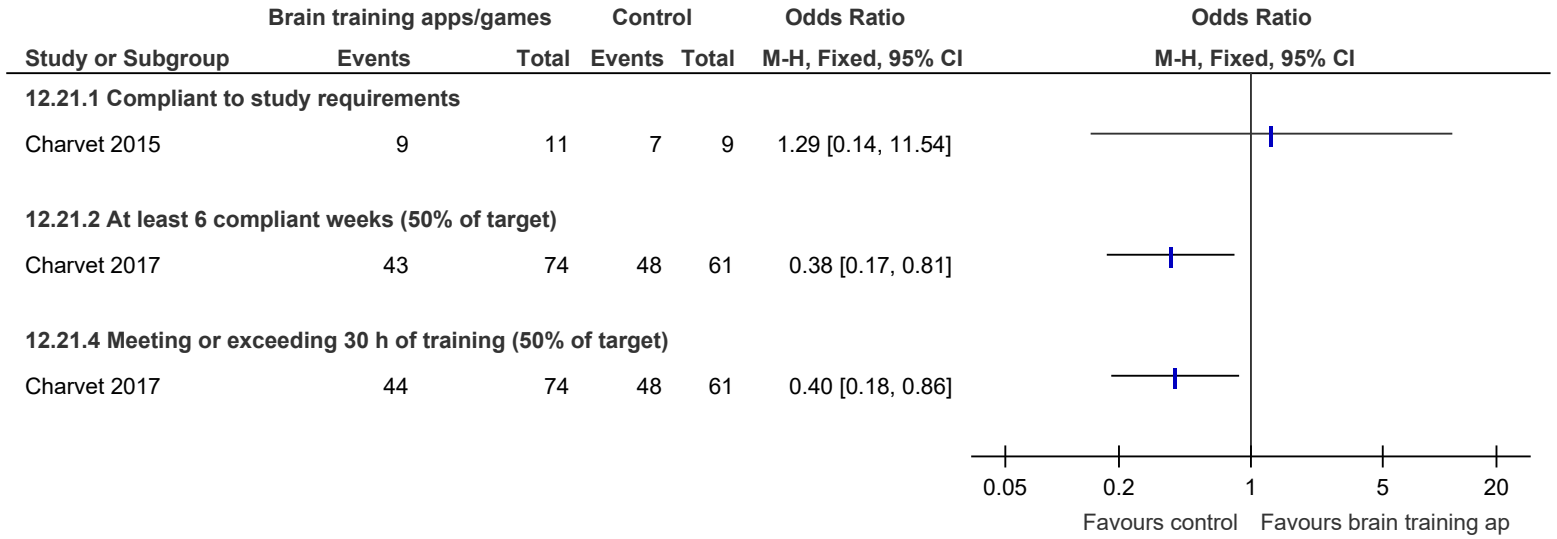


Figure 221: Adherence



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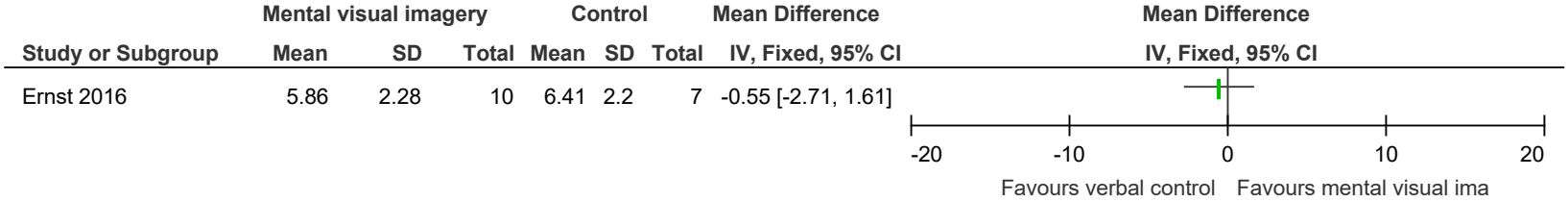
E.13 Mental visual imagery vs. control (sham verbal control), 6-8 weeks

Figure 222: Number of details provided (measure of mental visualisation ability; higher better)



E.14 Mindfulness vs. control, 4 weeks

Figure 223: SDMT (higher better)

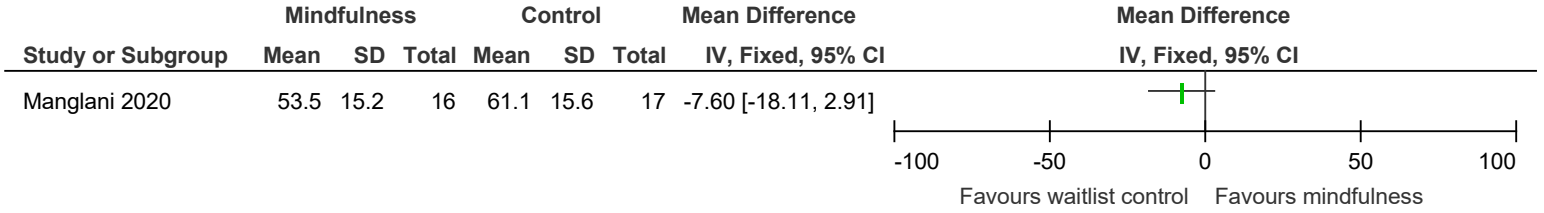


Figure 224: PASAT (higher better)

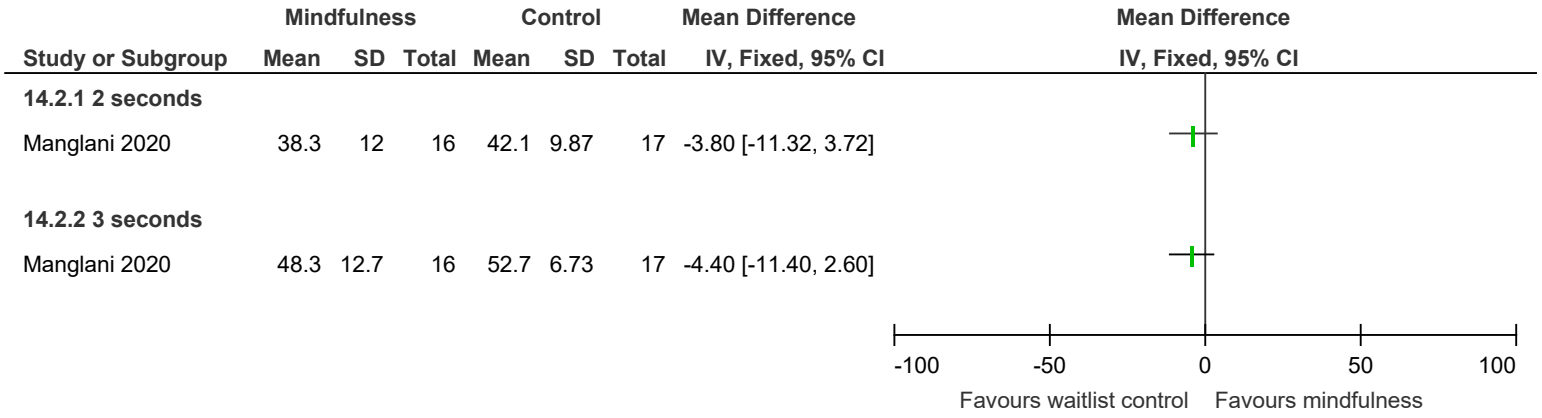


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Figure 225: Selective Reminding Test (higher better)

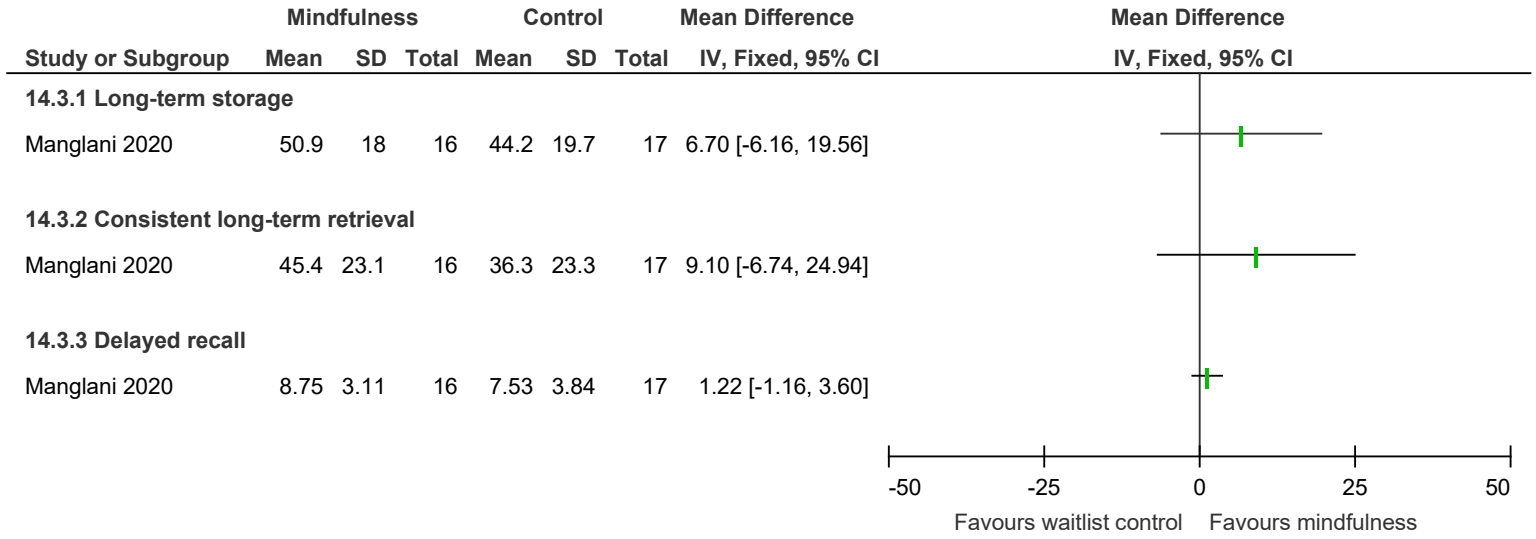

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Figure 226: Word List Generation Test (higher better)

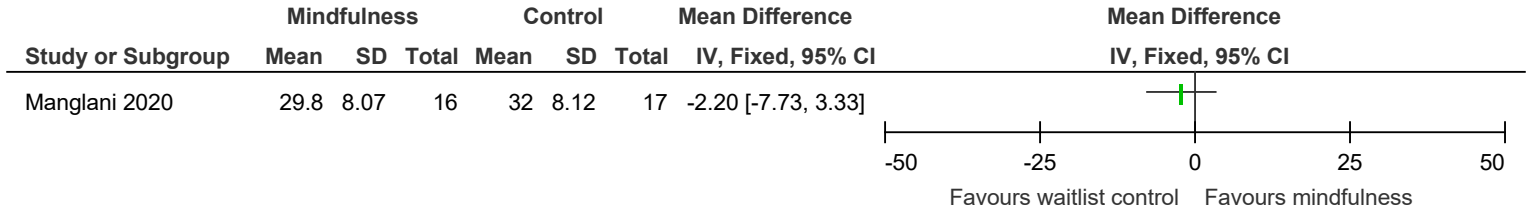


Figure 227: Spatial Recall Test (10/36 SPART; higher better)

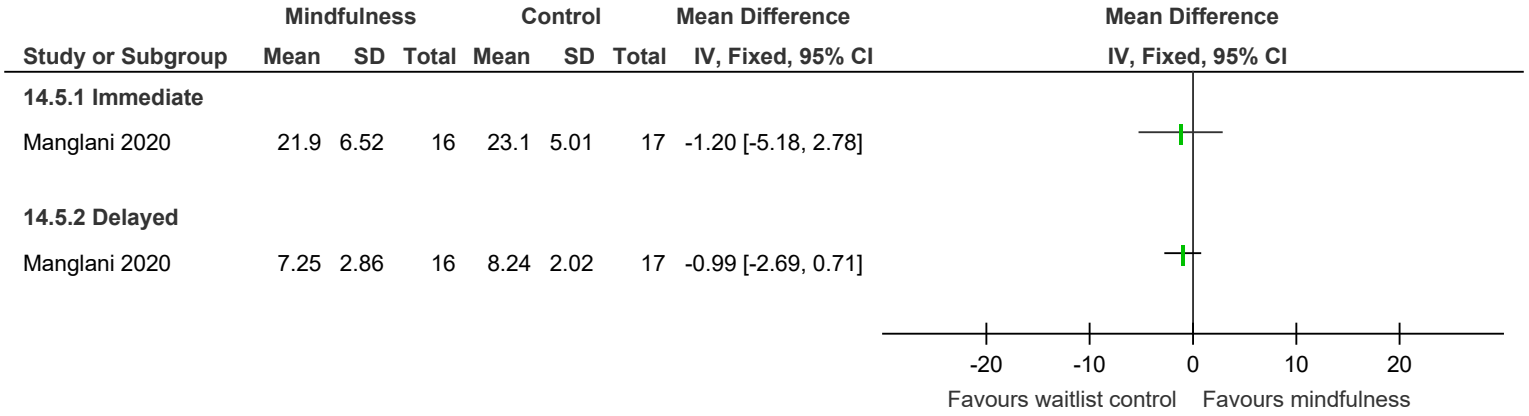


Figure 228: Beck Depression Inventory (scale 0-63; lower better)

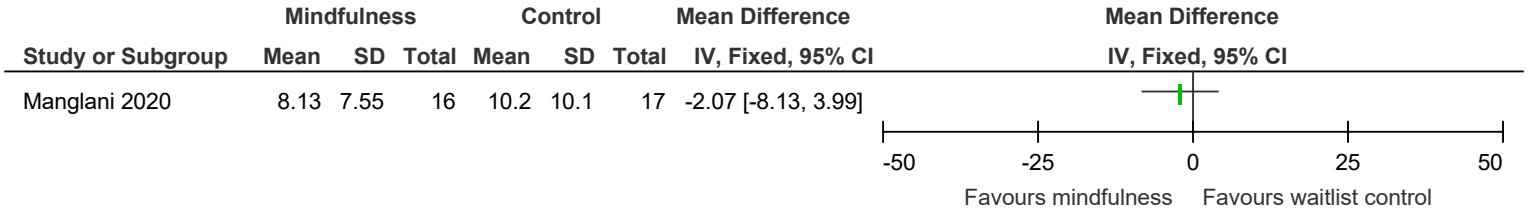


Figure 229: Penn State Worry Questionnaire (scale usually 16-80; lower better)

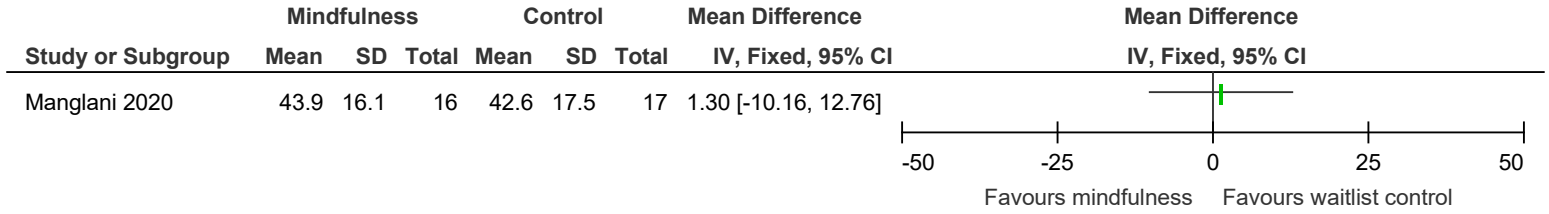


Figure 230: Difficulties in Emotion Regulation Scale (DERS; scale unclear; lower better)

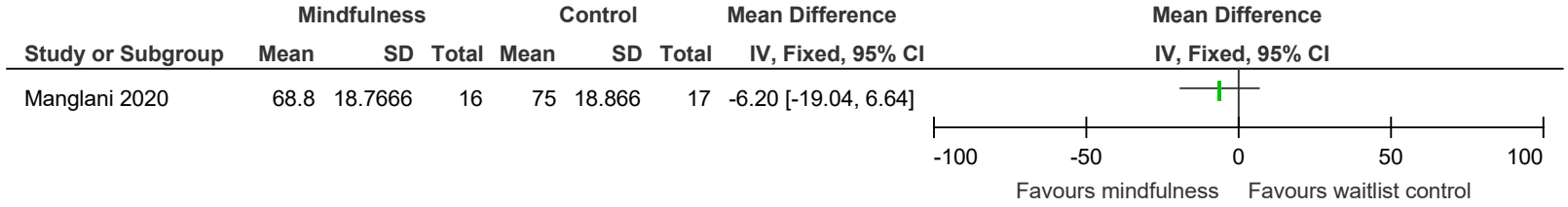
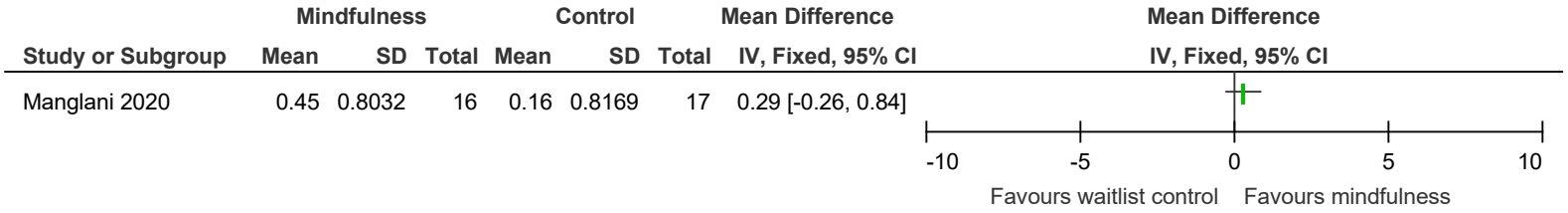


Figure 231: WHO Quality of Life and Satisfaction with Life Scale composite (z-score; higher better)



E.15 Mindfulness vs. control, 12 months

Figure 232: SDMT (higher better)

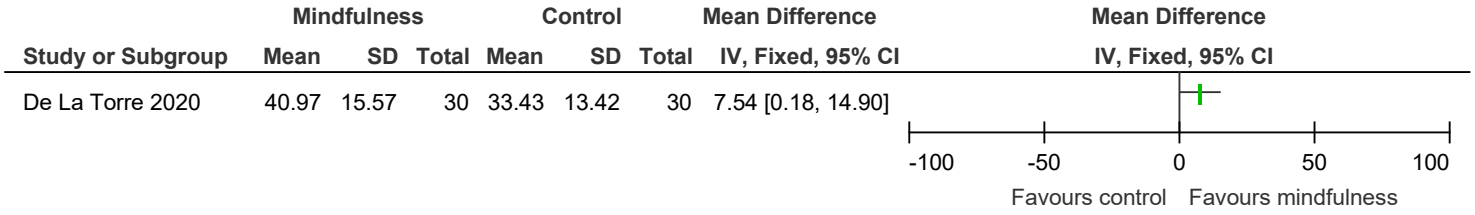


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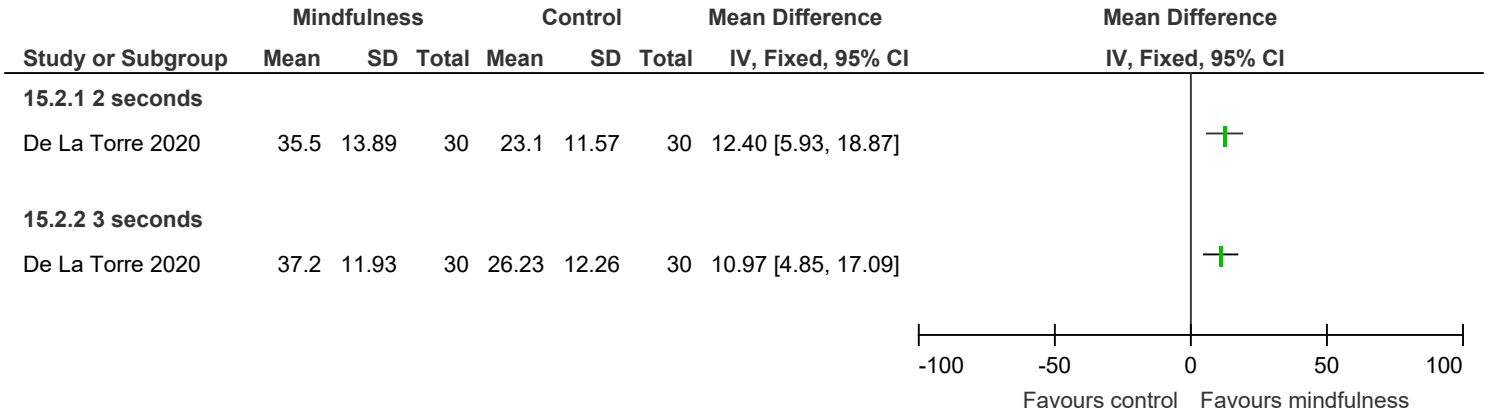
Figure 233: PASAT (higher better)



1

Figure 234: COWAT verbal fluency test (higher better)

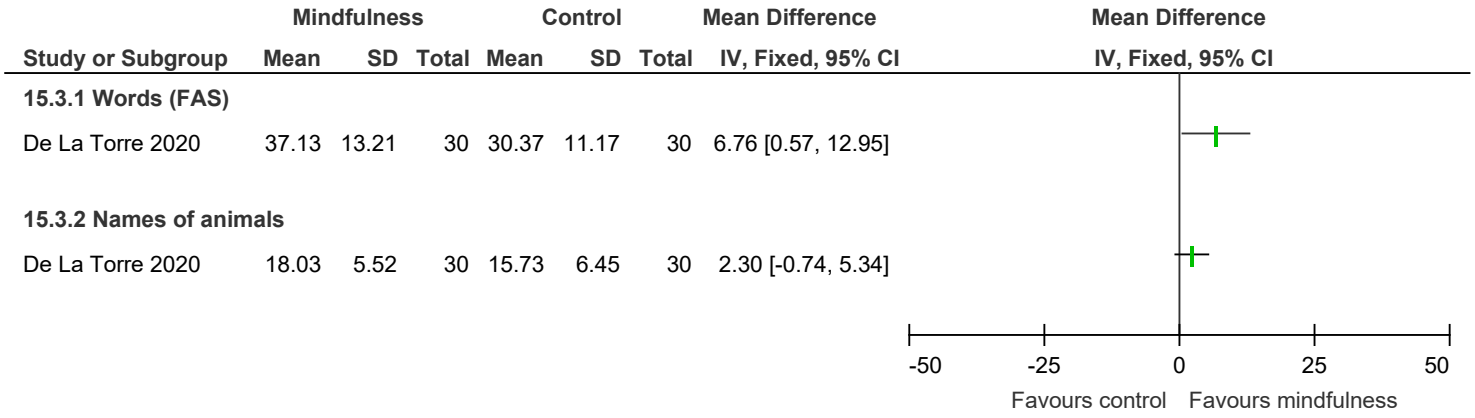
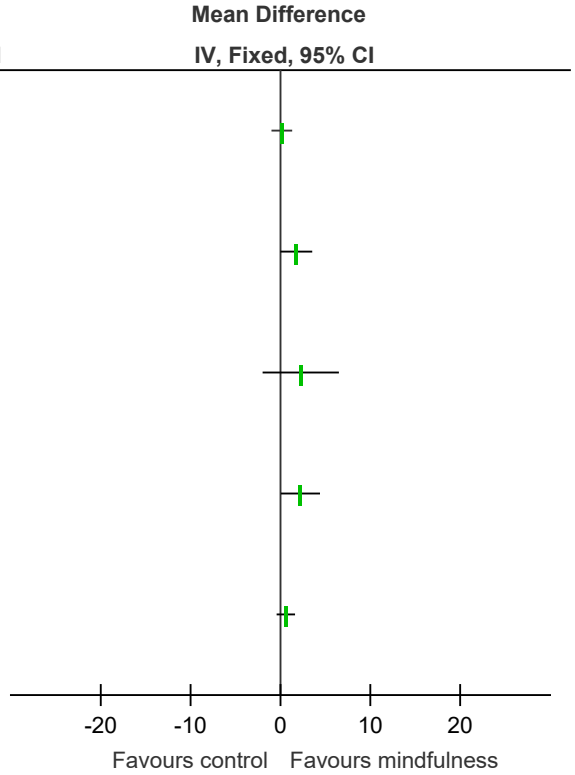


Figure 235: Wechsler Memory Scale III (Spanish version; higher better)

Study or Subgroup	Mindfulness Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
15.4.1 Attention							
De La Torre 2020	5.03	1.69	30	4.87	2.4	30	0.16 [-0.89, 1.21]
15.4.2 Long-term memory							
De La Torre 2020	7.87	2.78	30	6.1	3.74	30	1.77 [0.10, 3.44]
15.4.3 Short-term memory							
De La Torre 2020	29.43	6.64	30	27.17	9.48	30	2.26 [-1.88, 6.40]
15.4.4 Recognition							
De La Torre 2020	22.23	2.67	30	20	5.13	30	2.23 [0.16, 4.30]
15.4.5 Learning							
De La Torre 2020	3.97	1.96	30	3.37	1.65	30	0.60 [-0.32, 1.52]



1

Figure 236: Beck Depression Inventory (scale usually 0-63; lower better)

	Mindfulness			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
De La Torre 2020	14	7.52	30	18.67	10.68	30	-4.67 [-9.34, 0.00]	

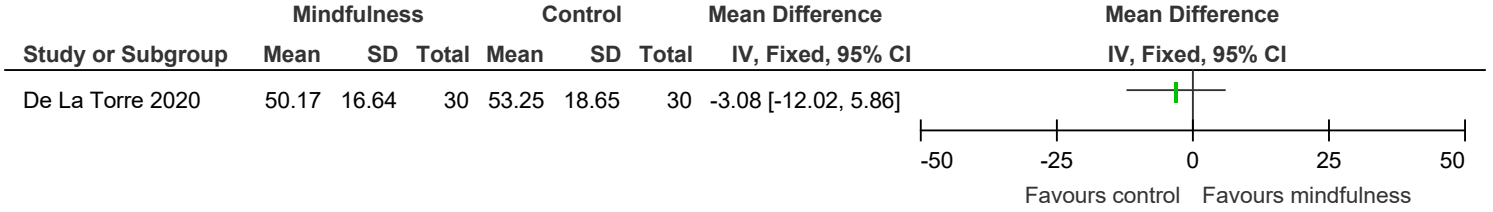
1

Figure 237: State-Trait Anxiety Inventory (unclear which subscale; scale usually 20-80 for each subscale; lower better)

	Mindfulness			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
De La Torre 2020	38.97	23	30	41.77	23.52	30	-2.80 [-14.57, 8.97]	

2

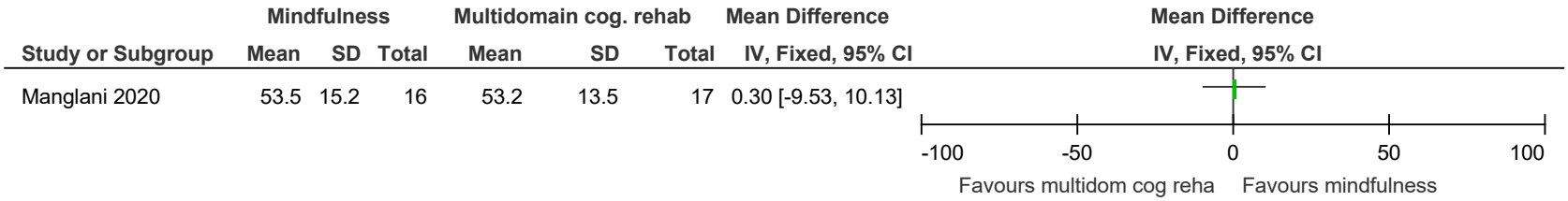
Figure 238: FIM + FAM composite (functional independence and assessment measures; scale unclear; higher better)



E.16 Mindfulness vs. general cognitive rehabilitation (multi-component and multi-domain), 4 weeks

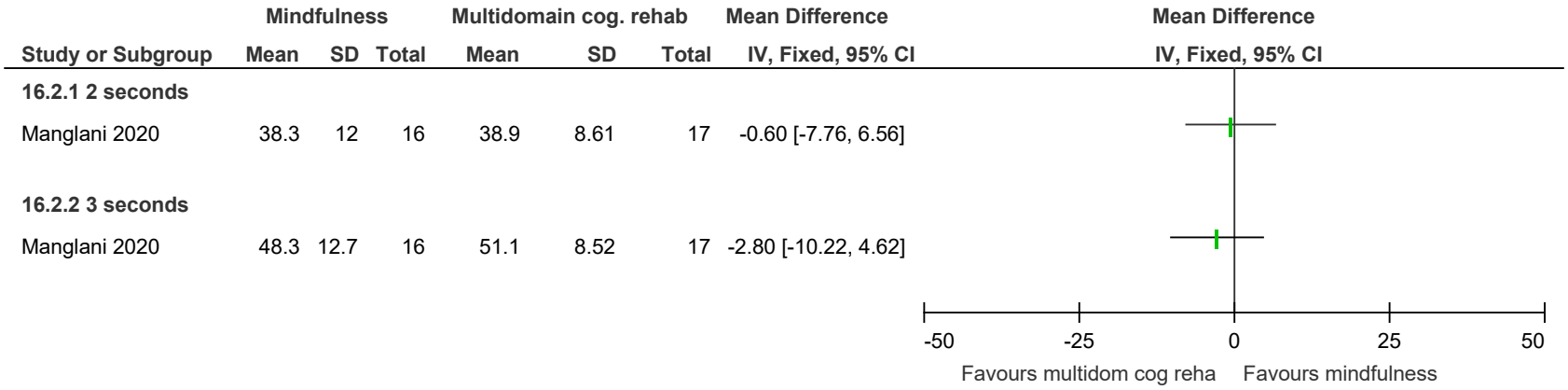
2

Figure 239: SDMT (higher better)



3

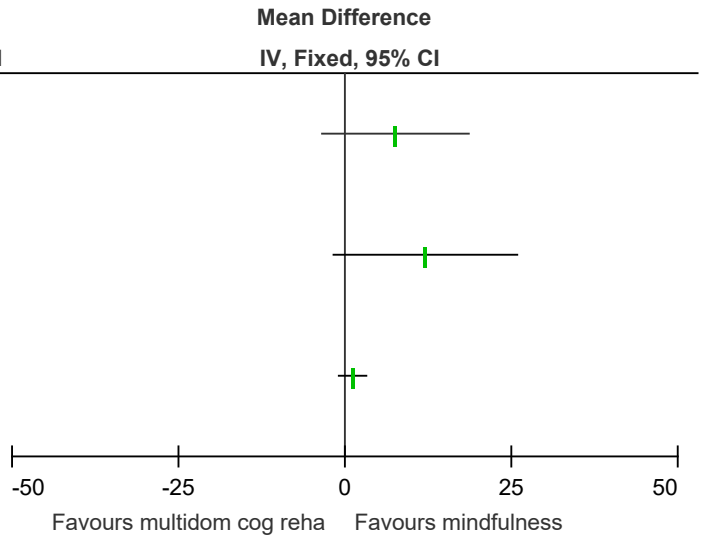
Figure 240: PASAT (higher better)



1

Figure 241: Selective Reminding Test (higher better)

Study or Subgroup	Mindfulness Mean	SD	Total	Multidomain cog. rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
16.3.1 Long-term storage							
Manglani 2020	50.9	18	16	43.3	13.9	17	7.60 [-3.42, 18.62]
16.3.2 Consistent long-term retrieval							
Manglani 2020	45.4	23.1	16	33.3	16.6	17	12.10 [-1.70, 25.90]
16.3.3 Delayed recall							
Manglani 2020	8.75	3.11	16	7.59	2.94	17	1.16 [-0.91, 3.23]



1

Figure 242: Word List Generation Test (higher better)

Study or Subgroup	Mindfulness Mean	SD	Total	Multidomain cog. rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Manglani 2020	29.8	8.07	16	33.9	8.58	17	-4.10 [-9.78, 1.58]

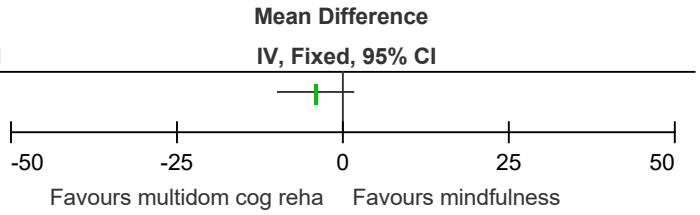


Figure 243: Spatial Recall Test (10/36 SPART; higher better)

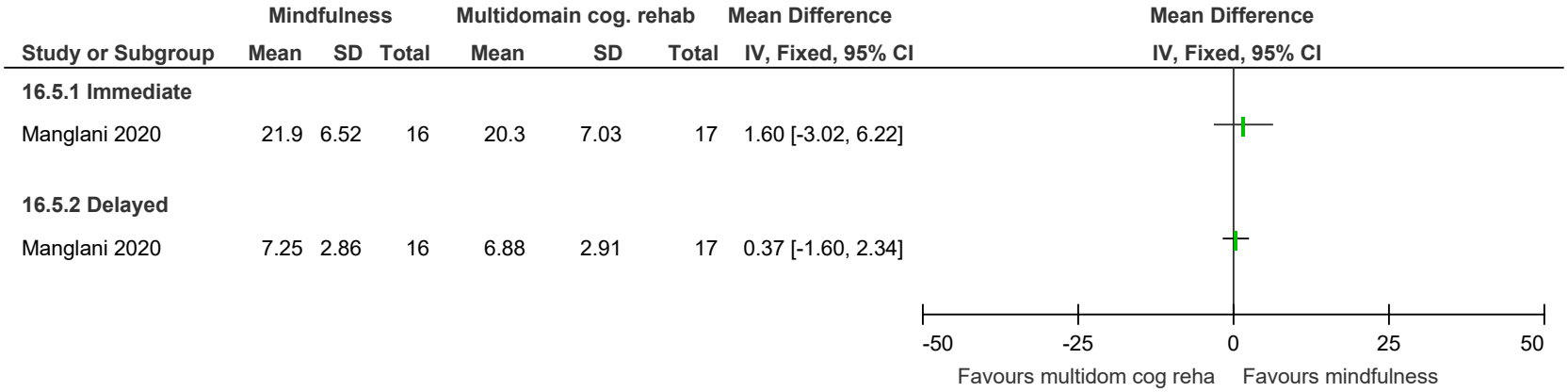


Figure 244: Beck Depression Inventory (scale 0-63; lower better)

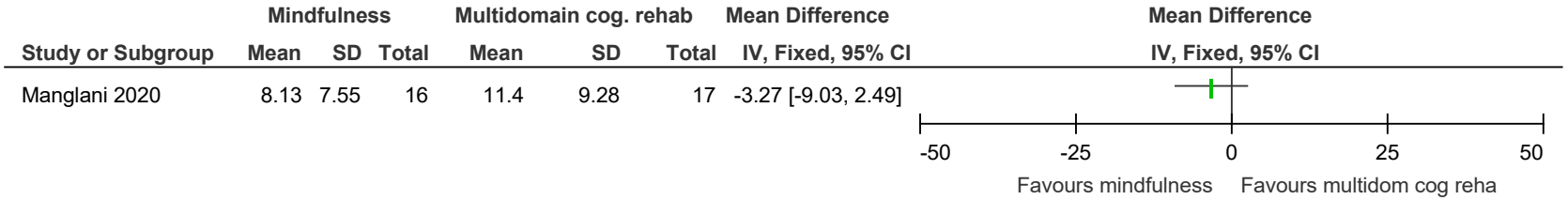


Figure 245: Penn State Worry Questionnaire (scale usually 16-80; lower better)

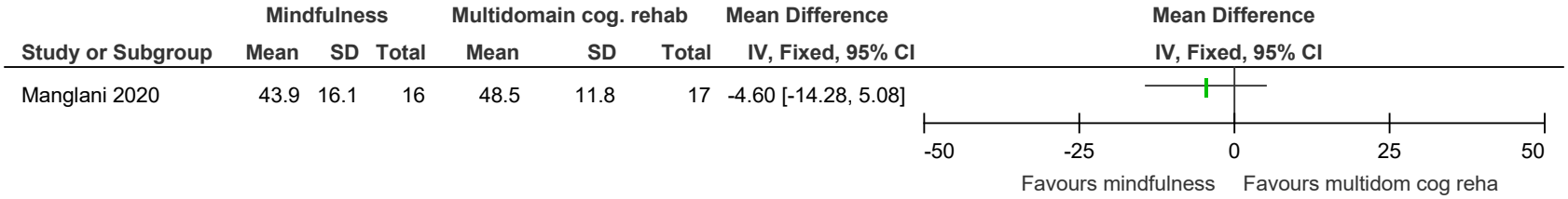


Figure 246: Difficulties in Emotion Regulation Scale (DERS; scale unclear; lower better)

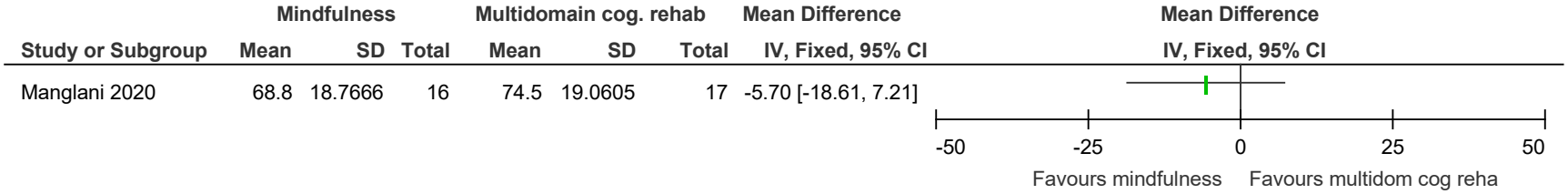
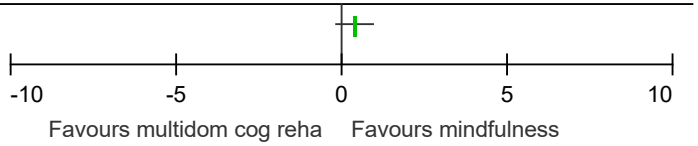


Figure 247: WHO Quality of Life and Satisfaction with Life Scale composite (z-score; higher better)

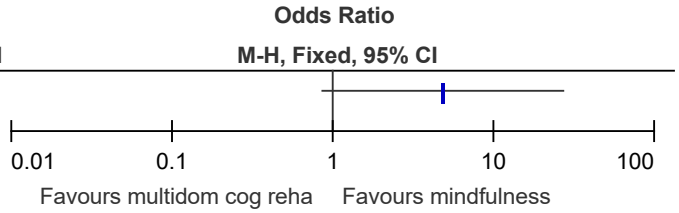
Study or Subgroup	Mindfulness Mean	SD	Total	Multidomain cog. rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Manglani 2020	0.45	0.8032	16	0.056	0.8285	17	0.39 [-0.16, 0.95]



1

Figure 248: Adherence – completing all four weekly sessions

Study or Subgroup	Mindfulness Events	Total	Multidomain cog. rehab Events	Total	Odds Ratio M-H, Fixed, 95% CI
Manglani 2020	18	20	13	20	4.85 [0.86, 27.22]



2

E.17 Mindfulness vs. medical treatment and counselling, 8 weeks

Figure 249: Wechsler Adult Intelligence Scale-Revised – Symbol Coding Test (higher better)

	Mindfulness			Medical treat. + counsel.			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Nazaribadie 2020/2021	50.4	9.26	27	45.88	10.58	26	4.52 [-0.84, 9.88]	

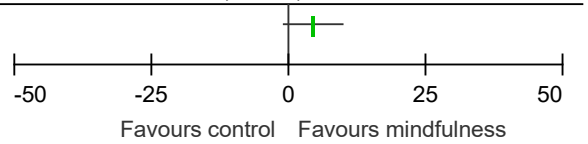


Figure 250: Wechsler Adult Intelligence Scale-Revised – Digit Span Test (higher better)

	Mindfulness			Medical treat. + counsel.			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Nazaribadie 2020/2021	6.74	1.53	27	5.38	1.2	26	1.36 [0.62, 2.10]	

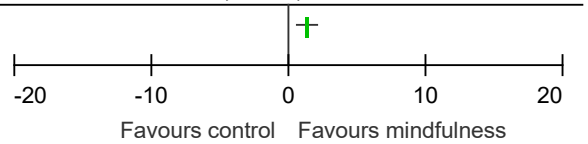


Figure 251: Rey Complex Figure Test – Recall (higher better)

Study or Subgroup	Mindfulness Mean	SD	Total	Medical treat. + counsel. Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Nazaribadie 2020/2021	24.77	5.29	27	22.8	3.28	26	1.97 [-0.39, 4.33]

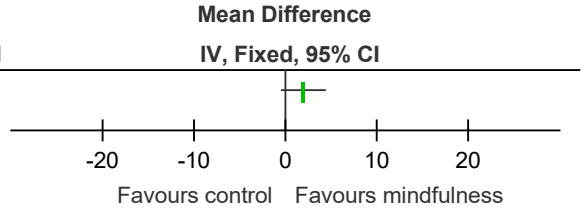


Figure 252: PASAT 3 seconds (higher better)

Study or Subgroup	Mindfulness Mean	SD	Total	Medical treat. + counsel. Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Nazaribadie 2020/2021	44.11	10.1	27	33.61	14.75	26	10.50 [3.67, 17.33]

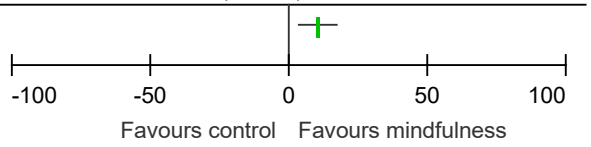


Figure 253: PASAT 2 seconds (higher better)

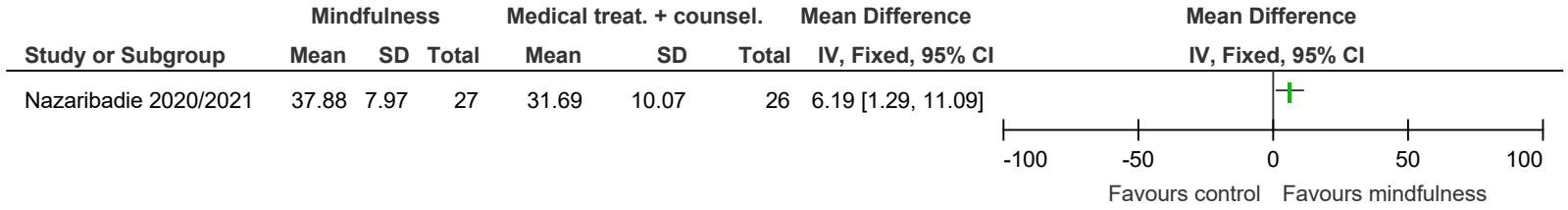


Figure 254: Wisconsin Card Sorting Test – category (higher better)

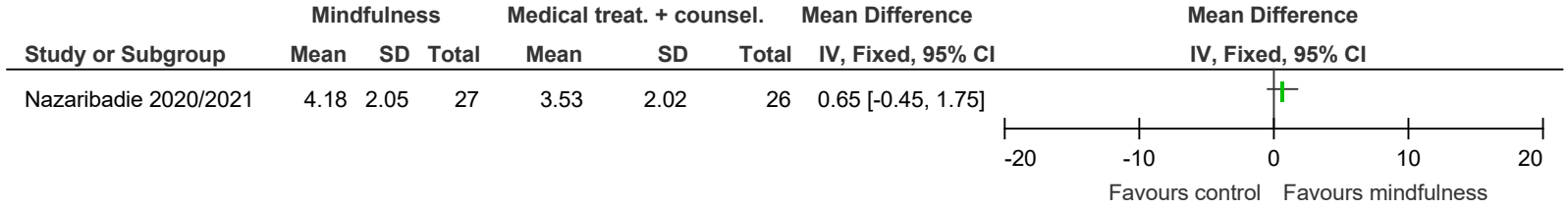


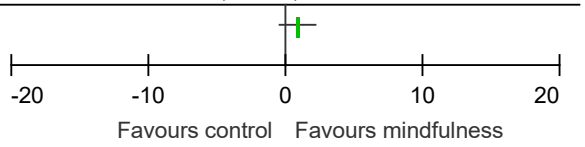
Figure 255: Wisconsin Card Sorting Test – perseveration (lower better)

	Mindfulness			Medical treat. + counsel.			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Nazaribadie 2020/2021	3.22	2.65	27	8	5.45	26	-4.78 [-7.10, -2.46]	

1

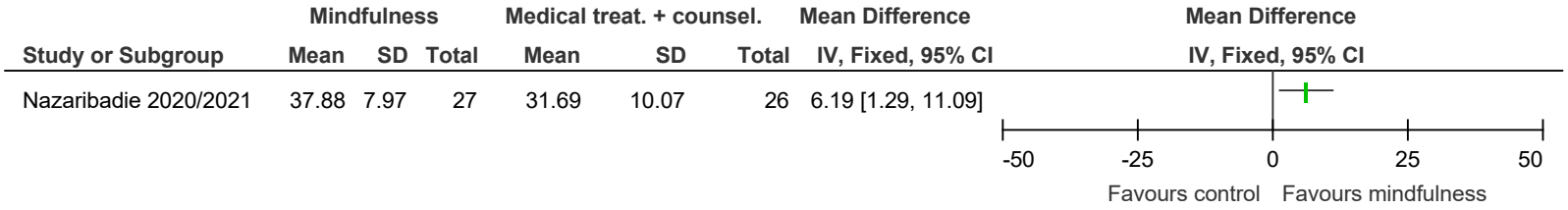
Figure 256: Wisconsin Card Sorting Test – conception responses (higher better)

	Mindfulness			Medical treat. + counsel.			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Nazaribadie 2020/2021	4.81	2.09	27	3.92	2.72	26	0.89 [-0.42, 2.20]	



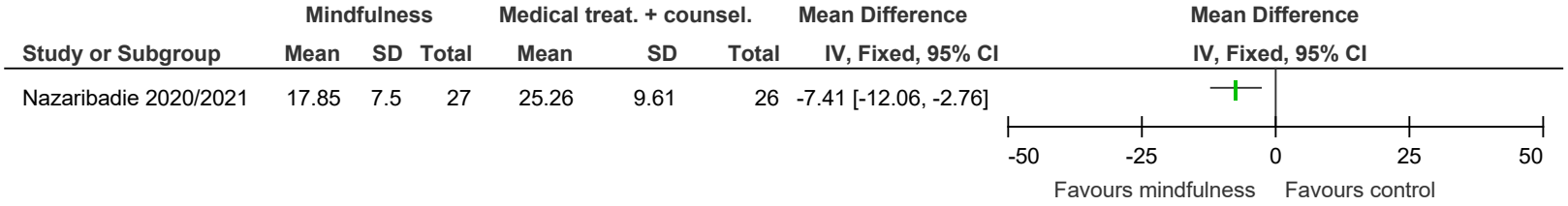
2

Figure 257: Wisconsin Card Sorting Test – total correct (higher better)



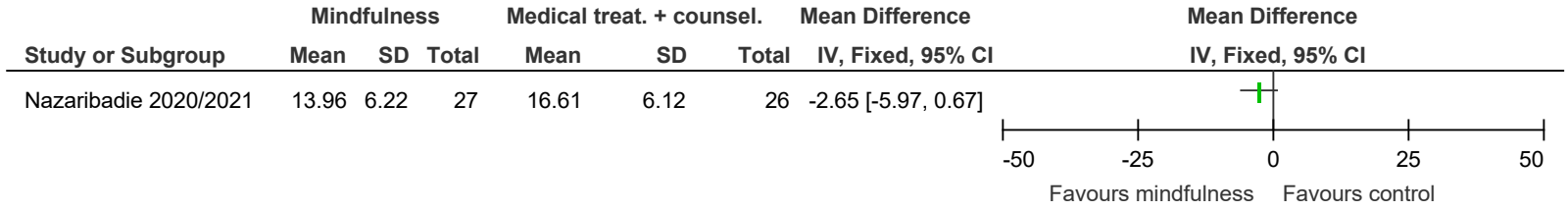
1

Figure 258: Wisconsin Card Sorting Test – number of errors (lower better)



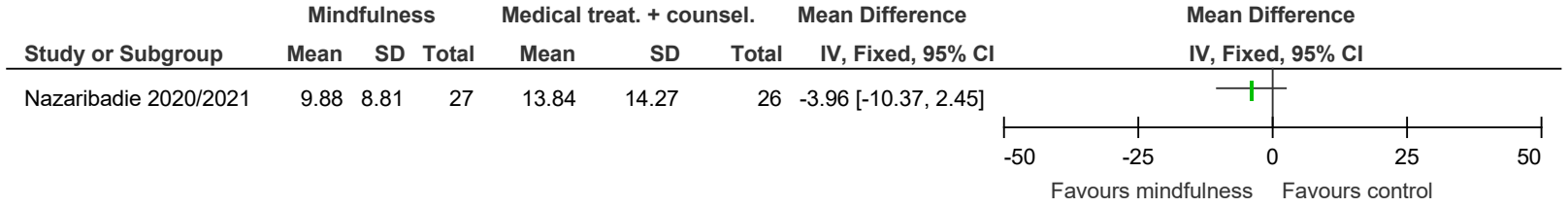
2

Figure 259: Wisconsin Card Sorting Test – other errors (lower better)



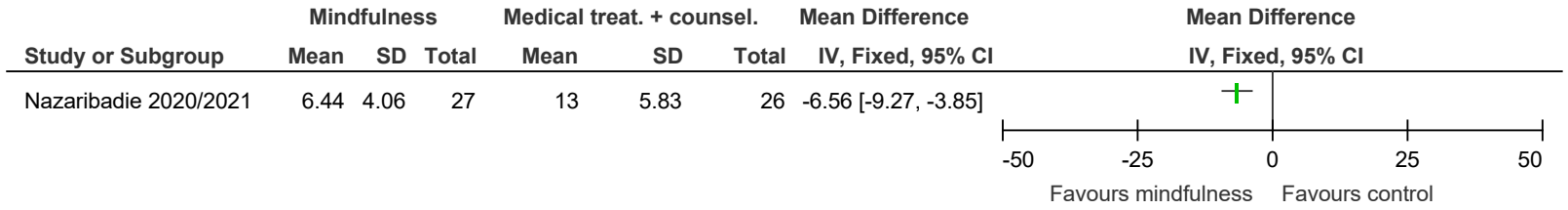
1

Figure 260: Wisconsin Card Sorting Test – first trial (lower better)



2

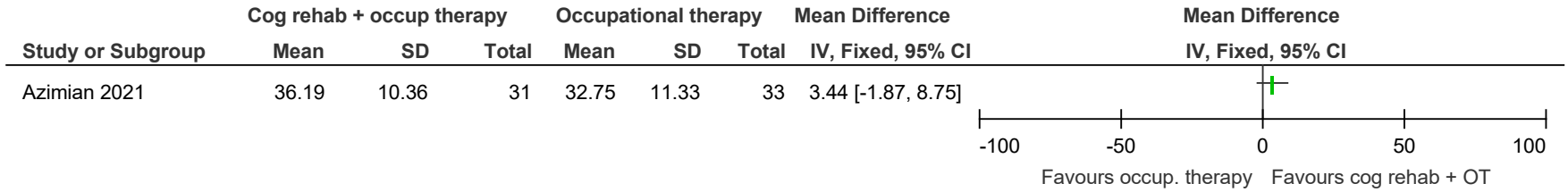
Figure 261: Hamilton Anxiety Scale (scale 0-56; lower better)



1

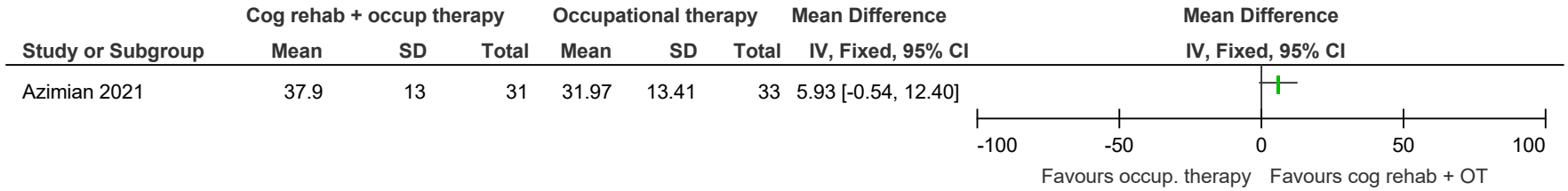
E.18 Information processing speed: cognitive rehabilitation software focused on processing speed + occupational therapy vs. occupational therapy only, 3 months

Figure 262: SDMT (higher better)



4

Figure 263: PASAT (higher better)



E.19 Information processing speed: cognitive rehabilitation software focused on processing speed vs. control (active game or no intervention), 5-6 weeks

Figure 264: SDMT (higher better)

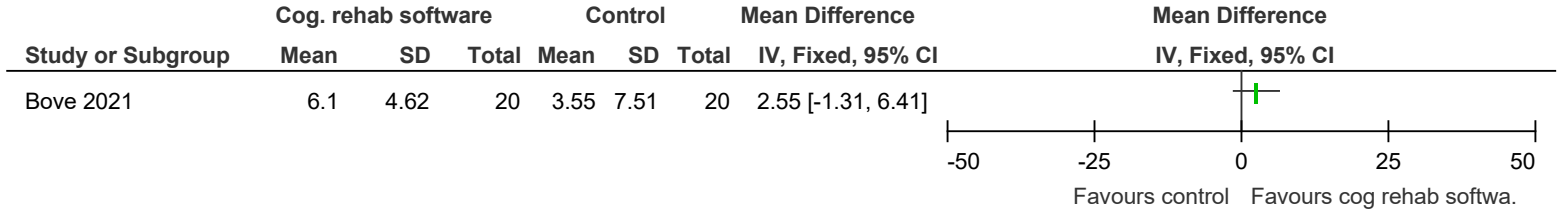
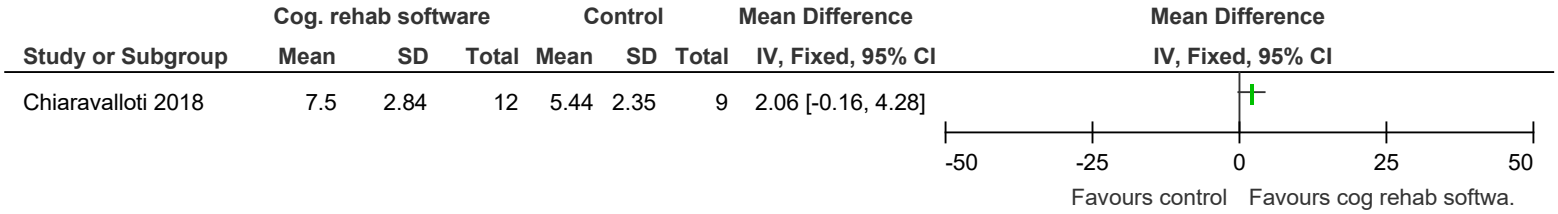
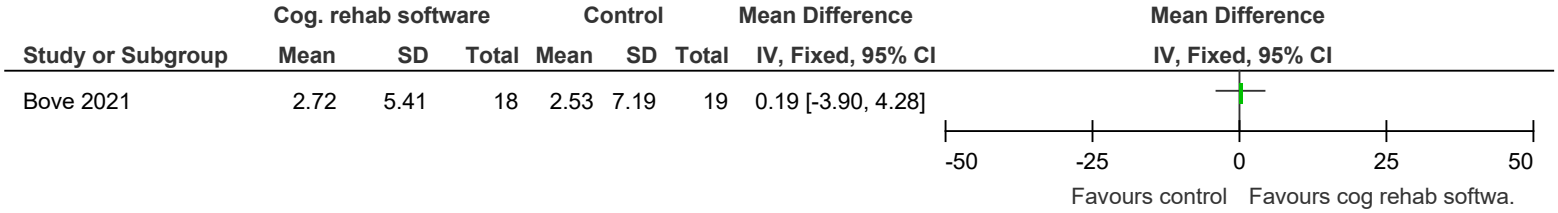


Figure 265: Wechsler Adult Intelligence Scale III – Digit-Symbol Coding Test (higher better)



1

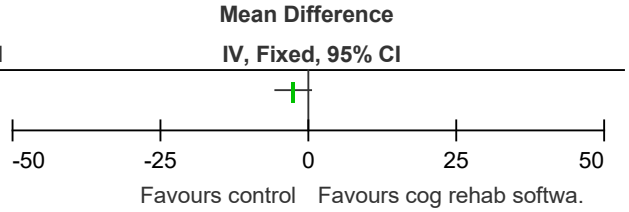
Figure 266: PASAT (higher better)



2

Figure 267: Brief Visuospatial Memory Test-Revised (higher better)

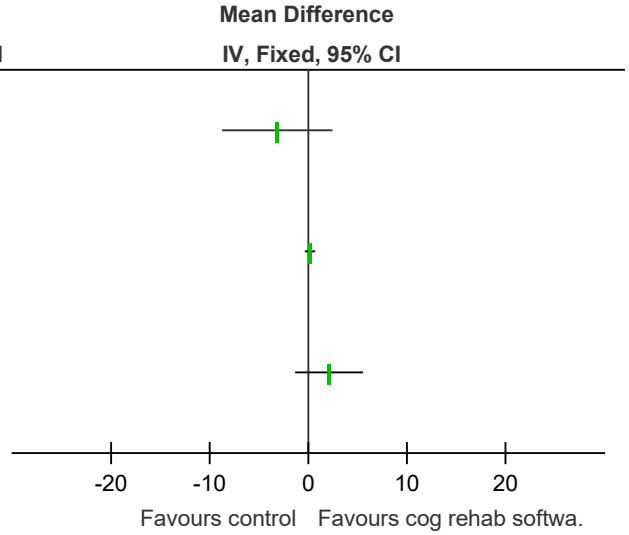
Study or Subgroup	Cog. rehab software Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Bove 2021	0.7	4.47	20	3.25	5.23	20	-2.55 [-5.57, 0.47]



1

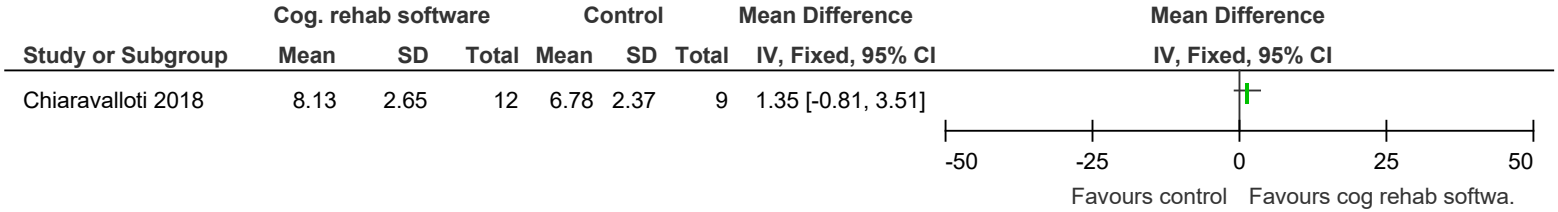
Figure 268: California Verbal Learning Test (higher better)

Study or Subgroup	Cog. rehab software Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
19.5.1 Number correct							
Bove 2021	2.05	9.14	20	5.2	8.6	20	-3.15 [-8.65, 2.35]
19.5.2 Learning slope							
Chiaravalloti 2018	1.17	0.61	12	0.99	0.4	9	0.18 [-0.25, 0.61]
19.5.3 Short-delay free recall							
Chiaravalloti 2018	8.75	4.27	12	6.65	3.54	9	2.10 [-1.24, 5.44]



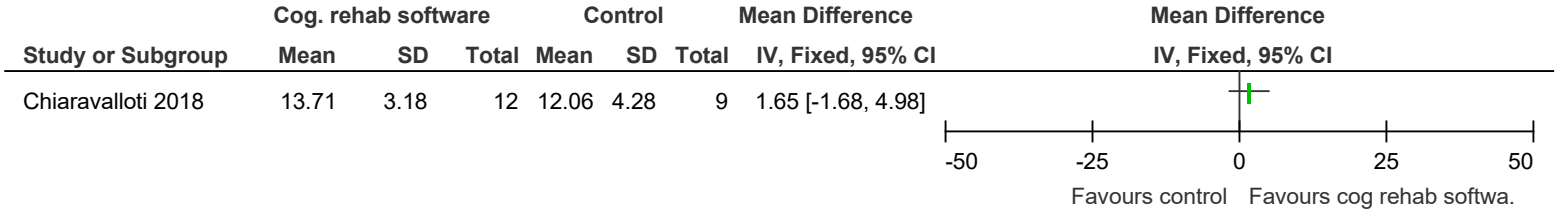
1

Figure 269: Letter comparison (perceptual speed; higher better)



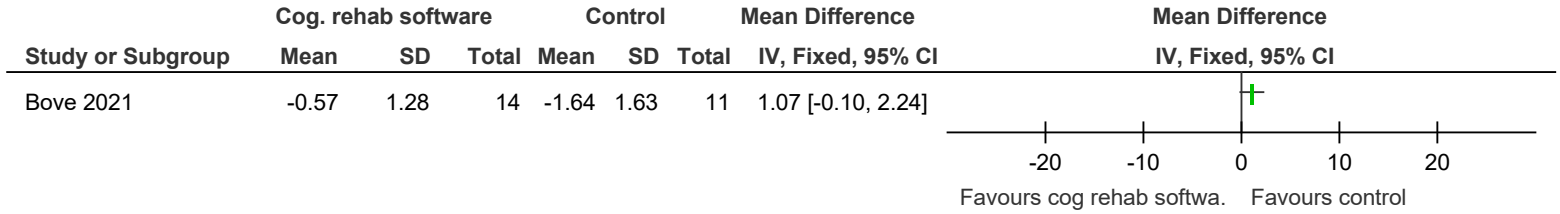
2

Figure 270: Pattern comparison (perceptual speed; higher better)



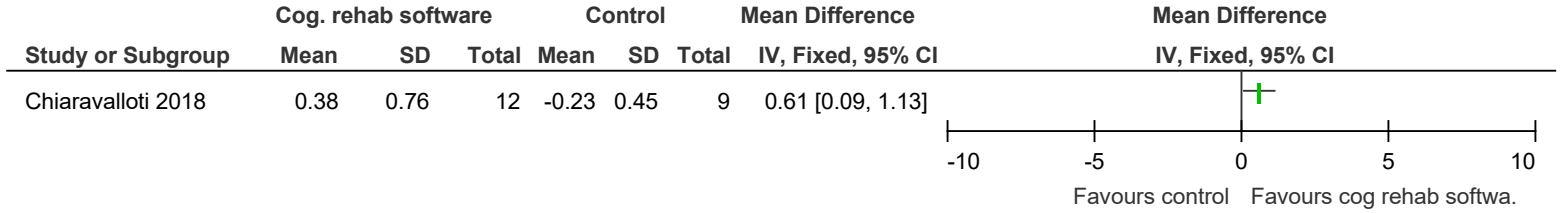
3

Figure 271: Perceived Deficits Questionnaire 5-item (scale usually 0-80; lower better)



1

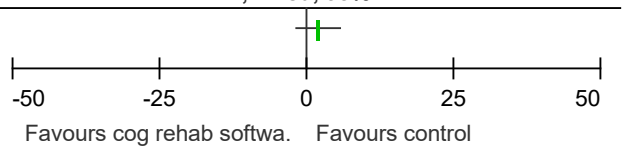
Figure 272: Timed Instrumental Activities of Daily Living Test (TIADL - z-score for speed and accuracy combined; higher better)



2

Figure 273: CES-D depression scale (scale usually 0-60; lower better)

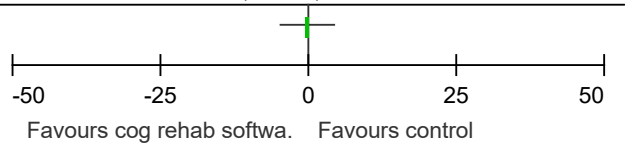
Study or Subgroup	Cog. rehab software Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Bove 2021	1.11	6.14	19	-0.9	5.57	19	2.01 [-1.72, 5.74]



1

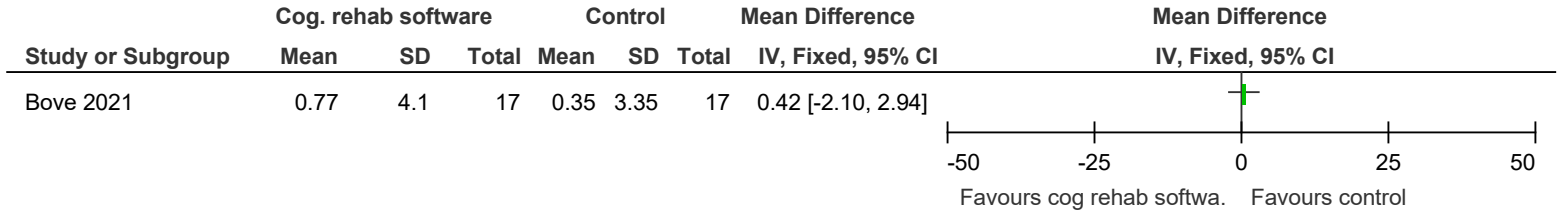
Figure 274: State-Trait Anxiety Index – State sub score (scale usually 20-80; lower better)

Study or Subgroup	Cog. rehab software Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Bove 2021	0.05	4.64	19	0.21	8.93	19	-0.16 [-4.69, 4.37]



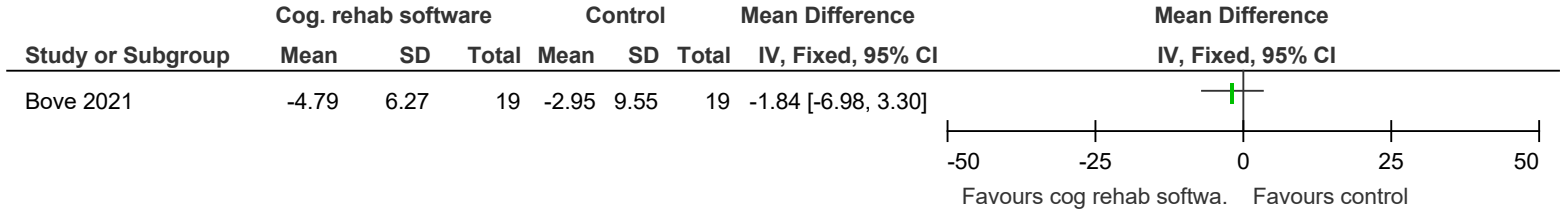
2

Figure 275: State-Trait Anxiety Index – Trait sub score (scale usually 20-80; lower better)



1

Figure 276: Modified Fatigue Impact Scale (scale usually 0-84; lower better)



2

E.20 Information processing speed + working memory: n-back training focused on processing speed + working memory vs. sham training (n-back with no increasing difficulty), 6 weeks

Figure 277: SDMT (higher better)

	N-back training for PS/WM			Sham training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hancock 2015	50.85	11.52	20	50.5	15.14	20	0.35 [-7.99, 8.69]	

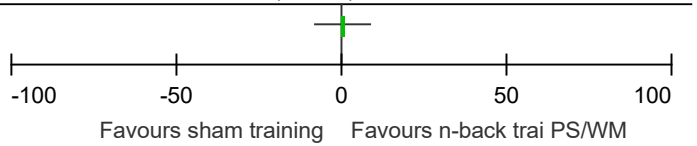


Figure 278: PASAT (higher better)

	N-back training for PS/WM			Sham training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hancock 2015	88.05	21.59	20	76.67	22.4	20	11.38 [-2.25, 25.01]	

Figure 279: Stroop Test (higher better)

Study or Subgroup	N-back training for PS/WM Mean	SD	Total	Sham training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hancock 2015	35.6	7.52	20	32.16	7.54	20	3.44 [-1.23, 8.11]

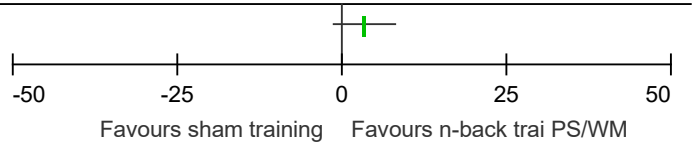


Figure 280: COWAT (higher better)

Study or Subgroup	N-back training for PS/WM Mean	SD	Total	Sham training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hancock 2015	42.15	15.23	20	37.95	14.23	20	4.20 [-4.93, 13.33]

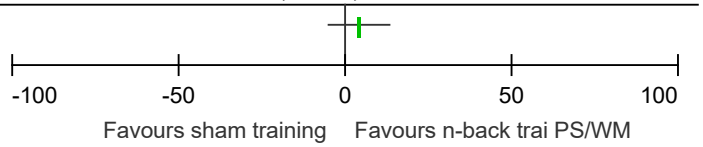


Figure 281: Letter-Number Sequencing (higher better)

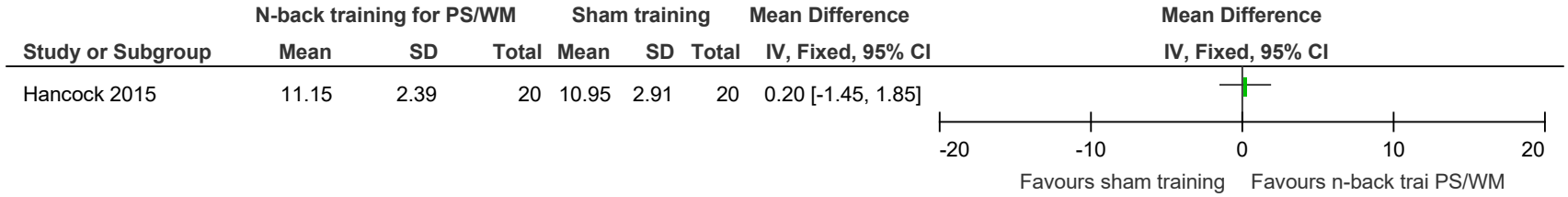


Figure 282: Digits Backwards (higher better)

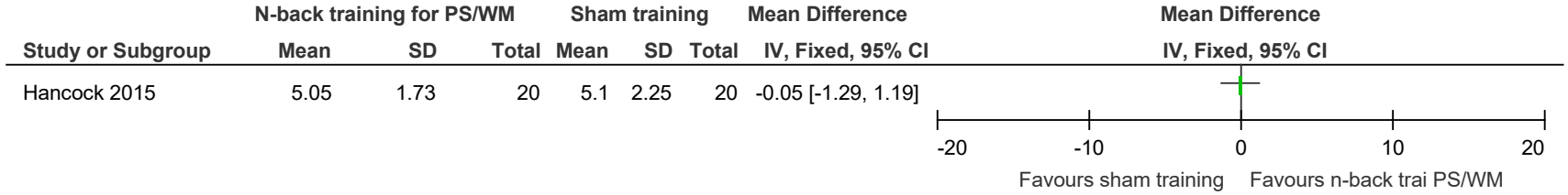
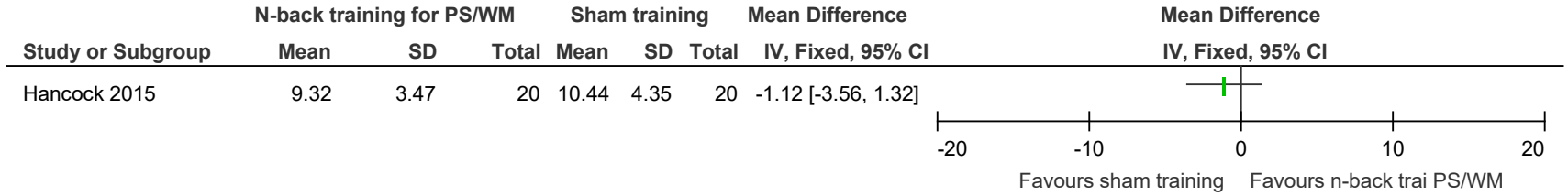
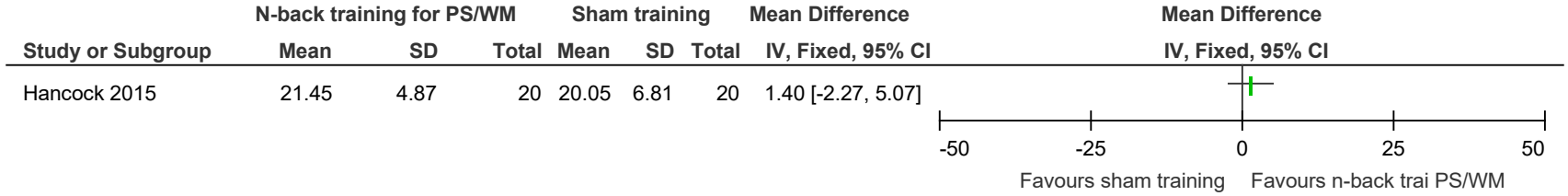


Figure 283: Raven's Advanced Progressive Matrices (test of fluid intelligence; higher better)



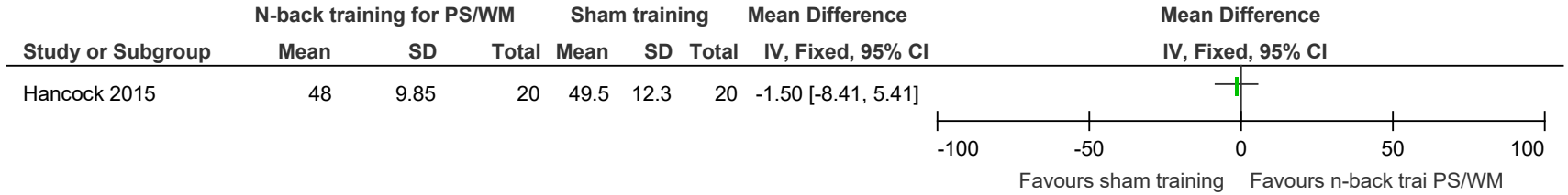
1

Figure 284: Brief Visuospatial Memory Test – Trials 1-3 (higher better)



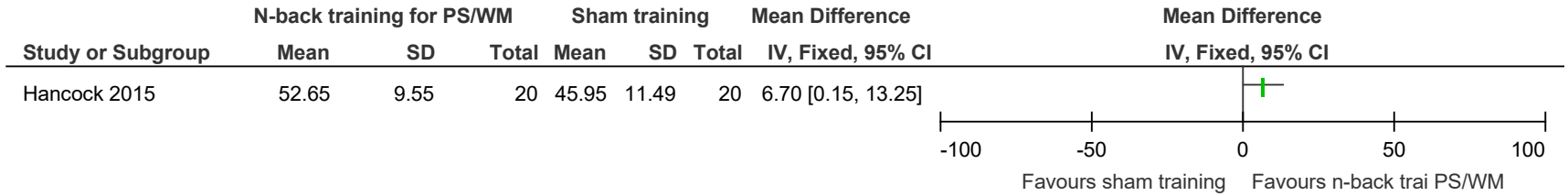
2

Figure 285: Conners' Continuous Performance Task Commissions - Speed (measures sustained attention and response inhibition, T-score; higher better)



1

Figure 286: Auditory Verbal Learning Task – Trials 1-5 (higher better)



2

Figure 287: MSQoL-54 (scale usually 0-100; higher better)

Study or Subgroup	N-back training for PS/WM Mean	SD	Total	Sham training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hancock 2015	70.5	12.77	20	75.45	15.12	20	-4.95 [-13.62, 3.72]

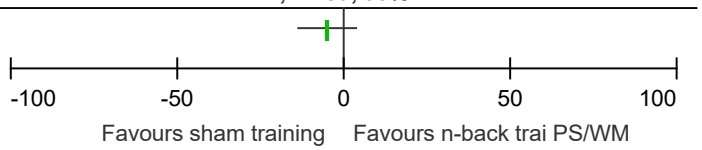


Figure 288: State-Trait Anxiety Inventory – State subscale (scale usually 20-80; lower better)

Study or Subgroup	N-back training for PS/WM Mean	SD	Total	Sham training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hancock 2015	45.6	6.29	20	44.33	5.73	20	1.27 [-2.46, 5.00]

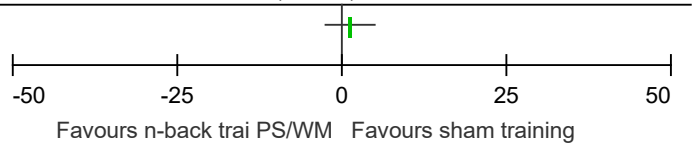
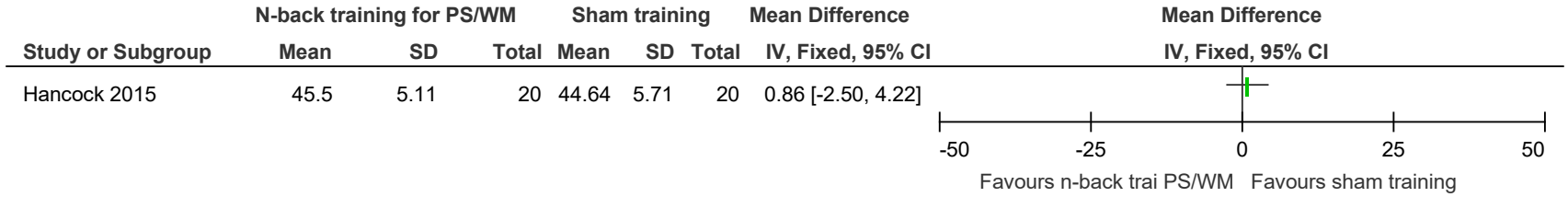
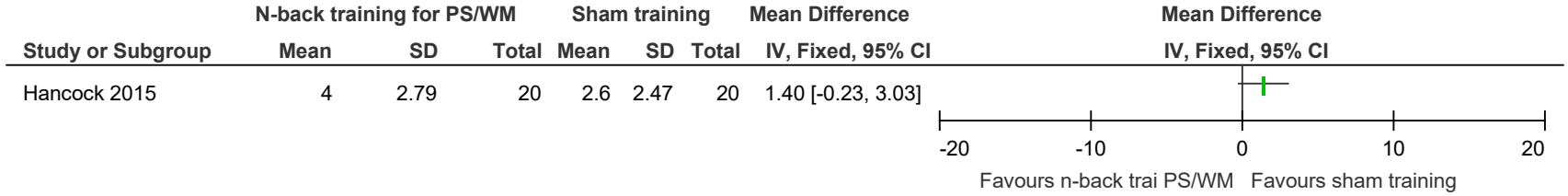


Figure 289: State-Trait Anxiety Inventory – Trait subscale (scale usually 20-80; lower better)



1

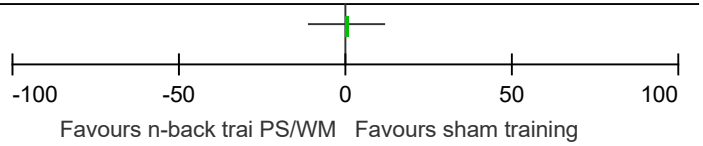
Figure 290: Beck Depression Inventory-Fast Screen (scale usually 0-21; lower better)



2

Figure 291: Modified Fatigue Impact Scale (scale usually 0-84; lower better)

	N-back training for PS/WM			Sham training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hancock 2015	43.95	17.45	20	43.6	18.98	20	0.35 [-10.95, 11.65]	



1

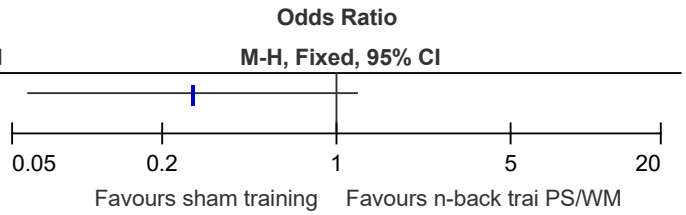
Figure 292: Adherence - % training completed (objective report; higher better)

	N-back training for PS/WM			Sham training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hancock 2015	94.63	12.58	20	95.3	12.01	20	-0.67 [-8.29, 6.95]	

2

Figure 293: Satisfaction – proportion very satisfied with overall study experience

	N-back training for PS/WM		Sham training		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Hancock 2015	12	20	17	20	0.26 [0.06, 1.21]



E.21 Attention/working memory: computer-aided RehaCom training (attention and information processing) vs. active control, 6 weeks

Figure 294: SDMT (higher better)

	RehaCom training			Active control tasks			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
21.1.1 Final values							
Cerasa 2013	38.69	9.9	12	37.3	8.45	11	1.39 [-6.11, 8.89]

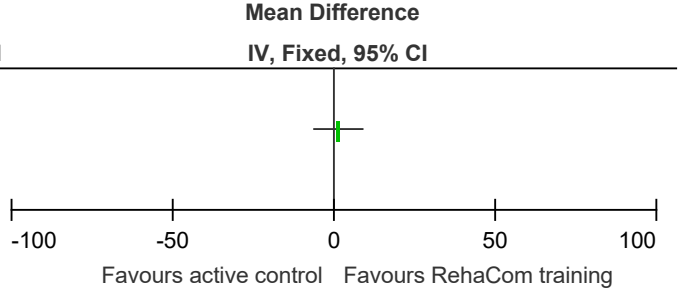
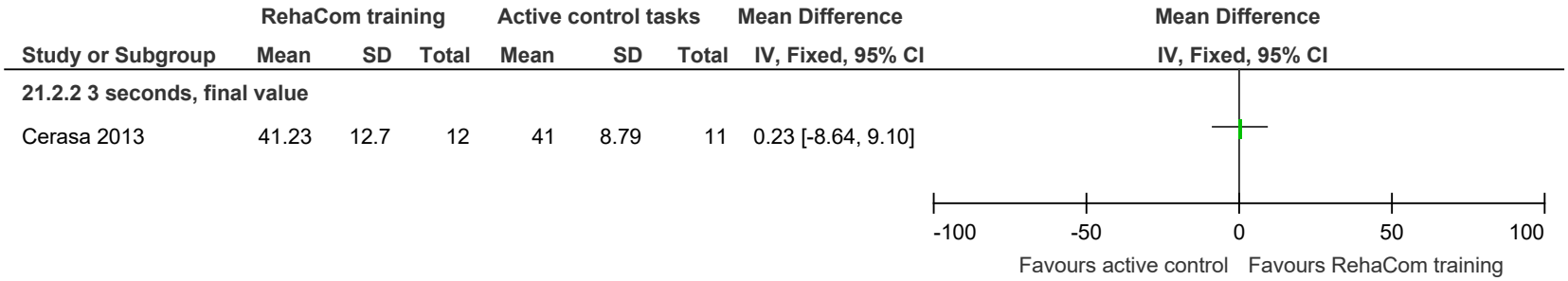
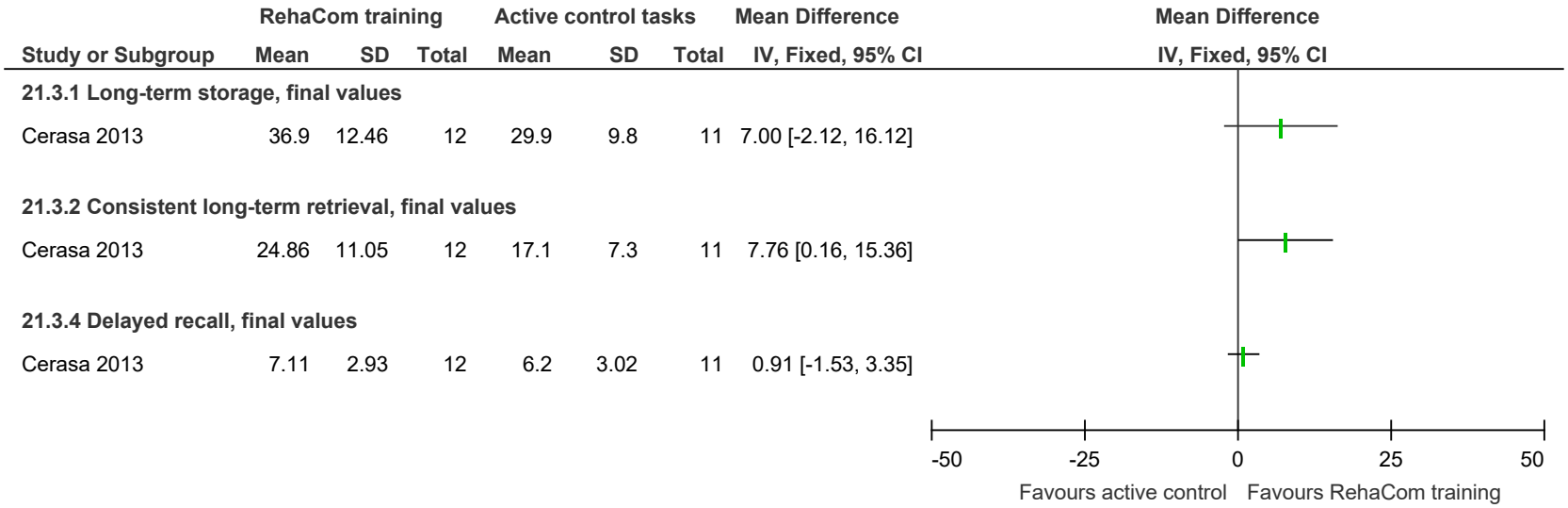


Figure 295: PASAT (higher better)



1

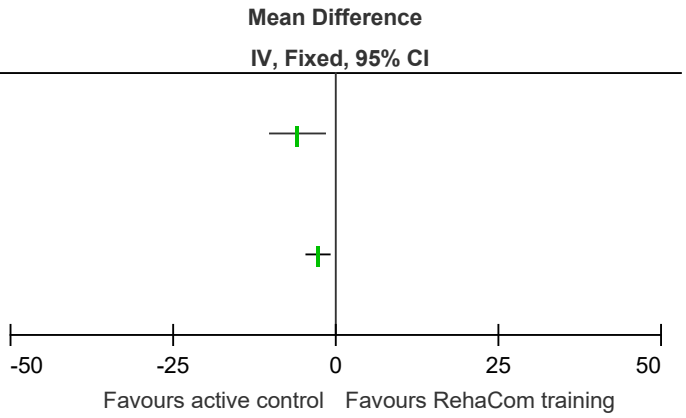
Figure 296: Selective Reminding Test (higher better)



1

Figure 297: Spatial Recall Test (SPART; higher better)

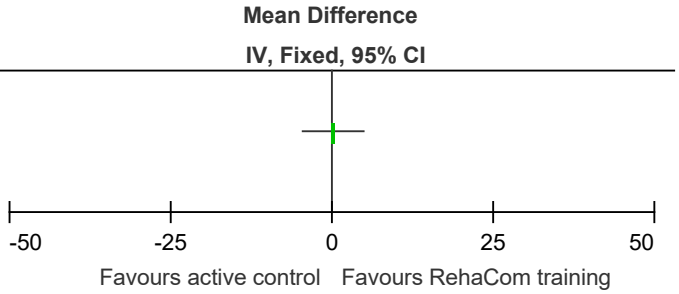
	RehaCom training			Active control tasks			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
21.4.1 Immediate, final values							
Cerasa 2013	18.42	6.22	12	24.3	3.99	11	-5.88 [-10.12, -1.64]
21.4.3 Delayed, final values							
Cerasa 2013	5.58	2.47	12	8.3	1.89	11	-2.72 [-4.51, -0.93]



1

Figure 298: Word List Generation test (higher better)

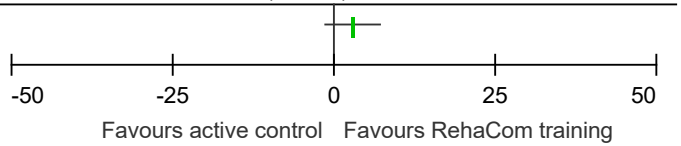
	RehaCom training			Active control tasks			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
21.5.1 Final values							
Cerasa 2013	20.8	5.96	12	20.6	5.59	11	0.20 [-4.52, 4.92]



1

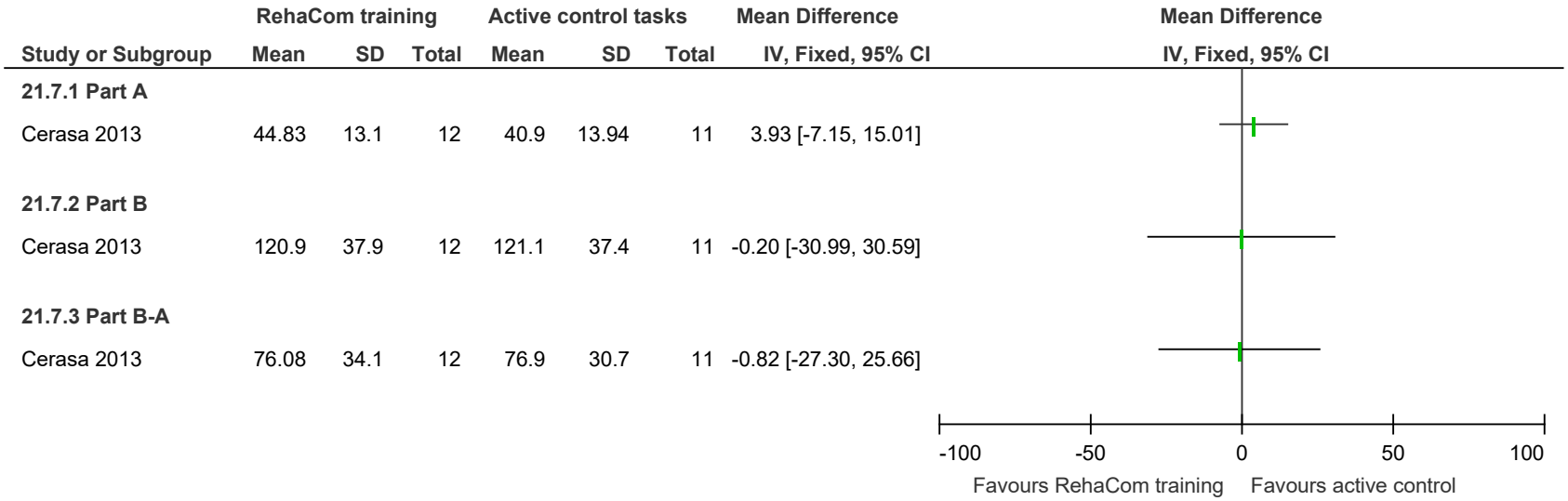
Figure 299: Stroop Test (higher better)

	RehaCom training			Active control tasks			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Cerasa 2013	19.41	5.14	12	16.5	5.22	11	2.91 [-1.33, 7.15]	



2

Figure 300: Trail Making Test (lower better)



1

Figure 301: State-Trait Anxiety Inventory Y1 (State?; scale usually 20-80; lower better)

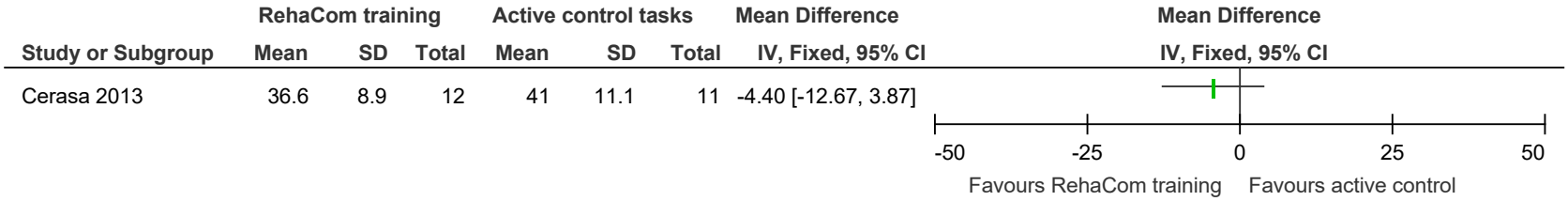


Figure 302: State-Trait Anxiety Inventory Y2 (Trait?; scale usually 20-80; lower better)

	RehaCom training			Active control tasks			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Cerasa 2013	35.5	8.6	12	46	11.1	11	-10.50 [-18.67, -2.33]	

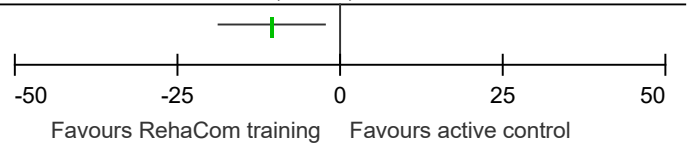


Figure 303: Beck Depression Inventory-II (scale usually 0-63; lower better)

	RehaCom training			Active control tasks			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Cerasa 2013	4.33	3.17	12	12.8	13.5	11	-8.47 [-16.65, -0.29]	

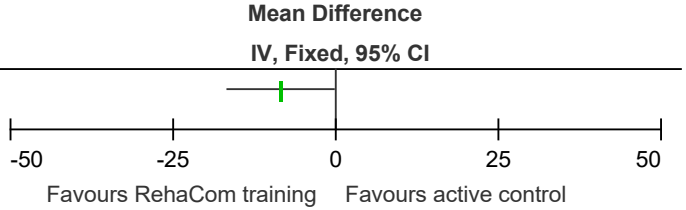
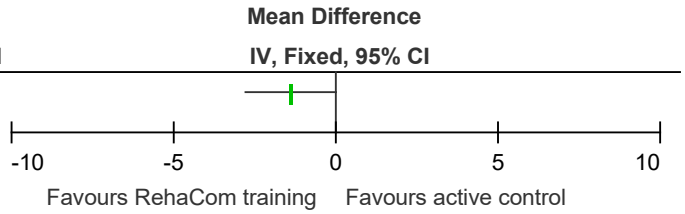


Figure 304: Fatigue Severity Scale (scale likely 1-7; lower better)

Study or Subgroup	RehaCom training Mean	SD	Total	Active control tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Cerasa 2013	2.83	1.63	12	4.22	1.77	11	-1.39 [-2.78, 0.00]



E.22 Attention/working memory: computer-aided training for attention/working memory vs. control, 18 weeks – 6 months

Figure 305: SDMT (higher better)

Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Blair 2021	39.73	7.51	11	40.64	9.79	11	25.5%	-0.91 [-8.20, 6.38]
Campbell 2016	3.35	4.17	17	4.57	7.21	14	74.5%	-1.22 [-5.49, 3.05]
Total (95% CI)			**28**			**25**	**100.0%**	**-1.14 [-4.82, 2.54]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%

Test for overall effect: Z = 0.61 (P = 0.54)

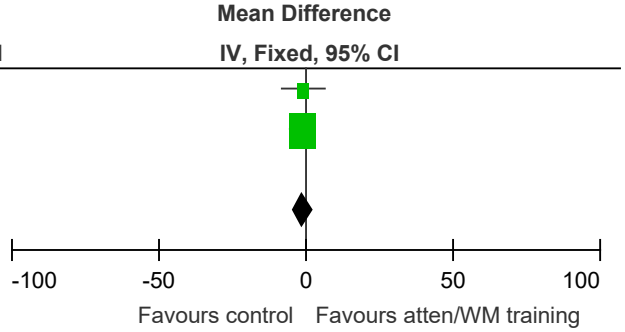
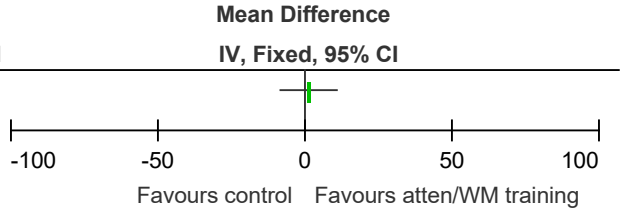


Figure 306: PASAT (higher better)

Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Blair 2021	35.18	10.69	11	33.91	12.2	11	1.27 [-8.32, 10.86]



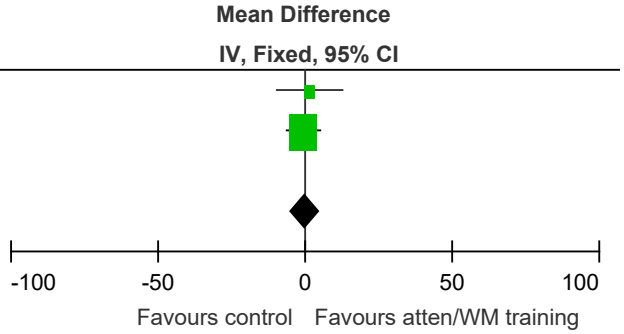
1

Figure 307: California Verbal Learning Test-II – Total Immediate Recall (higher better)

Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Blair 2021	46.55	13.53	11	45	13.09	11	20.8%	1.55 [-9.58, 12.68]
Campbell 2016	6.94	7.01	17	7.5	8.83	14	79.2%	-0.56 [-6.26, 5.14]
Total (95% CI)			**28**			**25**	**100.0%**	**-0.12 [-5.19, 4.95]**

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%

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



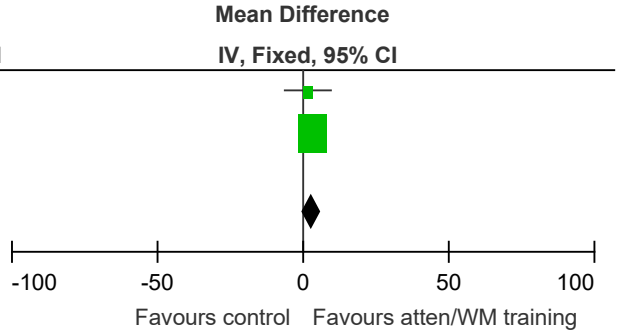
2

Figure 308: Brief Visuospatial Memory Test-Revised – Total Immediate Recall (higher better)

Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Blair 2021	19.27	10.43	11	17.64	8.38	11	17.8%	1.63 [-6.28, 9.54]
Campbell 2016	7.29	5.07	17	4.14	5.32	14	82.2%	3.15 [-0.53, 6.83]
Total (95% CI)			**28**			**25**	**100.0%**	**2.88 [-0.46, 6.22]**

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%

Test for overall effect: Z = 1.69 (P = 0.09)



1

Figure 309: Wechsler Memory Scale III – Spatial Span (higher better)

Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
22.5.1 Forward							
Blair 2021	6.09	1.22	11	6.82	1.47	11	-0.73 [-1.86, 0.40]
22.5.2 Backward							
Blair 2021	6.18	1.66	11	6.45	1.51	11	-0.27 [-1.60, 1.06]

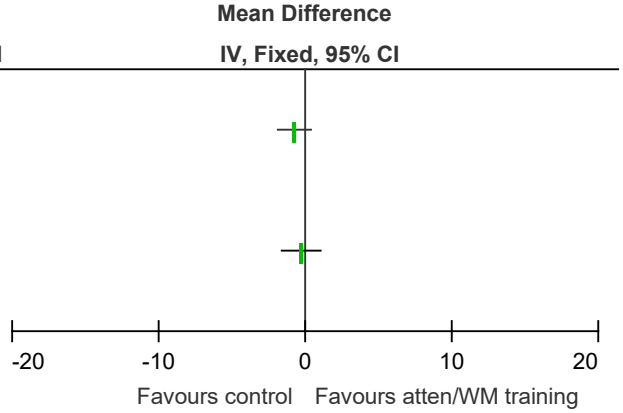


Figure 310: Wechsler Adult Intelligence Scale-III (higher better)

Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
22.6.1 Arithmetic							
Blair 2021	12	3	11	11	2.61	11	1.00 [-1.35, 3.35]
22.6.2 Letter-Number Sequencing							
Blair 2021	8.45	2.58	11	7.82	3.28	11	0.63 [-1.84, 3.10]
22.6.3 Digit span forward							
Blair 2021	9.18	2.32	11	8.82	1.66	11	0.36 [-1.33, 2.05]
22.6.4 Digit span backward							
Blair 2021	6.09	1.3	11	5.36	1.86	11	0.73 [-0.61, 2.07]

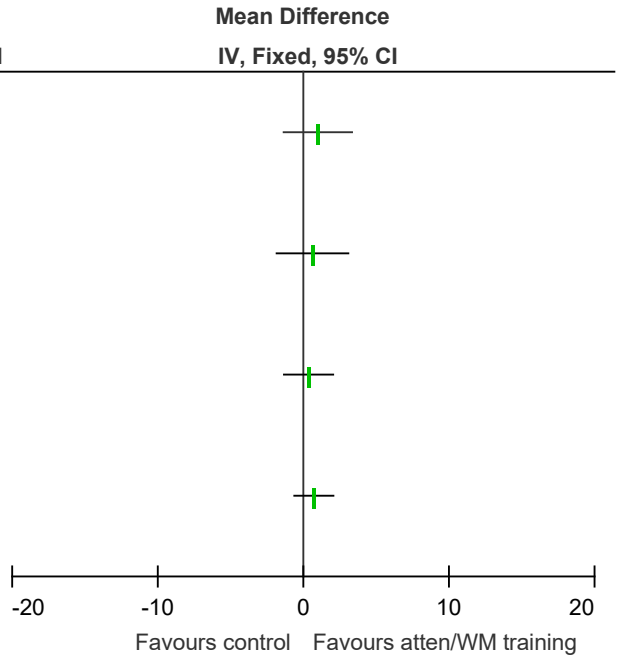
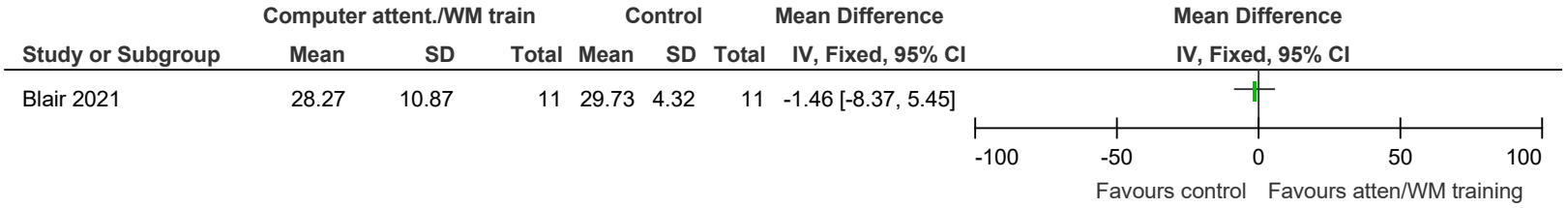


Figure 311: Delis-Kaplan Executive Function System (D-KEFS) – Color-Word Interference (higher better)



1

Figure 312: N-back test errors (lower better)

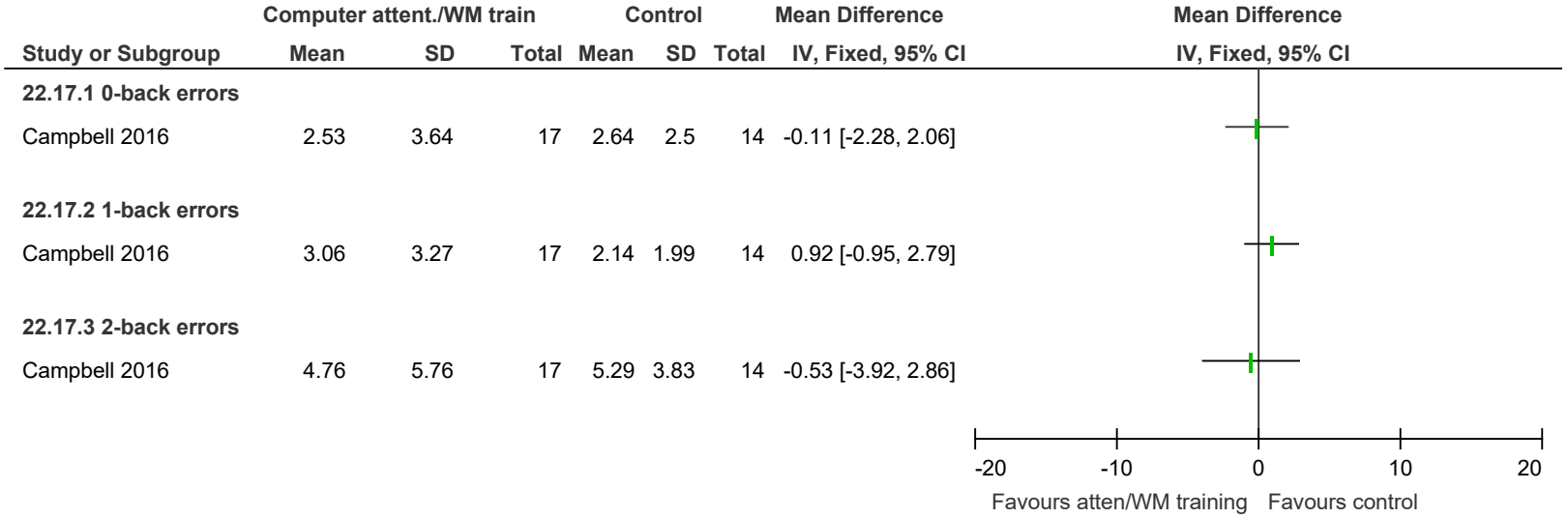


Figure 313: MS Neuropsychological Screening Questionnaire (scale usually 0-60; lower better)

	Computer attent./WM train			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Blair 2021	28.55	15.16	11	29.91	10.83	11	45.0%	-1.36 [-12.37, 9.65]
Campbell 2016	29.18	15.14	17	28.93	13.13	14	55.0%	0.25 [-9.70, 10.20]
Total (95% CI)			**28**			**25**	**100.0%**	**-0.47 [-7.86, 6.91]**

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%

Test for overall effect: Z = 0.13 (P = 0.90)

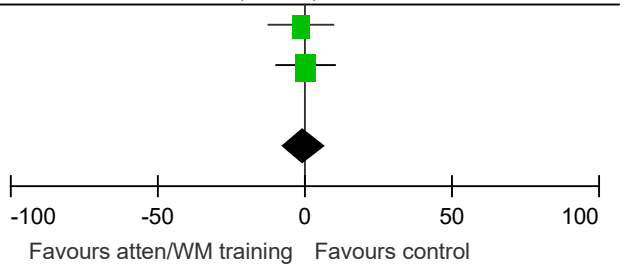


Figure 314: Cognitive Failure Questionnaire (scale usually 0-100; lower better)

	Computer attent./WM train			Control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Blair 2021	43.26	24.25	11	36.45	20.54	11	6.81 [-11.97, 25.59]

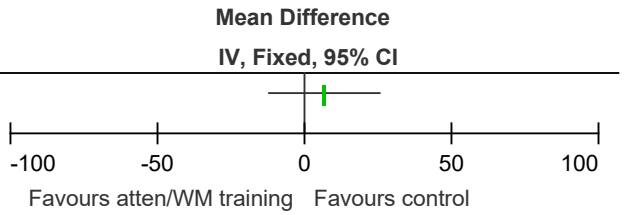
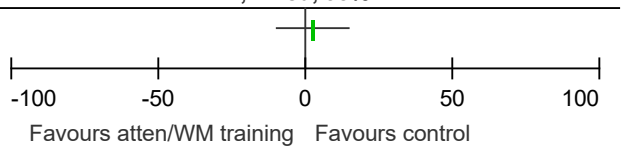


Figure 315: Dysexecutive Questionnaire (scale usually 0-80; lower better)

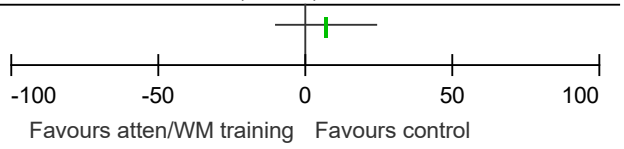
	Computer attent./WM train			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Blair 2021	23.09	17.68	11	20.55	10.82	11	2.54 [-9.71, 14.79]	



1

Figure 316: Perceived Deficits Questionnaire (scale usually 0-80; lower better)

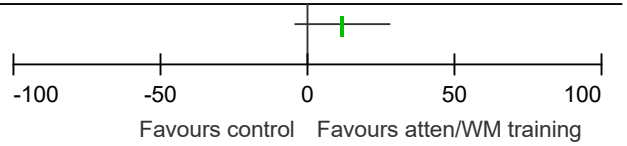
	Computer attent./WM train			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Blair 2021	37.82	24.19	11	30.73	15.74	11	7.09 [-9.96, 24.14]	



2

Figure 317: SF-36 quality of life (unclear which subscale or composite; scale usually 0-100; higher better)

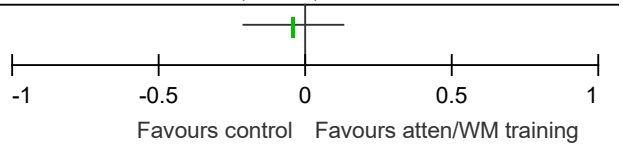
	Computer attent./WM train			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Blair 2021	56.45	23.79	11	44.55	12.78	11	11.90 [-4.06, 27.86]	



1

Figure 318: EQ-5D (scale 0-1; higher better)

	Computer attent./WM train			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Campbell 2016	0.53	0.2	17	0.57	0.27	14	-0.04 [-0.21, 0.13]	



2

Figure 319: Functional Assessment of MS (FAMS; scale usually 0-176; higher better)

	Computer attent./WM train			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Campbell 2016	89	30.99	17	101	32.4	14	-12.00 [-34.47, 10.47]	

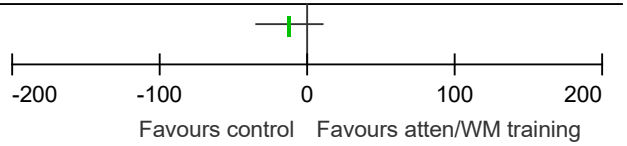


Figure 320: Beck Depression Inventory-Fast Screen (scale usually 0-21; lower better)

	Computer attent./WM train			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Blair 2021	2.64	3.26	11	2.73	3.52	11	-0.09 [-2.93, 2.75]	

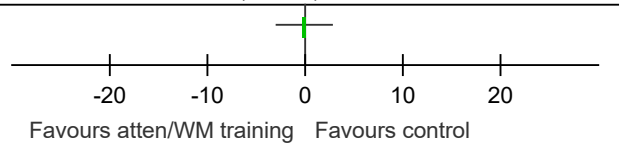
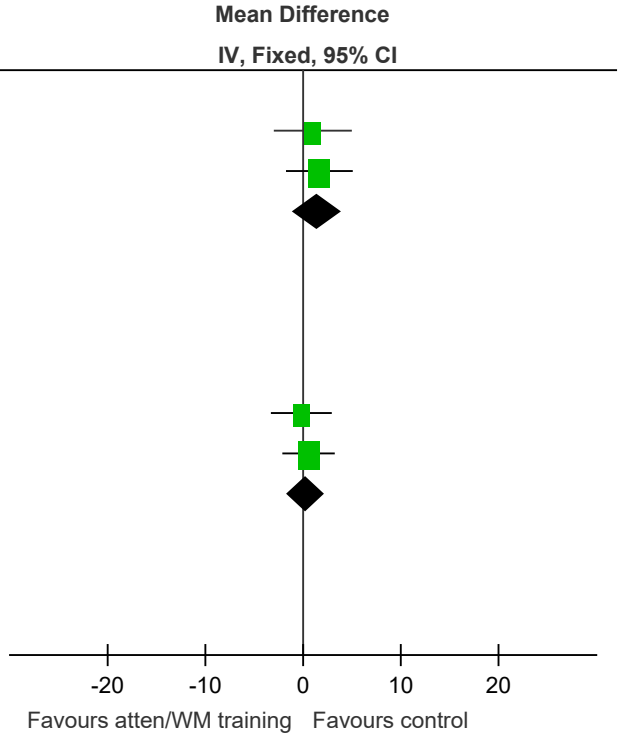


Figure 321: Hospital Anxiety and Depression Scale (HADS; scale usually 0-21; lower better)

Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
22.27.1 Anxiety								
Blair 2021	7.09	4.35	11	6.09	4.95	11	42.0%	1.00 [-2.89, 4.89]
Campbell 2016	8.53	4.38	17	6.86	4.93	14	58.0%	1.67 [-1.65, 4.99]
Subtotal (95% CI)			**28**			**25**	**100.0%**	**1.39 [-1.14, 3.91]**
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0%								
Test for overall effect: Z = 1.08 (P = 0.28)								
22.27.2 Depression								
Blair 2021	4.73	4.03	11	4.91	3.15	11	42.3%	-0.18 [-3.20, 2.84]
Campbell 2016	9.35	2.85	17	8.79	4.21	14	57.7%	0.56 [-2.03, 3.15]
Subtotal (95% CI)			**28**			**25**	**100.0%**	**0.25 [-1.72, 2.21]**
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%								
Test for overall effect: Z = 0.25 (P = 0.81)								



1

Figure 322: Fatigue Severity Scale (1-7 scale and 9-63 scale; lower better)

	Computer attent./WM train			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
22.28.1 1-7 scale								
Blair 2021	4.89	2.26	11	5.18	1.26	11	-0.29 [-1.82, 1.24]	
22.28.2 9-63 scale								
Campbell 2016	52.53	11.47	17	49.29	15.5	14	3.24 [-6.54, 13.02]	

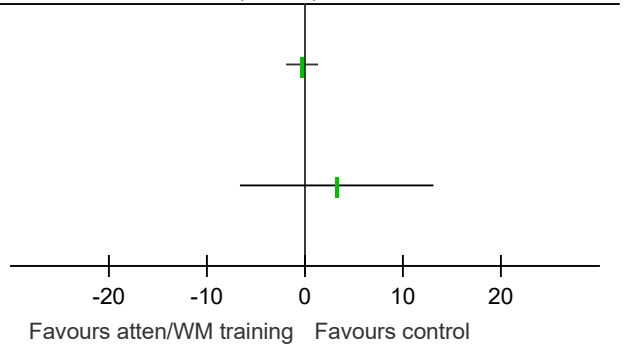


Figure 323: Patient Activation Measure-13 (PAM-13; measures engagement in health; scale usually 0-100; higher better)

	Computer attent./WM train			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Campbell 2016	58.79	15.52	17	62.1	15.9	14	-3.31 [-14.44, 7.82]	

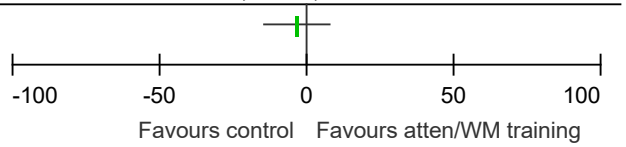
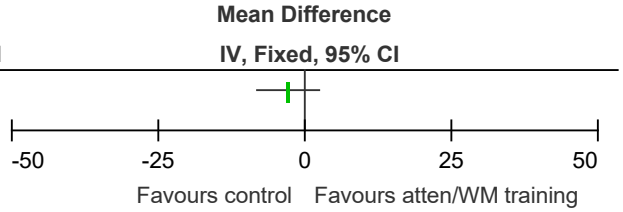


Figure 324: Unidimensional Self-Efficacy Scale for MS (USE-MS; scale unclear; higher better)

Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Campbell 2016	16.47	5.7	17	19.31	8.7	14	-2.84 [-8.14, 2.46]



E.23 Attention/working memory: high-intensity working memory training vs. distributed working memory training, 4-8 weeks

Figure 325: SDMT (higher better)

Study or Subgroup	High-intensity WM trainin Mean	SD	Total	Distributed WM training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Vogt 2009	53.87	14.78	15	62.22	16.22	15	-8.35 [-19.45, 2.75]

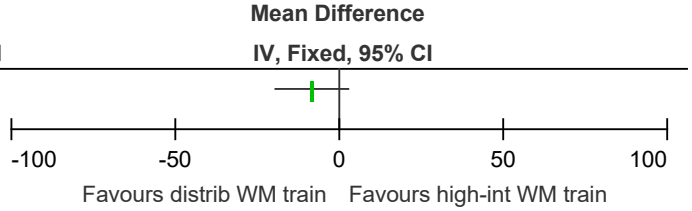
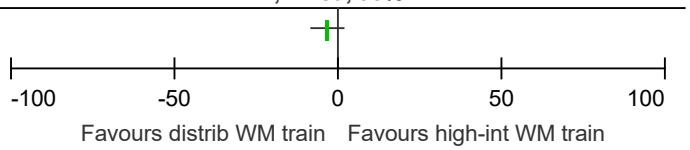


Figure 326: PASAT (higher better)

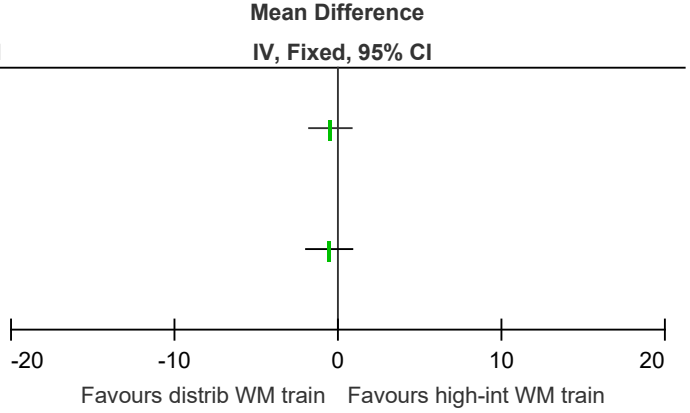
Study or Subgroup	High-intensity WM trainin Mean	SD	Total	Distributed WM training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Vogt 2009	50.41	7.91	15	53.61	5.69	15	-3.20 [-8.13, 1.73]



1

Figure 327: Corsi blocks (higher better)

Study or Subgroup	High-intensity WM trainin Mean	SD	Total	Distributed WM training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
23.3.1 Backward							
Vogt 2009	8.87	2.03	15	9.33	1.58	15	-0.46 [-1.76, 0.84]
23.3.2 Forward							
Vogt 2009	7.2	2.01	15	7.73	1.94	15	-0.53 [-1.94, 0.88]



2

Figure 328: Digit Span (higher better)

Study or Subgroup	High-intensity WM trainin Mean	SD	Total	Distributed WM training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
23.4.1 Backward							
Vogt 2009	7.87	2.38	15	7.41	1.72	15	0.46 [-1.03, 1.95]
23.4.2 Forward							
Vogt 2009	8.87	2.03	15	9.33	1.58	15	-0.46 [-1.76, 0.84]

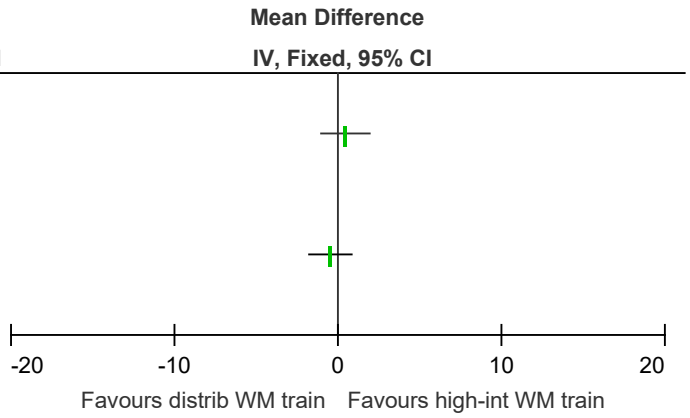


Figure 329: 2-back number correct (higher better)

Study or Subgroup	High-intensity WM trainin Mean	SD	Total	Distributed WM training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Vogt 2009	55.07	4.02	15	57.33	4.06	15	-2.26 [-5.15, 0.63]

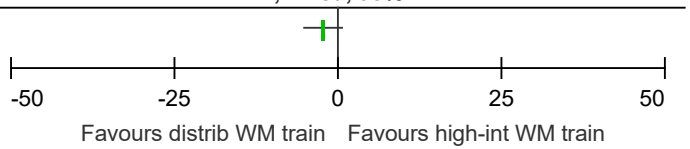
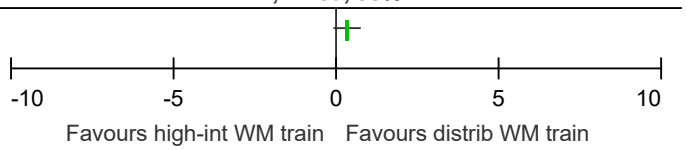


Figure 330: 2-back omissions (lower better)

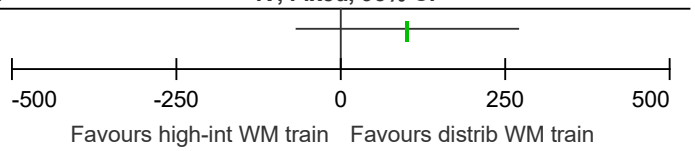
	High-intensity WM trainin			Distributed WM training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Vogt 2009	0.4	0.73	15	0.06	0.26	15	0.34 [-0.05, 0.73]	



1

Figure 331: 2-back reaction time (lower better)

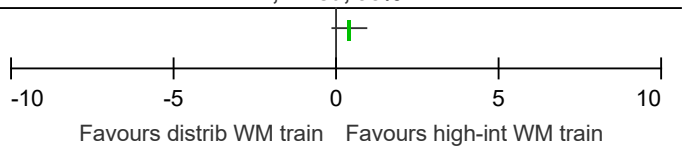
	High-intensity WM trainin			Distributed WM training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Vogt 2009	767.66	272.31	15	666.4	191.57	15	101.26 [-67.23, 269.75]	



2

Figure 332: Faces Symbol Test (higher better)

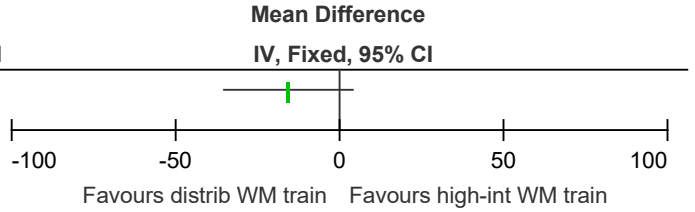
Study or Subgroup	High-intensity WM trainin Mean	SD	Total	Distributed WM training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Vogt 2009	2.54	0.73	15	2.13	0.73	15	0.41 [-0.11, 0.93]



1

Figure 333: Functional Assessment of MS (FAMS; scale usually 0-176; higher better)

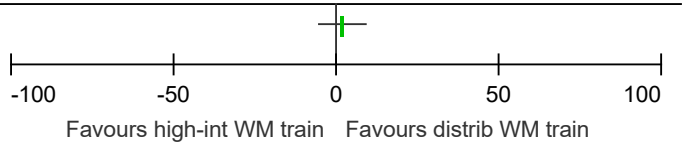
Study or Subgroup	High-intensity WM trainin Mean	SD	Total	Distributed WM training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Vogt 2009	118.61	34.08	15	134.2	18.57	15	-15.59 [-35.23, 4.05]



2

Figure 334: Allgemeine Depressionsskala (scale unclear; lower better)

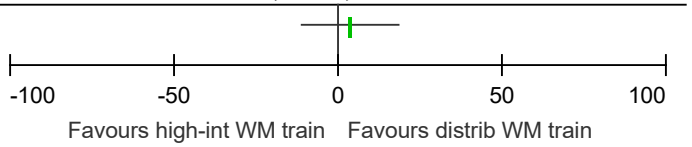
	High-intensity WM trainin			Distributed WM training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Vogt 2009	12.21	12.2	15	10.26	7.32	15	1.95 [-5.25, 9.15]	



1

Figure 335: Fatigue Scale for Motor and Cognitive Functions (scale usually 20-100; lower better)

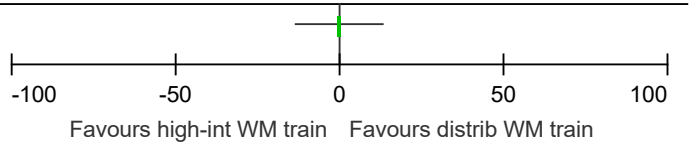
	High-intensity WM trainin			Distributed WM training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Vogt 2009	61.73	19.08	15	58	22.08	15	3.73 [-11.04, 18.50]	



2

Figure 336: Modified Fatigue Impact Scale (scale usually 0-84; lower better)

	High-intensity WM trainin			Distributed WM training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Vogt 2009	34.13	17.34	15	34.23	19.66	15	-0.10 [-13.37, 13.17]	



E.24 Attention/working memory: high-intensity working memory training vs. control (no training), 4 weeks

Figure 337: SDMT (higher better)

	High-intensity WM trainin			No training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Vogt 2009	53.87	14.78	15	58.67	19.19	15	-4.80 [-17.06, 7.46]	

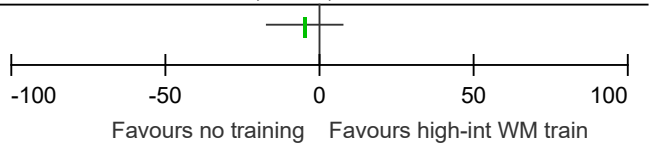
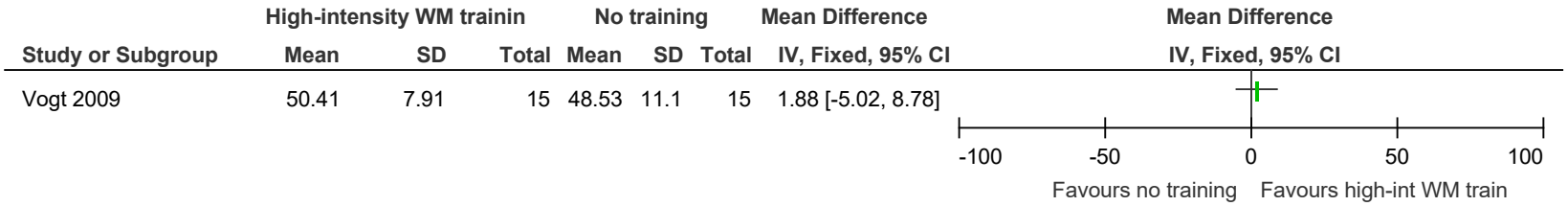
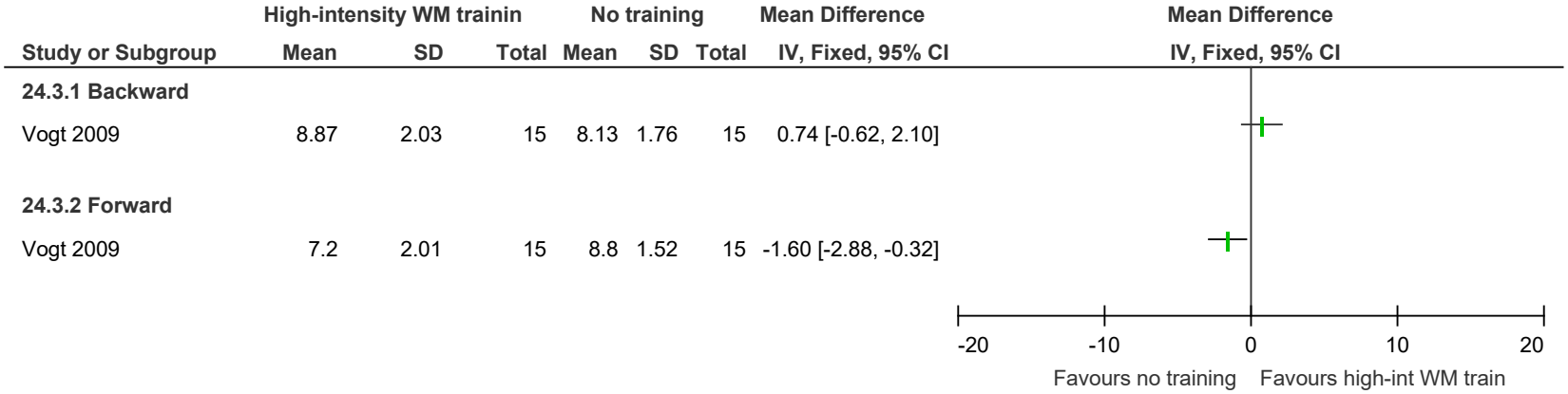


Figure 338: PASAT (higher better)



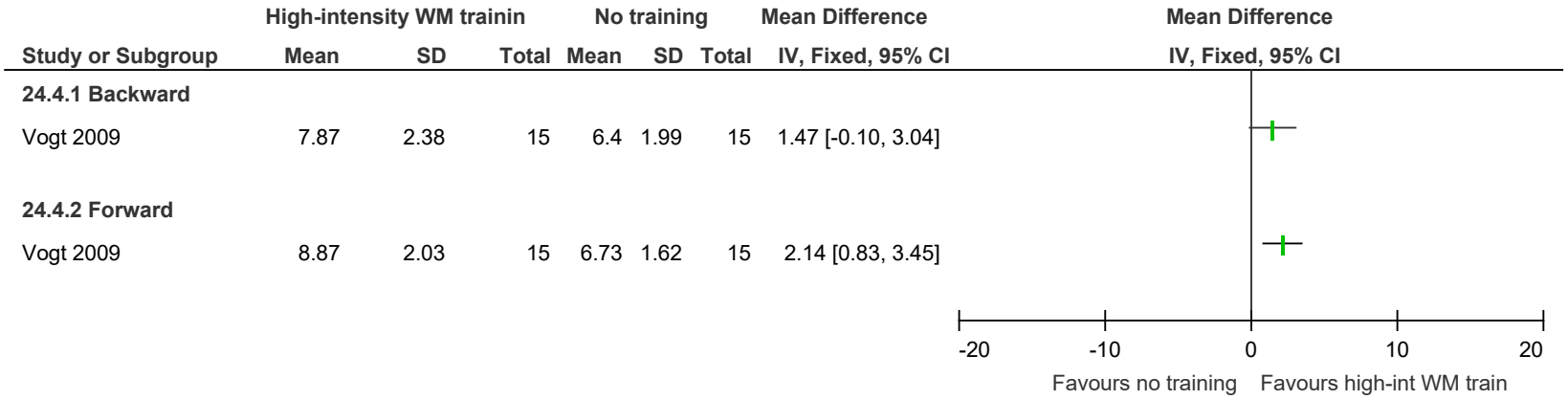
1

Figure 339: Corsi blocks (higher better)



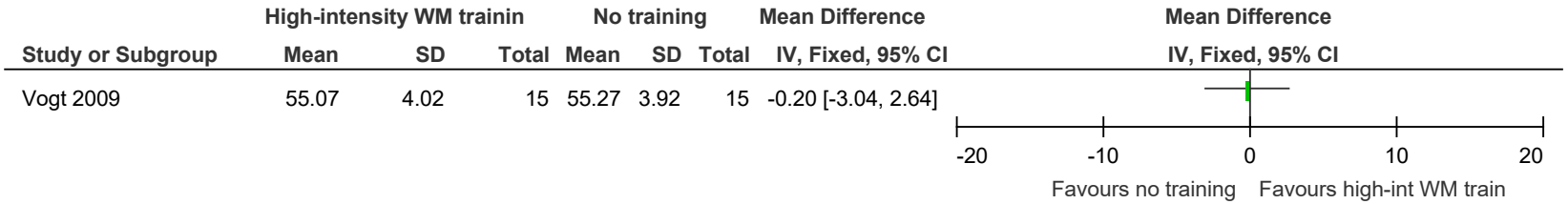
2

Figure 340: Digit Span (higher better)



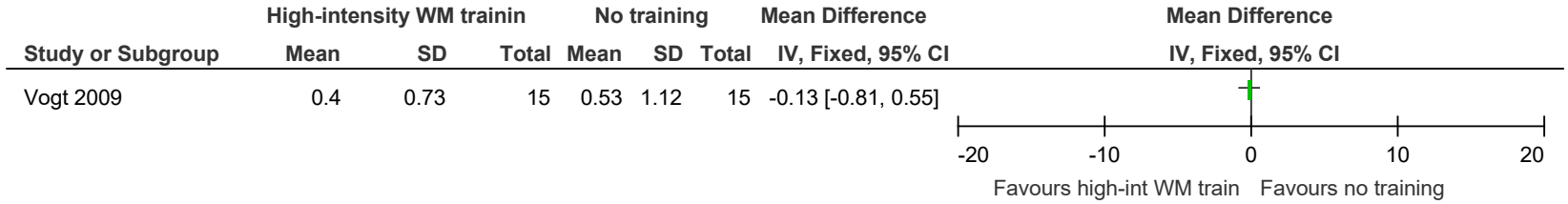
1

Figure 341: 2-back number correct (higher better)



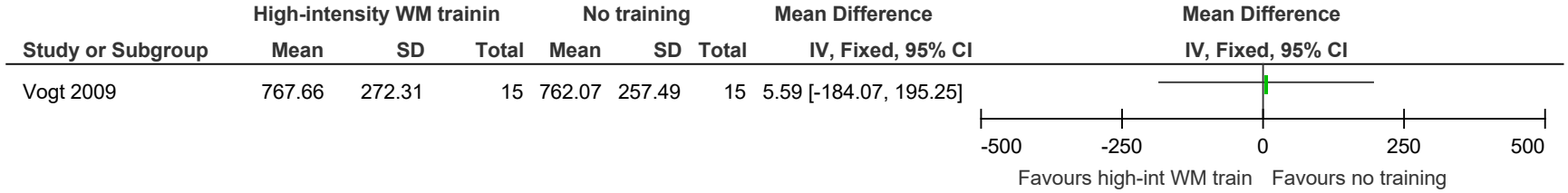
2

Figure 342: 2-back omissions (lower better)



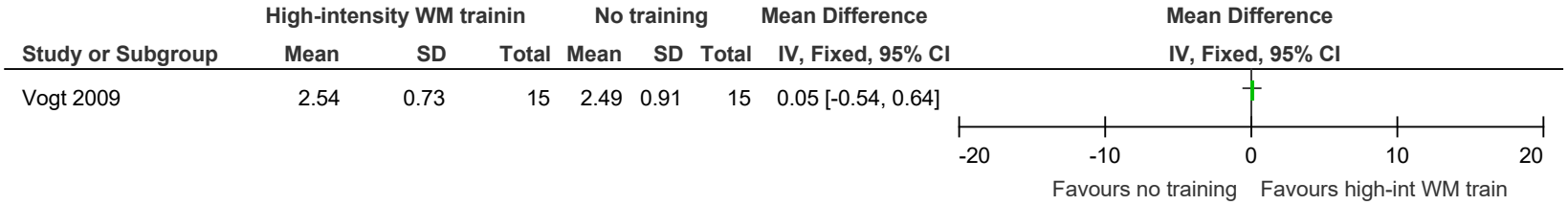
1

Figure 343: 2-back reaction time (lower better)



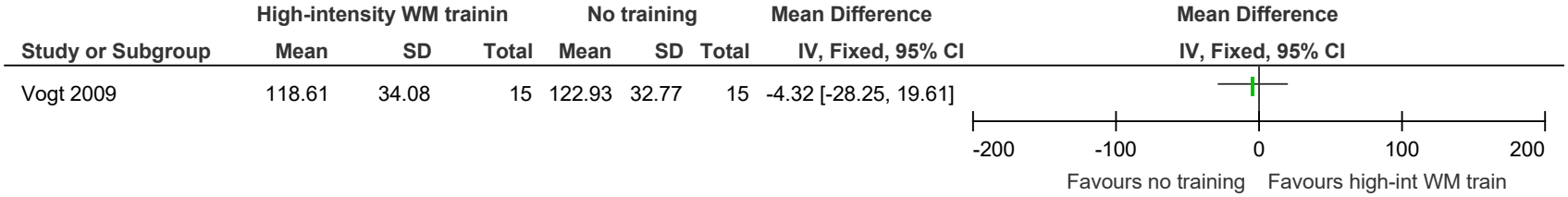
2

Figure 344: Faces Symbol Test (higher better)



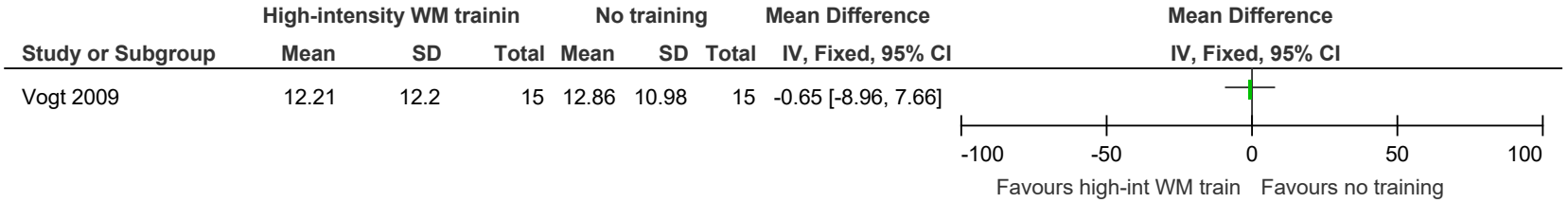
1

Figure 345: Functional Assessment of MS (FAMS; scale usually 0-176; higher better)



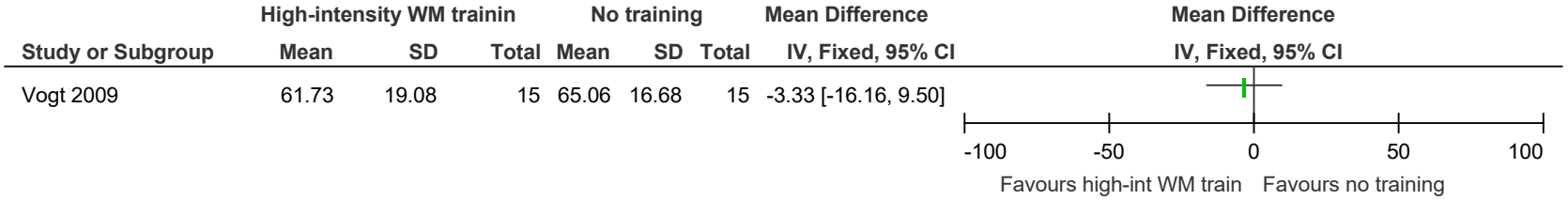
2

Figure 346: Allgemeine Depressionsskala (scale unclear; lower better)



1

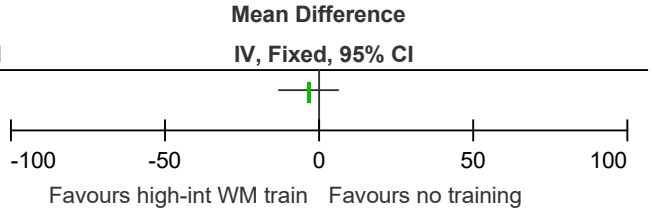
Figure 347: Fatigue Scale for Motor and Cognitive Functions (scale usually 20-100; lower better)



2

Figure 348: Modified Fatigue Impact Scale (scale usually 0-84; lower better)

Study or Subgroup	High-intensity WM trainin Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Vogt 2009	34.13	17.34	15	37.53	7.29	15	-3.40 [-12.92, 6.12]



E.25 Attention/working memory: distributed working memory training vs. control (no training), 4-8 weeks

Figure 349: SDMT (higher better)

Study or Subgroup	Distributed WM training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Vogt 2009	62.22	16.22	15	58.67	19.19	15	3.55 [-9.17, 16.27]

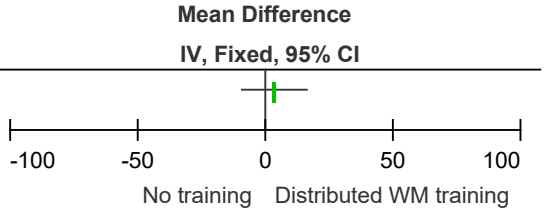
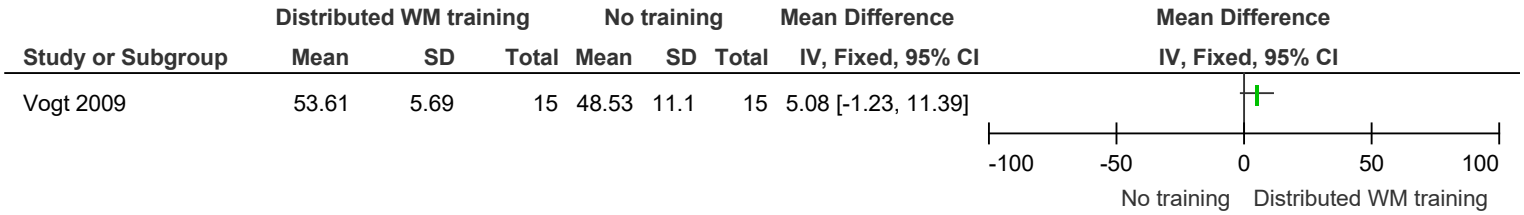
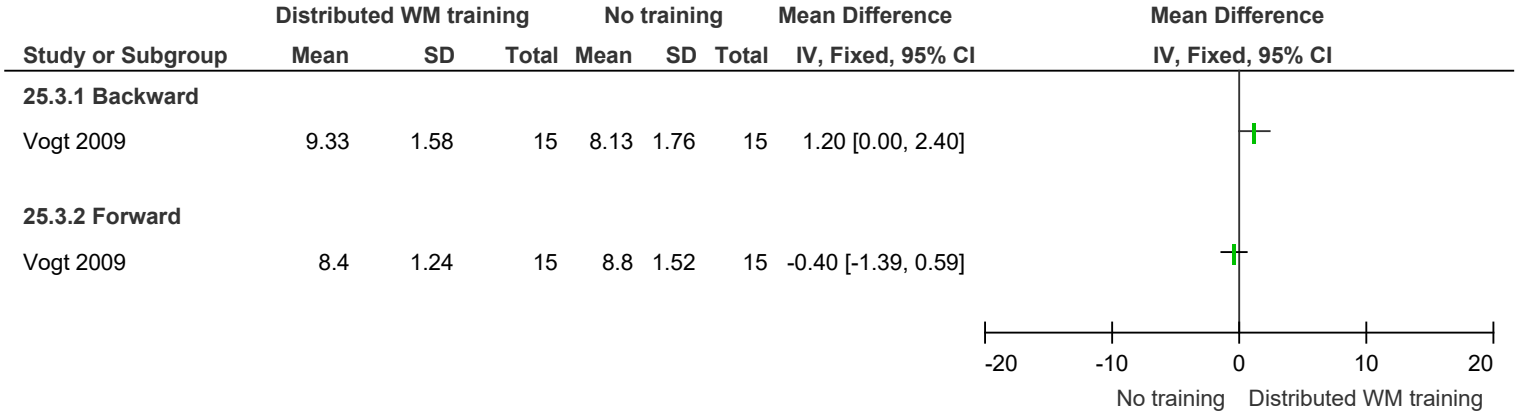


Figure 350: PASAT (higher better)



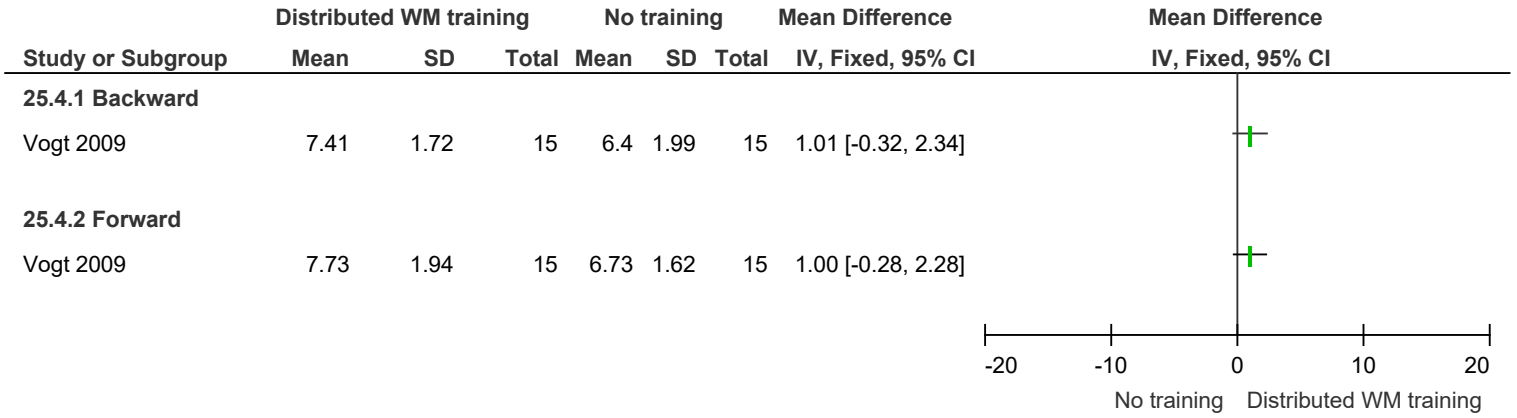
1

Figure 351: Corsi blocks (higher better)



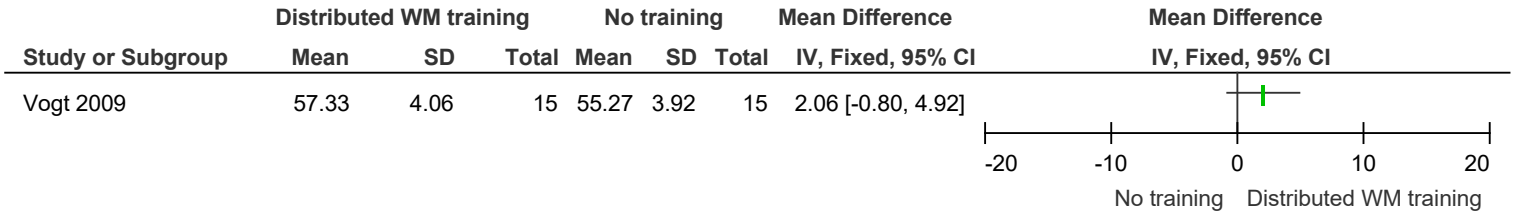
2

Figure 352: Digit Span (higher better)



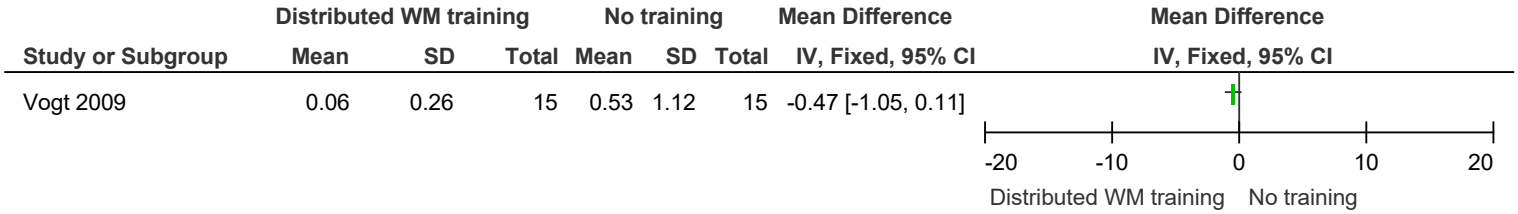
1

Figure 353: 2-back number correct (higher better)



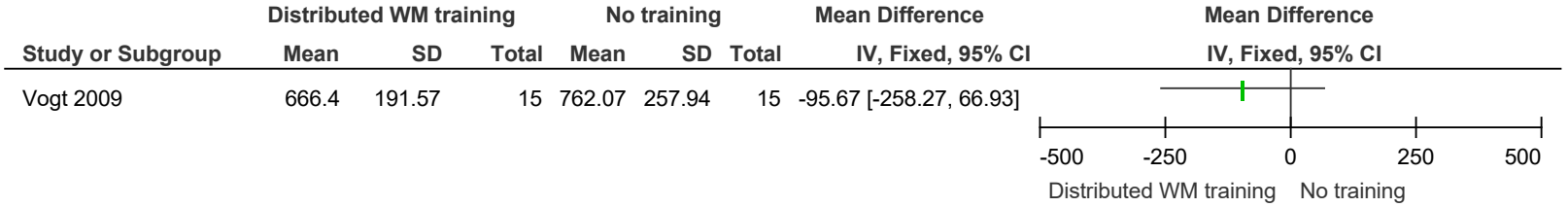
2

Figure 354: 2-back omissions (lower better)



1

Figure 355: 2-back reaction time (lower better)



2

Figure 356: Faces Symbol Test (higher better)

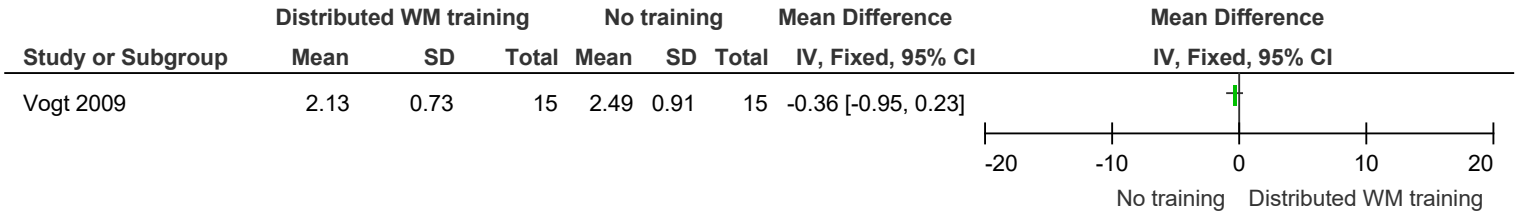


Figure 357: Functional Assessment of MS (FAMS; scale usually 0-176; higher better)

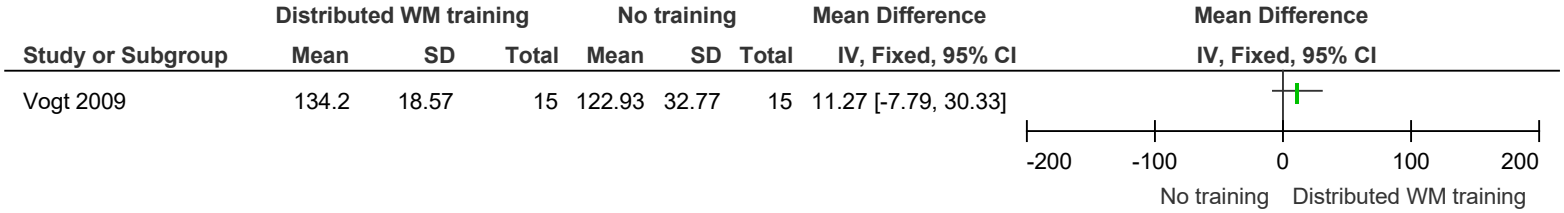
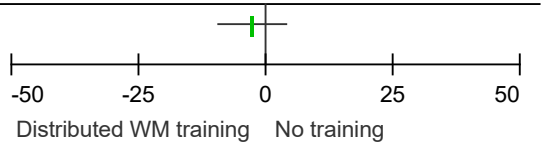


Figure 358: Allgemeine Depressionsskala (scale unclear; lower better)

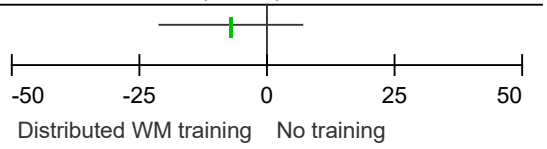
	Distributed WM training			No training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Vogt 2009	10.26	7.32	15	12.86	10.98	15	-2.60 [-9.28, 4.08]	



1

Figure 359: Fatigue Scale for Motor and Cognitive Functions (scale usually 20-100; lower better)

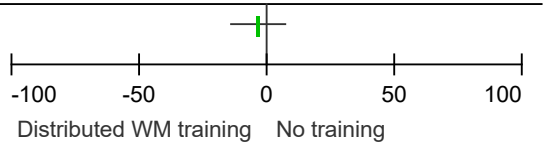
	Distributed WM training			No training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Vogt 2009	58	22.08	15	65.06	16.68	15	-7.06 [-21.06, 6.94]	



2

Figure 360: Modified Fatigue Impact Scale (scale usually 0-84; lower better)

Study or Subgroup	Distributed WM training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Vogt 2009	34.23	19.66	15	37.53	7.29	15	-3.30 [-13.91, 7.31]

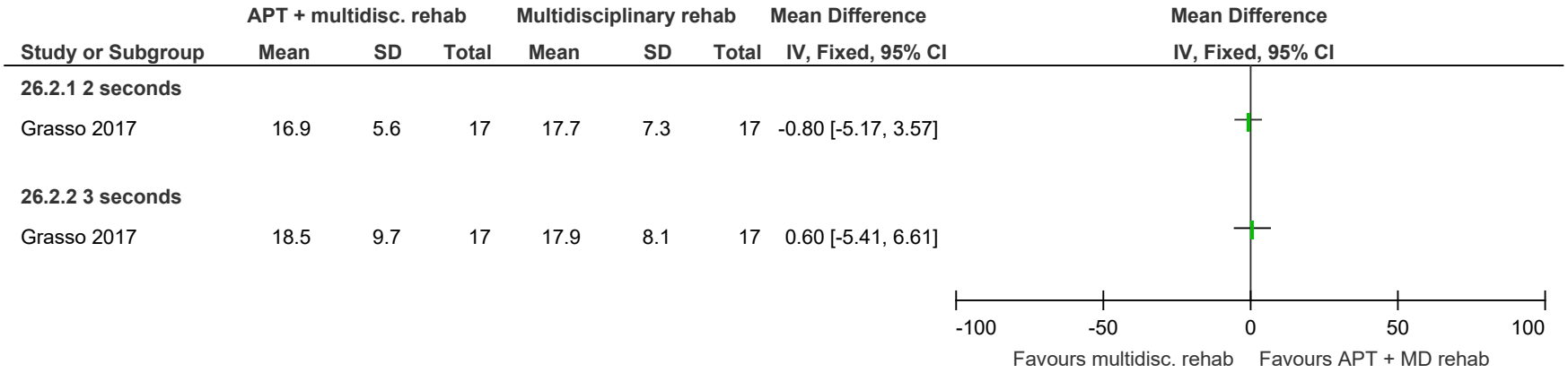


E.26 Attention/working memory: Attention Processing Training (APT) + multidisciplinary rehabilitation vs. multidisciplinary rehabilitation only, 3-6 months

Figure 361: SDMT (higher better)

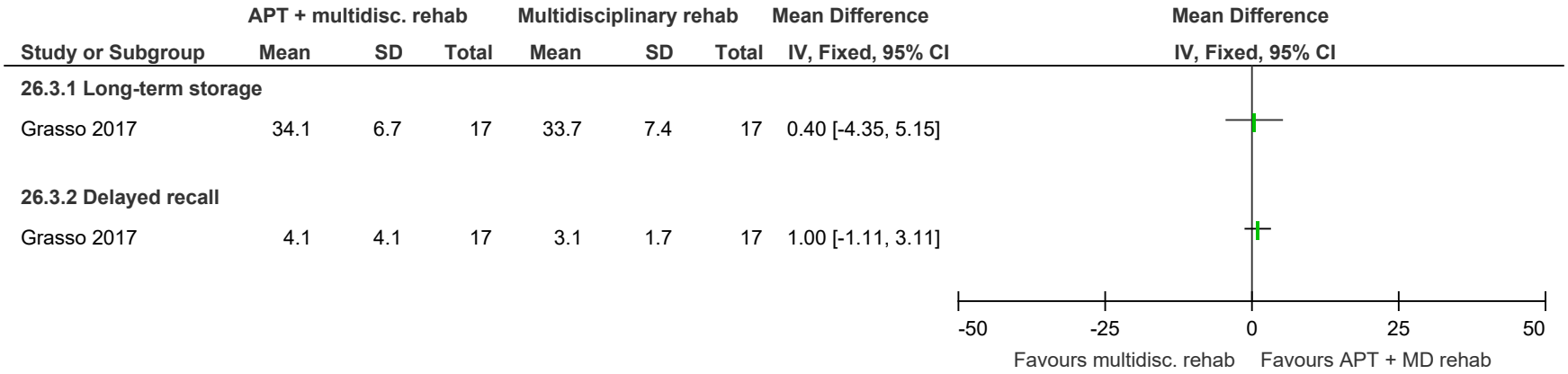
Study or Subgroup	APT + multidisc. rehab Mean	SD	Total	Multidisciplinary rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Grasso 2017	18.3	6.7	17	19.1	7.3	17	-0.80 [-5.51, 3.91]

Figure 362: PASAT (higher better)



1

Figure 363: Selective Reminding Test (higher better)



1

Figure 364: Spatial Recall Test (SPART; higher better)

	APT + multidisc. rehab			Multidisciplinary rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
26.4.1 Immediate							
Grasso 2017	13.7	6.7	17	14.7	7.1	17	-1.00 [-5.64, 3.64]
26.4.2 Delayed							
Grasso 2017	6.1	5.1	17	6	4.8	17	0.10 [-3.23, 3.43]

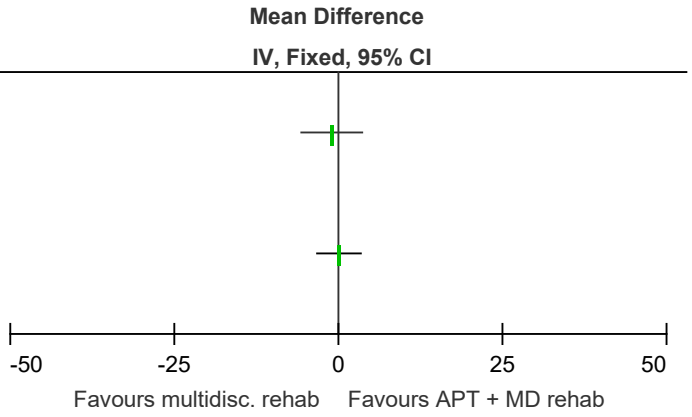


Figure 365: Word List Generation (higher better)

	APT + multidisc. rehab			Multidisciplinary rehab			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
Grasso 2017	12.5	8.9	17	14.1	9.1	17	-1.60 [-7.65, 4.45]

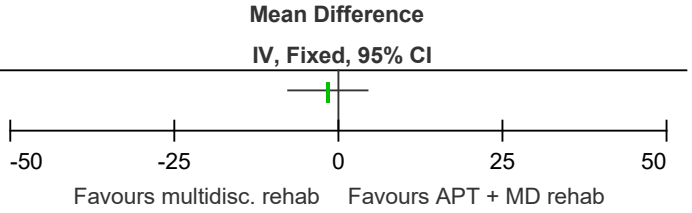
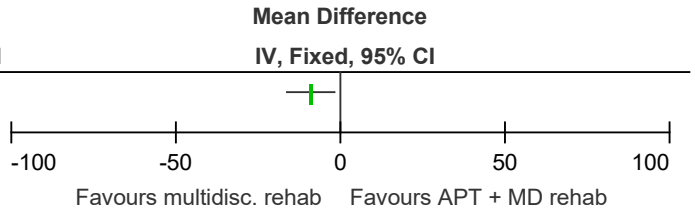


Figure 366: Stroop Test (higher better)

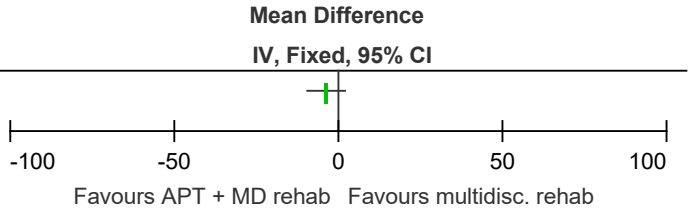
Study or Subgroup	APT + multidisc. rehab Mean	SD	Total	Multidisciplinary rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Grasso 2017	21.5	7.1	17	30.5	13.4	17	-9.00 [-16.21, -1.79]



1

Figure 367: Montgomery and Asberg Depression Rating Scale (scale possibly 0-60; lower better)

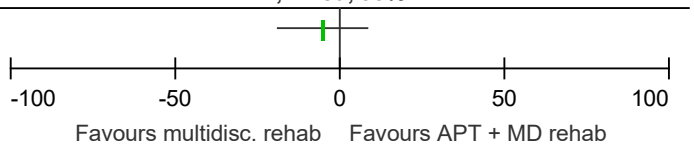
Study or Subgroup	APT + multidisc. rehab Mean	SD	Total	Multidisciplinary rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Grasso 2017	16.73	6.8	17	20.44	10	17	-3.71 [-9.46, 2.04]



2

Figure 368: Barthel Index (measure of activities of daily living; scale 0-100; higher better)

Study or Subgroup	APT + multidisc. rehab Mean	SD	Total	Multidisciplinary rehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Grasso 2017	39	20.8	17	44.22	19.6	17	-5.22 [-18.81, 8.37]



E.27 Attention/working memory: reaction time tasks + usual rehabilitation vs. active control (cognitive software with no time component), 2 weeks

Figure 369: Alertness – T-value indicating normal results (≥40)

Study or Subgroup	RT tasks + usual rehab Events	Total	Active control Events	Total	Odds Ratio M-H, Fixed, 95% CI
Flachenecker 2017	9	14	6	16	3.00 [0.68, 13.31]

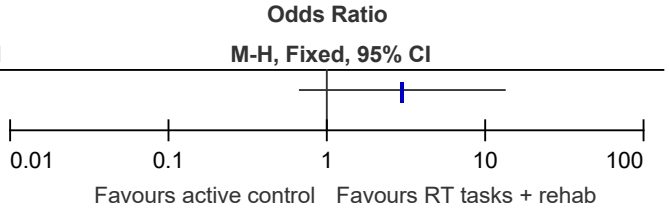


Figure 370: WEIMuS score indicating fatigue (≥32)

Study or Subgroup	RT tasks + usual rehab Events	Total	Active control Events	Total	Odds Ratio M-H, Fixed, 95% CI
Flachenecker 2017	6	14	11	16	0.34 [0.08, 1.52]

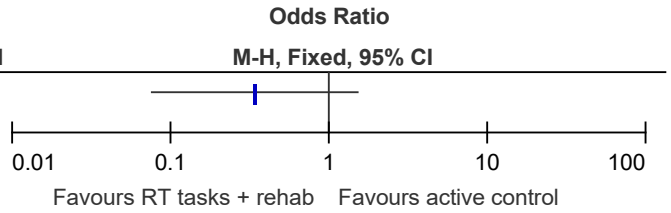
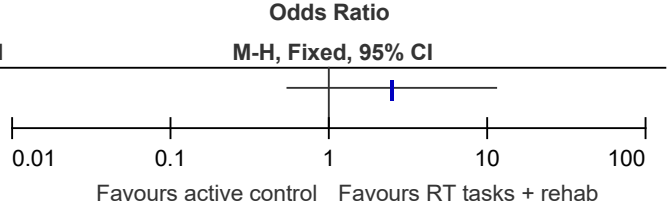


Figure 371: Adherence – completed training sessions of 10 h total

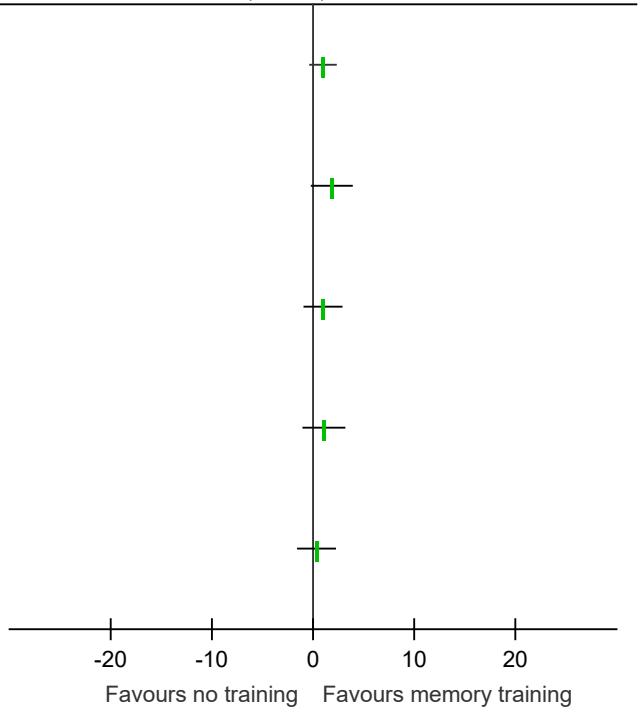
Study or Subgroup	RT tasks + usual rehab Events	Total	Active control Events	Total	Odds Ratio M-H, Fixed, 95% CI
Flachenecker 2017	10	14	8	16	2.50 [0.55, 11.41]



E.28 Memory: computer-aided training for memory (with or without attention components) vs. control (no training), 6-14 weeks

Figure 372: California Verbal Learning Test (higher better)

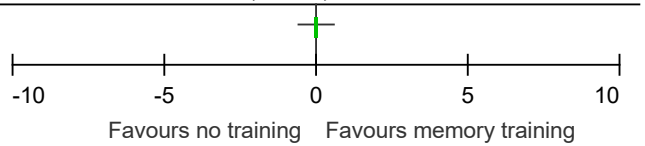
	Computer memory training			No training			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
28.1.1 Learning trials								
Hildebrandt 2007	12.29	2.12	17	11.3	1.94	25	0.99 [-0.27, 2.25]	
28.1.2 Short delay free recall								
Hildebrandt 2007	13.18	3.05	17	11.32	3.45	25	1.86 [-0.12, 3.84]	
28.1.3 Short delay cued recall								
Hildebrandt 2007	13.47	3	17	12.48	2.95	25	0.99 [-0.85, 2.83]	
28.1.4 Long delay free recall								
Hildebrandt 2007	13.24	3.35	17	12.16	3.22	25	1.08 [-0.95, 3.11]	
28.1.5 Long delay cued recall								
Hildebrandt 2007	13.31	3.16	17	12.96	2.69	25	0.35 [-1.49, 2.19]	



1

Figure 373: PASAT (higher better)

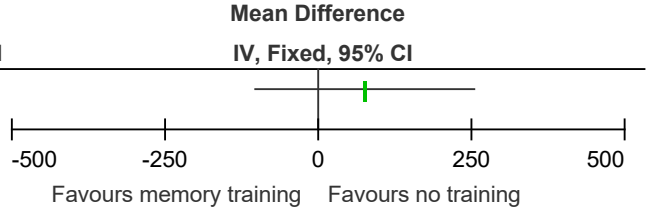
	Computer memory training			No training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hildebrandt 2007	0.017	0.83	17	0.01	1.09	25	0.01 [-0.57, 0.59]	



2

Figure 374: Objective Alternation reaction time (lower better)

	Computer memory training			No training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hildebrandt 2007	820	323	17	744	233	25	76.00 [-102.65, 254.65]	



3

Figure 375: Object Alternation errors (lower better)

Study or Subgroup	Computer memory training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hildebrandt 2007	1.18	1.7	17	2.16	3.04	25	-0.98 [-2.42, 0.46]

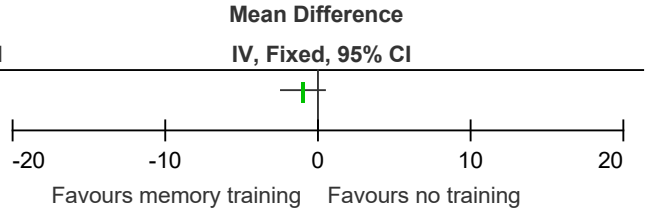


Figure 376: Alertness (higher better)

Study or Subgroup	Computer memory training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
28.5.1 Without cueing							
Hildebrandt 2007	248	85	17	233	45	25	15.00 [-29.09, 59.09]
28.5.2 With cueing							
Hildebrandt 2007	234	80	17	223	56	25	11.00 [-32.91, 54.91]

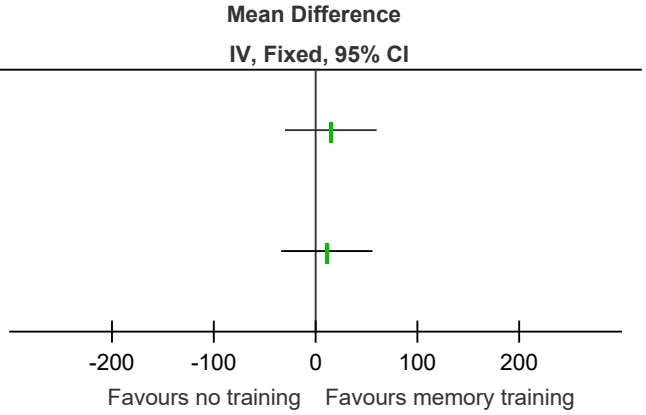


Figure 377: Spatial Span (Corsi) % change (higher better)

Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Mendozzi 1998	25.4	21.5	20	-1.1	15.5	20	26.50 [14.88, 38.12]

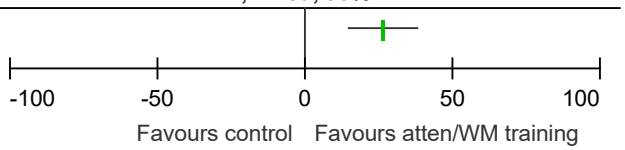


Figure 378: Paired Associates % change (higher better)

Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
28.7.1 Easy							
Mendozzi 1998	10.3	20.5	20	1.1	10.4	20	9.20 [-0.87, 19.27]
28.7.2 Hard							
Mendozzi 1998	59	87	20	2.21	64.8	20	56.79 [9.25, 104.33]

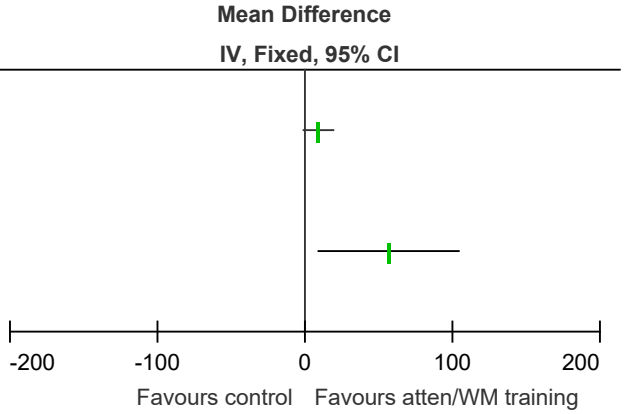
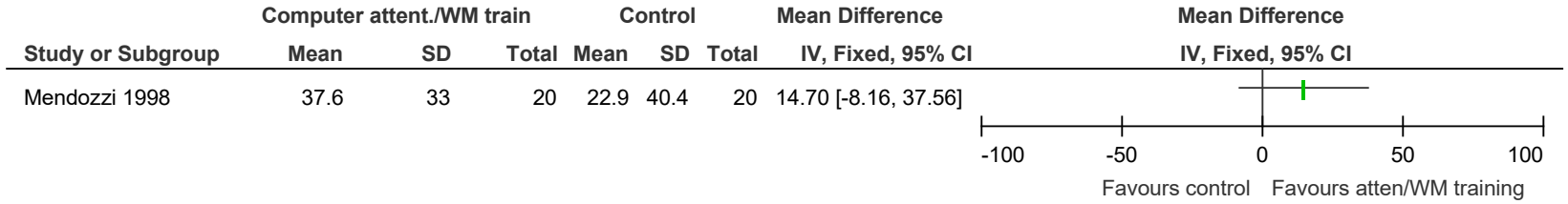
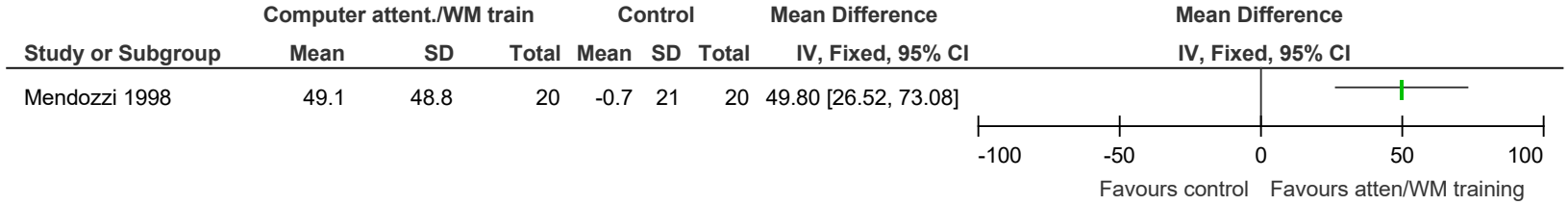


Figure 379: Short Story Recall % change (higher better)



1

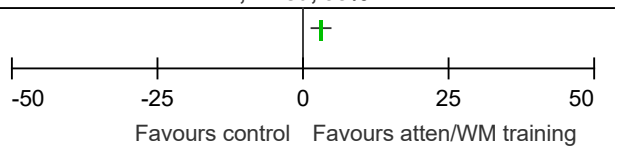
Figure 380: Visual Reproduction % change (higher better)



2

Figure 381: Luria-Nebraska Neuropsychological Battery Memory Scale % change (higher better)

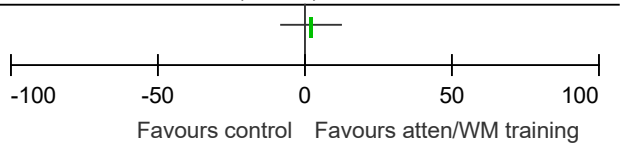
	Computer attent./WM train			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mendozzi 1998	2.5	3	20	-0.6	2.2	20	3.10 [1.47, 4.73]	



1

Figure 382: Signal Detection Hits % change (higher better)

	Computer attent./WM train			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mendozzi 1998	8.5	17.9	20	6.4	14.8	20	2.10 [-8.08, 12.28]	



2

Figure 383: Signal Detection Reaction Time % change (higher better)

Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Mendozzi 1998	9.4	10.3	20	1.7	9.7	20	7.70 [1.50, 13.90]

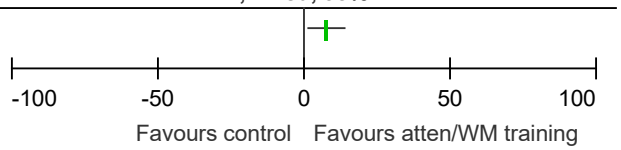


Figure 384: Recognition Memory % change (higher better)

Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Mendozzi 1998	5.5	5.4	20	-0.4	9.8	20	5.90 [1.00, 10.80]

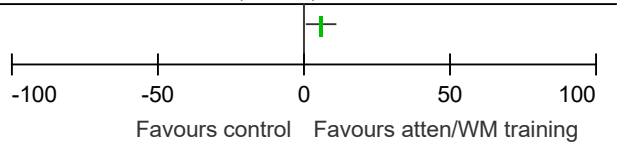
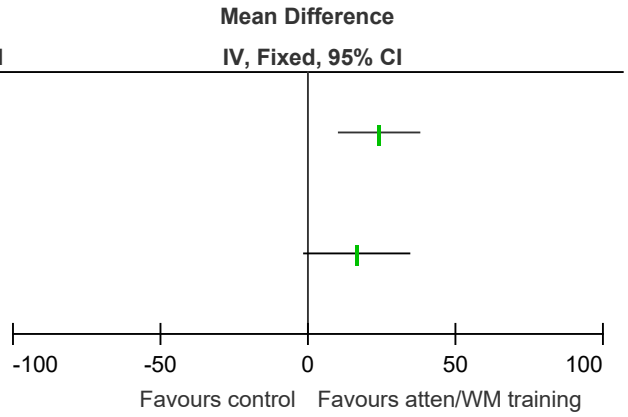


Figure 385: Digit Span % change (higher better)

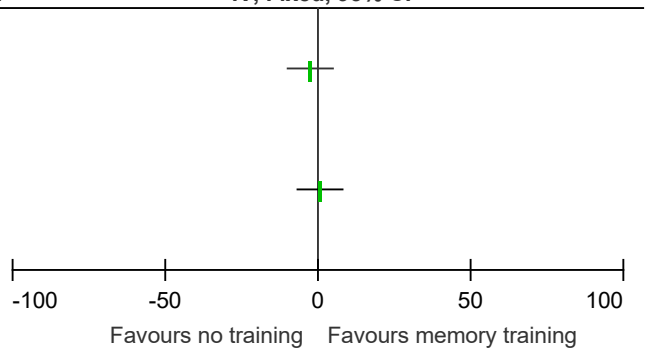
Study or Subgroup	Computer attent./WM train Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
28.14.1 Forward							
Mendozzi 1998	17.8	22.9	20	-6.35	21.1	20	24.15 [10.50, 37.80]
28.14.2 Backward							
Mendozzi 1998	10.8	29.4	20	-5.75	28.2	20	16.55 [-1.30, 34.40]



1

Figure 386: SF-12 quality of life (scale usually 0-100; higher better)

	Computer memory training			No training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
28.15.1 Bodily score								
Hildebrandt 2007	38.6	12.1	17	41.1	11.9	25	-2.50 [-9.91, 4.91]	
28.15.2 Mental score								
Hildebrandt 2007	48.5	13.3	17	47.8	9.7	25	0.70 [-6.68, 8.08]	



1

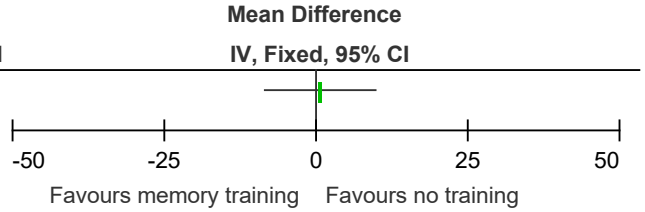
Figure 387: Beck Depression Inventory (scale usually 0-63; lower better)

	Computer memory training			No training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hildebrandt 2007	10.3	8.5	17	11	7.9	25	-0.70 [-5.79, 4.39]	

2

Figure 388: Fatigue Severity Scale (scale usually 9-63; lower better)

Study or Subgroup	Computer memory training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hildebrandt 2007	37.5	15	17	36.8	14.5	25	0.70 [-8.42, 9.82]



E.29 Memory: computer-aided RehaCom memory (and attention) training vs. active control, 14-16 weeks

Figure 389: SDMT % change (higher better)

Study or Subgroup	RehaCom training Mean	SD	Total	Active control tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
29.1.2 % change from baseline							
Solari 2004	15.4	26.8905	40	16.9	35.991	37	-1.50 [-15.78, 12.78]

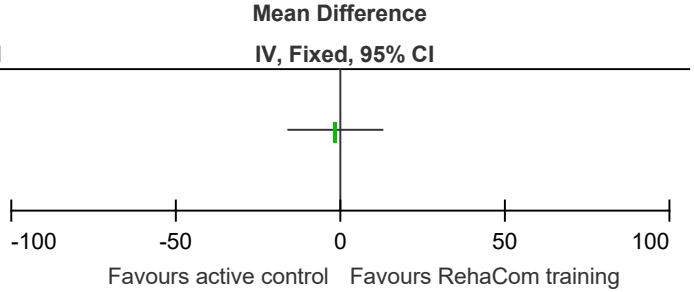
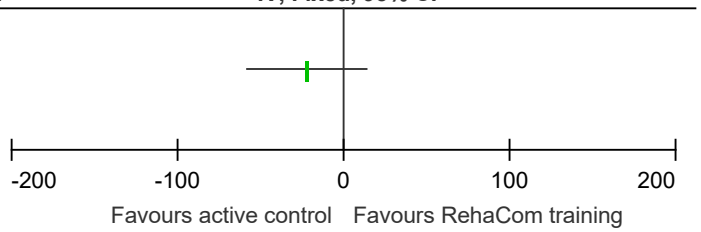


Figure 390: PASAT % change (higher better)

Study or Subgroup	RehaCom training Mean	SD	Total	Active control tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
29.2.1 2 seconds, % change from baseline							
Solari 2004	16.4	49.4035	40	38.5	101.0748	37	-22.10 [-58.09, 13.89]



1

Figure 391: Selective Reminding Test % change (higher better)

Study or Subgroup	RehaCom training Mean	SD	Total	Active control tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
29.3.3 Consistent long-term retrieval, % change from baseline							
Solari 2004	160	313.931	40	143.2	284.029	37	16.80 [-116.77, 150.37]
29.3.5 Delayed recall, % change from baseline							
Solari 2004	9.8	39.7104	40	44.3	98.0755	37	-34.50 [-68.41, -0.59]

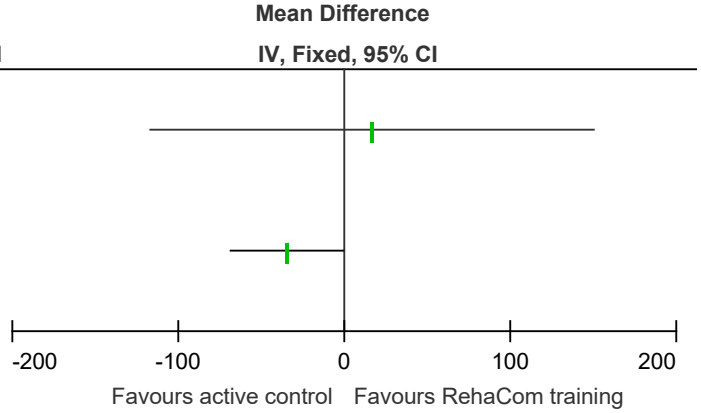


Figure 392: Spatial Recall Test (SPART) % change (higher better)

Study or Subgroup	RehaCom training Mean	SD	Total	Active control tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
29.4.2 Immediate, % change from baseline							
Solari 2004	17.4	53.1556	40	26.6	67.4831	37	-9.20 [-36.48, 18.08]
29.4.4 Delayed, % change from baseline							
Solari 2004	12	62.8487	40	77.1	149.9625	37	-65.10 [-117.20, -13.00]

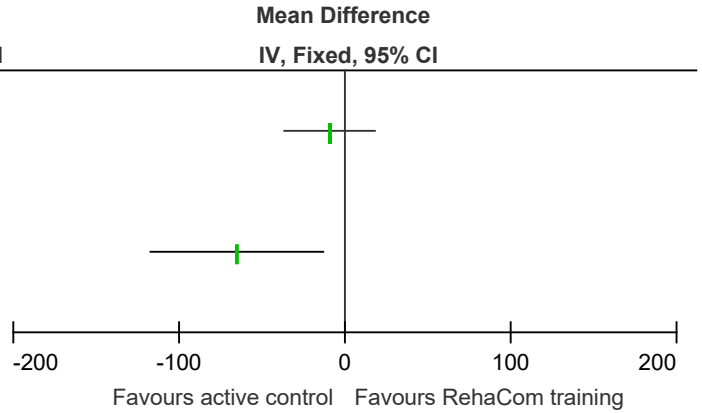


Figure 393: Word List Generation % change (higher better)

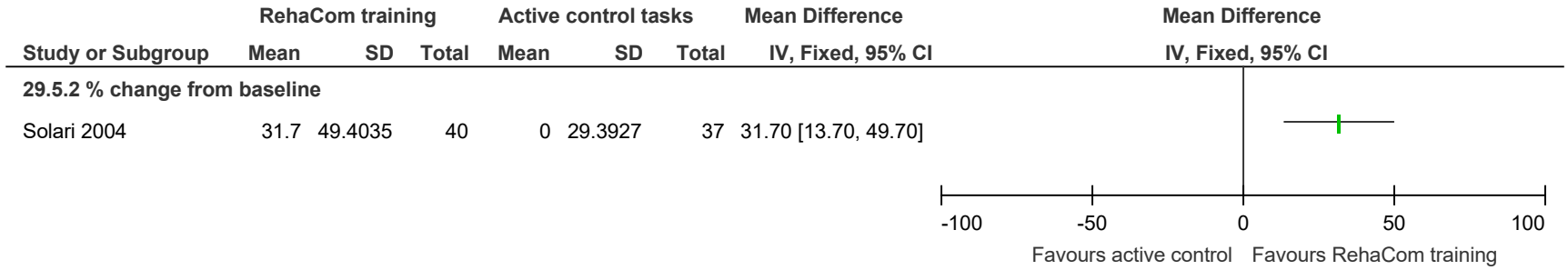


Figure 394: Spatial Span (Corsi) % change (higher better)

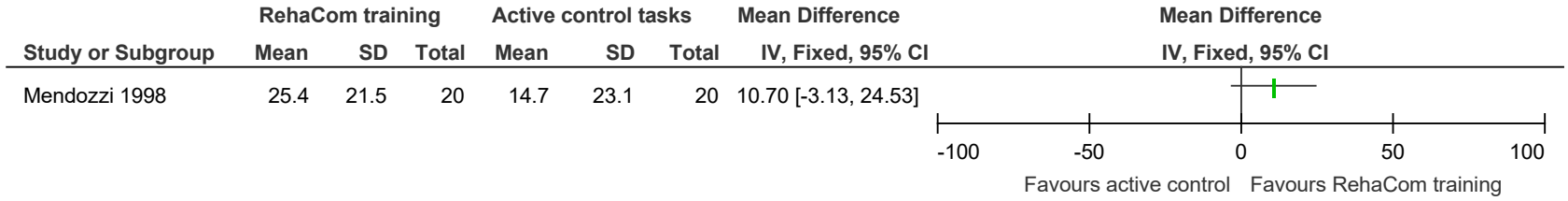
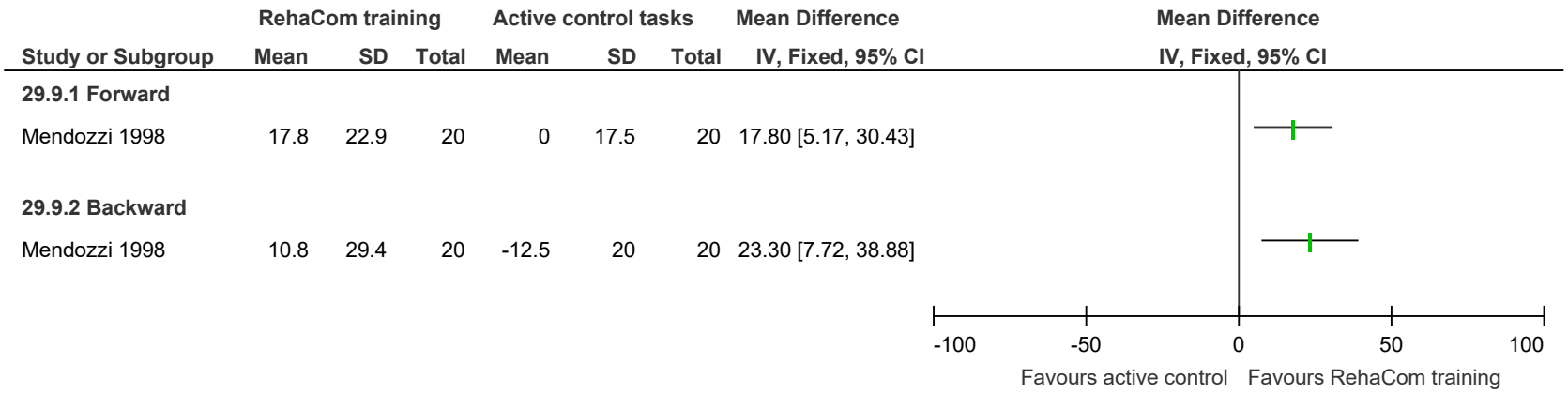


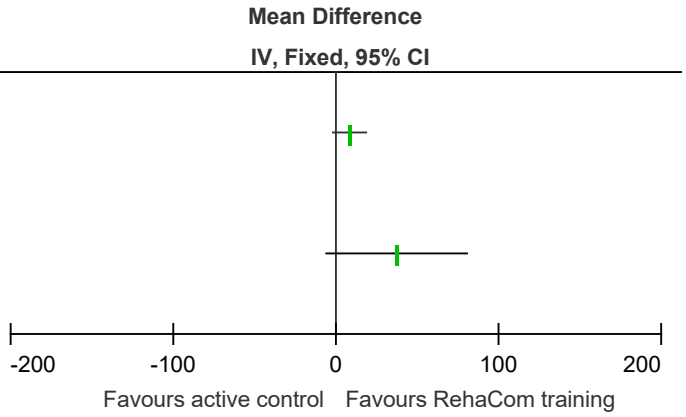
Figure 395: Digit Span % change



1

Figure 396: Paired Associates % change (higher better)

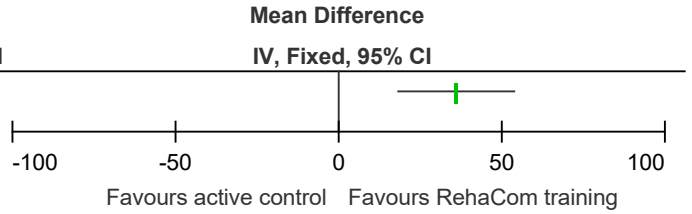
Study or Subgroup	RehaCom training Mean	SD	Total	Active control tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
29.10.1 Easy							
Mendozzi 1998	10.3	20.5	20	1.9	11.1	20	8.40 [-1.82, 18.62]
29.10.2 Hard							
Mendozzi 1998	59	87	20	21.6	46.5	20	37.40 [-5.83, 80.63]



1

Figure 397: Short Story Recall % change (higher better)

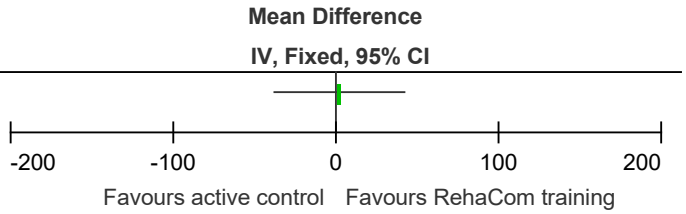
Study or Subgroup	RehaCom training Mean	SD	Total	Active control tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Mendozzi 1998	37.6	33	20	1.55	23.6	20	36.05 [18.27, 53.83]



2

Figure 398: Visual Reproduction % change (higher better)

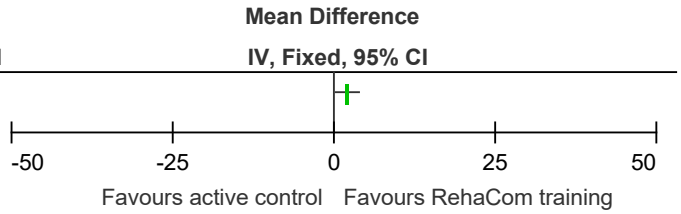
Study or Subgroup	RehaCom training Mean	SD	Total	Active control tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Mendozzi 1998	49.1	48.8	20	46.9	77.1	20	2.20 [-37.79, 42.19]



1

Figure 399: Luria-Nebraska Neuropsychological Battery Memory Scale % change (higher better)

Study or Subgroup	RehaCom training Mean	SD	Total	Active control tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Mendozzi 1998	2.5	3	20	0.4	2.8	20	2.10 [0.30, 3.90]



2

Figure 400: Recognition Memory % change (higher better)

Study or Subgroup	RehaCom training Mean	SD	Total	Active control tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Mendozzi 1998	5.5	5.4	20	6.8	13.3	20	-1.30 [-7.59, 4.99]

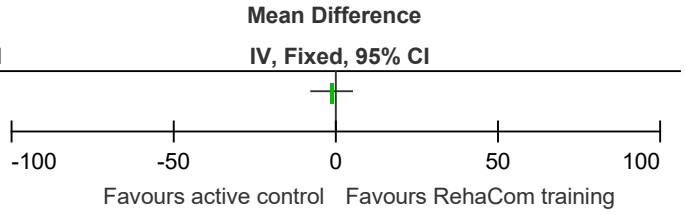


Figure 401: Signal Detection Hits % change (higher better)

	RehaCom training			Active control tasks			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mendozzi 1998	8.5	17.9	20	3.8	12.5	20	4.70 [-4.87, 14.27]	

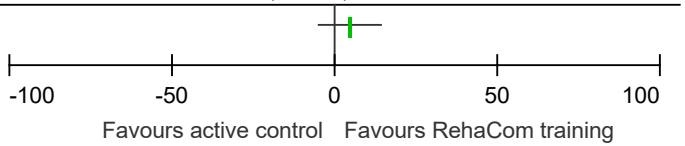


Figure 402: Signal Detection Reaction Time % change (higher better)

	RehaCom training			Active control tasks			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mendozzi 1998	9.4	10.3	20	4.5	8.8	20	4.90 [-1.04, 10.84]	

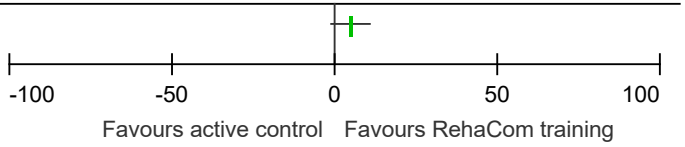
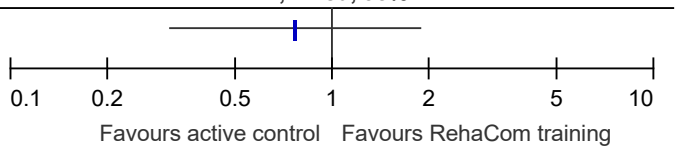


Figure 403: Improvement >20% in at least 5 of Brief Repeatable Battery of Neuropsychological Tests (BRBNT)

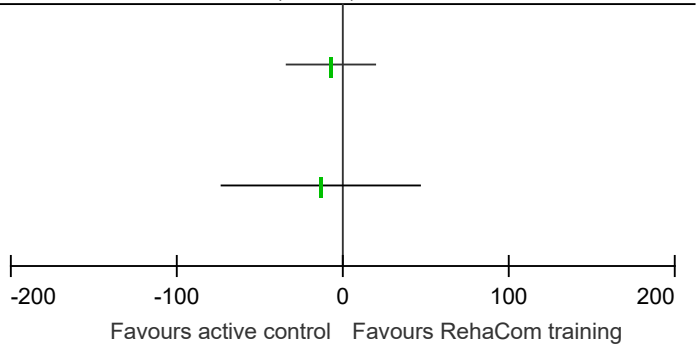
Study or Subgroup	RehaCom training Events	Total	Active control tasks Events	Total	Odds Ratio M-H, Fixed, 95% CI
Solari 2004	19	40	20	37	0.77 [0.31, 1.88]



1

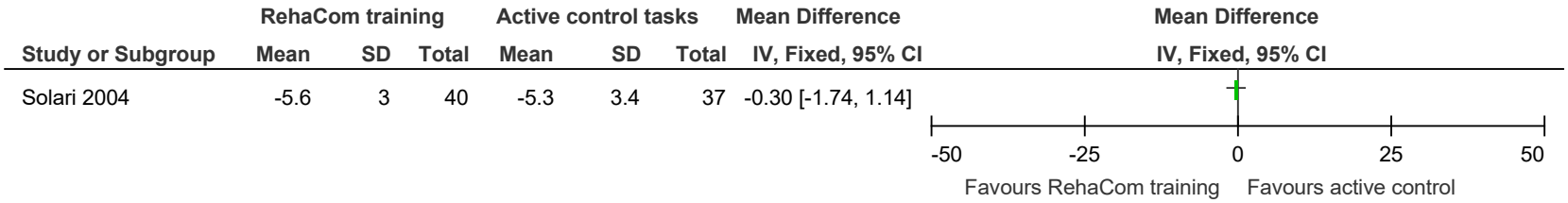
Figure 404: MSQoL-54 (scale usually 0-100; higher better)

Study or Subgroup	RehaCom training Mean	SD	Total	Active control tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
29.18.1 Physical composite							
Solari 2004	15.6	46.8017	40	22.7	69.3435	37	-7.10 [-33.74, 19.54]
29.18.2 Mental health composite							
Solari 2004	42.7	126.4911	40	55.9	139.9035	37	-13.20 [-72.94, 46.54]



2

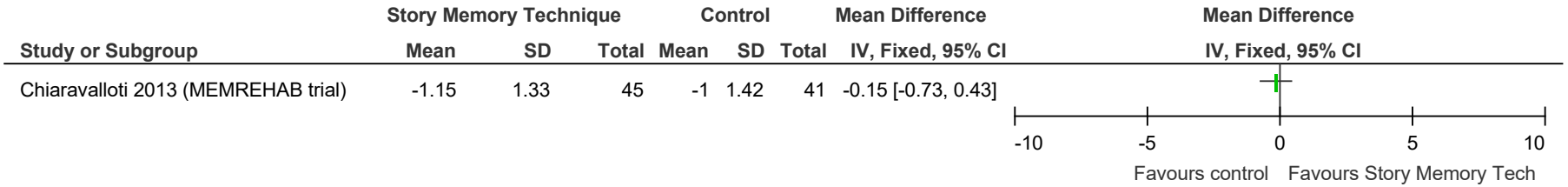
Figure 405: Chicago Mood Depression Inventory (scale unclear) % change (lower better)



1

E.30 Memory: Story Memory Technique vs. control, 5-11 weeks

Figure 406: SDMT (z-score; higher better)



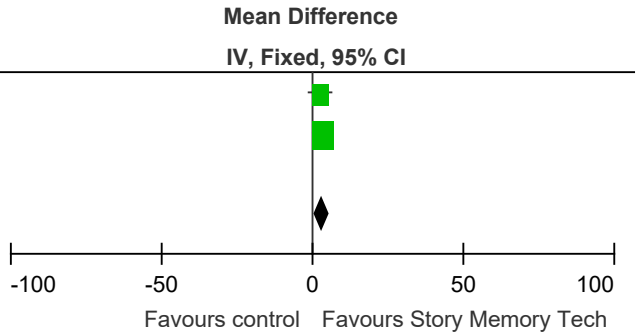
3

Figure 407: Hopkins Verbal Learning Test-Revised (higher better)

	Story Memory Technique			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Chiaravalloti 2005	3.07	5.88	14	0.57	4.2	14	41.6%	2.50 [-1.29, 6.29]
Krch 2019	25.27	3.6485	10	21.935	3.6415	10	58.4%	3.34 [0.14, 6.53]
Total (95% CI)			**24**			**24**	**100.0%**	**2.99 [0.55, 5.43]**

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%

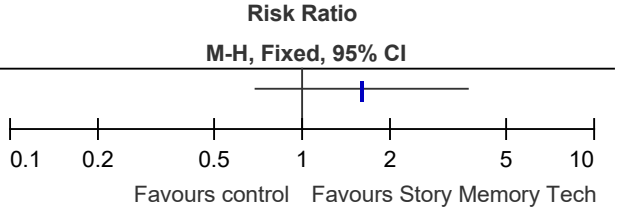
Test for overall effect: Z = 2.40 (P = 0.02)



1

Figure 408: Proportion with improvement on Hopkins Verbal Learning Test-Revised

	Story Memory Technique		Control		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Chiaravalloti 2005	8	14	5	14	1.60 [0.69, 3.69]



2

Figure 409: California Verbal Learning Test – Learning slope (higher better)

Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chiaravalloti 2013 (MEMREHAB trial)	1.885	0.7156	45	1.54	0.8871	41	77.3%	0.34 [0.00, 0.69]
Chiaravalloti 2020	1.29	0.1264	15	1.28	1.1584	13	22.7%	0.01 [-0.62, 0.64]
Total (95% CI)			**60**			**54**	**100.0%**	**0.27 [-0.03, 0.57]**

Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%

Test for overall effect: Z = 1.75 (P = 0.08)

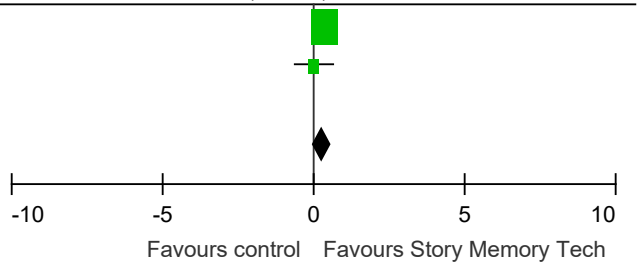


Figure 410: California Verbal Learning Test – Total Learning (T-score; higher better)

Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Chiaravalloti 2013 (MEMREHAB trial)	50.13	11.99	45	45.24	13.44	41	4.89 [-0.51, 10.29]

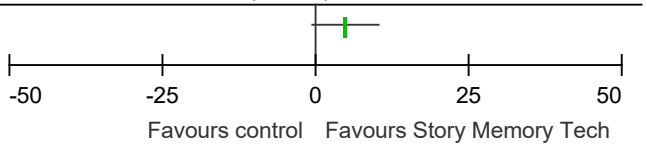


Figure 411: Proportion with >10% improvement on California Verbal Learning Test

Study or Subgroup	Story Memory Technique Events	Total	Control Events	Total	Odds Ratio M-H, Fixed, 95% CI
30.6.1 Short-delay recall					
Chiaravalloti 2012	6	8	2	8	9.00 [0.94, 86.52]
30.6.2 Learning slope					
Chiaravalloti 2013 (MEMREHAB trial)	28	45	15	41	2.85 [1.19, 6.85]

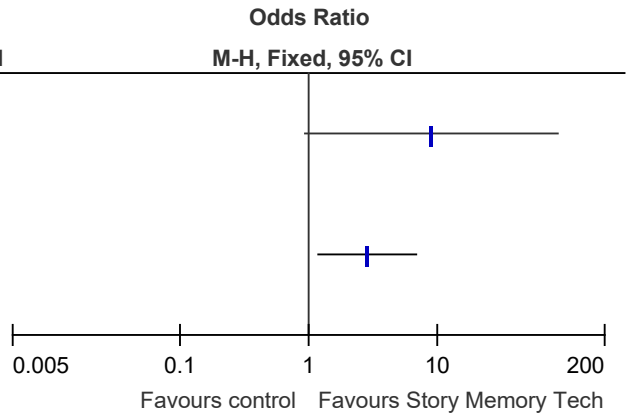


Figure 412: Objective Everyday Memory (Rivermead Behavioural Memory Test Story Memory; higher better)

Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Chiaravalloti 2013 (MEMREHAB trial)	1.5725	0.6341	45	1.25	0.6336	41	0.32 [0.05, 0.59]

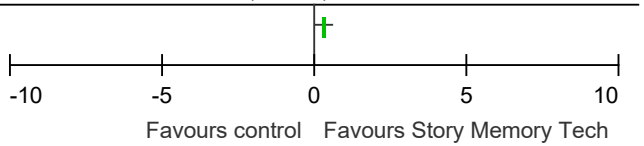
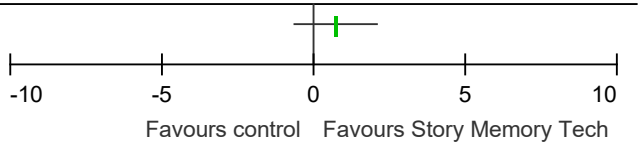


Figure 413: Letter-Number Sequencing Scaled Score (working memory; higher better)

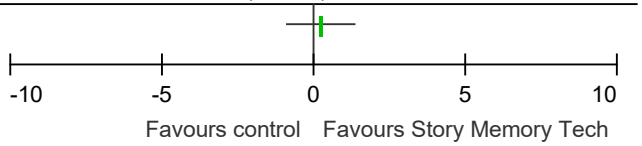
Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Chiaravalloti 2013 (MEMREHAB trial)	11.22	3.21	45	10.49	3.21	41	0.73 [-0.63, 2.09]



1

Figure 414: Attention – Digit Span Scaled Score (higher better)

Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Chiaravalloti 2013 (MEMREHAB trial)	10.51	2.36	45	10.27	2.86	41	0.24 [-0.87, 1.35]



2

Figure 415: Memory Functioning Questionnaire (Spanish version; scale 31-217; higher better)

Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Krch 2019	105.9	9.1423	10	110.8	9.1423	10	-4.90 [-12.91, 3.11]

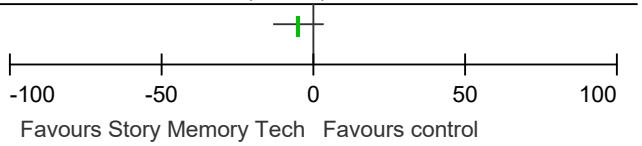


Figure 416: Awareness of Cognitive Deficits Questionnaire (scale possibly 17-85; higher better)

Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Chiaravalloti 2013 (MEMREHAB trial)	15.84	5.0381	15	11.58	5.312	13	4.26 [0.41, 8.11]

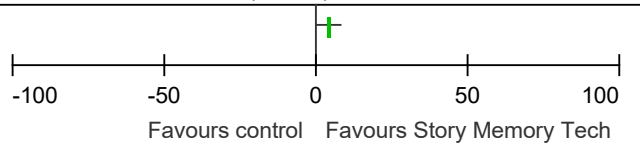


Figure 417: Functional Assessment of MS – General Contentment (scale 0-28; higher better)

Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Chiaravalloti 2013 (MEMREHAB trial)	19.8805	11.5849	45	15.4335	11.0268	41	4.45 [-0.33, 9.23]

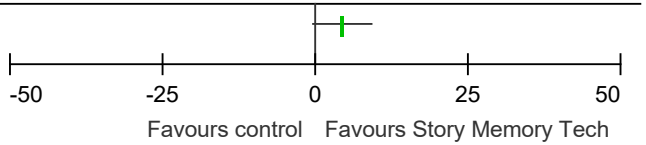


Figure 418: Frontal Systems Behaviour Scale (reported by significant others; scale indicated in figure; lower better)

Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
30.13.1 Apathy (scale unclear, possibly 14-70)							
Chiaravalloti 2013 (MEMREHAB trial)	34.144	11.9328	45	30.125	9.8594	41	4.02 [-0.59, 8.63]
30.13.2 Executive dysfunction (scale unclear, possibly 17-85)							
Chiaravalloti 2013 (MEMREHAB trial)	42.242	13.0578	45	38.109	10.832	41	4.13 [-0.92, 9.19]
30.13.3 Disinhibition after illness (scale unclear, possibly 15-75)							
Chiaravalloti 2020	27.465	3.1511	15	24.82	2.8959	13	2.64 [0.40, 4.89]

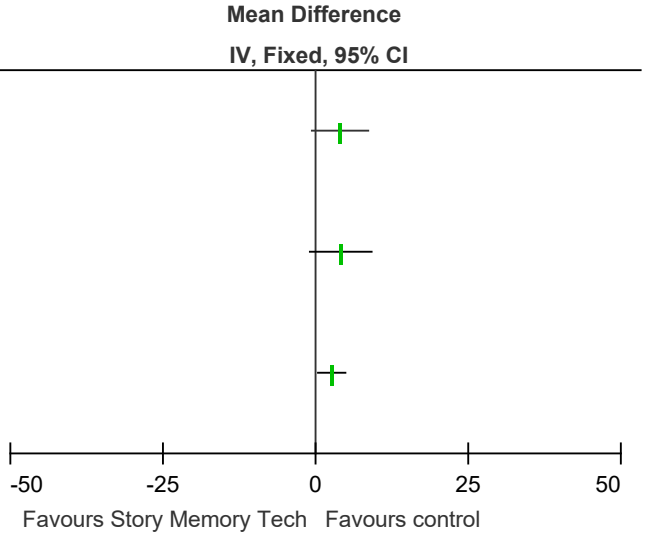


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Figure 419: State-Trait Anxiety Inventory (T-score; lower better)

	Story Memory Technique			Control			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
30.14.1 State score								
Chiaravalloti 2013 (MEMREHAB trial)	51.23	15.97	45	54.24	15.47	41	-3.01 [-9.66, 3.64]	
30.14.2 Trait score								
Chiaravalloti 2013 (MEMREHAB trial)	54.77	16.59	45	59.06	14.49	41	-4.29 [-10.86, 2.28]	

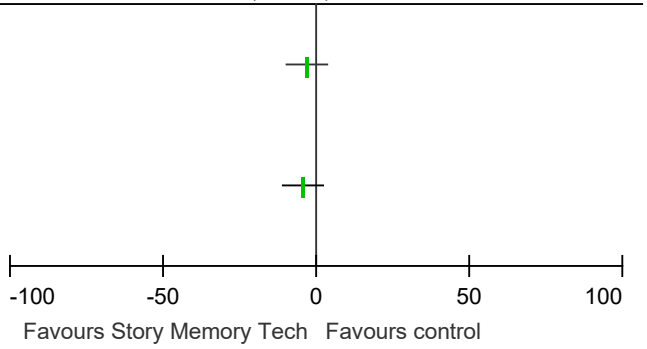


Figure 420: Chicago Multidimensional Depression Inventory T-score (lower better)

	Story Memory Technique			Control			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Chiaravalloti 2013 (MEMREHAB trial)	55.05	15.7	45	56.39	12.92	41	-1.34 [-7.40, 4.72]	

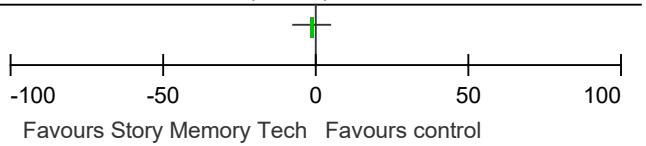
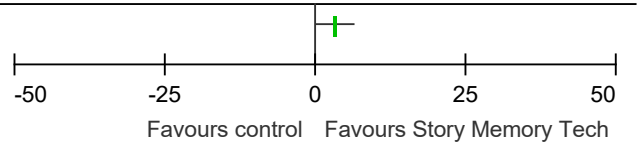


Figure 421: Satisfaction with Life Scale (scale usually 5-35; higher better)

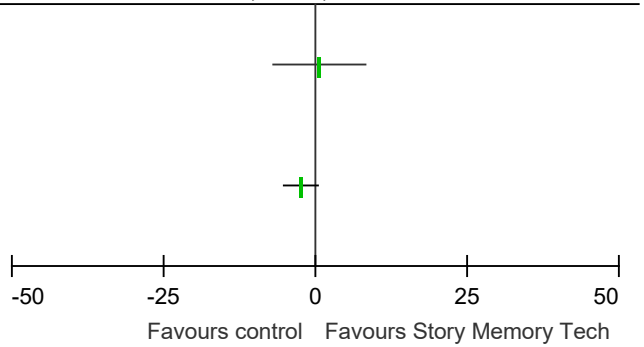
	Story Memory Technique			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Krch 2019	23.59	3.5647	10	20.31	3.5647	10	3.28 [0.16, 6.40]	



1

Figure 422: Patient Competency Rating Scale (scale usually 30-150; higher better)

	Story Memory Technique			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
30.17.1 Patient-reported								
Krch 2019	98.335	8.66	10	97.665	8.66	10	0.67 [-6.92, 8.26]	
30.17.2 Family-reported								
Krch 2019	102.41	3.2012	10	104.79	3.2012	10	-2.38 [-5.19, 0.43]	



2

E.31 Memory: Story Memory Technique vs. control, 7 months

Figure 423: SDMT (z-score; higher better)

Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Chiaravalloti 2013 (MEMREHAB trial)	-1	1.34	40	0.97	1.4	38	-1.97 [-2.58, -1.36]

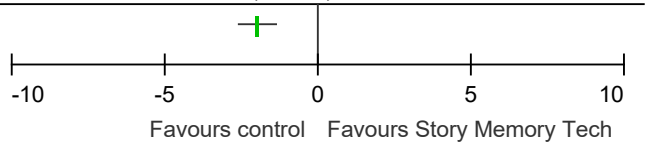


Figure 424: California Verbal Learning Test – Learning slope (z-score; higher better)

Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Chiaravalloti 2013 (MEMREHAB trial)	1.11	0.61	40	1	0.56	38	0.11 [-0.15, 0.37]

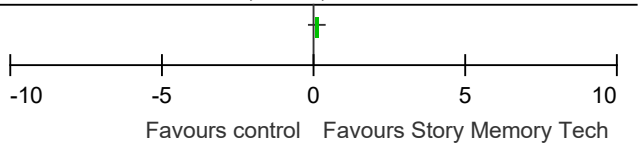


Figure 425: California Verbal Learning Test – Total Learning (T-score; higher better)

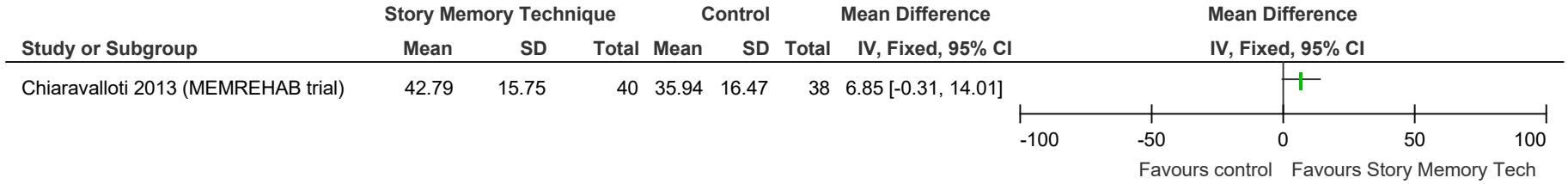


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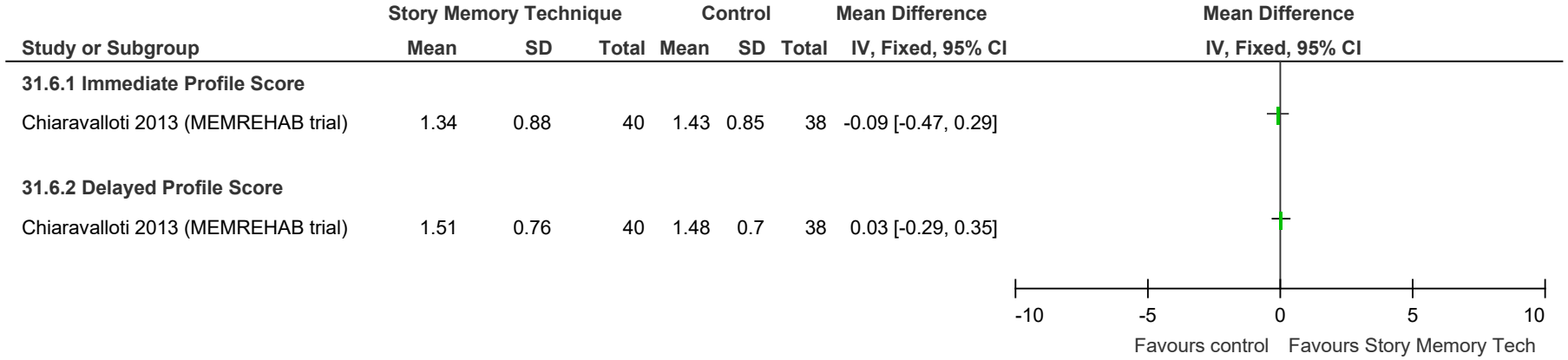
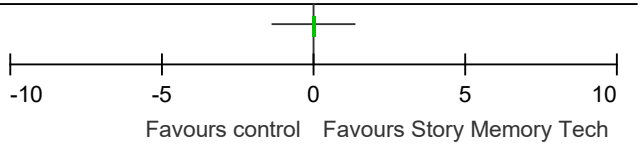
Figure 426: Objective Everyday Memory (Rivermead Behavioural Memory Test Story Memory; higher better)



2

Figure 427: Letter-Number Sequencing Scaled Score (working memory; higher better)

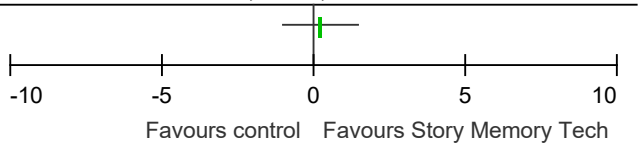
	Story Memory Technique			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Chiaravalloti 2013 (MEMREHAB trial)	10.37	3.04	40	10.37	3.05	38	0.00 [-1.35, 1.35]	



1

Figure 428: Attention – Digit Span Scaled Score (higher better)

	Story Memory Technique			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Chiaravalloti 2013 (MEMREHAB trial)	10.63	2.71	40	10.4	2.85	38	0.23 [-1.01, 1.47]	



2

Figure 429: Functional Assessment of MS – General Contentment (scale 0-28; higher better)

Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Chiaravalloti 2013 (MEMREHAB trial)	17.17	6.82	40	14.48	6.31	38	2.69 [-0.22, 5.60]

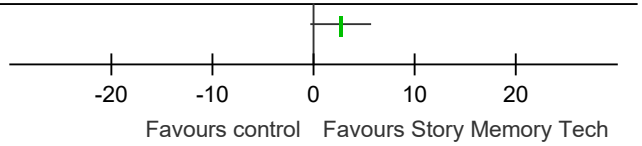


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Figure 430: Frontal Systems Behaviour Scale (reported by significant others; scale indicated in figure; lower better)

Study or Subgroup	Story Memory Technique Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
31.11.1 Apathy							
Chiaravalloti 2013 (MEMREHAB trial)	67.81	24.31	40	63.88	20.96	38	3.93 [-6.13, 13.99]
31.11.2 Executive dysfunction							
Chiaravalloti 2013 (MEMREHAB trial)	59.69	16.04	40	60.75	17.12	38	-1.06 [-8.43, 6.31]

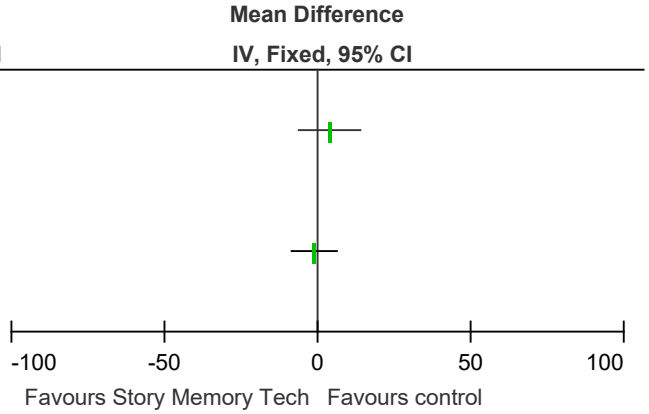

Figure 431: State-Trait Anxiety Inventory (T-score; lower better)

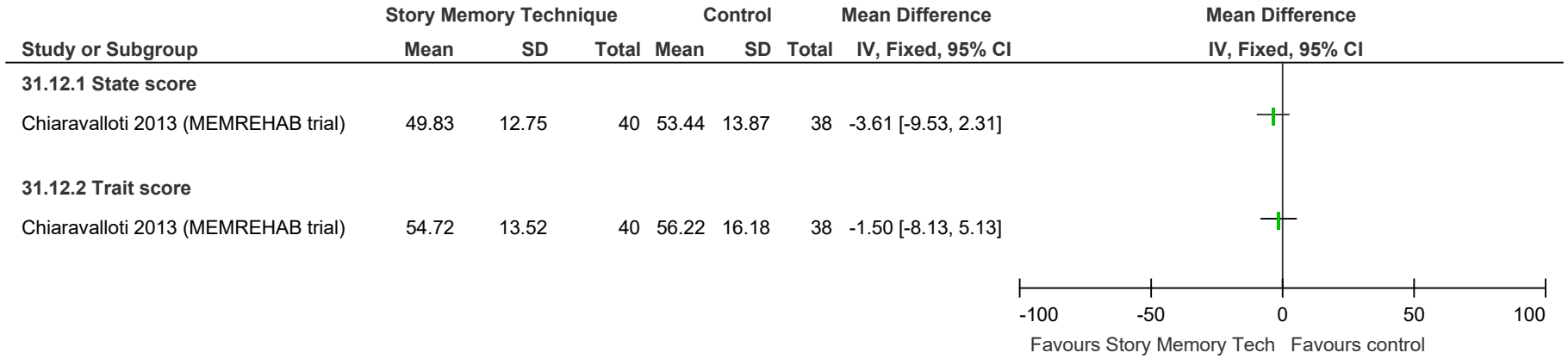

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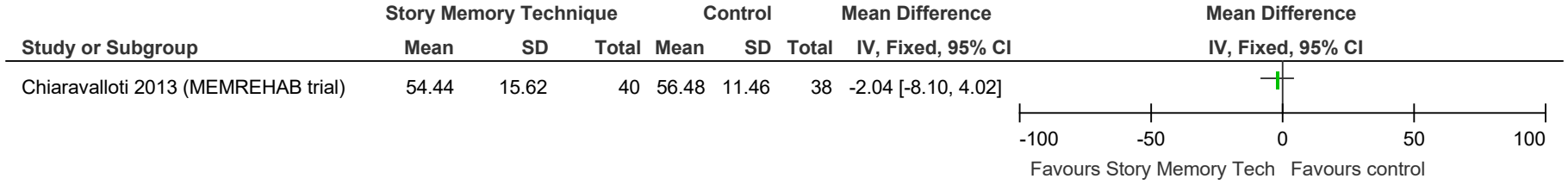
Figure 432: Chicago Multidimensional Depression Inventory (T-score; lower better)



E.32 Memory: group memory programme (various learning techniques) vs. control, 3-6 months

Figure 433: SDMT (higher better)

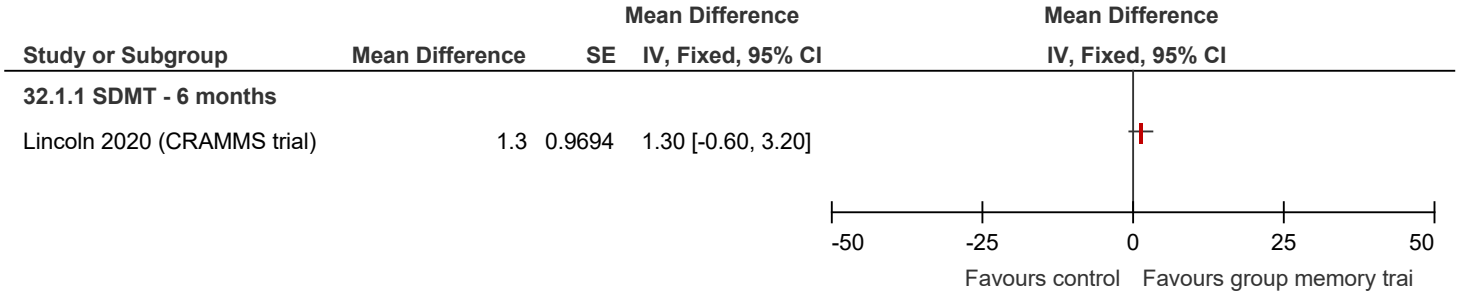
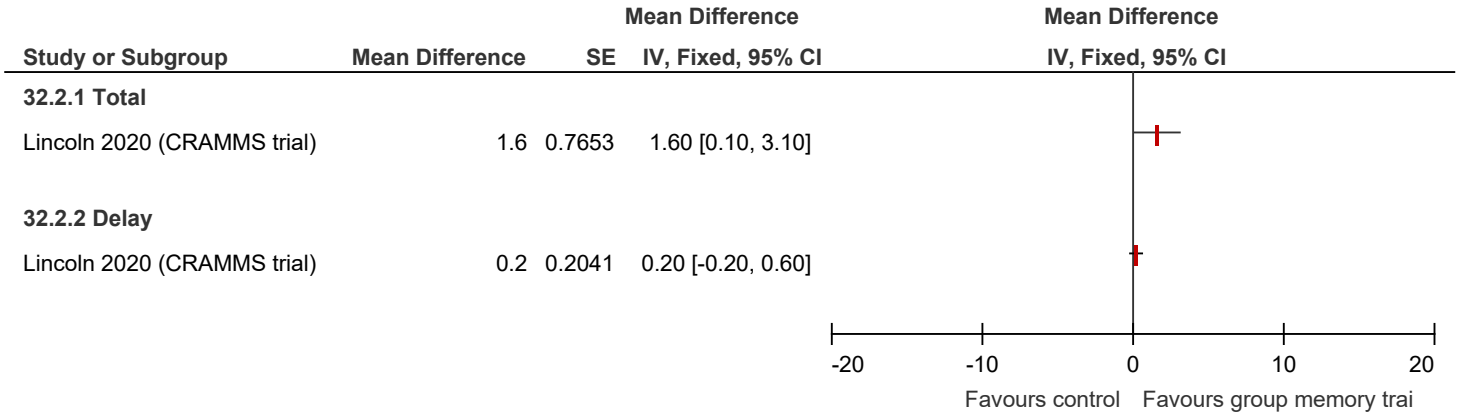
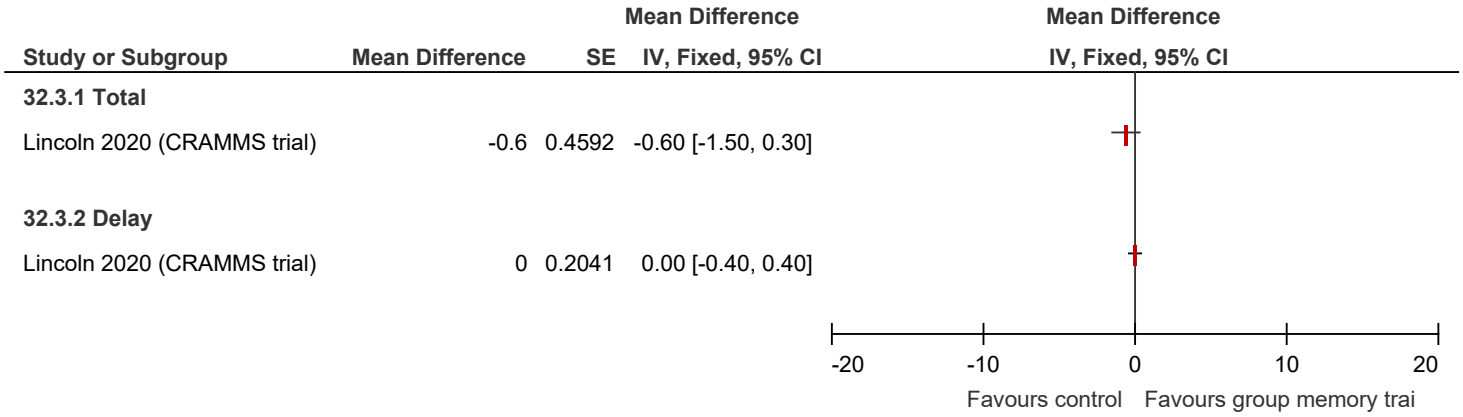


Figure 434: Selective Reminding Test (higher better)



1

Figure 435: Spatial Recall Test (10/36 SPART; higher better)



1

Figure 436: PASAT (higher better)

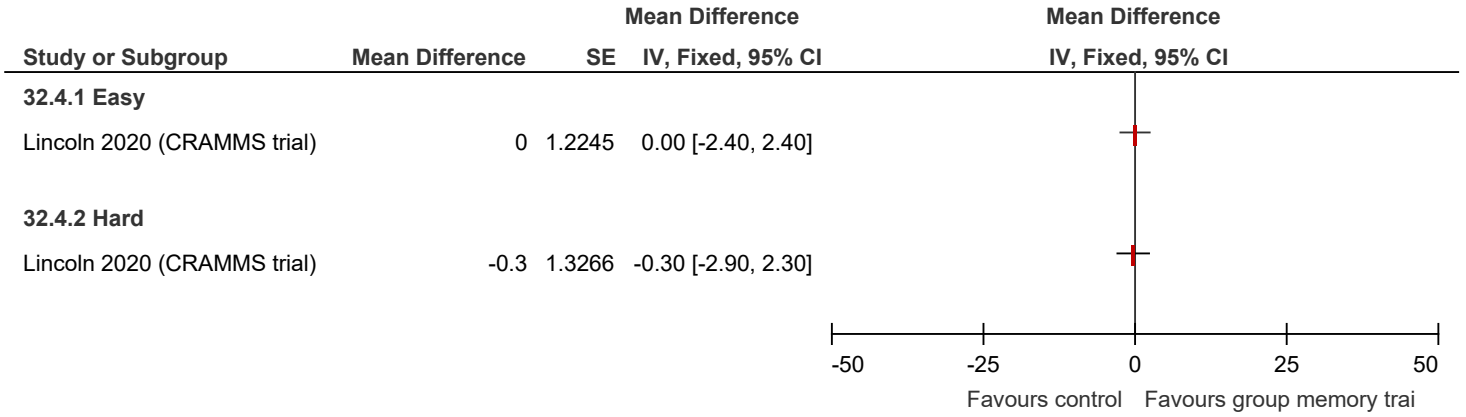


Figure 437: Trail Making Test (B-A; lower better)

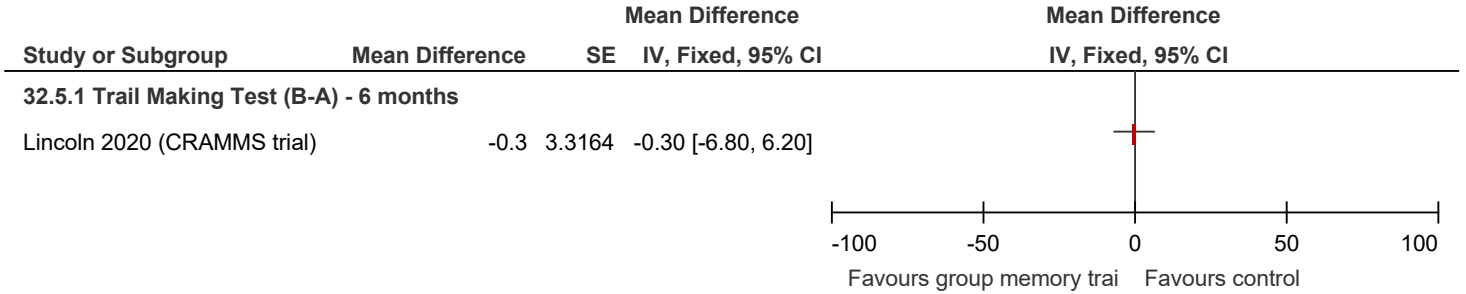


Figure 438: Word Fluency (higher better)

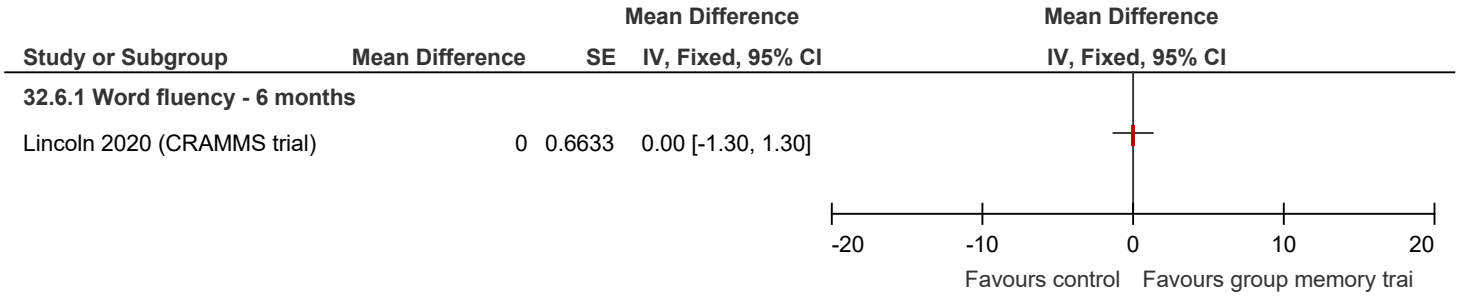


Figure 439: Working Memory (possibly Wechsler Memory Scale-III; higher better)

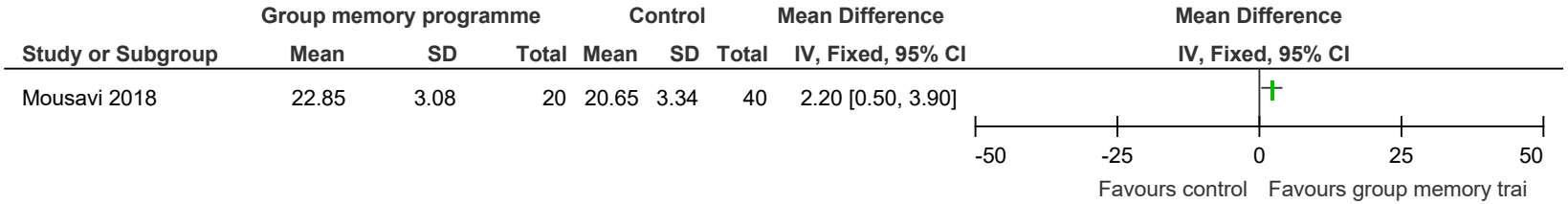
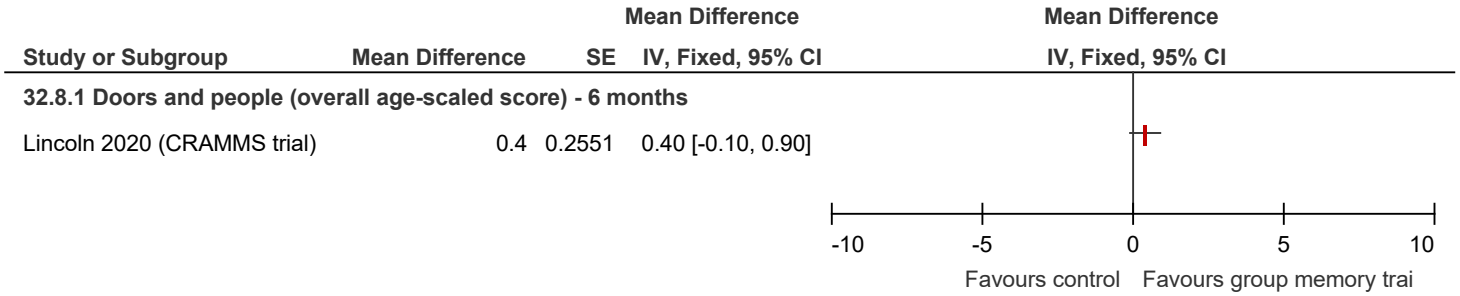
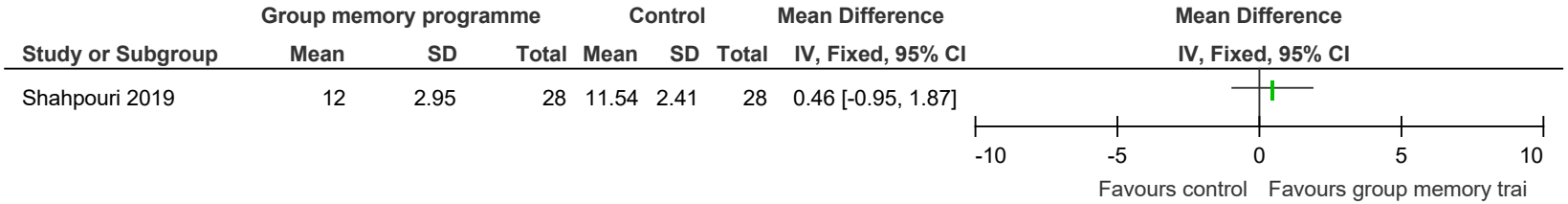


Figure 440: Doors and People (overall age-scaled score; higher better)



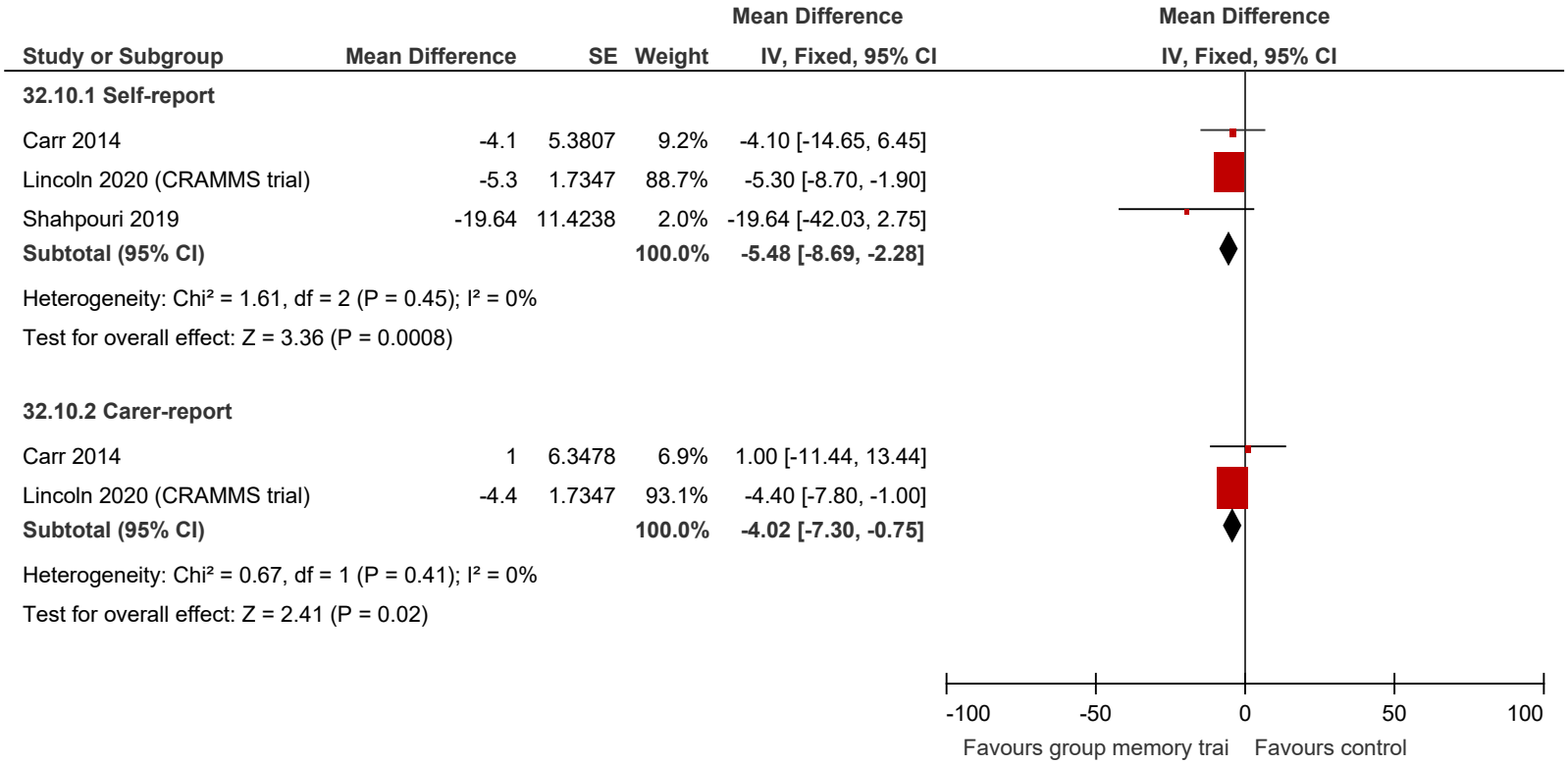
1

Figure 441: Digit Span Test for Attention (higher better)



2

Figure 442: Everyday Memory Questionnaire (Scale 0-140; lower better)



1

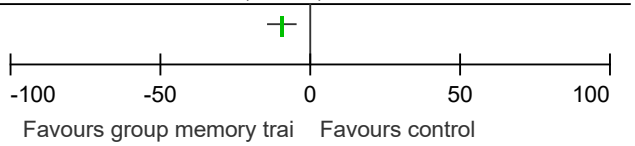
Figure 443: Everyday Memory Questionnaire (Scale 0-175; lower better)

	Group memory programme			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mousavi 2018	121.2	1.57	20	120.9	1.44	40	0.30 [-0.52, 1.12]	

1

Figure 444: Prospective and Retrospective Memory Questionnaire (scale 16-80?; lower better)

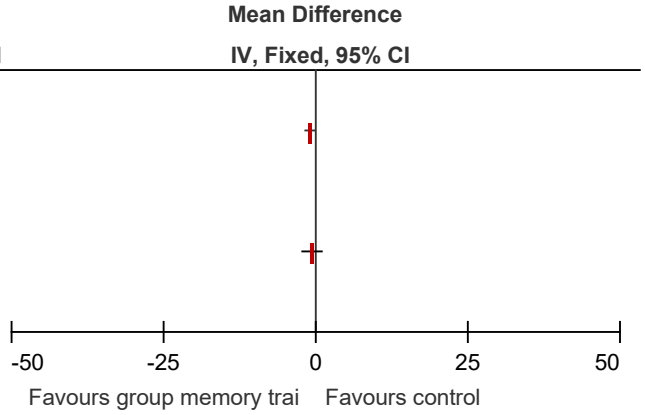
	Group memory programme			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shahpouri 2019	36.11	9.76	28	45.57	7.73	28	-9.46 [-14.07, -4.85]	



2

Figure 445: MSIS-29 quality of life (scale 0-100; lower better)

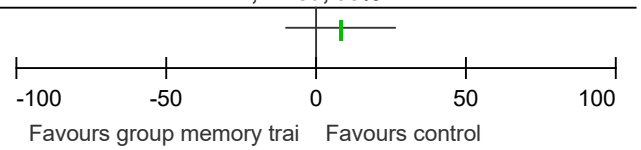
Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
32.13.1 Psychological			
Lincoln 2020 (CRAMMS trial)	-0.9	0.4082	-0.90 [-1.70, -0.10]
32.13.2 Physical			
Lincoln 2020 (CRAMMS trial)	-0.6	0.8163	-0.60 [-2.20, 1.00]



1

Figure 446: MSIS-29 quality of life (scale 29-145; lower better)

Study or Subgroup	Group memory programme Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Carr 2014	77.2	30.7	16	69	23.6	21	8.20 [-9.92, 26.32]



2

Figure 447: MSQoL-54 (scale 0-100; higher better)

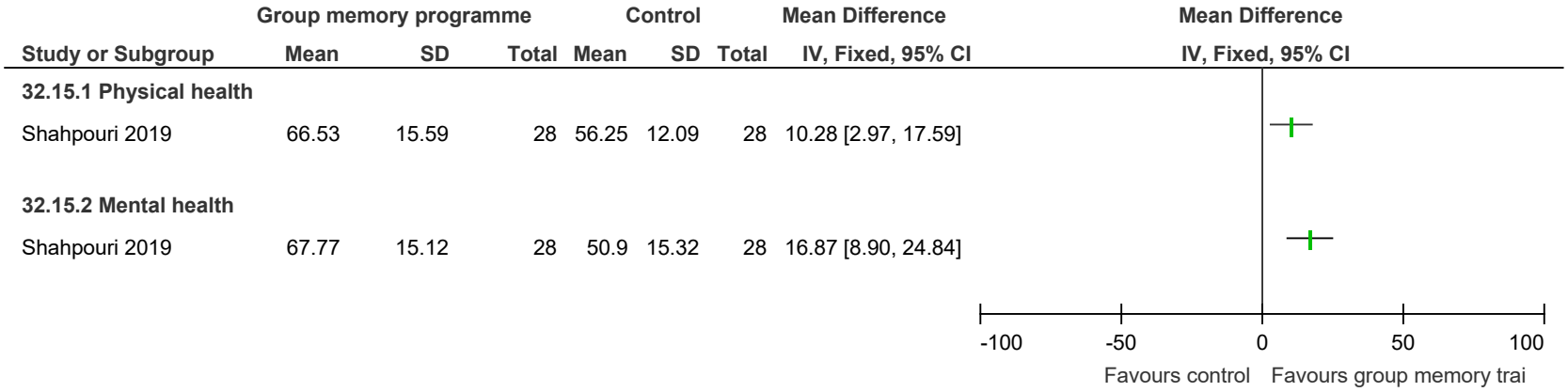


Figure 448: EQ-5D visual analogue scale (scale 0-100; higher better)

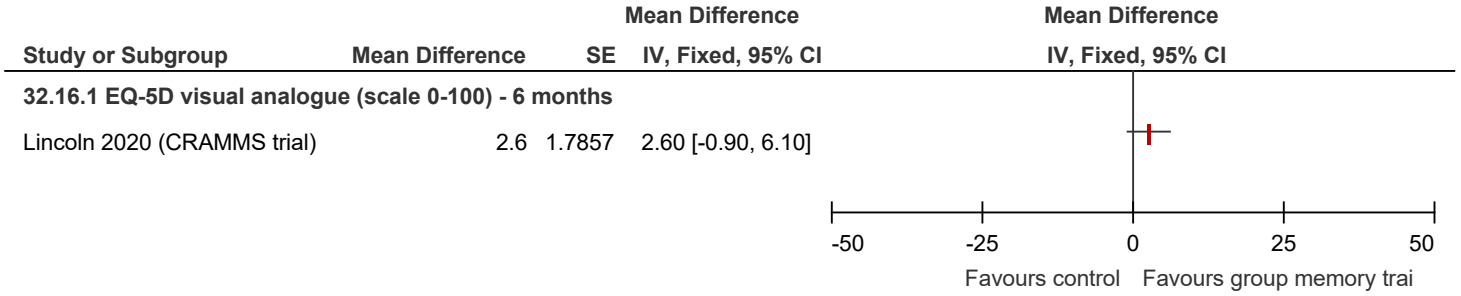


Figure 449: General Health Questionnaire (scale 0-28; lower better)

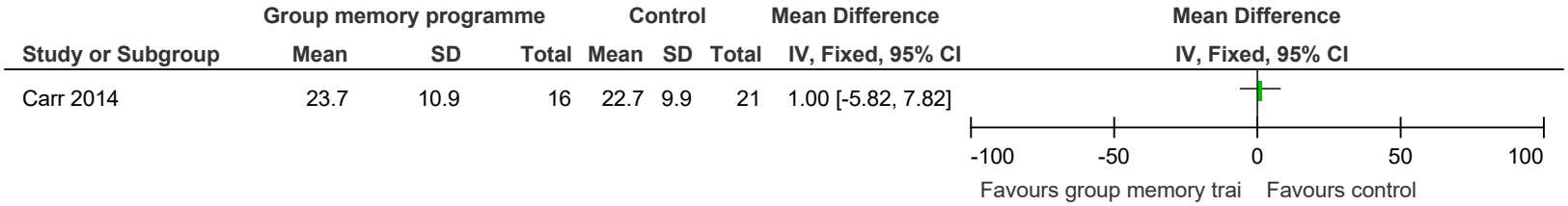


Figure 450: General Health Questionnaire-30 (scale 0-90; lower better)

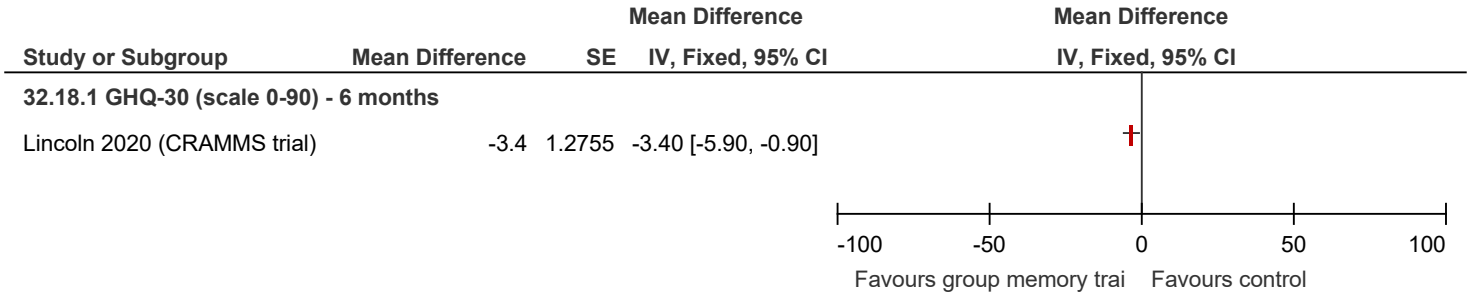
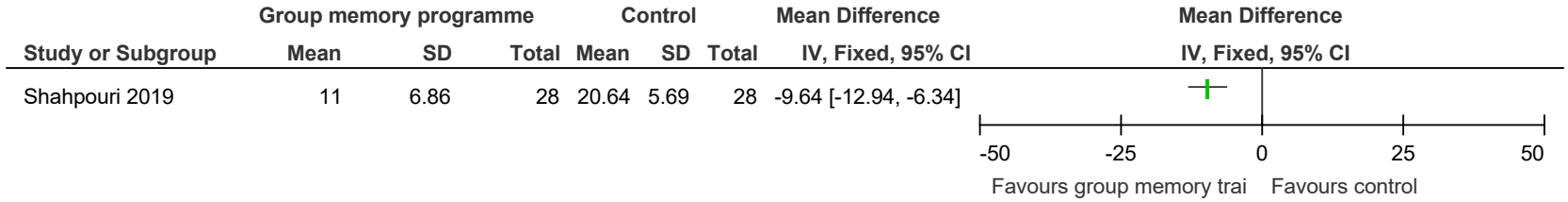
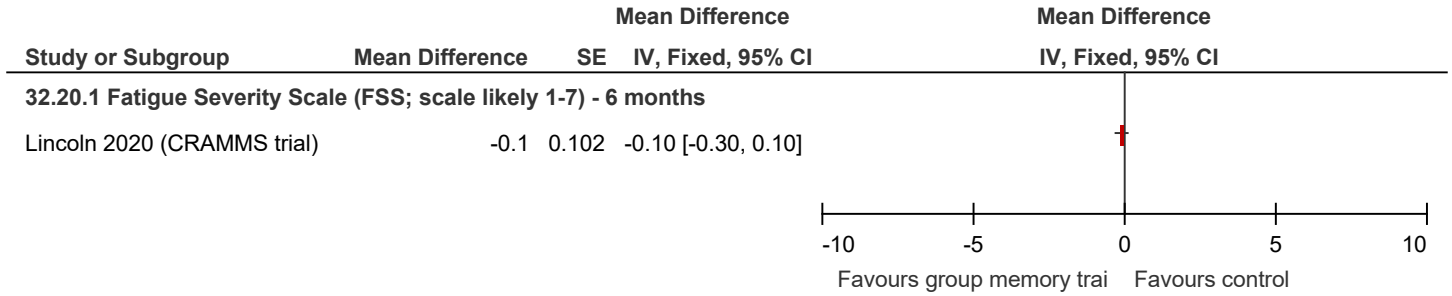


Figure 451: Beck Depression Inventory (scale usually 0-63; lower better)



1

Figure 452: Fatigue Severity Scale (scale likely 1-7; lower better)



2

Figure 453: Carer Strain Index (scale possible 0-13; lower better)

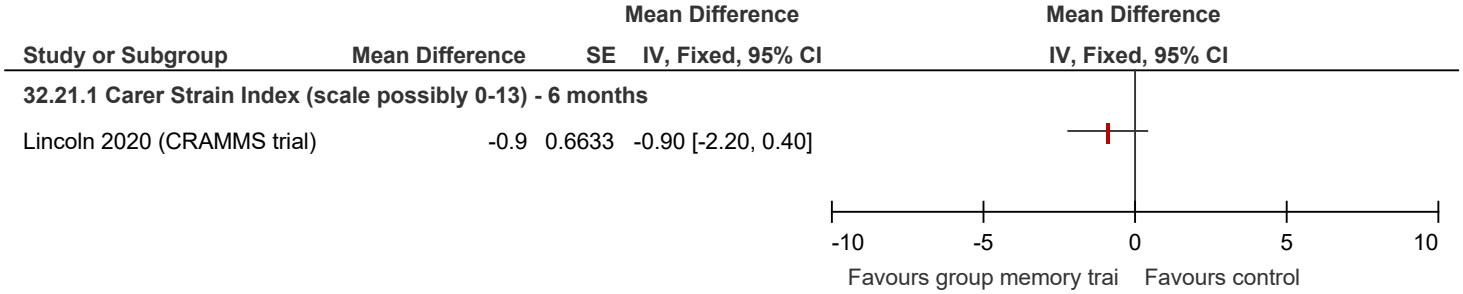
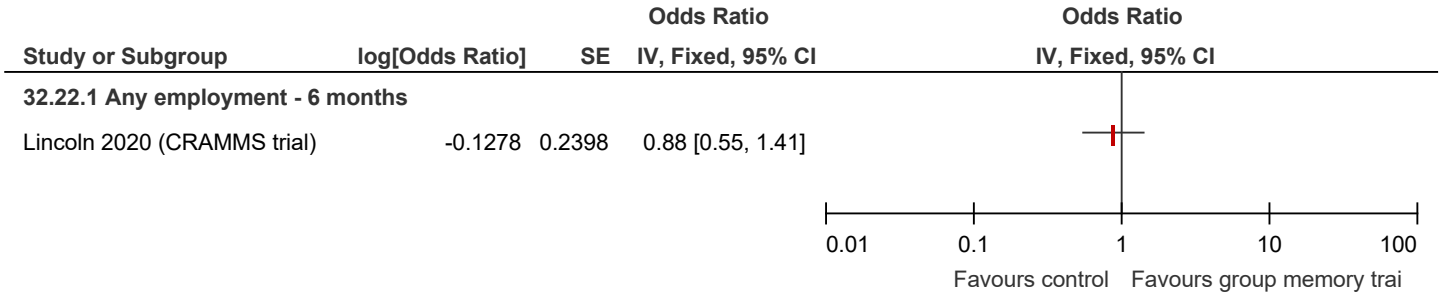


Figure 454: In any employment



E.33 Memory: group memory programme (various learning techniques) vs. control, 8-12 months

Figure 455: SDMT (higher better)

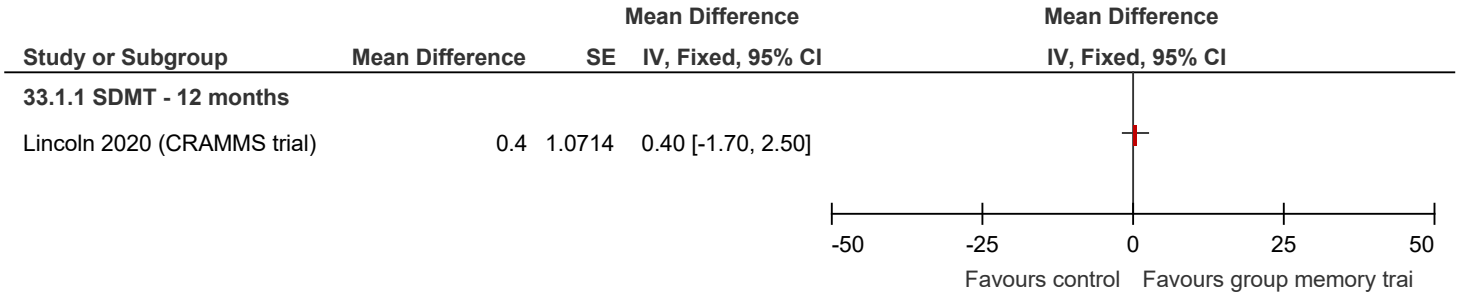


Figure 456: Selective Reminding Test (higher better)

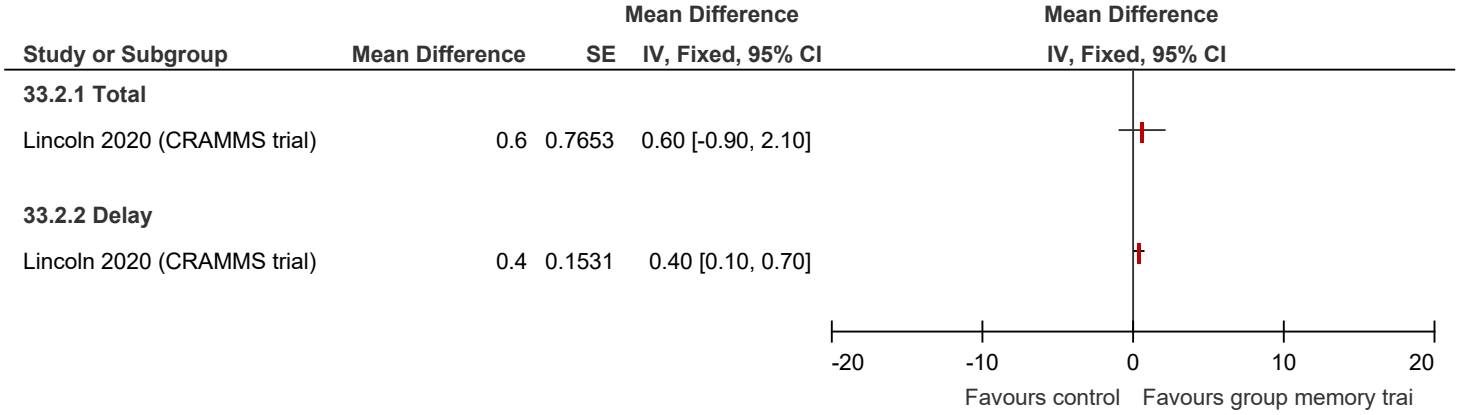
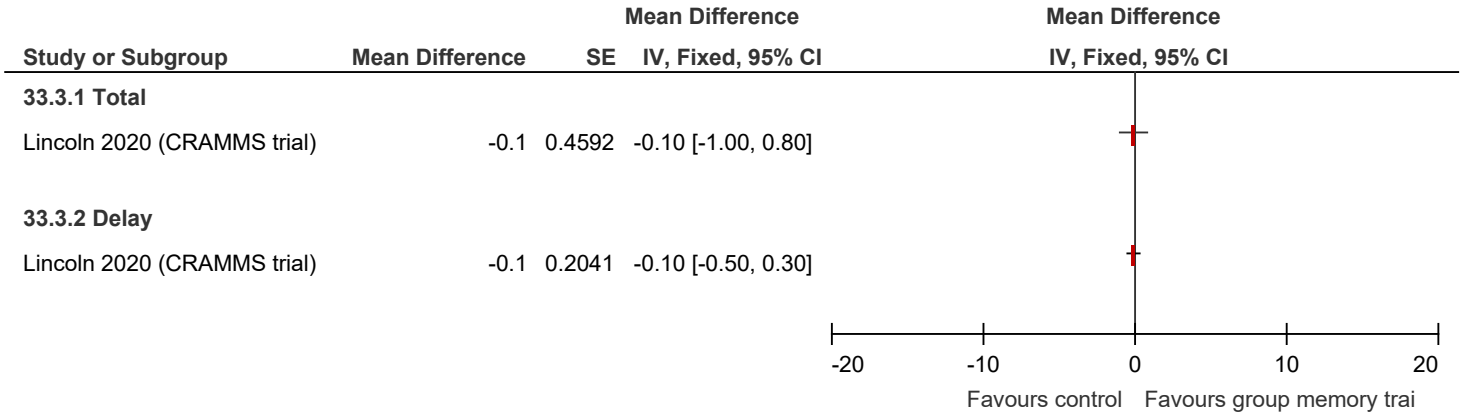
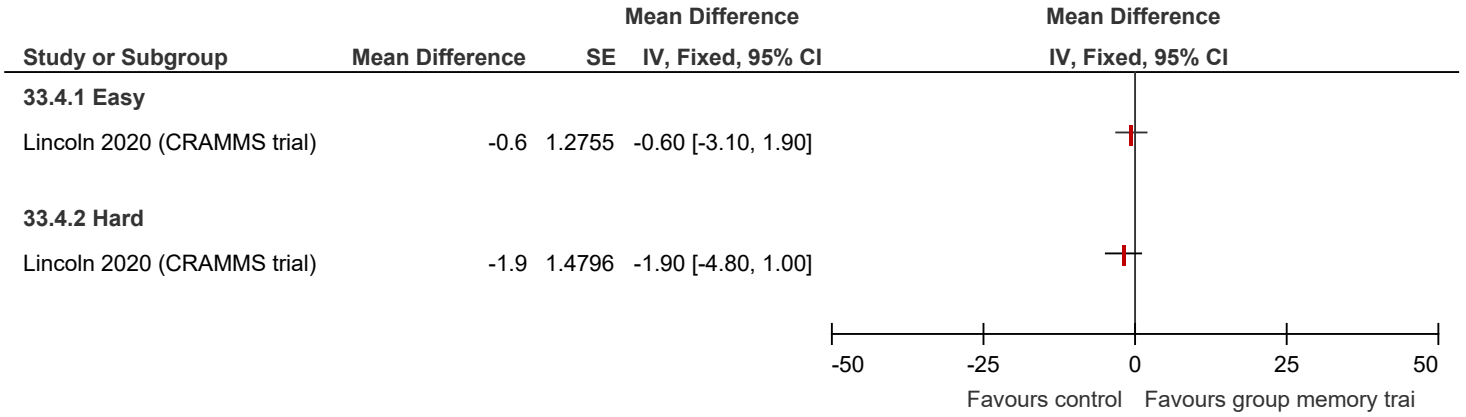


Figure 457: Spatial Recall Test (10/36 SPART; higher better)



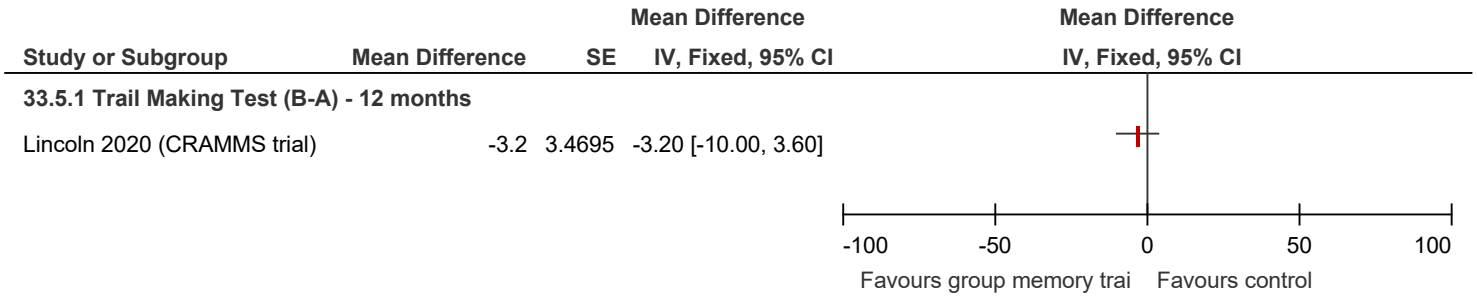
1

Figure 458: PASAT (higher better)



1

Figure 459: Trail Making Test (B-A; lower better)



2

Figure 460: Word Fluency (higher better)

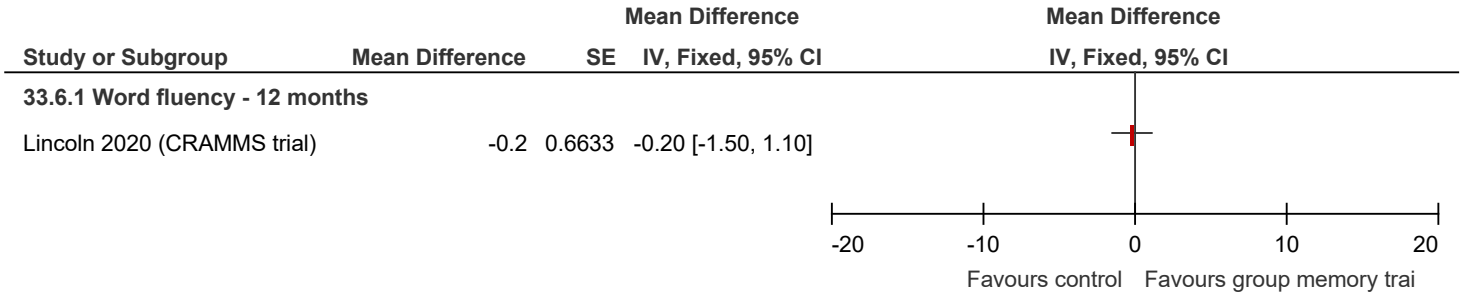


Figure 461: Doors and People (overall age-scaled score; higher better)

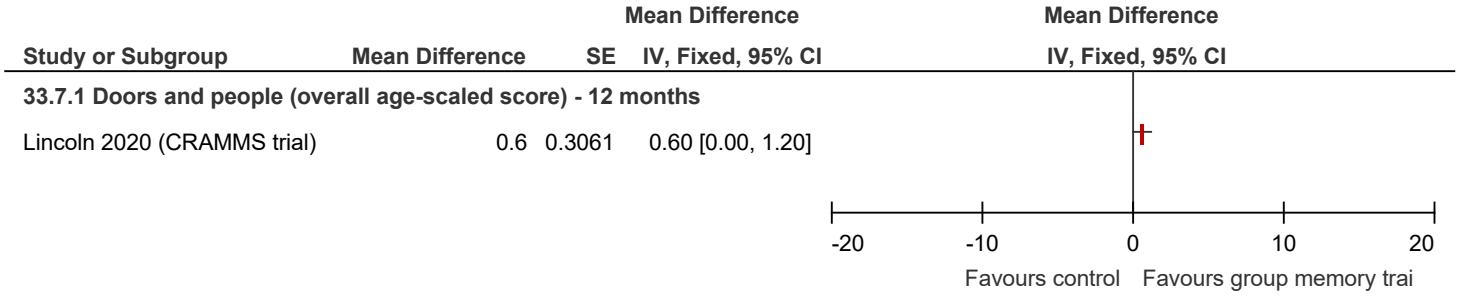


Figure 462: Everyday Memory Questionnaire (Scale 0-140; lower better)

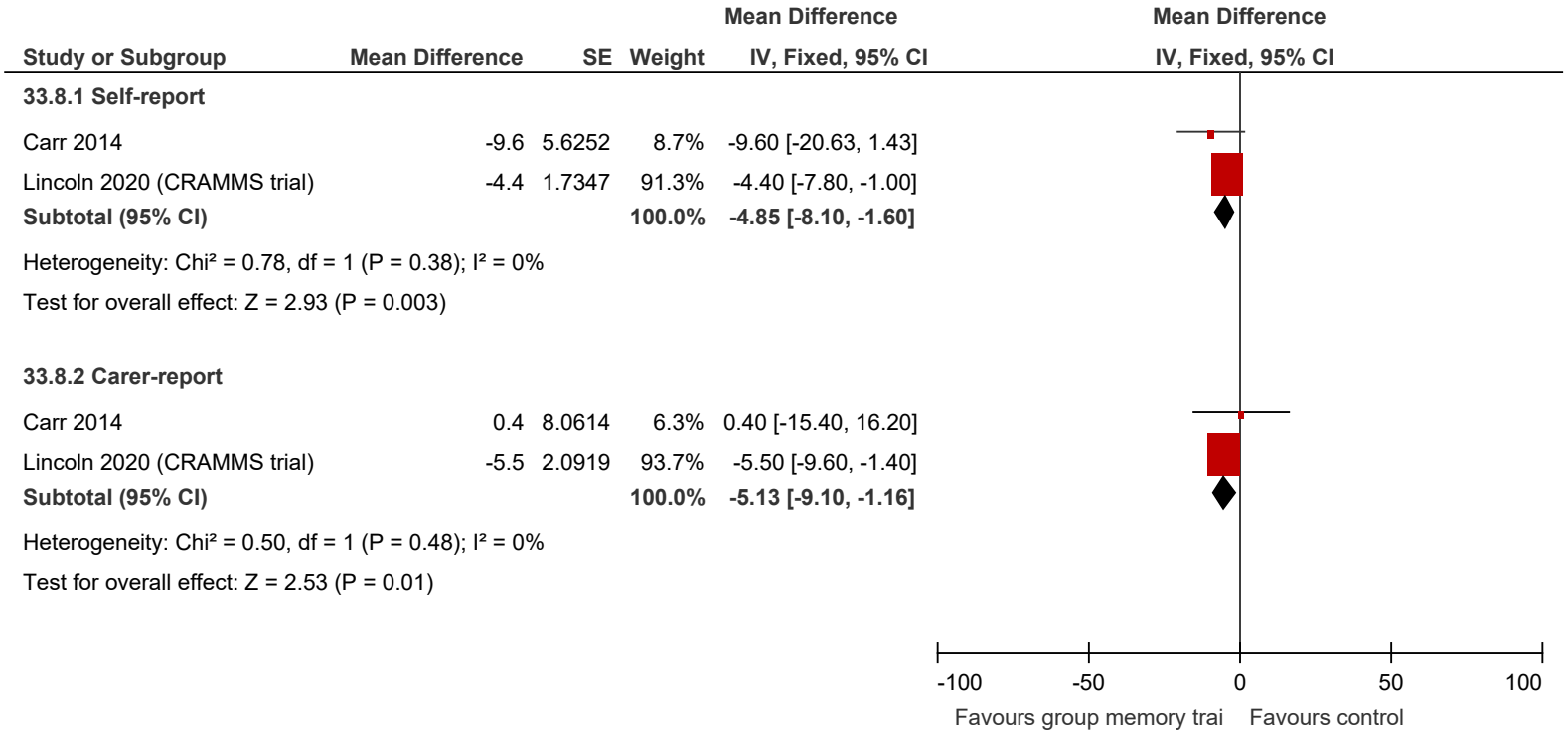


Figure 463: General Health Questionnaire (scale 0-84; lower better)

	Group memory programme			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Carr 2014	18.4	7	17	25.3	10.9	16	-6.90 [-13.19, -0.61]	

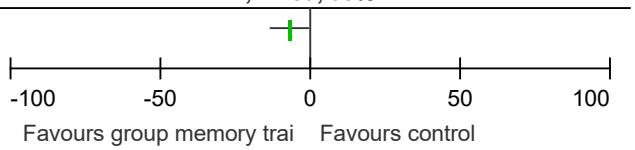
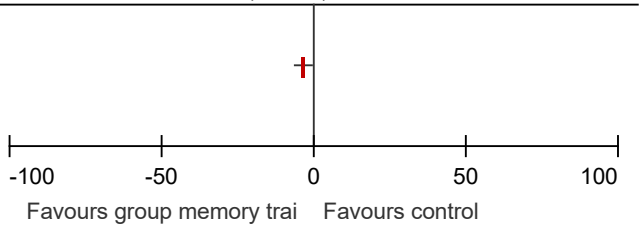


Figure 464: General Health Questionnaire-30 (scale 0-90; lower better)

			Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	IV, Fixed, 95% CI	IV, Fixed, 95% CI
33.13.1 GHQ-30 (scale 0-90) - 12 months				
Lincoln 2020 (CRAMMS trial)	-3.4	1.4286	-3.40 [-6.20, -0.60]	



1

Figure 465: MSIS-29 quality of life (scale 29-145; lower better)

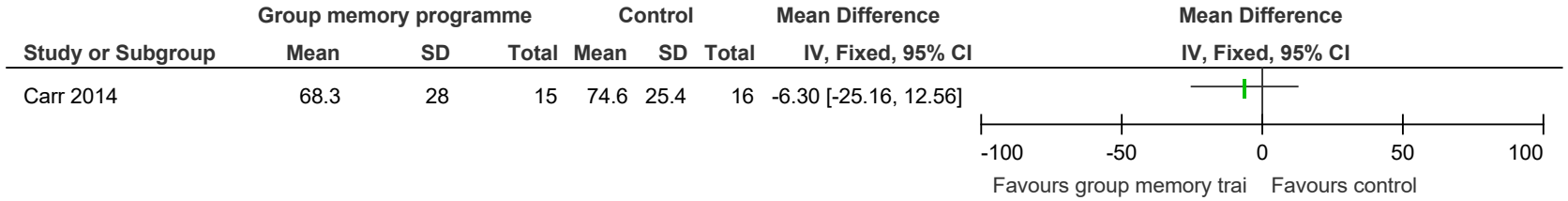


Figure 466: MSIS-29 quality of life (scale 0-100; lower better)

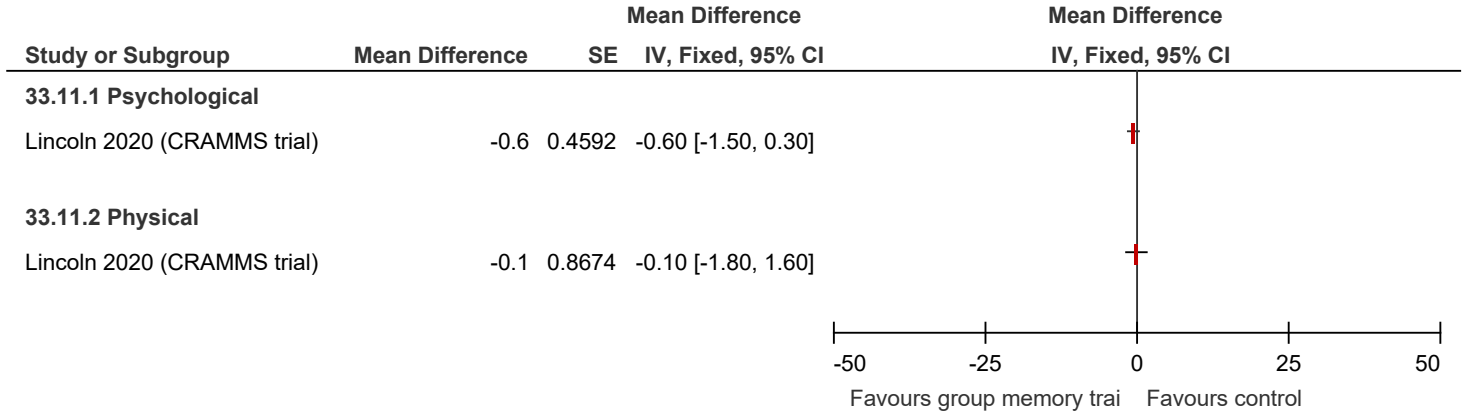


Figure 467: EQ-5D visual analogue scale (scale 0-100; higher better)

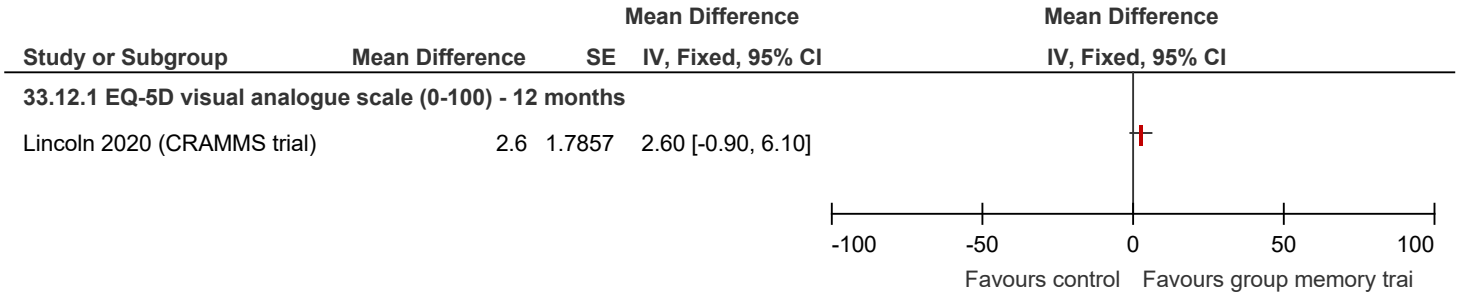


Figure 468: Fatigue Severity Scale (scale likely 1-7; lower better)

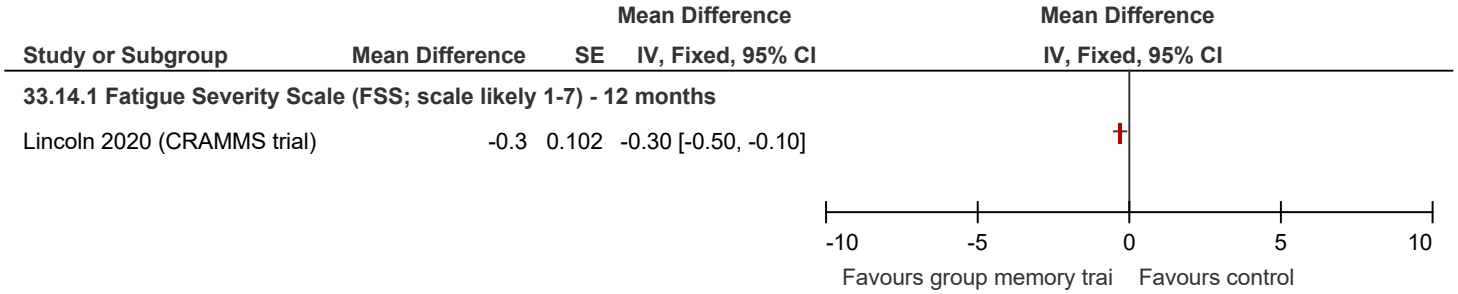
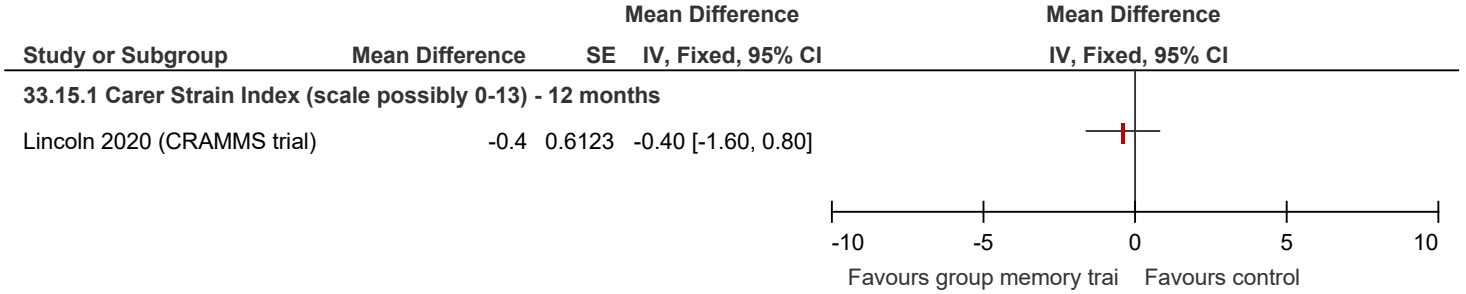
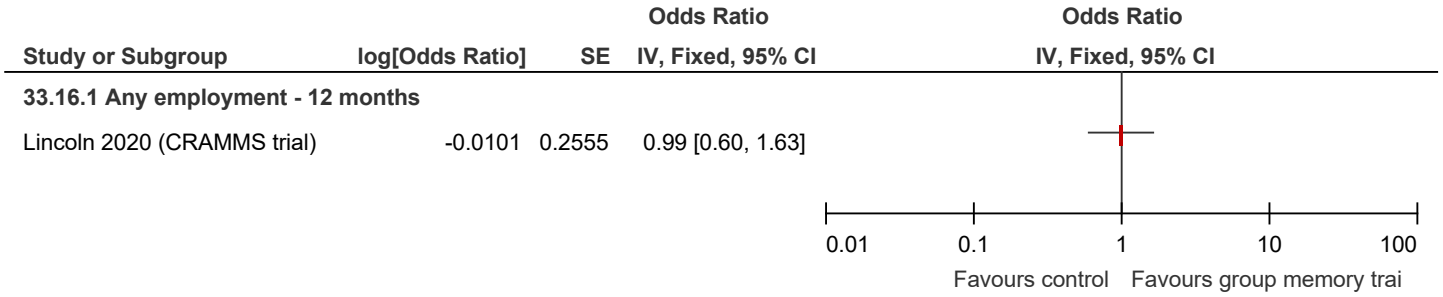


Figure 469: Carer Strain Index (scale possible 0-13; lower better)



1

Figure 470: In any employment



2

3

E.34 Memory: behaviour intervention (self-generated learning) vs. control (memory tasks with no self-generated learning taught), 3-4 weeks

Figure 471: California Verbal Learning Test-II (higher better)

Study or Subgroup	Self-generation learning Mean	SD	Total	Control memory tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
34.1.1 Five trials sum							
Goverover 2018 (Self-GEN trial)	53.5	10.5	19	52.1	10.6	16	1.40 [-5.62, 8.42]
34.1.2 Long delay							
Goverover 2018 (Self-GEN trial)	11.6	3.4	19	10.5	4	16	1.10 [-1.39, 3.59]

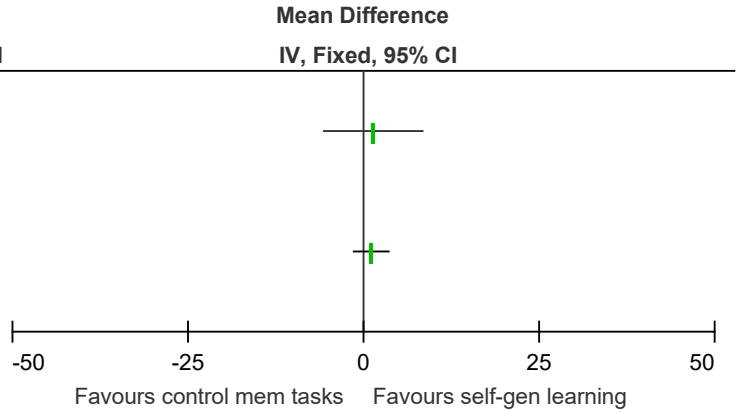


Figure 472: Contextual Memory Test (higher better)

Study or Subgroup	Self-generation learning Mean	SD	Total	Control memory tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
34.2.1 Immediate							
Goverover 2018 (Self-GEN trial)	15.6	2.6	19	11.6	2.7	16	4.00 [2.23, 5.77]
34.2.2 Delay							
Goverover 2018 (Self-GEN trial)	14	3.3	19	10.38	3.3	16	3.62 [1.43, 5.81]

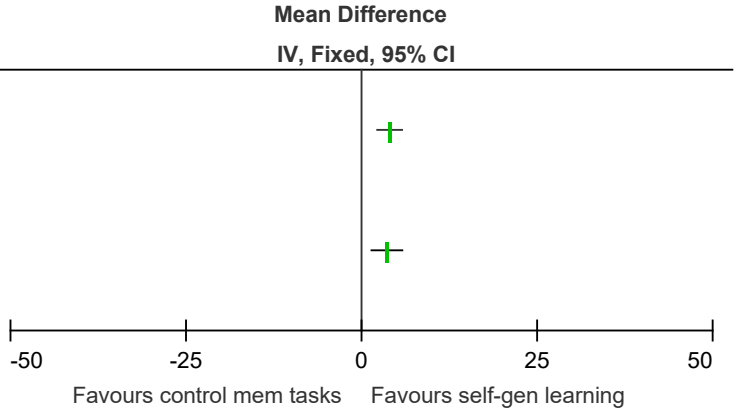


Figure 473: Memory for Intentions Test (MIST; higher better)

Study or Subgroup	Self-generation learning Mean	SD	Total	Control memory tasks Mean	SD	Total	Mean Difference IV, Random, 95% CI
Goverover 2018 (Self-GEN trial)	63.4	20.6	19	48.8	30	16	14.60 [-2.77, 31.97]

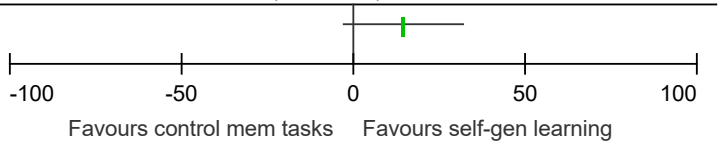
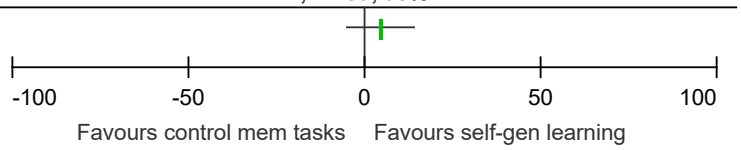


Figure 474: Verbal Fluency Test (total across three letters; higher better)

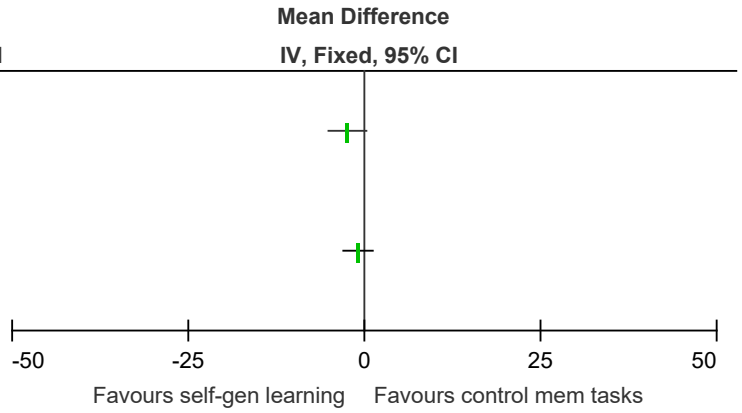
Study or Subgroup	Self-generation learning Mean	SD	Total	Control memory tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Goverover 2018 (Self-GEN trial)	40.25	14.1	19	35.7	14.5	16	4.55 [-4.97, 14.07]



1

Figure 475: Actual Reality™ Task (lower better)

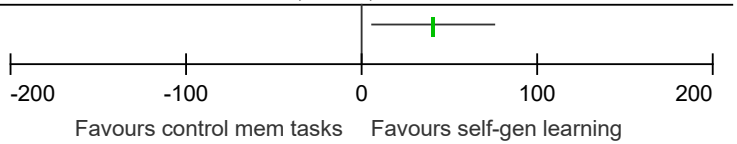
Study or Subgroup	Self-generation learning Mean	SD	Total	Control memory tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
34.5.1 Total errors							
Goverover 2018 (Self-GEN trial)	4.4	2.7	19	6.8	4.9	16	-2.40 [-5.09, 0.29]
34.5.2 Cognitive score (scale usually 0-20)							
Goverover 2018 (Self-GEN trial)	3.2	3.3	19	4.1	3	16	-0.90 [-2.99, 1.19]



2

Figure 476: Memory Functioning Questionnaire (scale usually 64-448; higher better)

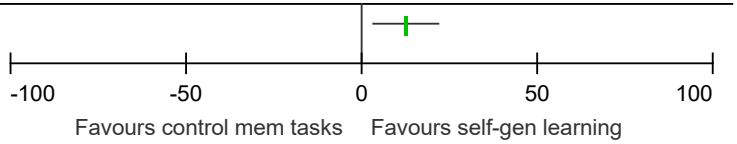
	Self-generation learning			Control memory tasks			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Goverover 2018 (Self-GEN trial)	250.2	47	19	209.4	56.3	16	40.80 [6.05, 75.55]	



1

Figure 477: Functional Behavioural Profile (scale possibly 0-108; higher better)

	Self-generation learning			Control memory tasks			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Goverover 2018 (Self-GEN trial)	101.5	10.5	19	88.9	16.3	16	12.60 [3.32, 21.88]	



2

Figure 478: Functional Assessment of MS (FAMS; scale usually 0-176; higher better)

	Self-generation learning			Control memory tasks			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Goverover 2018 (Self-GEN trial)	102.5	27.5	19	98.3	31.5	16	4.20 [-15.58, 23.98]	

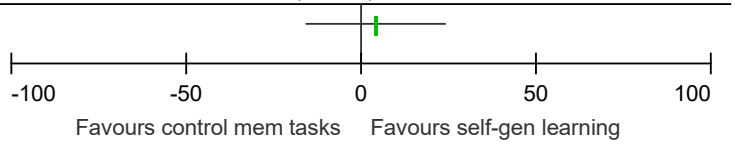


Figure 479: Self-awareness of Cognitive Deficits Questionnaire (scale usually 17-85; lower better)

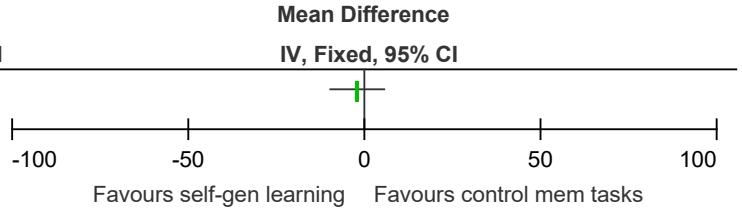
	Self-generation learning			Control memory tasks			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Goverover 2018 (Self-GEN trial)	8.6	8.1	19	4.8	4.8	16	3.80 [-0.54, 8.14]	

Figure 480: Self-regulation Skills Interview (self-awareness and strategy use; scale unclear; lower better)

	Self-generation learning			Control memory tasks			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Goverover 2018 (Self-GEN trial)	29.2	7.3	19	31.7	6.1	16	-2.50 [-6.94, 1.94]	

Figure 481: State-Trait Anxiety Inventory – Trait score (scale usually 20-80; lower better)

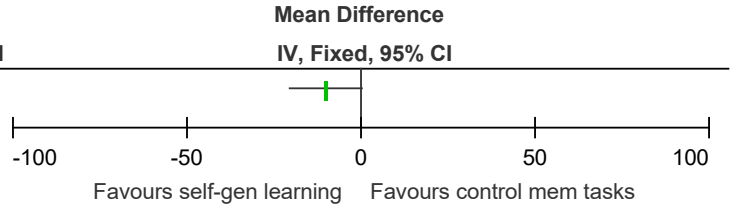
Study or Subgroup	Self-generation learning Mean	SD	Total	Control memory tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Goverover 2018 (Self-GEN trial)	39.4	12.6	19	41.4	10.5	16	-2.00 [-9.65, 5.65]



1

Figure 482: Chicago Multiscale Depression Inventory (scale possibly 42-210; lower better)

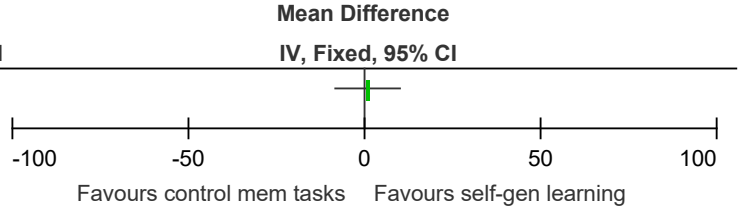
Study or Subgroup	Self-generation learning Mean	SD	Total	Control memory tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Goverover 2018 (Self-GEN trial)	53.1	15.8	19	63.2	15.4	16	-10.10 [-20.46, 0.26]



2

Figure 483: Satisfaction with Life Scale (scale usually 5-35; higher better)

Study or Subgroup	Self-generation learning Mean	SD	Total	Control memory tasks Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Goverover 2018 (Self-GEN trial)	19.19	18.3	19	18.3	8.3	16	0.89 [-8.29, 10.07]



E.35 Executive function: executive function-specific training vs. control (no training), 6 weeks

Figure 484: California Verbal Learning Test - Learning (higher better)

Study or Subgroup	Exec. function training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	12.1	2.1	11	11.5	2.1	15	0.60 [-1.03, 2.23]

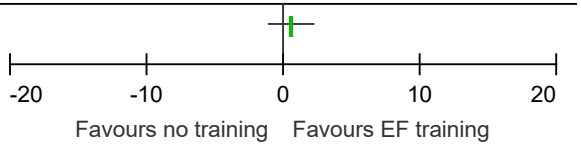


Figure 485: Wisconsin Card Sorting Test – Number of categories (higher better)

Study or Subgroup	Exec. function training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Sharifi 2019	4.8	1.13	10	3.5	0.7	10	1.30 [0.48, 2.12]

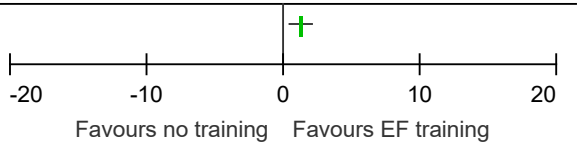
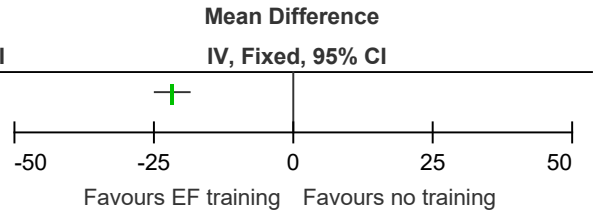


Figure 486: Wisconsin Card Sorting Test – Total errors (lower better)

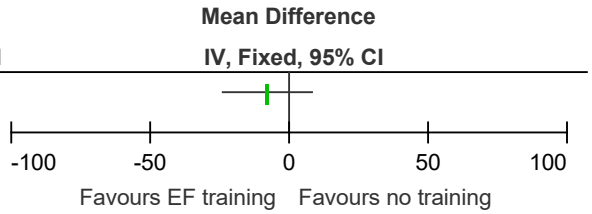
Study or Subgroup	Exec. function training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Sharifi 2019	19	4.39	10	40.7	2.45	10	-21.70 [-24.82, -18.58]



1

Figure 487: Preference shifting – trials to criterion (lower better)

Study or Subgroup	Exec. function training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	33	19	11	40.8	22.7	15	-7.80 [-23.86, 8.26]



2

Figure 488: Preference shifting – reaction time (lower better)

Study or Subgroup	Exec. function training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	638	185	11	697	144	15	-59.00 [-190.39, 72.39]

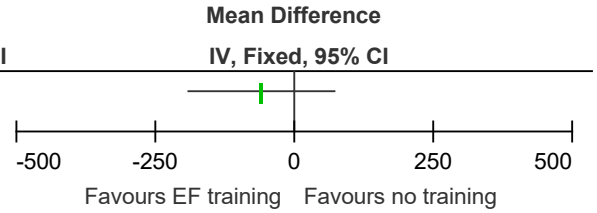


Figure 489: Response shifting – trials to criterion (lower better)

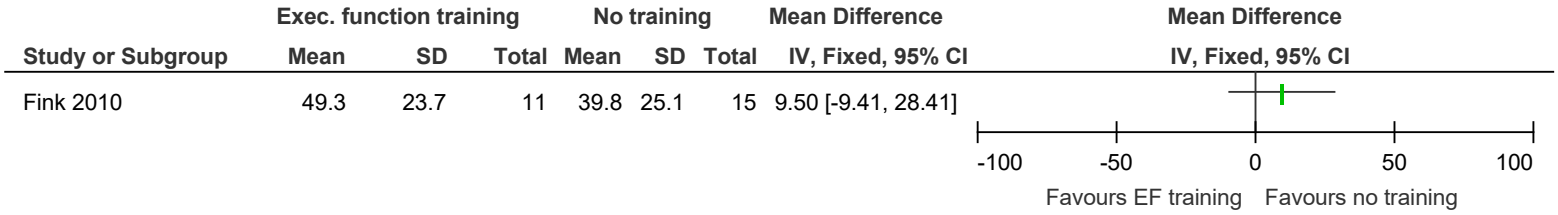


Figure 490: Response shifting – reaction time (lower better)

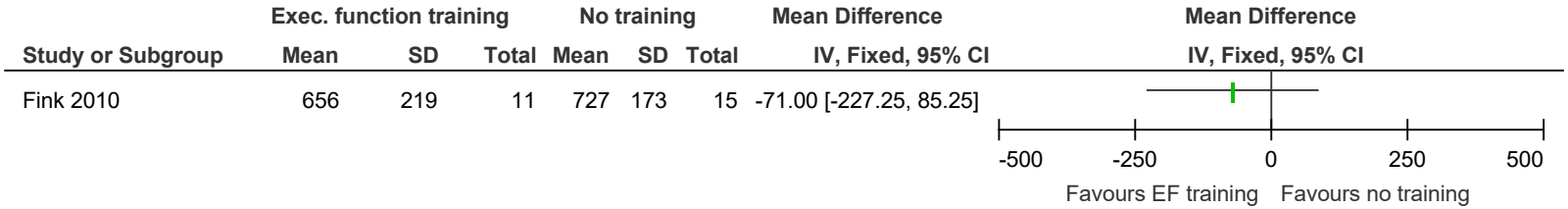
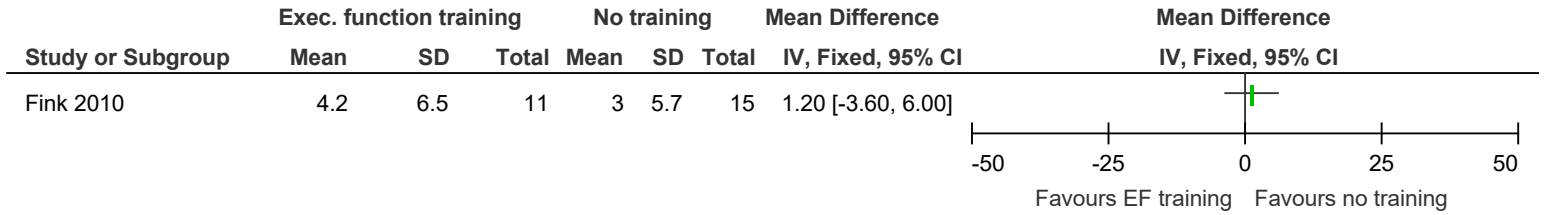
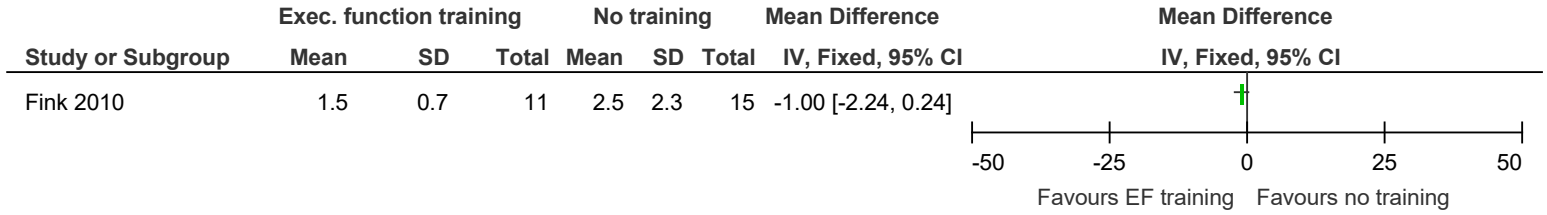


Figure 491: 2-back commissions (lower better)



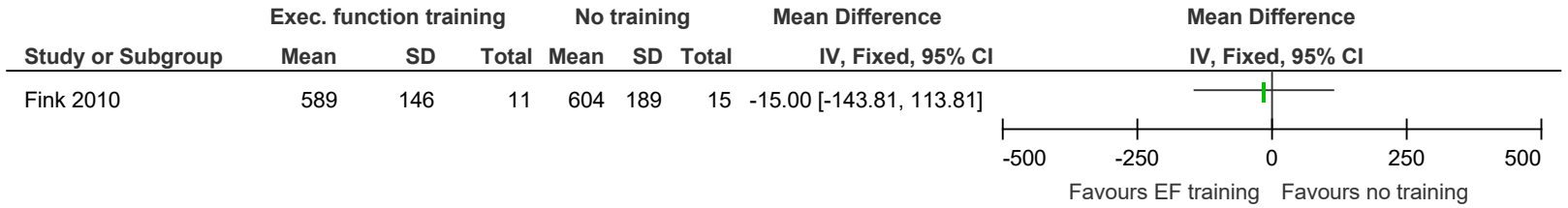
1

Figure 492: 2-back omissions (lower better)



2

Figure 493: 2-back reaction time (lower better)



E.36 Executive function: executive function-specific training vs. control (no training), 6 weeks

Figure 494: California Verbal Learning Test - Learning (higher better)

Study or Subgroup	Exec. function training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	11.5	2.1	6	12.3	1.8	6	-0.80 [-3.01, 1.41]

Figure 495: Preference shifting – trials to criterion (lower better)

Study or Subgroup	Exec. function training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	59.2	22.5	6	37.8	24.2	6	21.40 [-5.04, 47.84]

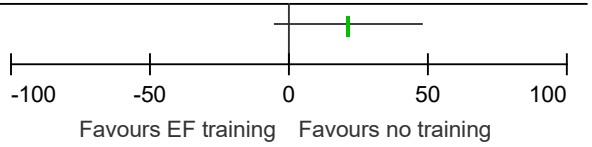
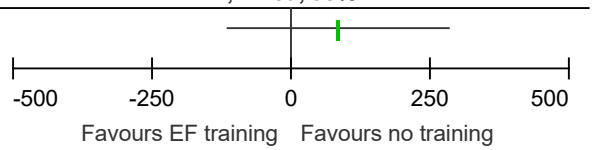


Figure 496: Preference shifting – reaction time (lower better)

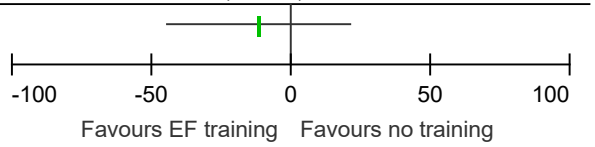
	Exec. function training			No training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fink 2010	685	142	6	600	204	6	85.00 [-113.88, 283.88]	



1

Figure 497: Response shifting – trials to criterion (lower better)

	Exec. function training			No training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fink 2010	40.4	31.6	6	51.9	26.2	6	-11.50 [-44.35, 21.35]	



2

Figure 498: Response shifting – reaction time (lower better)

	Exec. function training			No training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fink 2010	684	230	6	675	235	6	9.00 [-254.11, 272.11]	

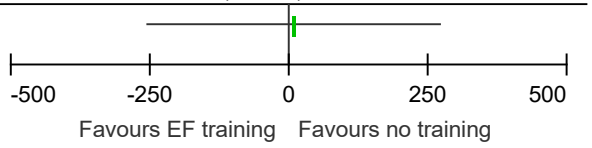


Figure 499: 2-back commissions (lower better)

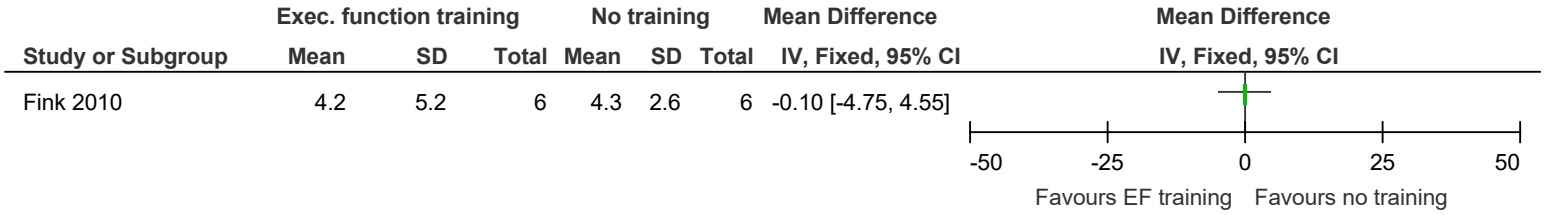


Figure 500: 2-back omissions (lower better)

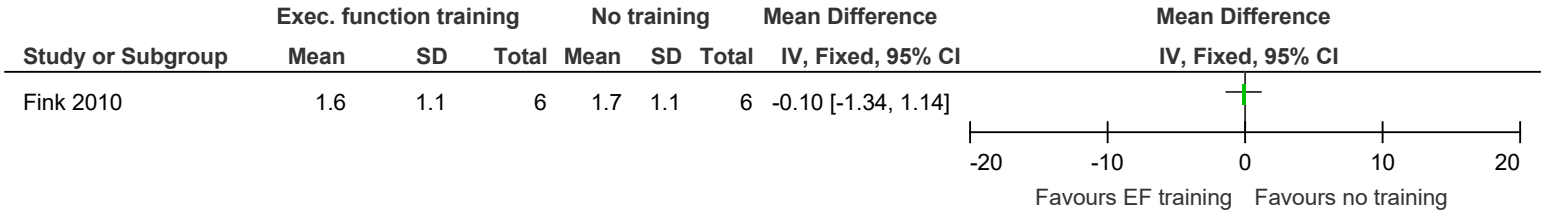
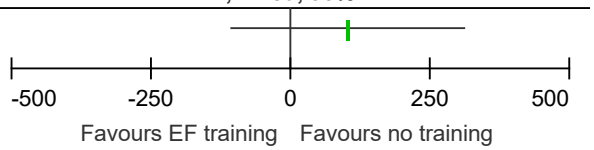


Figure 501: 2-back reaction time (lower better)

Study or Subgroup	Exec. function training Mean	SD	Total	No training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	685	184	6	582	185	6	103.00 [-105.78, 311.78]



E.37 Executive function: executive function-specific training vs. active control (responding quickly to visual stimuli), 6 weeks

Figure 502: California Verbal Learning Test - Learning (higher better)

Study or Subgroup	Exec. function training Mean	SD	Total	Active control training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	12.1	2.1	11	11.5	1.2	14	0.60 [-0.79, 1.99]

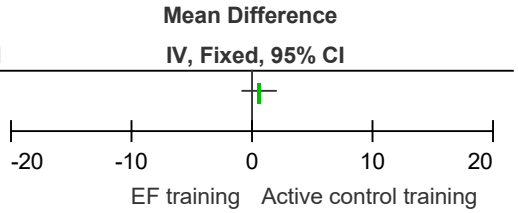
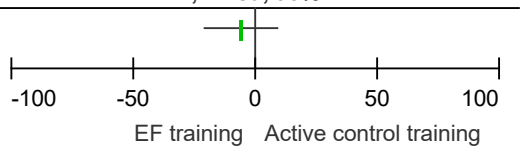


Figure 503: Preference shifting – trials to criterion (lower better)

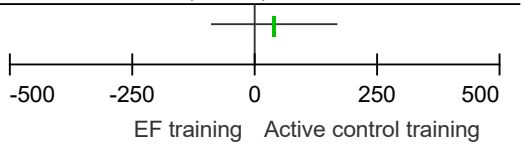
	Exec. function training			Active control training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fink 2010	33	19	11	38.8	18.7	14	-5.80 [-20.70, 9.10]	



1

Figure 504: Preference shifting – reaction time (lower better)

	Exec. function training			Active control training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fink 2010	638	185	11	598	124	14	40.00 [-87.17, 167.17]	



2

Figure 505: Response shifting – trials to criterion (lower better)

	Exec. function training			Active control training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fink 2010	49.3	23.7	11	49.9	27	14	-0.60 [-20.50, 19.30]	

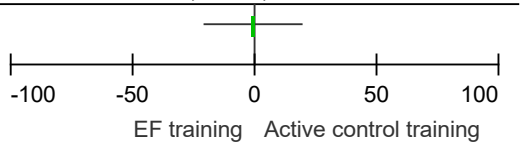


Figure 506: Response shifting – reaction time (lower better)

Study or Subgroup	Exec. function training Mean	SD	Total	Active control training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	656	219	11	676	170	14	-20.00 [-177.10, 137.10]

Figure 507: 2-back commissions (lower better)

Study or Subgroup	Exec. function training Mean	SD	Total	Active control training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	4.2	6.5	11	3.1	1.6	14	1.10 [-2.83, 5.03]

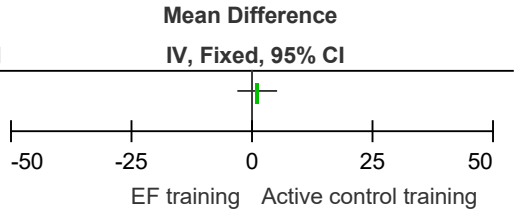


Figure 508: 2-back omissions (lower better)

Study or Subgroup	Exec. function training Mean	SD	Total	Active control training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	1.5	0.7	11	1.4	1.2	14	0.10 [-0.65, 0.85]

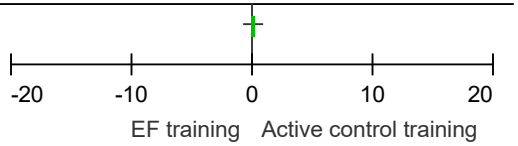
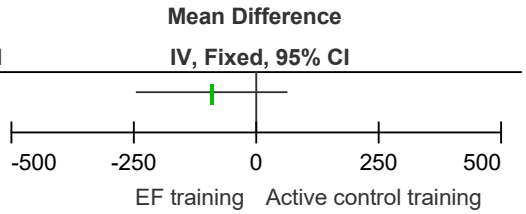


Figure 509: 2-back reaction time (lower better)

Study or Subgroup	Exec. function training Mean	SD	Total	Active control training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	589	146	11	680	241	14	-91.00 [-243.91, 61.91]



E.38 Executive function: executive function-specific training vs. active control (responding quickly to visual stimuli), 12 months

Figure 510: California Verbal Learning Test - Learning (higher better)

Study or Subgroup	Exec. function training Mean	SD	Total	Active control training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	11.5	2.1	6	11.5	1.1	8	0.00 [-1.85, 1.85]

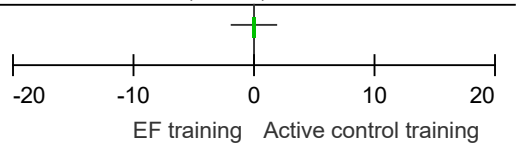


Figure 511: Preference shifting – trials to criterion (lower better)

Study or Subgroup	Exec. function training Mean	SD	Total	Active control training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	59.2	22.5	6	45.7	20.1	8	13.50 [-9.26, 36.26]

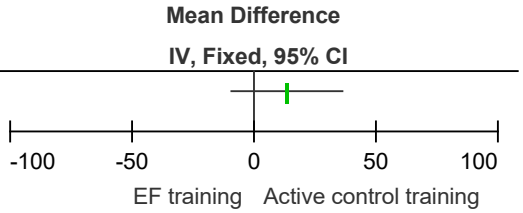


Figure 512: Preference shifting – reaction time (lower better)

Study or Subgroup	Exec. function training Mean	SD	Total	Active control training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	685	142	6	734	196	8	-49.00 [-226.08, 128.08]

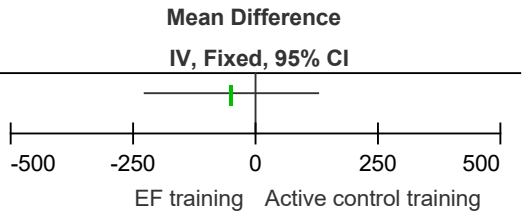


Figure 513: Response shifting – trials to criterion (lower better)

Study or Subgroup	Exec. function training Mean	SD	Total	Active control training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	40.4	31.6	6	49.9	25.2	8	-9.50 [-40.23, 21.23]

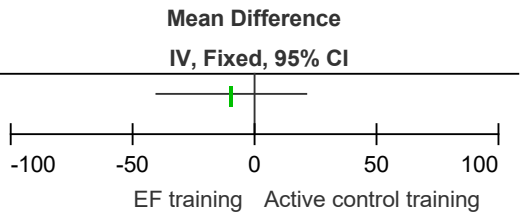


Figure 514: Response shifting – reaction time (lower better)

Study or Subgroup	Exec. function training Mean	SD	Total	Active control training Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fink 2010	684	230	6	747	230	8	-63.00 [-306.46, 180.46]

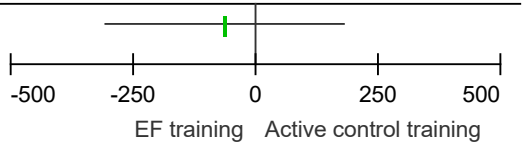
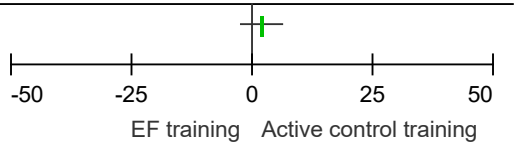


Figure 515: 2-back commissions (lower better)

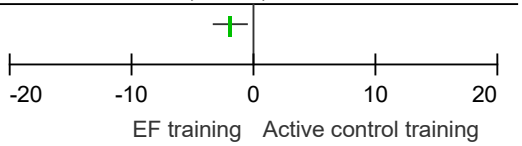
	Exec. function training			Active control training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fink 2010	4.2	5.2	6	2.2	1.5	8	2.00 [-2.29, 6.29]	



1

Figure 516: 2-back omissions (lower better)

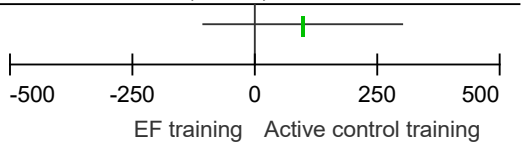
	Exec. function training			Active control training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fink 2010	1.6	1.1	6	3.5	1.5	8	-1.90 [-3.26, -0.54]	



2

Figure 517: 2-back reaction time (lower better)

	Exec. function training			Active control training			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fink 2010	685	184	6	587	202	8	98.00 [-105.15, 301.15]	



E.39 Executive function: goal management programme vs. psychoeducation, 9 weeks

Figure 518: Sustained Attention To Response Task (SART) errors (lower better)

Study or Subgroup	Goal management programme Mean	SD	Total	Psychoeducation Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
39.1.1 Commission errors (% of no-go trials)							
Richard 2013	39.4	29.6	13	28.3	22	14	11.10 [-8.69, 30.89]
39.1.2 Omission errors (% of go trials)							
Richard 2013	4.4	4.7	13	4.2	5	14	0.20 [-3.46, 3.86]

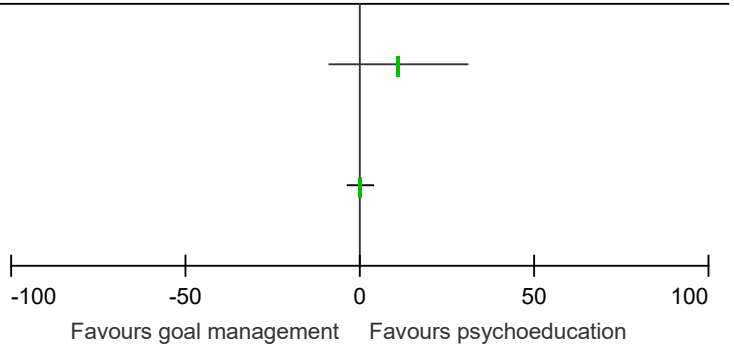
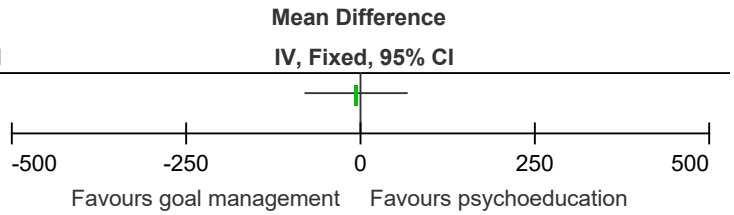


Figure 519: SART reaction time (lower better)

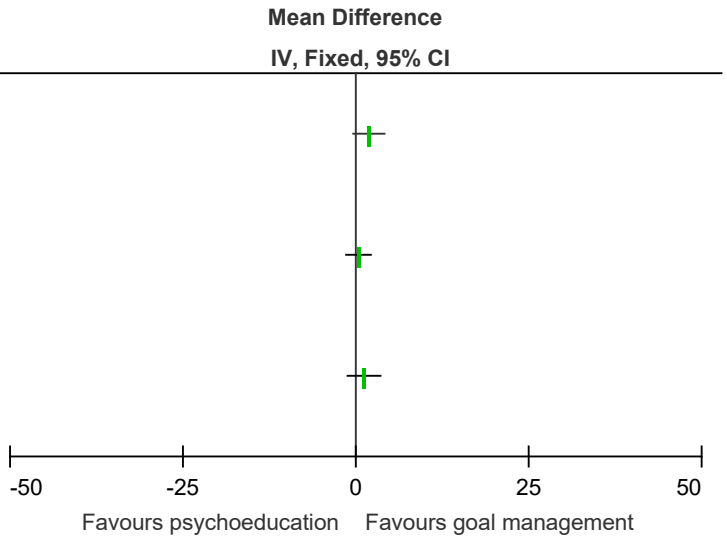
Study or Subgroup	Goal management programme Mean	SD	Total	Psychoeducation Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Richard 2013	447.8	108.8	13	454	80.4	14	-6.20 [-78.81, 66.41]



1

Figure 520: Test of Everyday Attention (higher better)

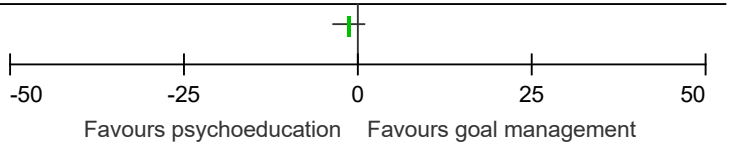
Study or Subgroup	Goal management programme Mean	SD	Total	Psychoeducation Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
39.3.1 Elevator counting with distraction							
Richard 2013	7.6	2.8	13	5.7	3.2	14	1.90 [-0.36, 4.16]
39.3.2 Visual elevator							
Richard 2013	8.4	2.5	13	8	2.2	14	0.40 [-1.38, 2.18]
39.3.3 Elevator counting with reversal							
Richard 2013	5.5	3	13	4.3	3.3	14	1.20 [-1.18, 3.58]



2

Figure 521: Delis-Kaplan Executive Function Scale (D-KEFS) Tower Test achievement score (higher better)

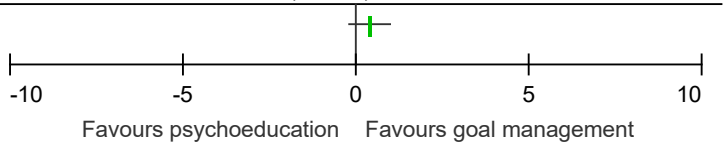
	Goal management programme			Psychoeducation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Richard 2013	7.6	2.9	13	8.9	3	14	-1.30 [-3.53, 0.93]	



1

Figure 522: Hotel Test – Tasks attempted (higher better)

	Goal management programme			Psychoeducation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Richard 2013	4.7	0.5	13	4.3	1	14	0.40 [-0.19, 0.99]	

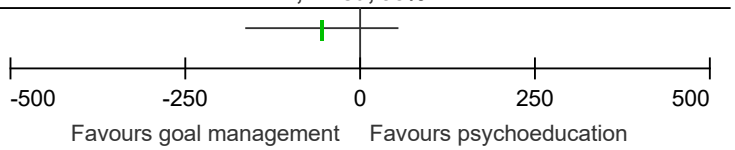


2

3

Figure 523: Hotel Test – deviation from optimal task time (lower better)

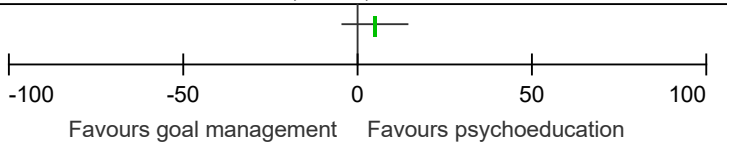
	Goal management programme			Psychoeducation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Richard 2013	403.6	111.7	13	458.3	170.9	14	-54.70 [-162.87, 53.47]	



1

Figure 524: Cognitive Failures Questionnaire (scale 0-100; lower better)

	Goal management programme			Psychoeducation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Richard 2013	42.3	11.3	13	37.3	13.4	14	5.00 [-4.33, 14.33]	



2

3

Figure 525: Dysexecutive Questionnaire (scale usually 0-80; lower better)

	Goal management programme			Psychoeducation			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
39.8.1 Self-reported							
Richard 2013	19	9.3	13	17.2	9.2	14	1.80 [-5.18, 8.78]
39.8.2 Informant-reported							
Richard 2013	21.5	18.8	13	22.5	17.7	14	-1.00 [-14.80, 12.80]

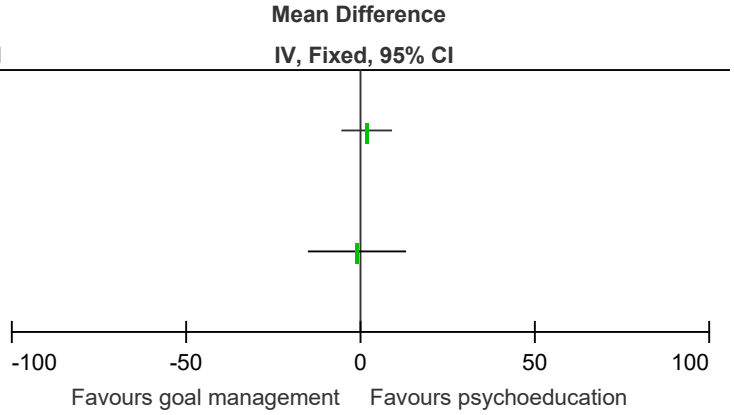


Figure 526: Profile of Mood States (POMS) – Total Mood Disturbance (scale usually 0-200; lower better)

	Goal management programme			Psychoeducation			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
Richard 2013	34.9	20.1	13	23	21.1	14	11.90 [-3.64, 27.44]

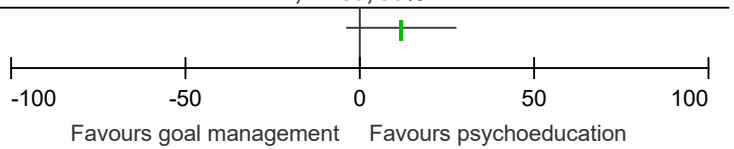


Figure 527: Pittsburgh Sleep Quality Index – Global Sleep Disturbance (scale usually 0-21; lower better)

	Goal management programme			Psychoeducation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Richard 2013	7	4.1	13	7.2	4.6	14	-0.20 [-3.48, 3.08]	

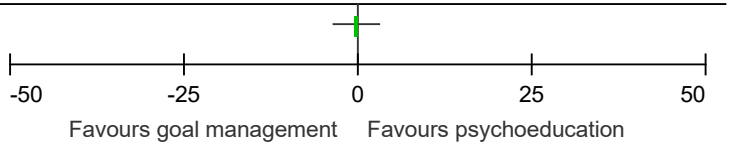
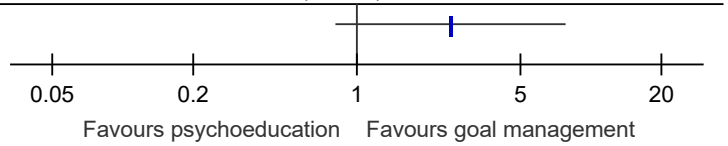


Figure 528: Goal Attainment post-intervention (proportion achieving or exceeding target goal)

	Goal management programme		Psychoeducation		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Richard 2013	7	13	3	14	2.51 [0.82, 7.72]	



E.40 Executive function: goal management programme vs. psychoeducation, 8 months

Figure 529: Sustained Attention To Response Task (SART) errors (lower better)

	Goal management programme			Psychoeducation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
40.1.1 Commission errors (% of no-go trials)								
Richard 2013	42	28	11	32	21.3	12	10.00 [-10.47, 30.47]	
40.1.2 Omission errors (% of go trials)								
Richard 2013	3.6	3.3	11	2.9	3.3	12	0.70 [-2.00, 3.40]	

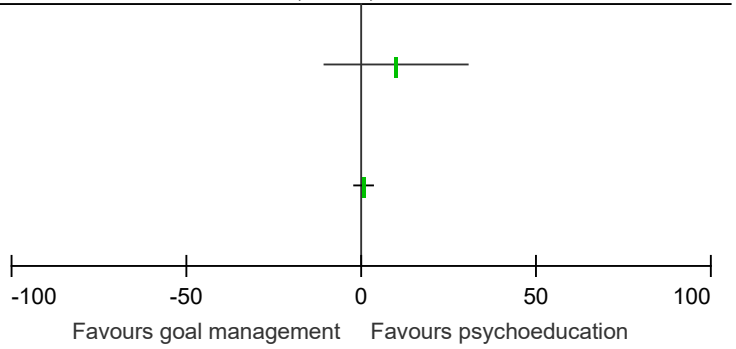


Figure 530: SART reaction time (lower better)

	Goal management programme			Psychoeducation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Richard 2013	423	116.1	11	433.8	79.3	12	-10.80 [-92.78, 71.18]	

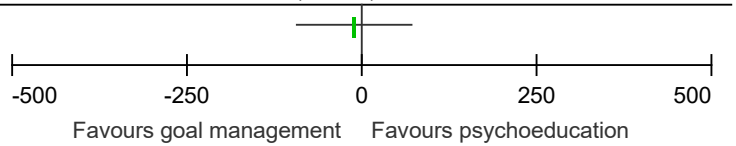
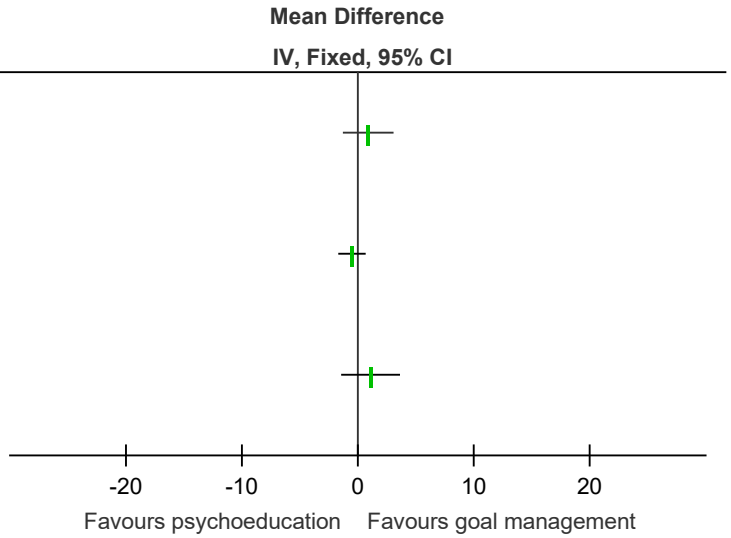


Figure 531: Test of Everyday Attention (higher better)

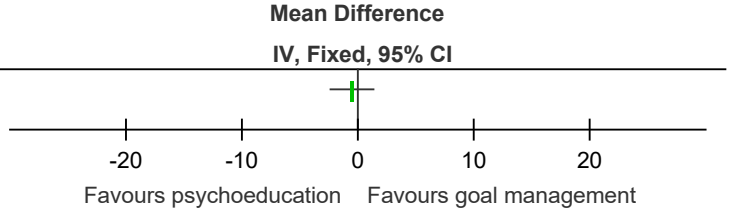
	Goal management programme			Psychoeducation			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
40.3.1 Elevator counting with distraction							
Richard 2013	7.6	2.8	11	6.7	2.3	12	0.90 [-1.21, 3.01]
40.3.2 Visual elevator							
Richard 2013	8.7	1.6	11	9.2	1	12	-0.50 [-1.60, 0.60]
40.3.3 Elevator counting with reversal							
Richard 2013	4.8	3	11	3.7	3	12	1.10 [-1.35, 3.55]



1

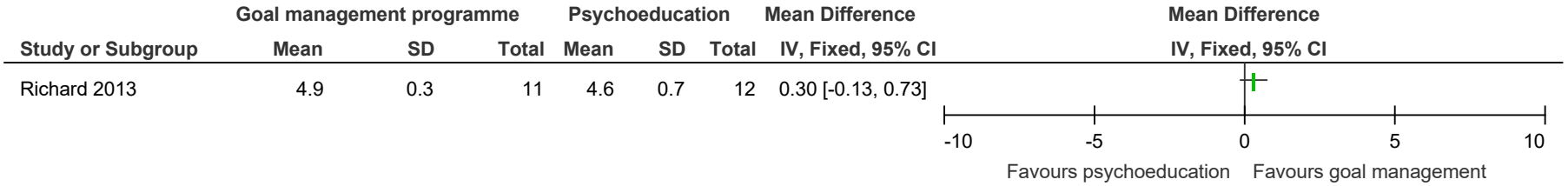
Figure 532: Delis-Kaplan Executive Function Scale (D-KEFS) Tower Test achievement score (higher better)

	Goal management programme			Psychoeducation			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
Richard 2013	7.8	2.4	11	8.3	2.1	12	-0.50 [-2.35, 1.35]



2

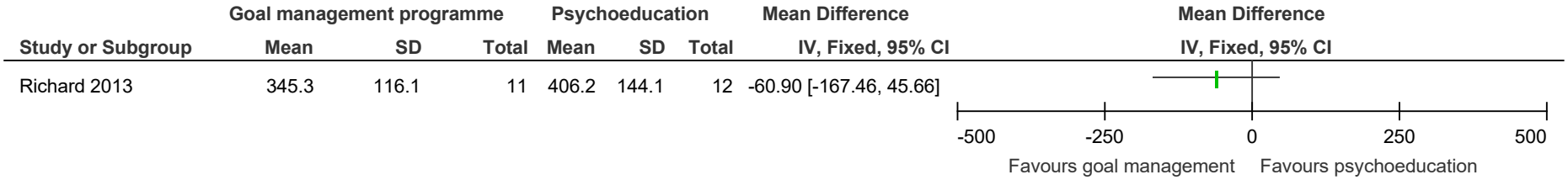
Figure 533: Hotel Test – Tasks attempted (higher better)



1

2

Figure 534: Hotel Test – deviation from optimal task time (lower better)



3

Figure 535: Cognitive Failures Questionnaire (scale 0-100; lower better)

	Goal management programme			Psychoeducation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Richard 2013	41.7	13.5	11	35.8	14.5	12	5.90 [-5.54, 17.34]	

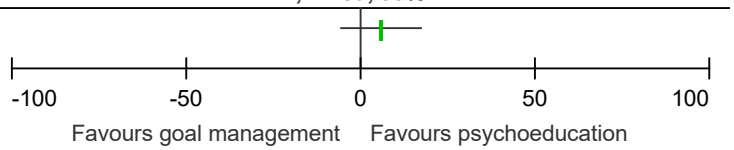


Figure 536: Dysexecutive Questionnaire (scale usually 0-80; lower better)

	Goal management programme			Psychoeducation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
40.8.1 Self-reported								
Richard 2013	20.1	8.9	11	16.9	10.9	12	3.20 [-4.91, 11.31]	
40.8.2 Informant-reported								
Richard 2013	15.7	10.4	11	18.4	13.2	12	-2.70 [-12.37, 6.97]	

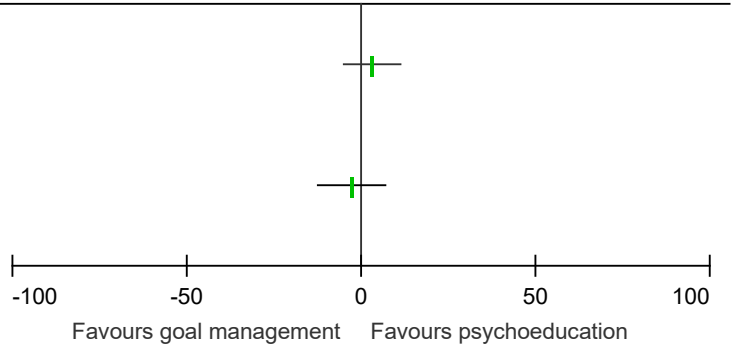


Figure 537: Profile of Mood States (POMS) – Total Mood Disturbance (scale usually 0-200; lower better)

	Goal management programme			Psychoeducation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Richard 2013	36.3	20.9	11	20.5	24.1	12	15.80 [-2.60, 34.20]	

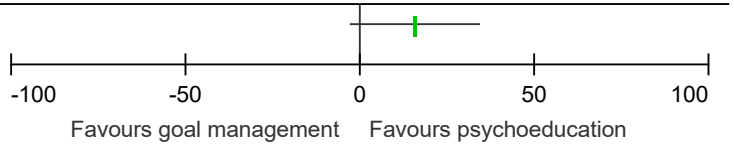
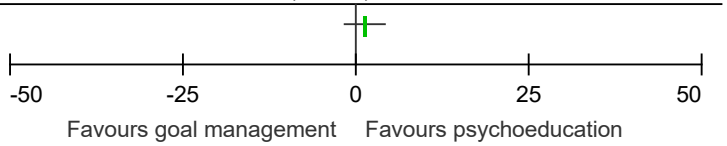


Figure 538: Pittsburgh Sleep Quality Index – Global Sleep Disturbance (scale usually 0-21; lower better)

	Goal management programme			Psychoeducation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Richard 2013	7.9	3.3	11	6.6	3.8	12	1.30 [-1.60, 4.20]	



E.41 Improving language: RehaCom verbal fluency training vs. control (no intervention), 5-10 weeks

Figure 539: California Verbal Learning Test-II (higher better)

Study or Subgroup	RehaCom training Mean	SD	Total	Control (no intervention) Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Arian Darestani 2020	54	14.17	27	46.62	10.1	26	7.38 [0.77, 13.99]

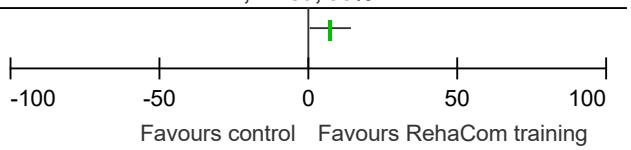


Figure 540: COWAT (higher better)

Study or Subgroup	RehaCom training Mean	SD	Total	Control (no intervention) Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Arian Darestani 2020	28.62	8.62	27	23.73	7.07	26	4.89 [0.65, 9.13]

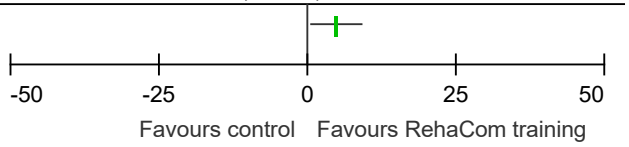
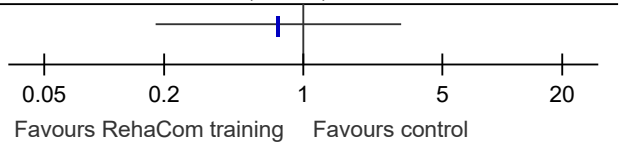


Figure 541: Adherence (optional dropout of treatment)

Study or Subgroup	RehaCom training Events	Total	Control (no intervention) Events	Total	Risk Ratio M-H, Fixed, 95% CI
Arian Darestani 2020	3	30	4	30	0.75 [0.18, 3.07]



Appendix F – GRADE tables

Table 3: Clinical evidence profile: General cognitive rehabilitation (multi-component and multi-domain) vs. control, 1-6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
Selective Reminding Test - Long-term storage (follow up: 1-6 months)												
2	randomised trials	not serious [a]	serious [b]	not serious	serious [c]	none	75	57	-	MD **2.19 higher** (2.48 lower to 6.86 higher)	⨁⨁◯◯ LOW	CRITICAL
Selective Reminding Test - Long-term storage - 1-6 months - Consistent long-term retrieval (follow up: 1-6 months)												
2	randomised trials	serious [a]	serious [b]	not serious	serious [d,e]	none	75	57	-	MD **3.06 higher** (2.91 lower to 9.02 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test - Long-term storage - 1-6 months - Delayed recall (follow up: 1-6 months)												
3	randomised trials	serious [a]	not serious	not serious	not serious [f]	none	127	106	-	MD **0.4 higher** (0.23 lower to 1.03 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Selective Reminding Test - 1-6 months - Mean free recall (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	not serious [g]	none	52	49	-	MD **0** (0.74 lower to 0.74 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Selective Reminding Test - 1-6 months - Learning index (follow up: 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [d,h]	none	52	49	-	MD **6.7 higher** (1.91 lower to 15.31 higher)	⨁⨁◯◯ LOW	CRITICAL
10/36 Spatial Recall Test - 1-6 months - Total score (follow up: 1-6 months)												
3	randomised trials	serious [a]	serious [i]	not serious	serious [d,j]	none	127	106	-	MD **1.15 higher** (1.3 lower to 3.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL
10/36 Spatial Recall Test - 1-6 months - Delayed recall (follow up: 1-6 months)												
3	randomised trials	serious [a]	serious [i]	not serious	very serious [d,k]	none	127	106	-	MD **0.06 higher** (1.21 lower to 1.32 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SDMT - 1-6 months - Similar at baseline (follow up: 1-6 months)												
4	randomised trials	very serious [a]	not serious	not serious	not serious [l]	none	202	174	-	MD **1.65 higher** (0.77 lower to 4.06 higher)	⨁⨁◯◯ LOW	CRITICAL
SDMT - 1-6 months - Larger difference at baseline (lower in intervention) (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [m]	serious [d,n]	none	21	21	-	MD **4.9 lower** (12.6 lower to 2.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT (2 seconds) - 1-6 months (follow up: 1-6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	very serious [a]	very serious [o]	not serious	serious [d,p]	none	202	174	-	MD **1.96 higher** (4.31 lower to 8.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL

PASAT (3 seconds) - 1-6 months (follow up: 1-6 months)

5	randomised trials	very serious [a]	not serious	serious [m]	not serious [q]	none	238	198	-	MD **2.69 higher** (1.37 higher to 4.01 higher)	⨁◯◯◯ VERY LOW	CRITICAL

COWAT - 5-6 months (follow up: 5-6 months)

3	randomised trials	very serious [a]	not serious	not serious	not serious [r]	none	185	157	-	MD **1.37 higher** (0.77 lower to 3.52 higher)	⨁⨁◯◯ LOW	CRITICAL

Stroop test time - 5-6 months - Colour naming time (follow up: 6 months)

1	randomised trials	serious [a]	not serious	not serious	not serious [s]	none	58	40	-	MD **3.3 lower** (10.45 lower to 3.85 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Stroop test time - 5-6 months - Colour/word interference time (follow up: 6 months)

1	randomised trials	serious [a]	not serious	not serious	not serious [t]	none	58	40	-	MD **0.2 higher** (13.03 lower to 13.43 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Stroop test time - 5-6 months - General 'Stroop test' (follow up: 5)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [m]	not serious [u]	none	36	24	-	MD **2.83 lower** (3.63 lower to 2.03 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Stroop test - 3 months - Word-color test (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [m]	very serious [d,v]	none	21	21	-	MD **1.05 lower** (7.99 lower to 5.89 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Stroop test - 3 months - Interference (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [m]	serious [d,w]	none	21	21	-	MD **2.55 higher** (1.78 lower to 6.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Trail Making Test time - 6 months - Part A (follow up: 3-6 months)												
2	randomised trials	serious [a]	not serious	not serious	not serious [x]	none	79	61	-	MD **1.62 higher** (2.34 lower to 5.59 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Trail Making Test time - 6 months - Part B (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	not serious [y]	none	58	40	-	MD **3.7 higher** (10.77 lower to 18.17 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
California Verbal Learning Test (CVLT) - 5 months - Total (follow up: 5 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	serious [d,z]	none	127	117	-	MD **2.93 higher** (0.26 lower to 6.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test (CVLT) - 5 months - Delayed (follow up: 5 months)												
2	randomised trials	very serious [a]	not serious	not serious	not serious [aa]	none	127	117	-	MD **0.4 higher** (0.53 lower to 1.33 higher)	⨁⨁◯◯ LOW	CRITICAL
Hopkins Verbal Learning Test - Revised - 3 months - Learning (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [m]	very serious [ab,d]	none	21	21	-	MD **0.33 lower** (3.07 lower to 2.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Hopkins Verbal Learning Test - Revised - 3 months - Recall (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [m]	serious [ac,d]	none	21	21	-	MD **0.77 lower** (2.15 lower to 0.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Brief Visuospatial Memory Test (BVMT) - 5 months - Total (follow up: 5 months)												
2	randomised trials	very serious [a]	not serious	not serious	not serious [ad]	none	127	117	-	MD **0.98 higher** (0.65 lower to 2.61 higher)	⨁⨁◯◯ LOW	CRITICAL
Brief Visuospatial Memory Test (BVMT) - 5 months - Delayed (follow up: 5 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	not serious [ae]	none	127	117	-	MD **0.5 higher** (0.14 lower to 1.14 higher)	⨁⨁◯◯ LOW	CRITICAL
Digit Span - 3-6 months - Forward (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [af,d]	none	52	49	-	MD **0.1 higher** (0.35 lower to 0.55 higher)	⨁⨁◯◯ LOW	CRITICAL
Digit Span - 3-6 months - Backward (follow up: 3-6 months)												
2	randomised trials	serious [a]	not serious	not serious	serious [ag,d]	none	73	70	-	MD **0.28 higher** (0.21 lower to 0.76 higher)	⨁⨁◯◯ LOW	CRITICAL
Word List Generation - 1 month (follow up: 1 months)												
1	randomised trials	very serious [a]	not serious	serious [ah]	serious [ai,d]	none	17	17	-	MD **1.9 higher** (3.72 lower to 7.52 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wisconsin Card Sorting Test (time as described as benefits in intervention group?) 5 months (follow up: 5 months)												
1	randomised trials	very serious [a]	not serious	serious [m]	not serious [aj]	none	36	24	-	MD **3.1 lower** (4.09 lower to 2.11 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Test of Attentional Performance (TAP) - Working Memory domain omissions - 6 months (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	not serious [ak]	none	52	49	-	MD **0.1 lower** (1.1 lower to 0.9 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
Test of Attentional Performance (TAP) - Flexibility domain correct answers - 6 months (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [al,d]	none	52	49	-	MD **4.6 lower** (8.8 lower to 0.4 lower)	⨁⨁◯◯ LOW	CRITICAL
Test of Attentional Performance (TAP) - Incompatibility domain correct answers - 6 months (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [am,d]	none	52	49	-	MD **3.3 lower** (7.41 lower to 0.81 higher)	⨁⨁◯◯ LOW	CRITICAL
Test of Attentional Performance (TAP) reaction time - 5 weeks - Alertness - simple (follow up: 5 weeks)												
1	randomised trials	very serious [a]	not serious	very serious [an]	serious [ao,d]	none	20	20	-	MD **19.2 lower** (34.64 lower to 3.76 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Test of Attentional Performance (TAP) reaction time - 5 weeks - Alertness - cued (follow up: 5 weeks)												
1	randomised trials	very serious [a]	not serious	very serious [an]	serious [ap,d]	none	20	20	-	MD **21.5 lower** (36.84 lower to 6.16 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Test of Attentional Performance (TAP) reaction time - 5 weeks - Divided Attention - acoustic (follow up: 5 weeks)												
1	randomised trials	very serious [a]	not serious	very serious [an]	serious [aq,d]	none	20	20	-	MD **29.6 lower** (99.47 lower to 40.27 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Test of Attentional Performance (TAP) reaction time - 5 weeks - Divided Attention - visual (follow up: 5 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	very serious [an]	serious [ar,d]	none	20	20	-	MD **59.5 lower** (105 lower to 14 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Brief Test of Attention - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [m]	serious [as,d]	none	21	21	-	MD **2.29 lower** (4.69 lower to 0.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Delis–Kaplan Executive Function System (D-KEFS) - 5 months - Descriptive (follow up: 5 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [at,d]	none	34	27	-	MD **2.1 lower** (7.02 lower to 2.82 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Delis–Kaplan Executive Function System (D-KEFS) - 5 months - Sort (follow up: 5 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [au,d]	none	34	27	-	MD **0.7 lower** (1.94 lower to 0.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Verbal fluency - 6 months - Letter M (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [av,d]	none	52	49	-	MD **0.6 higher** (1.06 lower to 2.26 higher)	⨁⨁◯◯ LOW	CRITICAL
Verbal fluency - 6 months - Animals (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [aw,d]	none	52	49	-	MD **1.4 higher** (0.81 lower to 3.61 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
Calibrated Ideational Fluency Assessment - 3 months - Animals (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [m]	very serious [ax,d]	none	21	21	-	MD **0.67 lower** (4.63 lower to 3.29 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Calibrated Ideational Fluency Assessment - 3 months - Supermarket (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [m]	serious [ay,d]	none	21	21	-	MD **2.29 lower** (6.45 lower to 1.87 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Calibrated Ideational Fluency Assessment - 3 months - P-words (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [m]	serious [az,d]	none	21	21	-	MD **2.95 lower** (8.58 lower to 2.68 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MUSIC (unclear which outcome set/measure this is referring to) - 5 weeks - Verbal memory (follow up: 5 weeks)												
1	randomised trials	very serious [a]	not serious	very serious [an]	very serious [ba,d]	none	20	20	-	MD **0.12 higher** (1.99 lower to 2.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MUSIC (unclear which outcome set/measure this is referring to) - 5 weeks - Verbal retrieval (follow up: 5 weeks)												
1	randomised trials	very serious [a]	not serious	very serious [an]	serious [bb,d]	none	20	20	-	MD **0.23 higher** (0.69 lower to 1.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MUSIC (unclear which outcome set/measure this is referring to) - 5 weeks - Verbal fluency (follow up: 5 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	very serious [an]	very serious [bc,d]	none	20	20	-	MD **0.16 lower** (2.29 lower to 1.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MUSIC (unclear which outcome set/measure this is referring to) - 5 weeks - Interferences (follow up: 5 weeks)												
1	randomised trials	very serious [a]	not serious	very serious [an]	serious [bd,d]	none	20	20	-	MD **2.82 lower** (6.73 lower to 1.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Judgement of Line Orientation (JLO) - 5 months (follow up: 5 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [be,d]	none	34	27	-	MD **0.4 higher** (1.66 lower to 2.46 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Salthouse Perceptual Comparison Test (baseline values not equal) - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [m]	serious [bf,d]	none	21	21	-	MD **2 lower** (7.03 lower to 3.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Code (assessing processing speed) - 6 months (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [bg,d]	none	52	49	-	MD **1.9 lower** (6.33 lower to 2.53 higher)	⨁◯◯◯ VERY LOW	CRITICAL
DO80 (assesses language) - Total score - 6 months (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	not serious [bh]	none	52	49	-	MD **0.4 higher** (0.52 lower to 1.32 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
DO80 (assesses language) - Time - 6 months (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [bi,d]	none	52	49	-	MD **10.2 lower** (31.05 lower to 10.65 higher)	⨁⨁◯◯ LOW	CRITICAL
Perceived Deficits Questionnaire - 6 months (follow up: 6 months; Scale from: 0 to 80)												
1	randomised trials	serious [a]	not serious	not serious	serious [bj,d]	none	58	40	-	MD **8.9 lower** (13.83 lower to 3.97 lower)	⨁⨁◯◯ LOW	CRITICAL
MS Neuropsychological Questionnaire - 5-6 months - Patient-reported (follow up: 5-6 months; Scale from: 0 to 60)												
2	randomised trials	serious [a]	serious [i]	not serious	very serious [bk,d]	none	92	67	-	MD **1.47 lower** (8.06 lower to 5.12 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MS Neuropsychological Questionnaire - 5-6 months - Informant-reported (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	not serious [bl,d]	none	58	40	-	MD **1.4 lower** (5.76 lower to 2.96 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
PROMIS - Applied Cognition Abilities short form 8a - 5 months (scale 8-40) (follow up: 5 months; Scale from: 8 to 40)												
1	randomised trials	very serious [a]	not serious	not serious	serious [bm,d]	none	93	90	-	MD **2.2 higher** (0.03 higher to 4.37 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 - 6 months (scale usually 0-100) - Physical (follow up: 6 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [bn,d]	none	58	40	-	MD **4.1 lower** (11.02 lower to 2.82 higher)	⨁⨁◯◯ LOW	CRITICAL
MSIS-29 - 6 months (scale usually 0-100) - Psychological (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [bo,d]	none	58	40	-	MD **2.2 lower** (9.32 lower to 4.92 higher)	⨁⨁◯◯ LOW	CRITICAL
MS International Quality of Life Questionnaire - Index (mean of 9 subdomains, scale 0-100) - 6 months (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	not serious [bp]	none	52	49	-	MD **1.1 higher** (4.63 lower to 6.83 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
WHO-BREF Quality of Life - 6 months (scale used unclear) - S1 Physical health (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [bq,d]	none	58	40	-	MD **0.6 higher** (0.34 lower to 1.54 higher)	⨁⨁◯◯ LOW	CRITICAL
WHO-BREF Quality of Life - 6 months (scale used unclear) - S2 Psychological (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [br,d]	none	58	40	-	MD **0.3 higher** (0.71 lower to 1.31 higher)	⨁⨁◯◯ LOW	CRITICAL
WHO-BREF Quality of Life - 6 months (scale used unclear) - S3 Social relationship (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [bs]	none	58	40	-	MD **0.1 lower** (1.25 lower to 1.05 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
WHO-BREF Quality of Life - 6 months (scale used unclear) - S4 environment (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [bt,d]	none	58	40	-	MD **0.5 higher** (0.46 lower to 1.46 higher)	⨁⨁◯◯ LOW	CRITICAL
WHO Quality of Life and Satisfaction with life composite, z-score - 1 month (follow up: 1 months; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	serious [ah]	serious [bu,d]	none	17	17	-	MD **0.1 lower** (0.66 lower to 0.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Memory span (t-score of various tests) - 6 months vs. baseline (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [bv,d]	none	16	16	-	MD **0.6 lower** (4.41 lower to 3.21 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Verbal learning (t-score of various tests) - 6 months vs. baseline (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [bw,d]	none	16	16	-	MD **1.6 higher** (2.07 lower to 5.27 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Visuo-spatial memory (t-score of various tests) - 6 months vs. baseline (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [bx,d]	none	16	16	-	MD **2.5 higher** (0.1 higher to 4.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Visuo-motor speed (t-score of various tests) - 6 months vs. baseline (follow up: 6 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [by,d]	none	16	16	-	MD **1.5 higher** (2.26 lower to 5.26 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Visual perception (t-score of various tests) - 6 months vs. baseline (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [bz,d]	none	16	16	-	MD **1.2 higher** (0.14 lower to 2.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Sum of 11 tests (t-score of various tests) - 6 months vs. baseline (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ca,d]	none	16	16	-	MD **2.1 higher** (0.25 lower to 4.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Information processing speed (unclear how measured) - 5 months (follow up: 5 months)												
1	randomised trials	very serious [a]	not serious	serious [m]	not serious [cb]	none	36	24	-	MD **81.1 lower** (118.05 lower to 44.15 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Adult Intelligence Scale - Similarities test (t-score) - 6 months vs. baseline (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [cc,d]	none	16	16	-	MD **0.6 lower** (5.45 lower to 4.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Adult Intelligence Scale - Picture arrangement (t-score) - 6 months vs. baseline (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [cd,d]	none	16	16	-	MD **0.5 lower** (6.44 lower to 5.44 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
Fatigue - FSMC cognitive subscale - 6 months (follow up: 6 months; Scale from: 10 to 50)												
1	randomised trials	serious [a]	not serious	not serious	serious [ce,d]	none	58	40	-	MD **2.6 lower** (6.39 lower to 1.19 higher)	⨁⨁◯◯ LOW	CRITICAL
Beck Depression Inventory - 1-6 months, mix of final value and change scores (scale usually 0-63) (follow up: 1-6 months; Scale from: 0 to 63)												
3	randomised trials	very serious [a]	serious [b]	not serious	serious [cf,d]	none	91	73	-	MD **1.38 lower** (4.21 lower to 1.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
CES-D depression - 5 months (scale usually 0-60) (follow up: 5 months; Scale from: 0 to 60)												
1	randomised trials	very serious [a]	not serious	not serious	serious [cg,d]	none	93	90	-	MD **1.6 lower** (3.46 lower to 0.26 higher)	⨁◯◯◯ VERY LOW	CRITICAL
State-Trait Anxiety Inventory (STAI) - State - 6 months vs. baseline (scale usually 20-80) (follow up: 6 months; Scale from: 20 to 80)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ch,d]	none	16	16	-	MD **2.7 lower** (9.17 lower to 3.77 higher)	⨁◯◯◯ VERY LOW	CRITICAL
State-Trait Anxiety Inventory (STAI) - Trait - 6 months vs. baseline (scale usually 20-80) (follow up: 6 months; Scale from: 20 to 80)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [ci,d]	none	16	16	-	MD **0.9 lower** (6.39 lower to 4.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Penn State Worry Questionnaire - 1 month (scale usually 16-80) (follow up: 1 months; Scale from: 16 to 80)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [ah]	serious [cj,d]	none	17	17	-	MD **5.9 higher** (4.13 lower to 15.93 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Difficulties in Emotional Regulation Scale (DERS) - 1 month (scale unclear) (follow up: 1 months)												
1	randomised trials	very serious [a]	not serious	serious [ah]	very serious [ck,d]	none	17	17	-	MD **0.5 lower** (13.25 lower to 12.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MS Self-Efficacy Scale - Control subscale (scale 90-900) - 5 months (follow up: 5 months; Scale from: 90 to 900)												
1	randomised trials	very serious [a]	not serious	not serious	serious [cl,d]	none	34	27	-	MD **23.46 higher** (69.09 lower to 116.01 higher)	⨁◯◯◯ VERY LOW	CRITICAL
General self-efficacy scale (scale possibly 17-85) - 5 months (follow up: 5 months; Scale from: 17 to 85)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [cm]	none	93	90	-	MD **1.5 higher** (1.69 lower to 4.69 higher)	⨁⨁◯◯ LOW	CRITICAL
Multi-factorial Memory Questionnaire - Strategy subscale (scale 0-76 and indicates use of memory strategies) - 5 months (follow up: 5 months; Scale from: 0 to 76)												
2	randomised trials	very serious [a]	not serious	not serious	not serious [cn]	none	127	117	-	MD **1.17 higher** (1.68 lower to 4.01 higher)	⨁⨁◯◯ LOW	CRITICAL
Everyday Problems Test - Revised (activities of daily living performance, scale unclear) - 5 months (follow up: 5 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, 1-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious [co]	none	93	90	-	MD **0.7 higher** (0.62 lower to 2.02 higher)	⨁⨁◯◯ LOW	CRITICAL

Adherence (follow up: 6 months)

1	randomised trials	not serious	not serious	not serious	very serious [d]	none	50/64 (78.1%)	68.8%	**OR 1.62** (0.73 to 3.59)	**93 more per 1,000** (from 71 fewer to 200 more)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as direction of point estimates varies between studies, which cannot be explained by prespecified subgroup analyses

c. MIDs used to assess imprecision were ±6.80

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MIDs used to assess imprecision were ±7.93

f. MIDs used to assess imprecision were ±1.33

g. MIDs used to assess imprecision were ±0.98

h. MIDs used to assess imprecision were ±10.98

i. Downgraded by 1 increment as statistical heterogeneity is present that cannot be explained by prespecified subgroup analyses, with I2>50%

j. MIDs used to assess imprecision were ±2.31

k. MIDs used to assess imprecision were ±1.13

l. MIDs used to assess imprecision were ±6.05

m. Downgraded by 1 increment as the majority of the evidence comes from studies that did not appear to have cognitive impairment as an inclusion criterion

n. MIDs used to assess imprecision were ± 5.67

o. Downgraded by 2 increments as statistical heterogeneity is present that cannot be explained by prespecified subgroup analyses and point estimates vary widely, with I2 >80%

p. MIDs used to assess imprecision were ±4.99

q. MIDs used to assess imprecision were ±5.63

r. MIDs used to assess imprecision were ±5.60

s. MIDs used to assess imprecision were ±11.18

t. MIDs used to assess imprecision were ±26.10

u. MIDs used to assess imprecision were ±0.84

v. MIDs used to assess imprecision were ±4.81

w. MIDs used to assess imprecision were ±3.44

x. MIDs used to assess imprecision were ±7.50

y. MIDs used to assess imprecision were ±19.98

z. MIDs used to assess imprecision were ±5.83

aa. MIDs used to assess imprecision were ±1.85

ab. MIDs used to assess imprecision were ±1.87

ac. MIDs used to assess imprecision were ±1.21

ad. MIDs used to assess imprecision were ±3.35

ae. MIDs used to assess imprecision were ±1.35

af. MIDs used to assess imprecision were ±0.53

ag. MIDs used to assess imprecision were ±0.70

ah. Downgraded by 1 increment as the majority of the evidence was reported at a time-point <3-month minimum specified in protocol

ai. MIDs used to assess imprecision were ±4.38

aj. MIDs used to assess imprecision were ±0.93

ak. MIDs used to assess imprecision were ±1.28

al. MIDs used to assess imprecision were ±6.15

am. MIDs used to assess imprecision were ±4.50

an. Downgraded by 2 increments as the majority of the evidence was reported at a time-point <3-month minimum specified in protocol and did not have cognitive impairment as an inclusion criterion

ao. MIDs used to assess imprecision were ±22.05

ap. MIDs used to assess imprecision were ±19.35

aq. MIDs used to assess imprecision were ±42.78

ar. MIDs used to assess imprecision were ±51.48

as. MIDs used to assess imprecision were ±1.90

at. MIDs used to assess imprecision were ±5.05

au. MIDs used to assess imprecision were ±1.33

av. MIDs used to assess imprecision were ±2.08

aw. MIDs used to assess imprecision were ±2.50

ax. MIDs used to assess imprecision were ±2.82

ay. MIDs used to assess imprecision were ±2.56

az. MIDs used to assess imprecision were ±5.03

ba. MIDs used to assess imprecision were ±1.62

bb. MIDs used to assess imprecision were ±0.76

bc. MIDs used to assess imprecision were ±1.75

bd. MIDs used to assess imprecision were ±2.91

be. MIDs used to assess imprecision were ±2.13

bf. MIDs used to assess imprecision were ±3.57

bg. MIDs used to assess imprecision were ±5.83

bh. MIDs used to assess imprecision were ±1.65

bi. MIDs used to assess imprecision were ±26.95

bj. MIDs used to assess imprecision were ±6.13

bk. MIDs used to assess imprecision were ±5.11

bl. MIDs used to assess imprecision were ±5.85

bm. MIDs used to assess imprecision were ±3.75

bn. MIDs used to assess imprecision were ±8.73

bo. MIDs used to assess imprecision were ±8.85

bp. MIDs used to assess imprecision were ±11.1

bq. MIDs used to assess imprecision were ±1.20

br. MIDs used to assess imprecision were ±1.25

bs. MIDs used to assess imprecision were ±1.43

bt. MIDs used to assess imprecision were ±1.08

bu. MIDs used to assess imprecision were ±0.48

bv. MIDs used to assess imprecision were ±2.75 (0.5 multiplied by SD calculated for control group for change from baseline score as no baseline values reported)

bw. MIDs used to assess imprecision were ±2.65 (0.5 multiplied by SD calculated for control group for change from baseline score as no baseline values reported)

bx. MIDs used to assess imprecision were ±1.73 (0.5 multiplied by SD calculated for control group for change from baseline score as no baseline values reported)

by. MIDs used to assess imprecision were ±2.71 (0.5 multiplied by SD calculated for control group for change from baseline score as no baseline values reported)

bz. MIDs used to assess imprecision were ±0.97 (0.5 multiplied by SD calculated for control group for change from baseline score as no baseline values reported)

ca. MIDs used to assess imprecision were ±1.70 (0.5 multiplied by SD calculated for control group for change from baseline score as no baseline values reported)

cb. MIDs used to assess imprecision were ±34.04

cc. MIDs used to assess imprecision were ±3.50 (0.5 multiplied by SD calculated for control group for change from baseline score as no baseline values reported)

cd. MIDs used to assess imprecision were ±4.28 (0.5 multiplied by SD calculated for control group for change from baseline score as no baseline values reported)

ce. MIDs used to assess imprecision were ±4.28

cf. MIDs used to assess imprecision were ±3.74

cg. MIDs used to assess imprecision were ±3.00

ch. MIDs used to assess imprecision were ±4.67 (0.5 multiplied by SD calculated for control group for change from baseline score as no baseline values reported)

ci. MIDs used to assess imprecision were ±3.96 (0.5 multiplied by SD calculated for control group for change from baseline score as no baseline values reported)

cj. MIDs used to assess imprecision were ±7.68

ck. MIDs used to assess imprecision were ±10.68

cl. MIDs used to assess imprecision were ±88.62

cm. MIDs used to assess imprecision were ±5.80

cn. MIDs used to assess imprecision were ±5.72

co. MIDs used to assess imprecision were ±2.38

Table 4: Clinical evidence profile: General cognitive rehabilitation (multi-component and multi-domain) vs. control, >6 months – 1 year

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, >6 months to 1 year	Relative (95% CI)	Absolute (95% CI)		
SDMT - 8 months (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	93	90	-	MD **2.6 higher** (0.97 lower to 6.17 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 7-8 months - 2 seconds (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [d]	none	93	90	-	MD **1.4 higher** (2.28 lower to 5.08 higher)	⨁⨁◯◯ LOW	CRITICAL
PASAT - 7-8 months - 3 seconds (follow up: 7-8 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, >6 months to 1 year	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	not serious [e]	none	129	114	-	MD **2.29 higher** (0.77 higher to 3.8 higher)	⨁⨁◯◯ LOW	CRITICAL
COWAT - 8 months (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,f]	none	93	90	-	MD **2.6 higher** (0.88 lower to 6.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Stroop test time - 7 months - General 'Stroop test' (follow up: 7 months)												
1	randomised trials	very serious [a]	not serious	serious [g]	not serious [h]	none	36	24	-	MD **2.19 lower** (2.92 lower to 1.46 lower)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test (CVLT) - 8 months - Total (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	93	90	-	MD **2.5 higher** (1.24 lower to 6.24 higher)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test (CVLT) - 8 months - Delayed (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,j]	none	93	90	-	MD **0.8 higher** (0.26 lower to 1.86 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Brief Visuospatial Memory Test (BVMT) - 8 months - Total (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,k]	none	93	90	-	MD **1.8 higher** (0.18 lower to 3.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, >6 months to 1 year	Relative (95% CI)	Absolute (95% CI)		
Brief Visuospatial Memory Test (BVMT) - 8 months - Delayed (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,l]	none	93	90	-	MD **0.7 higher** (0.08 lower to 1.48 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wisconsin Card Sorting Test (time as described benefits in intervention group?) 7 months (follow up: 7 months)												
1	randomised trials	very serious [a]	not serious	serious [g]	not serious [m]	none	36	24	-	MD **2.42 lower** (3.5 lower to 1.34 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Information processing speed (unclear how measured) - 7 months (follow up: 7 months)												
1	randomised trials	very serious [a]	not serious	serious [g]	serious [b,n]	none	36	24	-	MD **51 lower** (89.06 lower to 12.94 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Perceived Deficits Questionnaire - 1 year (follow up: 1 years; Scale from: 0 to 80)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,o]	none	50	28	-	MD **7.3 lower** (13.12 lower to 1.48 lower)	⨁⨁◯◯ LOW	CRITICAL
MS Neuropsychological Questionnaire - 1 year - Patient-reported (follow up: 1 years; Scale from: 0 to 60)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,p]	none	50	28	-	MD **6 lower** (11 lower to 1 lower)	⨁⨁◯◯ LOW	CRITICAL
MS Neuropsychological Questionnaire - 1 year - Informant-reported (follow up: 1 years; Scale from: 0 to 60)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, >6 months to 1 year	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,q]	none	50	28	-	MD **1.2 lower** (5.95 lower to 3.55 higher)	⨁⨁◯◯ LOW	CRITICAL
MSIS-29 - 1 year (scale usually 0-100) - Physical (follow up: 1 years; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	not serious [r]	none	50	28	-	MD **1.3 lower** (8.03 lower to 5.43 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
MSIS-29 - 1 year (scale usually 0-100) - Psychological (follow up: 1 years; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,s]	none	50	28	-	MD **1.1 higher** (6.7 lower to 8.9 higher)	⨁⨁◯◯ LOW	CRITICAL
WHO-BREF Quality of Life - 1 year (scale used unclear) - S1 Physical health (follow up: 1 years)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,t]	none	50	28	-	MD **0.7 higher** (0.44 lower to 1.84 higher)	⨁⨁◯◯ LOW	CRITICAL
WHO-BREF Quality of Life - 1 year (scale used unclear) - S2 Psychological (follow up: 1 years)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,u]	none	50	28	-	MD **0.5 higher** (0.69 lower to 1.69 higher)	⨁⨁◯◯ LOW	CRITICAL
WHO-BREF Quality of Life - 1 year (scale used unclear) - S3 Social relationship (follow up: 1 years)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,v]	none	50	28	-	MD **0.1 higher** (1.33 lower to 1.53 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, >6 months to 1 year	Relative (95% CI)	Absolute (95% CI)		
WHO-BREF Quality of Life - 1 year (scale used unclear) - S4 environment (follow up: 1 years)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,w]	none	50	28	-	MD **0.9 higher** (0.17 lower to 1.97 higher)	⨁⨁◯◯ LOW	CRITICAL
PROMIS - Applied Cognition Abilities short form 8a - 8 months (scale 8-40) (follow up: 8 months; Scale from: 8 to 40)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,x]	none	93	90	-	MD **2.6 higher** (0.4 higher to 4.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue - FSMC cognitive subscale - 1 year (follow up: 1 years; Scale from: 10 to 50)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,y]	none	50	28	-	MD **2.6 lower** (6.75 lower to 1.55 higher)	⨁⨁◯◯ LOW	CRITICAL
Beck Depression Inventory - 1 year (scale usually 0-63) (follow up: 1 years; Scale from: 0 to 63)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,z]	none	50	28	-	MD **1.1 higher** (2.26 lower to 4.46 higher)	⨁⨁◯◯ LOW	CRITICAL
CES-D depression - 8 months (scale usually 0-60) (follow up: 8 months; Scale from: 0 to 60)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [aa]	none	93	90	-	MD **0.4 lower** (2.15 lower to 1.35 higher)	⨁⨁◯◯ LOW	CRITICAL
General self-efficacy scale (scale possibly 17-85) - 8 months (follow up: 8 months; Scale from: 17 to 85)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	control, >6 months to 1 year	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [ab,b]	none	93	90	-	MD **2.6 higher** (0.75 lower to 5.95 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Multi-factorial Memory Questionnaire - Strategy subscale (scale 0-76 and indicates use of memory strategies) - 8 months (follow up: 8 months; Scale from: 0 to 76)

1	randomised trials	very serious [a]	not serious	not serious	not serious [ac]	none	93	90	-	MD **0.7 higher** (2.52 lower to 3.92 higher)	⨁⨁◯◯ LOW	CRITICAL

Everyday Problems Test - Revised (activities of daily living performance, scale unclear) - 8 months (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	not serious [ad]	none	93	90	-	MD **0.7 higher** (0.63 lower to 2.03 higher)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±6.05

d. MIDs used to assess imprecision were ±6.15

e. MIDs used to assess imprecision were ±4.07

f. MIDs used to assess imprecision were ±5.73

g. Downgraded by 1 increment as the majority of the evidence came from studies where cognitive impairment was not an inclusion criterion

h. MIDs used to assess imprecision were ±0.84

i. MIDs used to assess imprecision were ±5.58

j. MIDs used to assess imprecision were ±1.75

k. MIDs used to assess imprecision were ±3.33

l. MIDs used to assess imprecision were ±1.35

m. MIDs used to assess imprecision were ±0.93

n. MIDs used to assess imprecision were ±34.04

o. MIDs used to assess imprecision were ±6.13

p. MIDs used to assess imprecision were ±4.63

q. MIDs used to assess imprecision were ±5.85

r. MIDs used to assess imprecision were ±8.73

s. MIDs used to assess imprecision were ±8.85

t. MIDs used to assess imprecision were ±1.20

u. MIDs used to assess imprecision were ±1.25

v. MIDs used to assess imprecision were ±1.43

w. MIDs used to assess imprecision were ±1.08

x. MIDs used to assess imprecision were ±3.75

y. MIDs used to assess imprecision were ±4.28

z. MIDs used to assess imprecision were ±3.35

aa. MIDs used to assess imprecision were ±3.00

ab. MIDs used to assess imprecision were ±5.80

ac. MIDs used to assess imprecision were ±6.30

ad. MIDs used to assess imprecision were ±2.38

Table 5: Clinical evidence profile: General cognitive rehabilitation (multi-component and multi-domain) vs. psychoeducation + information-sharing, 3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	psychoeducation + information sharing, 3 months	Relative (95% CI)	Absolute (95% CI)		
Addenbrooke's cognitive examination - 3 months (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	15	15	-	MD **6.9 higher** (2.74 higher to 11.06 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wisconsin Card Sorting Test (WCST) - categories completed - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	15	15	-	MD **1.85 higher** (0.64 higher to 3.06 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wisconsin Card Sorting Test (WCST) - errors - 3 months - Perseverative errors (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [e]	none	15	15	-	MD **8.04 lower** (10.97 lower to 5.11 lower)	⨁⨁◯◯ LOW	CRITICAL
Wisconsin Card Sorting Test (WCST) - errors - 3 months - Non-perseverative errors (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,f]	none	15	15	-	MD **4.72 lower** (8.88 lower to 0.56 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Wisconsin Card Sorting Test (WCST) - time - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,g]	none	15	15	-	MD **32.7 lower** (97.03 lower to 31.63 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	psychoeducation + information sharing, 3 months	Relative (95% CI)	Absolute (95% CI)		
Behavior Rating Inventory of Executive Function-Adult (BRIEF-A) Global Executive Function - 3 months (follow up: 3 months; Scale from: 0 to 150)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [h]	none	15	15	-	MD **28.58 lower** (38.39 lower to 18.77 lower)	⨁⨁◯◯ LOW	CRITICAL
Memory Functioning Questionnaire (MFQ) - General rating (scale used unclear) - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	15	15	-	MD **6.87 higher** (2.27 higher to 11.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Weschler Memory Scale-Revised - 3 months - Visual memory (scale unclear) (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,j]	none	15	15	-	MD **4.58 higher** (2.1 higher to 7.06 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Weschler Memory Scale-Revised - 3 months - Verbal memory (scale unclear) (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,k]	none	15	15	-	MD **5.27 higher** (2.23 higher to 8.31 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±4.05

d. MIDs used to assess imprecision were ±0.98

e. MIDs used to assess imprecision were ±3.18

f. MIDs used to assess imprecision were ±2.47

g. MIDs used to assess imprecision were ±77.60

h. MIDs used to assess imprecision were ±12.65

i. MIDs used to assess imprecision were ±3.76

j. MIDs used to assess imprecision were ±2.34

k. MIDs used to assess imprecision were ±2.26

Table 6: Clinical evidence profile: General cognitive rehabilitation (multi-component and multi-domain) vs. non-specific cognitive rehabilitation programme, 4 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 4 months	Relative (95% CI)	Absolute (95% CI)		
SDMT - 4 months (follow up: 4 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,c]	none	18	17	-	MD **0.6 higher** (5.8 lower to 7 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Stroop test - time - 4 months - Colour naming (follow up: 4 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	18	17	-	MD **4.9 lower** (11.3 lower to 1.5 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Stroop test - time - 4 months - Word reading (follow up: 4 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 4 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,e]	none	18	17	-	MD **1.8 higher** (5.75 lower to 9.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Stroop test - time - 4 months - Interference (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,f]	none	18	17	-	MD **6.4 higher** (7.88 lower to 20.68 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Trail Making Test - time - 4 months - Part A (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,g]	none	18	17	-	MD **4.7 higher** (2.4 lower to 11.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Trail Making Test - time - 4 months - Part B (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,h]	none	18	17	-	MD **6.1 higher** (5.74 lower to 17.94 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 4 months - Learning trials - List A (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [a,i]	none	18	17	-	MD **2 lower** (7.59 lower to 3.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 4 months - Learning trials - List B (follow up: 4 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 4 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,j]	none	18	17	-	MD **0.4 lower** (1.89 lower to 1.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 4 months - Immediate recall (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,k]	none	18	17	-	MD **0.2 higher** (1.27 lower to 1.67 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 4 months - Delayed recall (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,l]	none	18	17	-	MD **0.1 higher** (1.06 lower to 1.26 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 4 months - Immediate cued recall (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,m]	none	18	17	-	MD **0.5 higher** (0.66 lower to 1.66 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 4 months - Delayed cued recall (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,n]	none	18	17	-	MD **0.2 lower** (1.43 lower to 1.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 4 months - Recognition (follow up: 4 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 4 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,o]	none	18	17	-	MD **0.3 lower** (0.84 lower to 0.24 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Alertness - Test of Attentional Performances subtest - reaction time - 4 months - Without warning (follow up: 4 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [p]	none	18	17	-	MD **23.2 lower** (50.96 lower to 4.56 higher)	⨁⨁◯◯ LOW	CRITICAL
Alertness - Test of Attentional Performances subtest - reaction time - 4 months - With warning (follow up: 4 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [q]	none	18	17	-	MD **13.7 lower** (42.43 lower to 15.03 higher)	⨁⨁◯◯ LOW	CRITICAL
Visual Scanning - Test of Attentional Performances subtest - correct answers - 4 months - With a target (follow up: 4 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,r]	none	18	17	-	MD **3.3 higher** (0.93 lower to 7.53 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Visual scanning - Test of Attentional Performances subtest - reaction time - 4 months - Without a target (follow up: 4 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,s]	none	18	17	-	MD **736.7 higher** (855.94 lower to 2329.34 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Visual scanning - Test of Attentional Performances subtest - reaction time - 4 months - With a target (follow up: 4 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 4 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,t]	none	18	17	-	MD **301.8 higher** (402.13 lower to 1005.73 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Divided Attention (visual attention) - Test of Attentional Performances subtest - correct answers - 4 months - Simple task (follow up: 4 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,u]	none	18	17	-	MD **0.3 lower** (1.2 lower to 0.6 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Divided Attention (visual attention) - Test of Attentional Performances subtest - correct answers - 4 months - Dual task (follow up: 4 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [v]	none	18	17	-	MD **0.2 higher** (0.48 lower to 0.88 higher)	⨁⨁◯◯ LOW	CRITICAL
Divided Attention (visual attention) - Test of Attentional Performances subtest - reaction time - 4 months - Simple task (follow up: 4 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,w]	none	18	17	-	MD **53.3 lower** (126.19 lower to 19.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Divided Attention (visual attention) - Test of Attentional Performances subtest - reaction time - 4 months - Dual task (follow up: 4 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,x]	none	18	17	-	MD **24.3 higher** (44.63 lower to 93.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Divided Attention (auditory attention) - Test of Attentional Performances subtest - correct answers - 4 months - Dual task (follow up: 4 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 4 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,y]	none	18	17	-	MD **0.4 higher** (0.37 lower to 1.17 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Divided Attention (auditory attention) - Test of Attentional Performances subtest - reaction time - 4 months - Simple task (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,z]	none	18	17	-	MD **34.7 lower** (105.37 lower to 35.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Divided Attention (auditory attention) - Test of Attentional Performances subtest - reaction time - 4 months - Dual task (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	not serious [aa]	none	18	17	-	MD **9.2 lower** (75.76 lower to 57.36 higher)	⨁⨁◯◯ LOW	CRITICAL

N-back - Test of Attentional Performances subtest - reaction time - 4 months (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [ab,b]	none	18	17	-	MD **49.8 lower** (164.08 lower to 64.48 higher)	⨁◯◯◯ VERY LOW	CRITICAL

N-back - Test of Attentional Performances subtest - correct answers - 4 months (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [ac,b]	none	18	17	-	MD **0.5 higher** (0.39 lower to 1.39 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Baddeley's Dual Task forward span - correct answers - 4 months (follow up: 4 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 4 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [ad,b]	none	18	17	-	MD **0.3 higher** (0.37 lower to 0.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Backward span - correct answers - 4 months (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [ae,b]	none	18	17	-	MD **0.4 higher** (0.26 lower to 1.06 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Fluency - correct answers - 4 months - Semantic (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	very serious [af,b]	none	18	17	-	MD **1.2 lower** (6.31 lower to 3.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Fluency - correct answers - 4 months - Phonemic (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	very serious [ag,b]	none	18	17	-	MD **0.6 lower** (3.97 lower to 2.77 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Rey complex figure (visuoconstruction and episodic memory) - correct answers - 4 months (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [ah,b]	none	18	17	-	MD **0.6 higher** (0.58 lower to 1.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Rey complex figure (visuoconstruction and episodic memory) - time - 4 months (follow up: 4 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 4 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [ai,b]	none	18	17	-	MD **29.5 higher** (17.03 lower to 76.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL

DO80 naming task - correct answers - 4 months (follow up: 4 months)

1	randomised trials	very serious [a]	not serious	not serious	very serious [aj,b]	none	18	17	-	MD **0.1 higher** (1.04 lower to 1.24 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Daily Cognitive Activities Questionnaire (scale 0-60) - 4 months (follow up: 4 months; Scale from: 0 to 60)

1	randomised trials	very serious [a]	not serious	not serious	serious [ak,b]	none	18	17	-	MD **6.7 higher** (3.64 lower to 17.04 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Beck Depression Inventory (scale usually 0-63) - 4 months (follow up: 4 years; Scale from: 0 to 63)

1	randomised trials	very serious [a]	not serious	not serious	serious [al,b]	none	18	17	-	MD **1 higher** (3.64 lower to 5.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL

State-Trait Anxiety Inventory (STAI; scale usually 20-80) - 4 months - STAI-A (state?) (follow up: 4 months; Scale from: 20 to 80)

1	randomised trials	very serious [a]	not serious	not serious	serious [am,b]	none	18	17	-	MD **4.7 higher** (3.74 lower to 13.14 higher)	⨁◯◯◯ VERY LOW	CRITICAL

State-Trait Anxiety Inventory (STAI; scale usually 20-80) - 4 months - STAI-B (trait?) (follow up: 4 months; Scale from: 20 to 80)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 4 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [an,b]	none	18	17	-	MD **3.1 higher** (4 lower to 10.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Modified Fatigue Impact Scale - Cognitive (scale usually 0-40) - 4 months (follow up: 4 months; Scale from: 0 to 40)

1	randomised trials	very serious [a]	not serious	not serious	very serious [ao,b]	none	18	17	-	MD **0.3 lower** (6.26 lower to 5.66 higher)	⨁◯◯◯ VERY LOW	CRITICAL

SF-36 quality of life (scale usually 0-100) - 4 months - Physical (follow up: 4 months; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	not serious	very serious [ap,b]	none	18	17	-	MD **2.3 higher** (10.13 lower to 14.73 higher)	⨁◯◯◯ VERY LOW	CRITICAL

SF-36 quality of life (scale usually 0-100) - 4 months - Psychological (follow up: 4 months; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	not serious	very serious [aq,b]	none	18	17	-	MD **2.1 higher** (10.51 lower to 14.71 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±4.75

d. MIDs used to assess imprecision were ±9.75

e. MIDs used to assess imprecision were ±8.40

f. MIDs used to assess imprecision were ±11.20

g. MIDs used to assess imprecision were ±8.50

h. MIDs used to assess imprecision were ±12.48

i. MIDs used to assess imprecision were ±4.08

j. MIDs used to assess imprecision were ±1.18

k. MIDs used to assess imprecision were ±1.30

l. MIDs used to assess imprecision were ±1.08

m. MIDs used to assess imprecision were ±0.90

n. MIDs used to assess imprecision were ±1.08

o. MIDs used to assess imprecision were ±0.58

p. MIDs used to assess imprecision were ±61.75

q. MIDs used to assess imprecision were ±66.18

r. MIDs used to assess imprecision were ±4.20

s. MIDs used to assess imprecision were ±894.08

t. MIDs used to assess imprecision were ±448.65

u. MIDs used to assess imprecision were ±0.83

v. MIDs used to assess imprecision were ±0.95

w. MIDs used to assess imprecision were ±61.93

x. MIDs used to assess imprecision were ±59.15

y. MIDs used to assess imprecision were ±1.08

z. MIDs used to assess imprecision were ±69.40

aa. MIDs used to assess imprecision were ±90.00

ab. MIDs used to assess imprecision were ±88.95

ac. MIDs used to assess imprecision were ±0.90

ad. MIDs used to assess imprecision were ±0.50

ae. MIDs used to assess imprecision were ±0.40

af. MIDs used to assess imprecision were ±3.55

ag. MIDs used to assess imprecision were ±2.68

ah. MIDs used to assess imprecision were ±1.25

ai. MIDs used to assess imprecision were ±41.68

aj. MIDs used to assess imprecision were ±0.60

ak. MIDs used to assess imprecision were ±10.08

al. MIDs used to assess imprecision were ±3.78

am. MIDs used to assess imprecision were ±4.85

an. MIDs used to assess imprecision were ±4.68

ao. MIDs used to assess imprecision were ±3.78

ap. MIDs used to assess imprecision were ±8.03

aq. MIDs used to assess imprecision were ±10.35

Table 7: Clinical evidence profile: General cognitive rehabilitation (multi-component and multi-domain) vs. non-specific cognitive rehabilitation programme, 8 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 8 months	Relative (95% CI)	Absolute (95% CI)		

SDMT - 8 months (follow up: 8 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 8 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,c]	none	18	17	-	MD **0.7 lower** (7.43 lower to 6.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Stroop test - time - 8 months - Colour naming (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	18	17	-	MD **3.3 lower** (10.14 lower to 3.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Stroop test - time - 8 months - Word reading (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	not serious [e]	none	18	17	-	MD **1.6 lower** (6.83 lower to 3.63 higher)	⨁⨁◯◯ LOW	CRITICAL

Stroop test - time - 8 months - Interference (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,f]	none	18	17	-	MD **1.8 lower** (12.03 lower to 8.43 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Trail Making Test - time - 8 months - Part A (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,g]	none	18	17	-	MD **2.7 higher** (3.63 lower to 9.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Trail Making Test - time - 8 months - Part B (follow up: 8 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 8 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,h]	none	18	17	-	MD **9.9 higher** (4.22 lower to 24.02 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 8 months - Learning trials - List A (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	18	17	-	MD **1.7 higher** (3.04 lower to 6.44 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 8 months - Learning trials - List B (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	very serious [b,j]	none	18	17	-	MD **0** (1.77 lower to 1.77 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 8 months - Immediate recall (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,k]	none	18	17	-	MD **0.6 lower** (2.06 lower to 0.86 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 8 months - Delayed recall (follow up: 8 months)

1	randomised trials	very serious [b]	not serious	not serious	very serious [b,l]	none	18	17	-	MD **0** (1.26 lower to 1.26 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 8 months - Immediate cued recall (follow up: 8 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 8 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,m]	none	18	17	-	MD **0.4 higher** (0.86 lower to 1.66 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 8 months - Delayed cued recall (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,l]	none	18	17	-	MD **0.2 higher** (0.83 lower to 1.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL

California Verbal Learning Test (CVLT) - correct answers - 8 months - Recognition (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	not serious [n]	none	18	17	-	MD **0.1 lower** (0.48 lower to 0.28 higher)	⨁⨁◯◯ LOW	CRITICAL

Alertness - Test of Attentional Performances subtest - reaction time - 8 months - Without warning (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	not serious [o]	none	18	17	-	MD **16.1 lower** (41.72 lower to 9.52 higher)	⨁⨁◯◯ LOW	CRITICAL

Alertness - Test of Attentional Performances subtest - reaction time - 8 months - With warning (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	not serious [p]	none	18	17	-	MD **12.5 higher** (25.19 lower to 50.19 higher)	⨁⨁◯◯ LOW	CRITICAL

Visual scanning - Test of Attentional Performances subtest - correct answers - 8 months - Without target (follow up: 8 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 8 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,q]	none	18	17	-	MD **0** (0.3 lower to 0.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Visual scanning - Test of Attentional Performances subtest - correct answers - 8 months - With target (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,r]	none	18	17	-	MD **2.3 lower** (5.77 lower to 1.17 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Visual scanning - Test of Attentional Performances subtest - reaction time - 8 months - Without target (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	very serious [b,s]	none	18	17	-	MD **139.9 higher** (1016.11 lower to 1295.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Visual scanning - Test of Attentional Performances subtest - reaction time - 8 months - With target (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,t]	none	18	17	-	MD **71 higher** (443.59 lower to 585.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Divided Attention (visual attention) - Test of Attentional Performances subtest - correct answers - 8 months - Simple task (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	very serious [b,u]	none	18	17	-	MD **0.1 lower** (1.31 lower to 1.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Divided Attention (visual attention) - Test of Attentional Performances subtest - correct answers - 8 months - Dual task (follow up: 8 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 8 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious [v]	none	18	17	-	MD **0.2 higher** (0.5 lower to 0.9 higher)	⨁⨁◯◯ LOW	CRITICAL

Divided Attention (visual attention) - Test of Attentional Performances subtest - reaction time - 8 months - Simple task (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,w]	none	18	17	-	MD **19.9 lower** (99.92 lower to 60.12 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Divided Attention (visual attention) - Test of Attentional Performances subtest - reaction time - 8 months - Dual task (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,x]	none	18	17	-	MD **28.3 lower** (94.19 lower to 37.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Divided Attention (auditory attention) - Test of Attentional Performances subtest - correct answers - 8 months - Simple task (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	not serious [y]	none	18	17	-	MD **0** (0.27 lower to 0.27 higher)	⨁⨁◯◯ LOW	CRITICAL

Divided Attention (auditory attention) - Test of Attentional Performances subtest - correct answers - 8 months - Dual task (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,z]	none	18	17	-	MD **0.4 higher** (0.49 lower to 1.29 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Divided Attention (auditory attention) - Test of Attentional Performances subtest - reaction time - 8 months - Simple task (follow up: 8 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 8 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious [aa]	none	18	17	-	MD **3.1 lower** (69.26 lower to 63.06 higher)	⨁⨁◯◯ LOW	CRITICAL
Divided Attention (auditory attention) - Test of Attentional Performances subtest - reaction time - 8 months - Dual task (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [ab]	none	18	17	-	MD **8.5 higher** (60.38 lower to 77.38 higher)	⨁⨁◯◯ LOW	CRITICAL
N-back - Test of Attentional Performances subtest - reaction time - 8 months (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ac,b]	none	18	17	-	MD **50.2 lower** (162.9 lower to 62.5 higher)	⨁◯◯◯ VERY LOW	CRITICAL
N-back - Test of Attentional Performances subtest - correct answers - 8 months (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ad,b]	none	18	17	-	MD **0.1 higher** (0.83 lower to 1.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Baddeley's Dual Task forward span - correct answers - 8 months (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ae,b]	none	18	17	-	MD **0.3 higher** (0.4 lower to 1 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Backward span - correct answers - 8 months (follow up: 8 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 8 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [af,b]	none	18	17	-	MD **0.5 higher** (0.16 lower to 1.16 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Fluency - correct answers - 8 months - Semantic (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	not serious [ag]	none	18	17	-	MD **0.3 higher** (0.37 lower to 0.97 higher)	⨁⨁◯◯ LOW	CRITICAL

Fluency - correct answers - 8 months - Phonemic (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	not serious [ah]	none	18	17	-	MD **0.3 higher** (0.37 lower to 0.97 higher)	⨁⨁◯◯ LOW	CRITICAL

Rey complex figure (visuoconstruction and episodic memory) - correct answers - 8 months (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [ai,b]	none	18	17	-	MD **1 higher** (0.16 higher to 1.84 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Rey complex figure (visuoconstruction and episodic memory) - time - 8 months (follow up: 8 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [aj,b]	none	18	17	-	MD **14.1 higher** (27.63 lower to 55.83 higher)	⨁◯◯◯ VERY LOW	CRITICAL

DO80 naming task - correct answers - 8 months (follow up: 8 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab - multi-component	non-specific cognitive rehab programme, 8 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [ak,b]	none	18	17	-	MD **0.3 higher** (0.56 lower to 1.16 higher)	⨁◯◯◯ VERY LOW	CRITICAL

1 a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

3 c. MIDs used to assess imprecision were ±4.75

4 d. MIDs used to assess imprecision were ±9.75

5 e. MIDs used to assess imprecision were ±8.40

6 f. MIDs used to assess imprecision were ±11.20

7 g. MIDs used to assess imprecision were ±8.50

8 h. MIDs used to assess imprecision were ±12.48

9 i. MIDs used to assess imprecision were ±4.08

10 j. MIDs used to assess imprecision were ±1.18

11 k. MIDs used to assess imprecision were ±1.30

12 l. MIDs used to assess imprecision were ±1.08

13 m. MIDs used to assess imprecision were ±0.90

14 n. MIDs used to assess imprecision were ±0.58

15 o. MIDs used to assess imprecision were ±61.75

16 p. MIDs used to assess imprecision were ±66.18

17 q. MIDs used to assess imprecision were ±0.20

r. MIDs used to assess imprecision were ±4.20

s. MIDs used to assess imprecision were ±894.08

t. MIDs used to assess imprecision were ±448.65

u. MIDs used to assess imprecision were ±0.83

v. MIDs used to assess imprecision were ±0.95

w. MIDs used to assess imprecision were ±61.93

x. MIDs used to assess imprecision were ±59.15

y. MIDs used to assess imprecision were ±0.60

z. MIDs used to assess imprecision were ±1.08

aa. MIDs used to assess imprecision were ±69.40

ab. MIDs used to assess imprecision were ±90.00

ac. MIDs used to assess imprecision were ±88.95

ad. MIDs used to assess imprecision were ±0.90

ae. MIDs used to assess imprecision were ±0.50

af. MIDs used to assess imprecision were ±0.40

ag. MIDs used to assess imprecision were ±3.55

ah. MIDs used to assess imprecision were ±2.68

ai. MIDs used to assess imprecision were ±1.25

aj. MIDs used to assess imprecision were ±41.68

ak. MIDs used to assess imprecision were ±0.60

Table 8: Clinical evidence profile: General cognitive rehabilitation (multi-component and multi-domain) tailored to individual + outpatient rehabilitation vs. outpatient rehabilitation only, 3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab + outpatient rehabilitation - multi-component and tailored to individual	control (outpatient rehabilitation only), 3 months	Relative (95% CI)	Absolute (95% CI)		
Computer-aided card sorting - correct - 3 months (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,c]	none	10	9	-	MD **11.8 lower** (27.87 lower to 4.27 higher)	⨁⨁◯◯ LOW	CRITICAL
Computer-aided card sorting - incorrect - 3 months (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,d]	none	10	9	-	MD **2.7 lower** (5.62 lower to 0.22 higher)	⨁⨁◯◯ LOW	CRITICAL
Sustained attention - correct - 3 months (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	10	9	-	MD **11.8 lower** (27.87 lower to 4.27 higher)	⨁⨁◯◯ LOW	CRITICAL
Sustained attention - incorrect - 3 months (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,e]	none	10	9	-	MD **5 lower** (18.62 lower to 8.62 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Sustained attention - reaction time - 3 months (follow up: 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab + outpatient rehabilitation - multi-component and tailored to individual	control (outpatient rehabilitation only), 3 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,f]	none	10	9	-	MD **4.1 lower** (11.86 lower to 3.66 higher)	⨁⨁◯◯ LOW	CRITICAL
Sustained attention - variation reaction time - 3 months (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,g]	none	10	9	-	MD **5.9 lower** (14.73 lower to 2.93 higher)	⨁⨁◯◯ LOW	CRITICAL
Verbal learning test - 3 months (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,h]	none	10	9	-	MD **6.5 higher** (5.54 lower to 18.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Spatial construction - 3 months (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,i]	none	10	9	-	MD **0.2 higher** (2.06 lower to 2.46 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Non-verbal learning test - 3 months (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,j]	none	10	9	-	MD **0.7 higher** (11.5 lower to 12.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory (scale usually 0-63) - 3 months (follow up: 3 months; Scale from: 0 to 63)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog. rehab + outpatient rehabilitation - multi-component and tailored to individual	control (outpatient rehabilitation only), 3 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b,k]	none	10	9	-	MD **0** (4.23 lower to 4.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Modified Fatigue Impact Scale (scale usually 0-84) - 3 months (follow up: 3 months; Scale from: 0 to 84)

1	randomised trials	serious [a]	not serious	serious [l]	serious [b,m]	none	10	9	-	MD **10.1 higher** (5.49 lower to 25.69 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±8.48

d. MIDs used to assess imprecision were ±2.10

e. MIDs used to assess imprecision were ±5.25

f. MIDs used to assess imprecision were ±4.00

g. MIDs used to assess imprecision were ±5.13

h. MIDs used to assess imprecision were ±4.68

i. MIDs used to assess imprecision were ±1.20

j. MIDs used to assess imprecision were ±3.10

k. MIDs used to assess imprecision were ±2.88

l. General Modified Fatigue Impact Scale rather than specifically the cognitive subdomain

m. MIDs used to assess imprecision were ±7.63

Table 9: Clinical evidence profile: Goal Attainment Scaling (GAS) goals (multi-component cognitive rehabilitation tailored to individual) + usual rehabilitation vs. usual rehabilitation only, 4 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog rehab - Goal Attainment Scaling (GAS) goals (multi-component cognitive rehab and tailored to individual) + usual rehab	control (usual rehab alone), 4 months	Relative (95% CI)	Absolute (95% CI)		
Behavior Rating Inventory of Executive Function – Adult (BRIEF-A) - General Executive Composite (T-score) - 4 months (follow up: 4 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	51	51	-	MD **0.3 lower** (4.84 lower to 4.24 higher)	⨁⨁◯◯ LOW	CRITICAL
BRIEF-A - Metacognition index (T-score) - 4 months (follow up: 4 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [c]	none	51	51	-	MD **0.4 higher** (3.97 lower to 4.77 higher)	⨁⨁◯◯ LOW	CRITICAL
MSIS-29 psychological subscale (Norweigian version, scale reported 9-45) - 4 months (follow up: 4 months; Scale from: 9 to 45)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,e]	none	51	51	-	MD **1.6 lower** (4.44 lower to 1.24 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Hopkins Symptom Checklist- 25 (measures psychological health; scale 1-4) - 4 months (follow up: 4 months; Scale from: 1 to 4)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog rehab - Goal Attainment Scaling (GAS) goals (multi-component cognitive rehab and tailored to individual) + usual rehab	control (usual rehab alone), 4 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [d,f]	none	51	51	-	MD **0.14 lower** (0.33 lower to 0.05 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. MIDs used to assess imprecision were ±5.40

c. MIDs used to assess imprecision were ±5.45

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MIDs used to assess imprecision were ±3.40

f. MIDs used to assess imprecision were ±0.24

Table 10: Clinical evidence profile: Goal Attainment Scaling (GAS) goals (multi-component cognitive rehabilitation tailored to individual) + usual rehabilitation vs. usual rehabilitation only, 7 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General cog rehab - Goal Attainment Scaling (GAS) goals (multi-component cognitive rehab and tailored to individual) + usual rehab	control (usual rehab alone), 7 months	Relative (95% CI)	Absolute (95% CI)		
Behavior Rating Inventory of Executive Function – Adult (BRIEF-A) - General Executive Composite (T-score) - 7 months (follow up: 7 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	54	48	-	MD **1.1 higher** (3.43 lower to 5.63 higher)	⨁◯◯◯ VERY LOW	CRITICAL
BRIEF-A - Metacognition index (T-score) - 7 months (follow up: 7 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [d]	none	54	48	-	MD **1 higher** (3.43 lower to 5.43 higher)	⨁⨁◯◯ LOW	CRITICAL
MSIS-29 psychological subscale (Norweigian version, scale reported 9-45) - 7 months (follow up: 7 months; Scale from: 9 to 45)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,e]	none	54	48	-	MD **2.3 lower** (5.27 lower to 0.67 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Hopkins Symptom Checklist- 25 (measures psychological health; scale 1-4) - 7 months (follow up: 7 months; Scale from: 1 to 4)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [f]	none	54	48	-	MD **0.03 lower** (0.23 lower to 0.17 higher)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±5.40

d. MIDs used to assess imprecision were ±5.45

e. MIDs used to assess imprecision were ±3.40

f. MIDs used to assess imprecision were ±0.24

Table 11: Clinical evidence profile: Multi-domain cognitive rehabilitation (pen/paper or computer tasks with no additional teaching strategies) vs. control, 2-6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
SDMT - 2-6 months (mix final values and change from baseline) - Similar at baseline or change from baseline reported (follow up: 2-6 months)												
4	randomised trials	serious [a]	serious [b]	serious [c]	not serious [d]	none	98	91	-	MD **5.57 higher** (3.69 higher to 7.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SDMT - 3 months - Larger difference at baseline (lower in intervention) (follow up: 3 months)												
2	randomised trials	very serious [a]	not serious	not serious	serious [e,f]	none	40	42	-	MD **1.57 lower** (7 lower to 3.86 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 2 seconds - 3 months (follow up: 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [e,g]	none	10	10	-	MD **12.8 higher** (1.83 higher to 23.77 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 3 seconds - 2.5-6 months (mix of final values and change from baseline) (follow up: 2.5-6 months)												
4	randomised trials	very serious [a]	serious [h]	not serious	serious [e,i]	none	87	90	-	MD **4.76 higher** (0.53 lower to 10.05 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Contralled Oral Word Association Test (COWAT) - 3 months - Phonemic cues (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [e,j]	none	10	10	-	MD **4.4 higher** (5.42 lower to 14.22 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Contralled Oral Word Association Test (COWAT) - 3 months - Semantic cues (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [e,k]	none	10	10	-	MD **2.6 higher** (6.55 lower to 11.75 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Contralled Oral Word Association Test (COWAT) - 3 months - Animals (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [e,l]	none	30	32	-	MD **0.4 lower** (2.89 lower to 2.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wisconsin Card Sorting Test (WCST) - 3 months - Total errors (follow up: 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [e,m]	none	10	10	-	MD **13.3 lower** (28.07 lower to 1.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Wisconsin Card Sorting Test (WCST) - 3 months - Perseverative errors (follow up: 3 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [e,n]	none	10	10	-	MD **14.3 lower** (32.66 lower to 4.06 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Wisconsin Card Sorting Test (WCST) - 3 months - Perseverative responses (follow up: 3 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [e,o]	none	10	10	-	MD **10.9 lower** (23.62 lower to 1.82 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Delis-Kaplan Executive Function System (D-KEFS) - card sorting test - 2.5 months - Verbal (follow up: 2.5 months)

1	randomised trials	very serious [a]	not serious	serious [c]	serious [e,p]	none	26	28	-	MD **4.61 higher** (1.14 lower to 10.36 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Delis-Kaplan Executive Function System (D-KEFS) - card sorting test - 2.5 months - Non-verbal (follow up: 2.5 months)

1	randomised trials	very serious [a]	not serious	serious [c]	serious [e,q]	none	26	28	-	MD **1.39 higher** (0.03 lower to 2.81 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Word List Generation Test - 6 months (change from baseline) - Word List Generation Test - 6 months (change from baseline) (follow up: 6 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious [r]	none	21	20	-	MD **3.6 higher** (0.83 higher to 6.37 higher)	⨁⨁◯◯ LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 3-6 months (mix final values and change from baseline) - Total (follow up: 3-6 months)												
2	randomised trials	very serious [a]	very serious [s]	not serious	serious [e,t]	none	51	52	-	MD **3.46 higher** (0.69 lower to 7.6 higher)	⨁◯◯◯ VERY LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 3-6 months (mix final values and change from baseline) - Long-term retrieval (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [e,u]	none	10	10	-	MD **0.3 lower** (4.43 lower to 3.83 higher)	⨁◯◯◯ VERY LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 3-6 months (mix final values and change from baseline) - Delayed recall (follow up: 3-6 months)												
3	randomised trials	very serious [a]	serious [h]	not serious	serious [e,v]	none	61	62	-	MD **0.67 higher** (0.9 lower to 2.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test (SRT) 2.5-6 months (change from baseline) - Total (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [w]	none	21	20	-	MD **1.63 higher** (2.76 lower to 6.02 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
Selective Reminding Test (SRT) 2.5-6 months (mix final values and change from baseline) - Long-term storage (follow up: 2.5-6 months)												
4	randomised trials	serious [a]	not serious	not serious	serious [x]	none	80	79	-	MD **6.18 higher** (3.36 higher to 8.99 higher)	⨁⨁◯◯ LOW	CRITICAL
Selective Reminding Test (SRT) 2.5-6 months (mix final values and change from baseline) - Delayed retrieval (follow up: 2.5-6 months)												
4	randomised trials	very serious [a]	not serious	not serious	serious [e,y]	none	80	79	-	MD **1.15 higher** (0.6 higher to 1.7 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test (SRT) 2.5-6 months (mix final values and change from baseline) - Consistent long-term retrieval (follow up: 3-6 months)												
3	randomised trials	very serious [a]	not serious	not serious	serious [e,z]	none	61	62	-	MD **5.11 higher** (0.49 lower to 10.7 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Brief Visuospatial Memory Test-Revised (BVMT-R) - 2-2.5 months (mix of final values and change from baseline) (follow up: 2-2.5 months)												
2	randomised trials	serious [a]	not serious	serious [c]	serious [aa,e]	none	51	43	-	MD **3.52 higher** (2.26 higher to 4.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Trail Making Test - 2.5-6 months (mix of final values and change from baseline) - Part A (follow up: 2.5-6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	serious [c]	serious [ab,e]	none	40	37	-	MD **11.59 lower** (18.85 lower to 4.33 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Trail Making Test - 2.5-6 months (change from baseline) - Part B, similar at baseline or change from baseline reported (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [ac,e]	none	21	20	-	MD **13.97 lower** (34.4 lower to 6.46 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Trail Making Test - 2.5-6 months - Part B, larger difference at baseline (lower in intervention) (follow up: 2.5 months)												
1	randomised trials	serious [a]	not serious	serious [c]	serious [ad,e]	none	19	17	-	MD **2.32 higher** (20.39 lower to 25.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Stroop neuropsychological screening test - 2.5 months (follow up: 2.5 months)												
1	randomised trials	serious [a]	not serious	serious [c]	serious [ae,e]	none	32	26	-	MD **5.9 higher** (1.23 lower to 13.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Test of Everyday Attention (TEA) median - 3 months - Auditory stimulus (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [af,e]	none	10	10	-	MD **137.5 higher** (8.81 higher to 266.19 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
Test of Everyday Attention (TEA) median - 3 months - Visual stimulus (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ag,e]	none	10	10	-	MD **89.6 lower** (234.87 lower to 55.67 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Test of Everyday Attention (TEA) errors/omissions - 3 months - Total omitted stimuli (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [ah]	none	10	10	-	MD **0.1 lower** (2.27 lower to 2.07 higher)	⨁⨁◯◯ LOW	CRITICAL
Test of Everyday Attention (TEA) errors/omissions - 3 months - Total errors (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ai,e]	none	10	10	-	MD **1.3 lower** (5.93 lower to 3.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Integrated Auditory Visual-2 (IVA-2) - 2.5 months - Visual attention (follow up: 2.5 months)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [aj,e]	none	26	28	-	MD **11.58 higher** (0.61 lower to 23.77 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Integrated Auditory Visual-2 (IVA-2) - 2.5 months - Auditory attention (follow up: 2.5 months)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [ak,e]	none	26	28	-	MD **13.31 higher** (1.71 higher to 24.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
Integrated Auditory Visual-2 (IVA-2) - 2.5 months - Visual response control (follow up: 2.5 months)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [al,e]	none	26	28	-	MD **11.61 higher** (1.37 higher to 21.85 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Integrated Auditory Visual-2 (IVA-2) - 2.5 months - Auditory response control (follow up: 2.5 months)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [am,e]	none	26	28	-	MD **15.73 higher** (5.68 higher to 25.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Integrated Auditory Visual-2 (IVA-2) - 2.5 months - Visual comprehension (follow up: 2.5 months)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [an,e]	none	26	28	-	MD **12.96 higher** (0.63 higher to 25.29 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Integrated Auditory Visual-2 (IVA-2) - 2.5 months - Auditory comprehension (follow up: 2.5 months)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [ao,e]	none	26	28	-	MD **11.58 higher** (1.19 lower to 24.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Integrated Auditory Visual-2 (IVA-2) - 2.5 months - Visual persistence attention (follow up: 2.5 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [c]	serious [ap,e]	none	26	28	-	MD **11.58 higher** (0.15 higher to 23.01 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Integrated Auditory Visual-2 (IVA-2) - 2.5 months - Auditory persistence attention (follow up: 2.5 months)

1	randomised trials	very serious [a]	not serious	serious [c]	not serious [aq]	none	26	28	-	MD **14.26 higher** (7.55 higher to 20.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Integrated Auditory Visual-2 (IVA-2) - 2.5 months - Visual sensory-motor attention (follow up: 2.5 months)

1	randomised trials	very serious [a]	not serious	serious [c]	serious [ar,e]	none	26	28	-	MD **12.31 higher** (2.8 higher to 21.82 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Integrated Auditory Visual-2 (IVA-2) - 2.5 months - Auditory sensory-motor attention (follow up: 2.5 months)

1	randomised trials	very serious [a]	not serious	serious [c]	serious [as,e]	none	26	28	-	MD **9.7 higher** (1.34 lower to 20.74 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Integrated Auditory Visual-2 (IVA-2) - 2.5 months - Fine motor hyperactivity (follow up: 2.5 months)

1	randomised trials	very serious [a]	not serious	serious [c]	serious [at,e]	none	26	28	-	MD **12.16 higher** (3.6 lower to 27.92 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
Digit span (Weschler Adult Intelligence Scale III) - 6 months (change from baseline) - Forward (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [au,e]	none	21	20	-	MD **0.43 higher** (0.34 lower to 1.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Digit span (Weschler Adult Intelligence Scale III) - 6 months (change from baseline) - Backward (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [av,e]	none	21	20	-	MD **0.92 higher** (0.2 lower to 2.04 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Block design (Weschler Adult Intelligence Scale III) - 6 months (change from baseline) - Block design (Weschler Adult Intelligence Scale III) - 6 months (change from baseline) (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [aw,e]	none	21	20	-	MD **4.35 higher** (1.01 lower to 9.71 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Letter-number sequencing (Weschler Adult Intelligence Scale III) - 6 months (change from baseline) - Letter-number sequencing (Weschler Adult Intelligence Scale III) - 6 months (change from baseline) (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ax,e]	none	21	20	-	MD **1.48 higher** (0.06 higher to 2.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Judgement of line orientation - 2.5 months (follow up: 2.5 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [c]	serious [ay,e]	none	26	28	-	MD **1.92 higher** (0.24 higher to 3.6 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Boston Naming Test - 6 months (change from baseline) - Boston Naming Test - 6 months (change from baseline) (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [ax]	none	21	20	-	MD **2.58 higher** (1.16 higher to 4 higher)	⨁⨁◯◯ LOW	CRITICAL
FAS test (verbal fluency) - 3-6 months (change from baseline) - Similar at baseline or change from baseline values reported (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [az,e]	none	21	20	-	MD **1.55 higher** (3.48 lower to 6.58 higher)	⨁◯◯◯ VERY LOW	CRITICAL
FAS test (verbal fluency) - 3-6 months - Larger difference at baseline (lower in intervention group) (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ba,e]	none	30	32	-	MD **0.9 lower** (6.1 lower to 4.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Verbal fluency test - 2.5 months - Phonemic (follow up: 2.5 months)												
1	randomised trials	serious [a]	not serious	serious [c]	serious [bb,e]	none	32	26	-	MD **3.18 higher** (0.7 lower to 7.06 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
Verbal fluency test - 2.5 months - Semantic (follow up: 2.5 months)												
1	randomised trials	serious [a]	not serious	serious [c]	serious [bc,e]	none	32	26	-	MD **3.98 higher** (0.78 lower to 8.74 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Greek Verbal Learning Test - 2 months (change from baseline) (follow up: 2 months)												
1	randomised trials	serious [a]	not serious	serious [c]	not serious [bd]	none	19	17	-	MD **9.04 higher** (6.15 higher to 11.93 higher)	⨁⨁◯◯ LOW	CRITICAL
MS Neuropsychological Questionnaire (MNSQ, scale usually 0-60) - 3 months (follow up: 3 months; Scale from: 0 to 60)												
1	randomised trials	very serious [a]	not serious	not serious	serious [be,e]	none	30	32	-	MD **1.76 lower** (7.65 lower to 4.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQoL-54 (scale usually 0-100) - 2.5 months - Physical composite (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [bf,e]	none	30	32	-	MD **10.25 lower** (19.3 lower to 1.2 lower)	⨁◯◯◯ VERY LOW	CRITICAL
MSQoL-54 (scale usually 0-100) - 3 months - Mental composite (follow up: 3 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [bg,e]	none	30	32	-	MD **10.93 lower** (19.86 lower to 2 lower)	⨁◯◯◯ VERY LOW	CRITICAL
MS quality of life (scale unclear) - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [bh,e]	none	10	10	-	MD **30.88 higher** (1.83 lower to 63.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL
EQ-5D visual analogue (scale usually 0-100) - 2 months (change from baseline) (follow up: 2 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [bi,e]	none	19	17	-	MD **10.59 higher** (6.38 higher to 14.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory-Fast Screen (scale usually 0-21) - 2 months (change from baseline) (follow up: 2 months; Scale from: 0 to 21)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [bj,e]	none	19	17	-	MD **2.86 lower** (4.57 lower to 1.15 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Montgomery-Asberg Depression Scale (scale usually 0-60) - 3 months (follow up: 3 months; Scale from: 0 to 60)												
1	randomised trials	very serious [a]	not serious	not serious	serious [bk,e]	none	10	10	-	MD **8.8 lower** (15.35 lower to 2.25 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	control, 2-6 months	Relative (95% CI)	Absolute (95% CI)		
HADS - 3-6 months (scale usually 0-21, mix of final values and change from baseline) - Anxiety (follow up: 3-6 months; Scale from: 0 to 21)												
2	randomised trials	very serious [a]	not serious	not serious	serious [bl,e]	none	51	52	-	MD **1.63 lower** (2.9 lower to 0.36 lower)	⨁◯◯◯ VERY LOW	CRITICAL
HADS - 3-6 months (scale usually 0-21, mix of final values and change from baseline) - Depression (follow up: 3-6 months; Scale from: 0 to 21)												
2	randomised trials	very serious [a]	not serious	not serious	serious [bm,e]	none	51	52	-	MD **1.08 lower** (2.33 lower to 0.16 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale (MFIS) - cognitive (scale usually 0-40) - 2 months (change from baseline) (follow up: 2 months; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	serious [c]	not serious [bn]	none	19	17	-	MD **4.8 lower** (6.52 lower to 3.08 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (FSS, scale usually 9-63) - 3 months (follow up: 3 months; Scale from: 9 to 63)												
1	randomised trials	very serious [a]	not serious	serious [bo]	serious [bp,e]	none	30	32	-	MD **1.3 higher** (9.19 lower to 11.79 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as point estimates vary in size of effect, which cannot be explained by prespecified subgrouping analyses

c. Downgraded by 1 increment as the majority of the evidence came from studies reporting the results at a time-point <3-month minimum specified in the protocol

d. MIDs used to assess imprecision were ±2.80

e. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

f. MIDs used to assess imprecision were ±6.03

g. MIDs used to assess imprecision were ±4.60

h. Downgraded by 1 increment as statistical heterogeneity is present that cannot be explained by prespecified subgroup analyses, with I2 >50%

i. MIDs used to assess imprecision were ±7.10

j. MIDs used to assess imprecision were ±4.28

k. MIDs used to assess imprecision were ±4.65

l. MIDs used to assess imprecision were ±2.38

m. MIDs used to assess imprecision were ±8.65

n. MIDs used to assess imprecision were ±6.10

o. MIDs used to assess imprecision were ±9.20

p. MIDs used to assess imprecision were ±5.53

q. MIDs used to assess imprecision were ±1.35

r. MIDs used to assess imprecision were ±0.49 (based on 0.5 multiplied by the SD of the change score in the control group as there were no baseline values reported)

s. Downgraded by 2 increments as statistical heterogeneity is present, with I2 ≥80% and point estimates differing in size of the effect and that could not be explained by prespecified subgroup analyses

t. MIDs used to assess imprecision were ±2.33

u. MIDs used to assess imprecision were ±2.05

v. MIDs used to assess imprecision were ±1.22

w. MIDs used to assess imprecision were ±0.77 (based on 0.5 multiplied by the SD of the change score in the control group as there were no baseline values reported)

x. MIDs used to assess imprecision were ±5.20

y. MIDs used to assess imprecision were ±1.02

z. MIDs used to assess imprecision were ±6.67

aa. MIDs used to assess imprecision were ±2.66

ab. MIDs used to assess imprecision were ±10.91

ac. MIDs used to assess imprecision were ±3.50 (based on 0.5 multiplied by the SD of the change score in the control group as there were no baseline values reported)

ad. MIDs used to assess imprecision were ±21.05

ae. MIDs used to assess imprecision were ±8.20

af. MIDs used to assess imprecision were ±115.95

ag. MIDs used to assess imprecision were ±144.95

ah. MIDs used to assess imprecision were ±2.35

ai. MIDs used to assess imprecision were ±3.60

aj. MIDs used to assess imprecision were ±12.20

ak. MIDs used to assess imprecision were ±12.03

al. MIDs used to assess imprecision were ±9.76

am. MIDs used to assess imprecision were ±10.47

an. MIDs used to assess imprecision were ±11.97

ao. MIDs used to assess imprecision were ±14.50

ap. MIDs used to assess imprecision were ±9.29

aq. MIDs used to assess imprecision were ±6.94

ar. MIDs used to assess imprecision were ±9.37

as. MIDs used to assess imprecision were ±11.70

at. MIDs used to assess imprecision were ±15.73

au. MIDs used to assess imprecision were ±0.14 (based on 0.5 multiplied by the SD of the change score in the control group as there were no baseline values reported)

av. MIDs used to assess imprecision were ±0.20 (based on 0.5 multiplied by the SD of the change score in the control group as there were no baseline values reported)

aw. MIDs used to assess imprecision were ±0.97 (based on 0.5 multiplied by the SD of the change score in the control group as there were no baseline values reported)

ax. MIDs used to assess imprecision were ±0.26 (based on 0.5 multiplied by the SD of the change score in the control group as there were no baseline values reported)

ay. MIDs used to assess imprecision were ±1.89

az. MIDs used to assess imprecision were ±0.90 (based on 0.5 multiplied by the SD of the change score in the control group as there were no baseline values reported)

ba. MIDs used to assess imprecision were ±4.96

bb. MIDs used to assess imprecision were ±4.17

bc. MIDs used to assess imprecision were ±4.40

bd. MIDs used to assess imprecision were ±4.55

be. MIDs used to assess imprecision were ±5.89

bf. MIDs used to assess imprecision were ±8.78

bg. MIDs used to assess imprecision were ±9.12

bh. MIDs used to assess imprecision were ±19.65

bi. MIDs used to assess imprecision were ±7.70

bj. MIDs used to assess imprecision were ±1.65

bk. MIDs used to assess imprecision were ±4.90

bl. MIDs used to assess imprecision were ±1.89

bm. MIDs used to assess imprecision were ±1.73

bn. MIDs used to assess imprecision were ±1.73

bo. Downgraded by 1 increment as general Fatigue Severity Scale reported rather than specifically cognitive fatigue

bp. MIDs used to assess imprecision were ±10.94

Table 12: Clinical evidence profile: Multi-domain cognitive rehabilitation (pen/paper or computer tasks with no additional teaching strategies) vs. control, 9 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	memory and cognitive problems in MS, 9 months	Relative (95% CI)	Absolute (95% CI)		
PASAT - 9 months - 2 seconds (follow up: 9 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	9	9	-	MD **11.2 higher** (0.01 lower to 22.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 9 months - 3 seconds (follow up: 9 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	9	9	-	MD **14.3 higher** (1.06 lower to 29.66 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SDMT - 9 months (follow up: 9 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,e]	none	9	9	-	MD **0.3 higher** (12.92 lower to 13.52 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Contralled Oral Word Association (COWA) - 9 months - Phonemic cues (follow up: 9 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,f]	none	9	9	-	MD **0.2 higher** (7.99 lower to 8.39 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Contralled Oral Word Association (COWA) - 9 months - Semantic cues (follow up: 9 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	memory and cognitive problems in MS, 9 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,g]	none	9	9	-	MD **7.3 higher** (1.89 lower to 16.49 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Wisconsin Card Sorting Test (WCST) - 9 months - Total errors (follow up: 9 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,h]	none	9	9	-	MD **19.4 lower** (36.03 lower to 2.77 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Wisconsin Card Sorting Test (WCST) - 9 months - Perseverative errors (follow up: 9 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	9	9	-	MD **12.6 lower** (29.56 lower to 4.36 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Wisconsin Card Sorting Test (WCST) - 9 months - Perseverative responses (follow up: 9 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,j]	none	9	9	-	MD **12.42 lower** (23.77 lower to 1.07 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Selective Reminding Test (SRT) - 9 months - Long-term storage (follow up: 9 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,k]	none	9	9	-	MD **5.6 higher** (5.16 lower to 16.36 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Selective Reminding Test (SRT) - 9 months - Consistent long-term retrieval (follow up: 9 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	memory and cognitive problems in MS, 9 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,l]	none	9	9	-	MD **2.2 higher** (11.85 lower to 16.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test (SRT) - 9 months - Delayed retrieval (follow up: 9 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,m]	none	9	9	-	MD **1.4 higher** (0.84 lower to 3.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 9 months - Long-term retrieval (follow up: 9 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,n]	none	9	9	-	MD **0.4 lower** (4.18 lower to 3.38 higher)	⨁◯◯◯ VERY LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 9 months - Delayed recall (follow up: 9 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,o]	none	9	9	-	MD **0.2 lower** (2.37 lower to 1.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Test of Everyday Attention (TEA) median - 9 months - Auditory stimulus (follow up: 9 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,p]	none	9	9	-	MD **172.6 higher** (40.85 lower to 386.05 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Test of Everyday Attention (TEA) median - 9 months - Visual stimulus (follow up: 9 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab (pen/paper or computer tasks, with no additional teaching strategies)	memory and cognitive problems in MS, 9 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,q]	none	9	9	-	MD **228.2 higher** (68.89 lower to 525.29 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MS quality of life (scale unclear) - 9 months (follow up: 9 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,r]	none	9	10	-	MD **27.37 higher** (6.15 lower to 60.89 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Montgomery-Asberg Depression Scale (scale usually 0-60) - 9 months (follow up: 9 months; Scale from: 0 to 60)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,s]	none	9	9	-	MD **9.8 lower** (19.15 lower to 0.45 lower)	⨁◯◯◯ VERY LOW	CRITICAL

1 a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

3 c. MIDs used to assess imprecision were ±4.60

4 d. MIDs used to assess imprecision were ±6.48

5 e. MIDs used to assess imprecision were ±6.55

6 f. MIDs used to assess imprecision were ±4.28

7 g. MIDs used to assess imprecision were ±4.65

8 h. MIDs used to assess imprecision were ±8.65

i. MIDs used to assess imprecision were ±6.10

j. MIDs used to assess imprecision were ±9.20

k. MIDs used to assess imprecision were ±5.20

l. MIDs used to assess imprecision were ±5.28

m. MIDs used to assess imprecision were ±0.99

n. MIDs used to assess imprecision were ±2.05

o. MIDs used to assess imprecision were ±1.03

p. MIDs used to assess imprecision were ±115.95

q. MIDs used to assess imprecision were ±144.95

r. MIDs used to assess imprecision were ±19.65

s. MIDs used to assess imprecision were ±4.90

Table 13: Clinical evidence profile: Multi-domain cognitive rehabilitation tailored to individual (CogniFit – computer tasks, with no additional teaching strategies) vs. control, 3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab tailored to individual (CogniFit - computer tasks, with no additional teaching strategies)	control, 3 months	Relative (95% CI)	Absolute (95% CI)		
Divided attention - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [c]	none	22	24	-	MD **0.04 lower** (0.47 lower to 0.39 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab tailored to individual (CogniFit - computer tasks, with no additional teaching strategies)	control, 3 months	Relative (95% CI)	Absolute (95% CI)		
Avoiding distractions - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [d]	none	22	24	-	MD **0.03 higher** (0.31 lower to 0.37 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Hand-eye coordination - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [e,f]	none	22	24	-	MD **0.3 lower** (0.81 lower to 0.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL
General memory - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [f,g]	none	22	24	-	MD **0.57 higher** (0.01 higher to 1.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Naming - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [f,h]	none	22	24	-	MD **0.14 higher** (0.27 lower to 0.55 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Response time - 3 months (follow up: 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab tailored to individual (CogniFit - computer tasks, with no additional teaching strategies)	control, 3 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [f,i]	none	22	24	-	MD **0.12 lower** (0.53 lower to 0.29 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Shifting attention - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [f,j]	none	22	24	-	MD **0.11 lower** (0.56 lower to 0.34 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Spatial perception - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [g]	none	22	24	-	MD **0.08 lower** (0.47 lower to 0.31 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Time estimation - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [f,k]	none	22	24	-	MD **0.28 higher** (0.19 lower to 0.75 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Visual working memory - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,f]	none	22	24	-	MD **0.5 higher** (0.04 lower to 1.04 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi-domain cog. rehab tailored to individual (CogniFit - computer tasks, with no additional teaching strategies)	control, 3 months	Relative (95% CI)	Absolute (95% CI)		
Visual scanning - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,f]	none	22	24	-	MD **0.04 lower** (0.53 lower to 0.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Verbal auditory working memory - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [f,i]	none	22	24	-	MD **0.56 higher** (0.03 higher to 1.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as cognitive impairment does not appear to be an inclusion criterion

c. MIDs used to assess imprecision were ±0.50

d. MIDs used to assess imprecision were ±0.39

e. MIDs used to assess imprecision were ±0.58

f. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

g. MIDs used to assess imprecision were ±0.49

h. MIDs used to assess imprecision were ±0.43

i. MIDs used to assess imprecision were ±0.35

j. MIDs used to assess imprecision were ±0.41

k. MIDs used to assess imprecision were ±0.56

l. MIDs used to assess imprecision were ±0.47

Table 14: Clinical evidence profile: Brain training apps/games (targeting general cognitive function/multiple domains) vs. control, 1.5-3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brain training apps/games	control, 1.5-3 months	Relative (95% CI)	Absolute (95% CI)		
Trail Making Test - 1.5-2 months - Part A, difference at baseline (higher in intervention) (follow up: 1.5 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	23	24	-	MD **5.2 lower** (16.92 lower to 6.52 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Trail Making Test - 1.5-2 months - Part A, difference at baseline (lower in intervention) (follow up: 2 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	26	17	-	MD **18.2 lower** (37.27 lower to 0.87 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Trail Making Test - 1.5-2 months - Part B, difference at baseline (higher in intervention) (follow up: 1.5 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [f]	none	23	24	-	MD **9.1 lower** (23.73 lower to 5.53 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Trail Making Test - 1.5-2 months - Part B, difference at baseline (lower in intervention) (follow up: 2 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,g]	none	26	17	-	MD **39.8 lower** (74.24 lower to 5.36 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brain training apps/games	control, 1.5-3 months	Relative (95% CI)	Absolute (95% CI)		
Stroop test - 1.5-2 months - General 'Stroop Test' (follow up: 2 months)												
2	randomised trials	serious [a]	not serious	serious [b]	serious [c,h]	none	30	28	-	MD **4.03 higher** (0.21 higher to 7.85 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Stroop test - 1.5-2 months - Color (follow up: 1.5 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,i]	none	23	24	-	MD **7.7 higher** (4.08 lower to 19.48 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Stroop test - 1.5-2 months - Color-Word (follow up: 1.5 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,j]	none	23	24	-	MD **5.2 higher** (2.26 lower to 12.66 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 2 months - 2 seconds (follow up: 2 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,k]	none	14	14	-	MD **1.22 higher** (8.69 lower to 11.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 2 months - 3 seconds (follow up: 2 months)												
3	randomised trials	serious [a]	not serious	serious [b]	serious [c,l]	none	44	42	-	MD **5.91 higher** (1.6 higher to 10.22 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 3 months (z-score) - 2 second (follow up: 3 months; Scale from: -5 to 5)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brain training apps/games	control, 1.5-3 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,m]	none	11	9	-	MD **0.2 higher** (0.78 lower to 1.18 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 3 months (z-score) - 3 second (follow up: 3 months; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,n]	none	11	9	-	MD **0.56 higher** (0.26 lower to 1.38 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SDMT - 1.5-2 months (follow up: 1.5-2 months)												
4	randomised trials	very serious [a]	not serious	serious [b]	serious [c,o]	none	67	66	-	MD **7.17 higher** (3.15 higher to 11.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test (SRT) - 2 months - Long-term storage (follow up: 2 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,p]	none	14	14	-	MD **3.78 lower** (15.71 lower to 8.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test (SRT) - 2 months - Consecutive long-term retrieval (follow up: 2 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,q]	none	14	14	-	MD **1.14 higher** (14.3 lower to 16.58 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test (SRT) - 2 months - Delayed recall (follow up: 2 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brain training apps/games	control, 1.5-3 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,r]	none	14	14	-	MD **0.43 lower** (2.08 lower to 1.22 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test (SRT) - 3 months (z-score) - Learning trials (follow up: 3 months; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,s]	none	11	9	-	MD **0.37 higher** (0.65 lower to 1.39 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test (SRT) - 3 months (z-score) - Delay (follow up: 3 months; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,t]	none	11	9	-	MD **0.29 higher** (0.83 lower to 1.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 2 months - Correct (follow up: 2 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,u]	none	14	14	-	MD **2.57 higher** (2.22 lower to 7.36 higher)	⨁◯◯◯ VERY LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 2 months - Delayed (follow up: 2 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,v]	none	14	14	-	MD **1.07 higher** (1.38 lower to 3.52 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Word List Generation Test - 2 months (follow up: 2 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brain training apps/games	control, 1.5-3 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,w]	none	14	14	-	MD **0.28 lower** (6.09 lower to 5.53 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Brief Visuospatial Memory Test-Revised (BVMT-R) - 1.5 months (follow up: 1.5 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,x]	none	23	24	-	MD **5 higher** (0.45 lower to 10.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Brief Visuospatial Memory Test-Revised (BVMT-R) - 3 months (z-score) - Learning trials (follow up: 3 months; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,y]	none	11	9	-	MD **0.1 higher** (1.31 lower to 1.51 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Brief Visuospatial Memory Test-Revised (BVMT-R) - 3 months (z-score) - Delay (follow up: 3 months; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,z]	none	11	9	-	MD **0.16 higher** (1.22 lower to 1.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Greek Verbal Learning Test - 1.5 months (follow up: 1.5 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [aa,c]	none	23	24	-	MD **9.3 higher** (0.38 higher to 18.22 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) - 2 months - Immediate memory (scale 40-152?) (follow up: 2 months; Scale from: 40 to 152)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brain training apps/games	control, 1.5-3 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	serious [ab,c]	none	26	17	-	MD **10.1 higher** (0.45 lower to 20.65 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) - 2 months - Visuospatial/constructional (scale 50-131?) (follow up: 2 months; Scale from: 50 to 131)

1	randomised trials	serious [a]	not serious	serious [b]	serious [ac,c]	none	26	17	-	MD **5 higher** (3.39 lower to 13.39 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) - 2 months - Language (scale 40-134?) (follow up: 2 months; Scale from: 40 to 134)

1	randomised trials	serious [a]	not serious	serious [b]	serious [ad,c]	none	26	17	-	MD **7.3 higher** (0.6 lower to 15.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) - 2 months - Attention (scale 40-150?) (follow up: 2 months; Scale from: 40 to 150)

1	randomised trials	serious [a]	not serious	serious [b]	serious [ae,c]	none	26	17	-	MD **13.4 higher** (3.89 higher to 22.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) - 2 months - Delayed memory (scale 40-133?) (follow up: 2 months; Scale from: 40 to 133)

1	randomised trials	serious [a]	not serious	serious [b]	serious [af,c]	none	26	17	-	MD **9.6 higher** (0.16 higher to 19.04 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) - 2 months - Total score (scale 40-160?) (follow up: 2 months; Scale from: 40 to 160)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brain training apps/games	control, 1.5-3 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	serious [ag,c]	none	26	17	-	MD **12.4 higher** (2.35 higher to 22.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler adult intelligence scale IV (WAIS-IV) Letter-Number Sequencing - 3 months (z-score) (follow up: 3 months; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [ah,c]	none	11	9	-	MD **0** (0.64 lower to 0.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Visual span (Corsi block tapping test) - 3 months (z-score) (follow up: 3 months; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ai,c]	none	11	9	-	MD **0.26 higher** (0.33 lower to 0.85 higher)	⨁◯◯◯ VERY LOW	CRITICAL
DelisKaplan executive function system (DKEFS) - 3 months (z-score) - Trail 5 (follow up: 3 months; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [aj,c]	none	11	9	-	MD **0.01 higher** (0.3 lower to 0.32 higher)	⨁◯◯◯ VERY LOW	CRITICAL
DelisKaplan executive function system (DKEFS) - 3 months (z-score) - Trails 2/3 combo (follow up: 3 months; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [ak,c]	none	11	9	-	MD **0.27 higher** (0.57 lower to 1.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL
General cognitive composite (average of multiple cognitive tests) - 3 months change from baseline (z-score) (follow up: 3 months; Scale from: -5 to 5)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brain training apps/games	control, 1.5-3 months	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	serious [al]	not serious	serious [am,c]	none	85	70	-	MD **0.32 higher** (0.09 lower to 0.74 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Self-reported improvement in cognition - 3 months (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	42/74 (56.8%)	31.2%	**OR 2.90** (1.43 to 5.91)	**256 more per 1,000** (from 81 more to 416 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Modified Fatigue Impact Scale (MFIS) - Cognitive (scale usually 0-40) - 2 months (follow up: 2 months; Scale from: 0 to 40)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [an,c]	none	26	17	-	MD **7 lower** (12.03 lower to 1.97 lower)	⨁◯◯◯ VERY LOW	CRITICAL
MSQoL-54 (scale usually 0-100) - 2 months - Physical composite (follow up: 2 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [ao,c]	none	18	16	-	MD **0.02 lower** (9.12 lower to 9.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQoL-54 (scale usually 0-100) - 2 months - Mental health composite (follow up: 2 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [ap,c]	none	18	16	-	MD **7.47 higher** (2.38 lower to 17.32 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence (varying definitions) - Compliant to study requirements (follow up: 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brain training apps/games	control, 1.5-3 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	9/11 (81.8%)	77.8%	**OR 1.29** (0.14 to 11.54)	**41 more per 1,000** (from 449 fewer to 198 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence (varying definitions) - At least 6 compliant weeks (50% of target) (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	43/74 (58.1%)	78.7%	**OR 0.38** (0.17 to 0.81)	**203 fewer per 1,000** (from 401 fewer to 37 fewer)	⨁⨁◯◯ LOW	CRITICAL
Adherence (varying definitions) - Meeting or exceeding 30 h of training (50% of target) (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	44/74 (59.5%)	78.7%	**OR 0.40** (0.18 to 0.86)	**191 fewer per 1,000** (from 388 fewer to 26 fewer)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence came from studies that reported the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±11.25

e. MIDs used to assess imprecision were ±15.78

f. MIDs used to assess imprecision were ±29.00

g. MIDs used to assess imprecision were ±23.90

h. MIDs used to assess imprecision were ±3.15

i. MIDs used to assess imprecision were ±11.50

j. MIDs used to assess imprecision were ±5.25

k. MIDs used to assess imprecision were ±6.19

l. MIDs used to assess imprecision were ±5.57

m. MIDs used to assess imprecision were ±0.62

n. MIDs used to assess imprecision were ±0.73

o. MIDs used to assess imprecision were ±5.21

p. MIDs used to assess imprecision were ±9.18

q. MIDs used to assess imprecision were ±10.87

r. MIDs used to assess imprecision were ±1.41

s. MIDs used to assess imprecision were ±0.72

t. MIDs used to assess imprecision were ±0.55

u. MIDs used to assess imprecision were ±2.75

v. MIDs used to assess imprecision were ±1.42

w. MIDs used to assess imprecision were ±3.90

x. MIDs used to assess imprecision were ±6.25

y. MIDs used to assess imprecision were ±0.68

z. MIDs used to assess imprecision were ±0.66

aa. MIDs used to assess imprecision were ±10.00

ab. MIDs used to assess imprecision were ±8.23

ac. MIDs used to assess imprecision were ±7.55

ad. MIDs used to assess imprecision were ±5.98

ae. MIDs used to assess imprecision were ±7.68

af. MIDs used to assess imprecision were ±7.23

ag. MIDs used to assess imprecision were ±9.98

ah. MIDs used to assess imprecision were ±0.38

ai. MIDs used to assess imprecision were ±0.56

aj. MIDs used to assess imprecision were ±0.20

ak. MIDs used to assess imprecision were ±0.48

al. Downgraded by 1 increment as statistical heterogeneity is present, with I2>50%, that cannot be explained by prespecified subgroup analyses

am. MIDs used to assess imprecision were ±0.39

an. MIDs used to assess imprecision were ±4.05

ao. MIDs used to assess imprecision were ±6.50

ap. MIDs used to assess imprecision were ±8.90

Table 15: Clinical evidence profile: Mental visual imagery vs. control (sham verbal control), 6-8 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mental visual imagery	control (sham verbal control), 6-8 weeks	Relative (95% CI)	Absolute (95% CI)		
Number of details provided (Measure of mental visualisation ability) (follow up: 6-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	10	7	-	MD **0.55 lower** (2.71 lower to 1.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence came from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±0.65

Table 16: Clinical evidence profile: Mindfulness vs. control, 4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	control (waitlist control), 4 weeks	Relative (95% CI)	Absolute (95% CI)		
SDMT - 4 weeks (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	16	17	-	MD **7.6 lower** (18.11 lower to 2.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 4 weeks - 2 seconds (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	16	17	-	MD **3.8 lower** (11.32 lower to 3.72 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 4 weeks - 3 seconds (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,f]	none	16	17	-	MD **4.4 lower** (11.4 lower to 2.6 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test - 4 weeks - Long-term storage (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,g]	none	16	17	-	MD **6.7 higher** (6.16 lower to 19.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test - 4 weeks - Consistent long-term retrieval (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,h]	none	16	17	-	MD **9.1 higher** (6.74 lower to 24.94 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test - 4 weeks - Delayed recall (follow up: 4 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	control (waitlist control), 4 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,i]	none	16	17	-	MD **1.22 higher** (1.16 lower to 3.6 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Word List Generation - 4 weeks (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,j]	none	16	17	-	MD **2.2 lower** (7.73 lower to 3.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 4 weeks - Immediate (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,k]	none	16	17	-	MD **1.2 lower** (5.18 lower to 2.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 4 weeks - Delayed (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,l]	none	16	17	-	MD **0.99 lower** (2.69 lower to 0.71 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory (scale usually 0-63) - 4 weeks (follow up: 4 weeks; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,m]	none	16	17	-	MD **2.07 lower** (8.13 lower to 3.99 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Penn State Worry Questionnaire (scale usually 16-80) - 4 weeks (follow up: 4 weeks; Scale from: 16 to 80)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,n]	none	16	17	-	MD **1.3 higher** (10.16 lower to 12.76 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	control (waitlist control), 4 weeks	Relative (95% CI)	Absolute (95% CI)		
Difficulties in Emotion Regulation (DERS, scale unclear) - 4 weeks (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,o]	none	16	17	-	MD **6.2 lower** (19.04 lower to 6.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
WHO Quality of Life and Satisfaction With Life Scale composite (z-score) - 4 weeks (follow up: 4 weeks; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,p]	none	16	17	-	MD **0.29 higher** (0.26 lower to 0.84 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence was from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±7.25

e. MIDs used to assess imprecision were ±5.44

f. MIDs used to assess imprecision were ±5.60

g. MIDs used to assess imprecision were ±9.85

h. MIDs used to assess imprecision were ±11.10

i. MIDs used to assess imprecision were ±1.59

j. MIDs used to assess imprecision were ±4.48

k. MIDs used to assess imprecision were ±2.40

l. MIDs used to assess imprecision were ±1.23

m. MIDs used to assess imprecision were ±5.63

n. MIDs used to assess imprecision were ±8.30

o. MIDs used to assess imprecision were ±10.68

p. MIDs used to assess imprecision were ±0.48

Table 17: Clinical evidence profile: Mindfulness vs. control, 12 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	control (pharma only), 12 months	Relative (95% CI)	Absolute (95% CI)		
SDMT - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	30	30	-	MD **7.54 higher** (0.18 higher to 14.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 12 months - 2 seconds (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [d]	none	30	30	-	MD **12.4 higher** (5.93 higher to 18.87 higher)	⨁⨁◯◯ LOW	CRITICAL
PASAT - 12 months - 3 seconds (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,e]	none	30	30	-	MD **10.97 higher** (4.85 higher to 17.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
COWAT verbal fluency test - 12 months - Words (FAS) (follow up: 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	control (pharma only), 12 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,f]	none	30	30	-	MD **6.76 higher** (0.57 higher to 12.95 higher)	⨁◯◯◯ VERY LOW	CRITICAL
COWAT verbal fluency test - 12 months - Names of animals (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,g]	none	30	30	-	MD **2.3 higher** (0.74 lower to 5.34 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Memory Scale - III Spanish Version - 12 months - Attention (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,h]	none	30	30	-	MD **0.16 higher** (0.89 lower to 1.21 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Memory Scale - III Spanish Version - 12 months - Long-term memory (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	30	30	-	MD **1.77 higher** (0.1 higher to 3.44 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Memory Scale - III Spanish Version - 12 months - Short-term memory (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,j]	none	30	30	-	MD **2.26 higher** (1.88 lower to 6.4 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Memory Scale - III Spanish Version - 12 months - Recognition (follow up: 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	control (pharma only), 12 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,k]	none	30	30	-	MD **2.23 higher** (0.16 higher to 4.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Memory Scale - III Spanish Version - 12 months - Learning (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,l]	none	30	30	-	MD **0.6 higher** (0.32 lower to 1.52 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory (scale usually 0-63) - 12 months (follow up: 12 months; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,m]	none	30	30	-	MD **4.67 lower** (9.34 lower to 0)	⨁◯◯◯ VERY LOW	CRITICAL
State-Trait Anxiety Inventory (unclear if state or trait subscale or both combined, scale usually 20-80 for each subscale) - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [n]	none	30	30	-	MD **2.8 lower** (14.57 lower to 8.97 higher)	⨁⨁◯◯ LOW	CRITICAL
FIM + FAM composite (functional independence and assessment measures, scale used unclear) - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,o]	none	30	30	-	MD **3.08 lower** (12.02 lower to 5.86 higher)	⨁◯◯◯ VERY LOW	CRITICAL

1 a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

3 c. MIDs used to assess imprecision were ±7.94

d. MIDs used to assess imprecision were ±5.12

e. MIDs used to assess imprecision were ±5.43

f. MIDs used to assess imprecision were ±6.75

g. MIDs used to assess imprecision were ±3.15

h. MIDs used to assess imprecision were ±0.81

i. MIDs used to assess imprecision were ±1.61

j. MIDs used to assess imprecision were ±3.59

k. MIDs used to assess imprecision were ±1.95

l. MIDs used to assess imprecision were ±1.06

m. MIDs used to assess imprecision were ±6.16

n. MIDs used to assess imprecision were ±16.68

o. MIDs used to assess imprecision were ±5.04

Table 18: Clinical evidence profile: Mindfulness vs. general cognitive rehabilitation (multi-component and multi-domain), 4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	general cogn. rehab (multi-component), 4 weeks	Relative (95% CI)	Absolute (95% CI)		
SDMT - 4 weeks (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,d]	none	16	17	-	MD **0.3 higher** (9.53 lower to 10.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 4 weeks - 2 seconds (follow up: 4 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	general cogn. rehab (multi-component), 4 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,e]	none	16	17	-	MD **0.6 lower** (7.76 lower to 6.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL

PASAT - 4 weeks - 3 seconds (follow up: 4 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,f]	none	16	17	-	MD **2.8 lower** (10.22 lower to 4.62 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Selective Reminding Test - 4 weeks - Long-term storage (follow up: 4 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,g]	none	16	17	-	MD **7.6 higher** (3.42 lower to 18.62 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Selective Reminding Test - 4 weeks - Consistent long-term retrieval (follow up: 4 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,h]	none	16	17	-	MD **12.1 higher** (1.7 lower to 25.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Selective Reminding Test - 4 weeks - Delayed recall (follow up: 4 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,i]	none	16	17	-	MD **1.16 higher** (0.91 lower to 3.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Word List Generation - 4 weeks (follow up: 4 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	general cogn. rehab (multi-component), 4 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,j]	none	16	17	-	MD **4.1 lower** (9.78 lower to 1.58 higher)	⨁◯◯◯ VERY LOW	CRITICAL

10/36 SPART (Spatial Recall Test) - 4 weeks - Immediate (follow up: 4 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,k]	none	16	17	-	MD **1.6 higher** (3.02 lower to 6.22 higher)	⨁◯◯◯ VERY LOW	CRITICAL

10/36 SPART (Spatial Recall Test) - 4 weeks - Delayed (follow up: 4 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,l]	none	16	17	-	MD **0.37 higher** (1.6 lower to 2.34 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Beck Depression Inventory (scale usually 0-63) - 4 weeks (follow up: 4 weeks; Scale from: 0 to 63)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,m]	none	16	17	-	MD **3.27 lower** (9.03 lower to 2.49 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Penn State Worry Questionnaire (scale usually 16-80) - 4 weeks (follow up: 4 weeks; Scale from: 16 to 80)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,n]	none	16	17	-	MD **4.6 lower** (14.28 lower to 5.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Difficulties in Emotion Regulation (DERS, scale unclear) - 4 weeks (follow up: 4 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	general cogn. rehab (multi-component), 4 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,o]	none	16	17	-	MD **5.7 lower** (18.61 lower to 7.21 higher)	⨁◯◯◯ VERY LOW	CRITICAL

WHO Quality of Life and Satisfaction With Life Scale composite (z-score) - 4 weeks (follow up: 4 weeks; Scale from: -5 to 5)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,p]	none	16	17	-	MD **0.39 higher** (0.16 lower to 0.95 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Adherence - completing all four weekly sessions (follow up: 4 weeks)

1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	18/20 (90.0%)	65.0%	**OR 4.85** (0.86 to 27.22)	**250 more per 1,000** (from 35 fewer to 331 more)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence came from studies that reported the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±6.83

e. MIDs used to assess imprecision were ±5.50

f. MIDs used to assess imprecision were ±5.80

g. MIDs used to assess imprecision were ±8.70

h. MIDs used to assess imprecision were ±9.40

i. MIDs used to assess imprecision were ±1.38

j. MIDs used to assess imprecision were ±4.35

k. MIDs used to assess imprecision were ±2.59

l. MIDs used to assess imprecision were ±1.16

m. MIDs used to assess imprecision were ±4.36

n. MIDs used to assess imprecision were ±7.55

o. MIDs used to assess imprecision were ±10.69

p. MIDs used to assess imprecision were ±0.47

Table 19: Clinical evidence profile: Mindfulness vs. medical treatment and counselling, 8 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	medical treatment and counselling, 8 weeks	Relative (95% CI)	Absolute (95% CI)		
Wechsler Adult Intelligence Scale-Revised (WAIS-R) - symbol coding test (follow up: 16 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	27	26	-	MD **4.52 higher** (0.84 lower to 9.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Adult Intelligence Scale-Revised (WAIS-R) - digit span test (follow up: 16 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	27	26	-	MD **1.36 higher** (0.62 higher to 2.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Rey Complex Figure Test - recall (follow up: 16 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	medical treatment and counselling, 8 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,e]	none	27	26	-	MD **1.97 higher** (0.39 lower to 4.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL

PASAT 3 seconds (follow up: 16 weeks)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,f]	none	27	26	-	MD **10.5 higher** (3.67 higher to 17.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL

PASAT 2 seconds (follow up: 16 weeks)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,g]	none	27	26	-	MD **6.19 higher** (1.29 higher to 11.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Wisconsin Card Sorting Test - category (follow up: 16 weeks)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,h]	none	27	26	-	MD **0.65 higher** (0.45 lower to 1.75 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Wisconsin Card Sorting Test - perseveration (follow up: 16 weeks)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	27	26	-	MD **4.78 lower** (7.1 lower to 2.46 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Wisconsin Card Sorting Test - conception responses (follow up: 16 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	medical treatment and counselling, 8 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,j]	none	27	26	-	MD **0.89 higher** (0.42 lower to 2.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Wisconsin Card Sorting Test - total correct (follow up: 16 weeks)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,k]	none	27	26	-	MD **6.19 higher** (1.29 higher to 11.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Wisconsin Card Sorting Test - number of errors (follow up: 16 weeks)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,l]	none	27	26	-	MD **7.41 lower** (12.06 lower to 2.76 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Wisconsin Card Sorting Test - other errors (follow up: 16 weeks)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,m]	none	27	26	-	MD **2.65 lower** (5.97 lower to 0.67 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Wisconsin Card Sorting Test - first trial (follow up: 16 weeks)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,n]	none	27	26	-	MD **3.96 lower** (10.37 lower to 2.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Hamilton Anxiety Scale (scale 0-56) (follow up: 16 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	medical treatment and counselling, 8 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious [o]	none	27	26	-	MD **6.56 lower** (9.27 lower to 3.85 lower)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±4.45

d. MIDs used to assess imprecision were ±0.72

e. MIDs used to assess imprecision were ±2.57

f. MIDs used to assess imprecision were ±5.59

g. MIDs used to assess imprecision were ±3.93

h. MIDs used to assess imprecision were ±0.80

i. MIDs used to assess imprecision were ±2.59

j. MIDs used to assess imprecision were ±1.27

k. MIDs used to assess imprecision were ±3.93

l. MIDs used to assess imprecision were ±4.18

m. MIDs used to assess imprecision were ±2.43

n. MIDs used to assess imprecision were ±9.28

o. MIDs used to assess imprecision were ±2.68

Table 20: Clinical evidence profile: Information processing speed: cognitive rehabilitation software focused on processing speed + occupational therapy vs. occupational therapy only, 3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Info processing speed: cogn. rehab focused on processing speed + occupational therapy	occupational therapy alone, 3 months	Relative (95% CI)	Absolute (95% CI)		
SDMT - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	31	33	-	MD **3.44 higher** (1.87 lower to 8.75 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 3 months (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	31	33	-	MD **5.93 higher** (0.54 lower to 12.4 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±5.54

d. MIDs used to assess imprecision were ±6.81

Table 21: Clinical evidence profile: Information processing speed: cognitive rehabilitation software focused on processing speed vs. control (active game or no intervention), 5-6 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Info processing speed: cogn. rehab software focused on processing speed	control (active game or no intervention), 5-6 weeks	Relative (95% CI)	Absolute (95% CI)		
SDMT - 6 weeks (change from baseline) (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	20	20	-	MD **2.55 higher** (1.31 lower to 6.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Adult Intelligence Scale-III - Digit Symbol Coding Subtest - 5 weeks (follow up: 5 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,e]	none	12	9	-	MD **2.06 higher** (0.16 lower to 4.28 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 6 weeks (change from baseline) (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [f]	none	18	19	-	MD **0.19 higher** (3.9 lower to 4.28 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Brief Visuospatial Memory Test-Revised (BVMT-R) - 6 weeks (change from baseline) (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,g]	none	20	20	-	MD **2.55 lower** (5.57 lower to 0.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test-II (CVLT-II) - 6 weeks (change from baseline) - Number correct (follow up: 6 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Info processing speed: cogn. rehab software focused on processing speed	control (active game or no intervention), 5-6 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,h]	none	20	20	-	MD **3.15 lower** (8.65 lower to 2.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test-II (CVLT-II) - 5- weeks - Learning slope (follow up: 5 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,i]	none	12	9	-	MD **0.18 higher** (0.25 lower to 0.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test-II (CVLT-II) - 5 weeks - Short-delay free recall (follow up: 5 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,j]	none	12	9	-	MD **2.1 higher** (1.24 lower to 5.44 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Letter comparison (perceptual speed) - 5 weeks (follow up: 5 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,k]	none	12	9	-	MD **1.35 higher** (0.81 lower to 3.51 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pattern comparison (perceptual speed) - 5 weeks (follow up: 5 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c,l]	none	12	9	-	MD **1.65 higher** (1.68 lower to 4.98 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Perceived Deficits Questionnaire (5-item, scale usually 0-80) - 6 weeks (change from baseline) (follow up: 6 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Info processing speed: cogn. rehab software focused on processing speed	control (active game or no intervention), 5-6 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,m]	none	14	11	-	MD **1.07 higher** (0.1 lower to 2.24 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Timed Instrumental Activities of Daily Living Test (TIADL - z-score for speed and accuracy combined) - 5 weeks (follow up: 5 weeks; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,n]	none	12	9	-	MD **0.61 higher** (0.09 higher to 1.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL
CES-D depression (scale usually 0-60) - 6 weeks (change from baseline) (follow up: 6 weeks; Scale from: 0 to 60)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,o]	none	19	19	-	MD **2.01 higher** (1.72 lower to 5.74 higher)	⨁◯◯◯ VERY LOW	CRITICAL
State-Trait Anxiety Index - State sub score (STAI-S; scale usually 20-80) - 6 weeks (change from baseline) (follow up: 6 weeks; Scale from: 20 to 80)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,p]	none	19	19	-	MD **0.16 lower** (4.69 lower to 4.37 higher)	⨁◯◯◯ VERY LOW	CRITICAL
State-Trait Anxiety Index - Trait sub score (STAI-T; scale usually 20-80) - 6 weeks (change from baseline) (follow up: 6 weeks; Scale from: 20 to 80)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,q]	none	17	17	-	MD **0.42 higher** (2.1 lower to 2.94 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Info processing speed: cogn. rehab software focused on processing speed	control (active game or no intervention), 5-6 weeks	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact Scale (MFIS; scale usually 0-84) - 6 weeks (change from baseline) (follow up: 6 weeks; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	very serious [b,r]	not serious [s]	none	19	19	-	MD **1.84 lower** (6.98 lower to 3.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL

1 a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 b. Downgraded by 1 increment as the majority of the evidence came from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

3 c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

4 d. MIDs used to assess imprecision were ±4.05

5 e. MIDs used to assess imprecision were ±1.24

6 f. MIDs used to assess imprecision were ±5.58

7 g. MIDs used to assess imprecision were ±2.78

8 h. MIDs used to assess imprecision were ±4.95

9 i. MIDs used to assess imprecision were ±0.27

10 j. MIDs used to assess imprecision were ±1.97

11 k. MIDs used to assess imprecision were ±1.49

12 l. MIDs used to assess imprecision were ±1.63

13 m. MIDs used to assess imprecision were ±1.53

14 n. MIDs used to assess imprecision were ±0.39

15 o. MIDs used to assess imprecision were ±5.03

p. MIDs used to assess imprecision were ±3.80

q. MIDs used to assess imprecision were ±1.60

r. Downgraded by 1 increment as general Modified Fatigue Impact Scale reported rather than specifically the cognitive subdomain

s. MIDs used to assess imprecision were ±8.30

Table 22: Clinical evidence profile: Information processing speed + working memory: n-back training focused on processing speed + working memory vs. sham training (n-back with no increasing difficulty), 6 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Info processing speed + working memory: n-back training focused on processing speed + working memory	sham training (n-back with no increasing difficulty), 6 weeks	Relative (95% CI)	Absolute (95% CI)		
SDMT - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,d]	none	20	20	-	MD **0.35 higher** (7.99 lower to 8.69 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	20	20	-	MD **11.38 higher** (2.25 lower to 25.01 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Stroop Test - 6 weeks (follow up: 6 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Info processing speed + working memory: n-back training focused on processing speed + working memory	sham training (n-back with no increasing difficulty), 6 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,f]	none	20	20	-	MD **3.44 higher** (1.23 lower to 8.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL

COWAT - 6 weeks (follow up: 6 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,g]	none	20	20	-	MD **4.2 higher** (4.93 lower to 13.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Letter-Number Sequencing - 6 weeks (follow up: 6 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,h]	none	20	20	-	MD **0.2 higher** (1.45 lower to 1.85 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Digits backwards - 6 weeks (follow up: 6 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,i]	none	20	20	-	MD **0.05 lower** (1.29 lower to 1.19 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Raven's Advanced Progressive Matrices (test of fluid intelligence) - 6 weeks (follow up: 6 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,j]	none	20	20	-	MD **1.12 lower** (3.56 lower to 1.32 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Brief Visuospatial Memory Test (BVMT) - Trials 1-3 - 6 weeks (follow up: 6 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Info processing speed + working memory: n-back training focused on processing speed + working memory	sham training (n-back with no increasing difficulty), 6 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,k]	none	20	20	-	MD **1.4 higher** (2.27 lower to 5.07 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Conners' Continuous Performance Task Commissions - Speed (measures sustained attention and response inhibition, T-score) - 6 weeks (follow up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,l]	none	20	20	-	MD **1.5 lower** (8.41 lower to 5.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Auditory Verbal Learning Task (AVLT) - Trials 1-5 - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,m]	none	20	20	-	MD **6.7 higher** (0.15 higher to 13.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQoL-54 (scale usually 0-100) - 6 weeks (follow up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,n]	none	20	20	-	MD **4.95 lower** (13.62 lower to 3.72 higher)	⨁◯◯◯ VERY LOW	CRITICAL
State-Trait Anxiety Inventory - State subscale (STAI; scale usually 20-80) - 6 weeks (follow up: 6 weeks; Scale from: 20 to 80)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,o]	none	20	20	-	MD **1.27 higher** (2.46 lower to 5 higher)	⨁◯◯◯ VERY LOW	CRITICAL
State-Trait Anxiety Inventory - Trait subscale (STAI; scale usually 20-80) - 6 weeks (follow up: 6 weeks; Scale from: 20 to 80)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Info processing speed + working memory: n-back training focused on processing speed + working memory	sham training (n-back with no increasing difficulty), 6 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,p]	none	20	20	-	MD **0.86 higher** (2.5 lower to 4.22 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory-Fast Screen (scale usually 0-21) - 6 weeks (follow up: 6 weeks; Scale from: 0 to 21)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,q]	none	20	20	-	MD **1.4 higher** (0.23 lower to 3.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale (MFIS; scale usually 0-84) - 6 weeks (follow up: 6 weeks; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	very serious [b,r]	very serious [c,s]	none	20	20	-	MD **0.35 higher** (10.95 lower to 11.65 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence - % training completed (objective report) - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,t]	none	20	20	-	MD **0.67 lower** (8.29 lower to 6.95 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Satisfaction - proportion very satisfied with overall study experience (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	12/20 (60.0%)	85.0%	**OR 0.26** (0.06 to 1.21)	**254 fewer per 1,000** (from 596 fewer to 23 more)	⨁◯◯◯ VERY LOW	CRITICAL

1 a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence came from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±6.96

e. MIDs used to assess imprecision were ±10.78

f. MIDs used to assess imprecision were ±3.70

g. MIDs used to assess imprecision were ±6.31

h. MIDs used to assess imprecision were ±1.39

i. MIDs used to assess imprecision were ±0.93

j. MIDs used to assess imprecision were ±2.04

k. MIDs used to assess imprecision were ±2.98

l. MIDs used to assess imprecision were ±5.14

m. MIDs used to assess imprecision were ±4.76

n. MIDs used to assess imprecision were ±7.36

o. MIDs used to assess imprecision were ±3.12

p. MIDs used to assess imprecision were ±2.61

q. MIDs used to assess imprecision were ±1.62

r. Downgraded by 1 increment as general Modified Fatigue Impact Scale reported rather than specifically the cognitive subdomain

s. MIDs used to assess imprecision were ±7.20

t. MIDs used to assess imprecision were ±6.01 (based on 0.5 multiplied by the SD of the value in the control group as no baseline values available for this outcome)

Table 23: Clinical evidence profile: Attention/working memory: computer-aided RehaCom training (attention and information processing) vs. active control, 6 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: computer-aided RehaCom training (attention and info processing)	active control, 6 weeks	Relative (95% CI)	Absolute (95% CI)		
SDMT - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,d]	none	12	11	-	MD **1.39 higher** (6.11 lower to 8.89 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT 3 seconds - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,e]	none	12	11	-	MD **0.23 higher** (8.64 lower to 9.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective reminding test (SRT) - 6 weeks - Long-term storage (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,f]	none	12	11	-	MD **7 higher** (2.12 lower to 16.12 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective reminding test (SRT) - 6 weeks - Consistent long-term retrieval (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,g]	none	12	11	-	MD **7.76 higher** (0.16 higher to 15.36 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective reminding test (SRT) - 6 weeks - Delayed recall (follow up: 6 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: computer-aided RehaCom training (attention and info processing)	active control, 6 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,h]	none	12	11	-	MD **0.91 higher** (1.53 lower to 3.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL

10/36 SPART (Spatial Recall Test) - 6 weeks - Immediate (follow up: 6 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,i]	none	12	11	-	MD **5.88 lower** (10.12 lower to 1.64 lower)	⨁◯◯◯ VERY LOW	CRITICAL

10/36 SPART (Spatial Recall Test) - 6 weeks - Delayed (follow up: 6 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,j]	none	12	11	-	MD **2.72 lower** (4.51 lower to 0.93 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Word List Generation - 6 weeks (follow up: 6 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,k]	none	12	11	-	MD **0.2 higher** (4.52 lower to 4.92 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Stroop Test - 6 weeks (follow up: 6 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	12	11	-	MD **2.91 higher** (1.33 lower to 7.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Trail Making Test - 6 weeks - Part A (follow up: 6 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: computer-aided RehaCom training (attention and info processing)	active control, 6 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,l]	none	12	11	-	MD **3.93 higher** (7.15 lower to 15.01 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Trail Making Test - 6 weeks - Part B (follow up: 6 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,m]	none	12	11	-	MD **0.2 lower** (30.99 lower to 30.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Trail Making Test - 6 weeks - Part B-A (follow up: 6 weeks)

1	randomised trials	very serious [b]	not serious	serious [b]	very serious [c,n]	none	12	11	-	MD **0.82 lower** (27.3 lower to 25.66 higher)	⨁◯◯◯ VERY LOW	CRITICAL

State-Trait Anxiety Inventory Y1 (State?; scale usually 20-80) - 6 weeks (follow up: 6 weeks; Scale from: 20 to 80)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,o]	none	12	11	-	MD **4.4 lower** (12.67 lower to 3.87 higher)	⨁◯◯◯ VERY LOW	CRITICAL

State-Trait Anxiety Inventory Y2 (Trait?; scale usually 20-80) - 6 weeks (follow up: 6 weeks; Scale from: 20 to 80)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,p]	none	12	11	-	MD **10.5 lower** (18.67 lower to 2.33 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Beck Depression Inventory-II (scale usually 0-63) - 6 weeks (follow up: 6 weeks; Scale from: 0 to 63)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: computer-aided RehaCom training (attention and info processing)	active control, 6 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,q]	none	12	11	-	MD **8.47 lower** (16.65 lower to 0.29 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Fatigue severity scale (FSS; scale likely 1-7) - 6 weeks (follow up: 6 weeks; Scale from: 1 to 7)

1	randomised trials	very serious [a]	not serious	very serious [b,r]	serious [c,s]	none	12	11	-	MD **1.39 lower** (2.78 lower to 0)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence comes from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±2.69

e. MIDs used to assess imprecision were ±5.04

f. MIDs used to assess imprecision were ±5.40

g. MIDs used to assess imprecision were ±5.82

h. MIDs used to assess imprecision were ±1.19

i. MIDs used to assess imprecision were ±2.20

j. MIDs used to assess imprecision were ±0.98

k. MIDs used to assess imprecision were ±1.60

l. MIDs used to assess imprecision were ±7.72

m. MIDs used to assess imprecision were ±25.47

n. MIDs used to assess imprecision were ±22.39

o. MIDs used to assess imprecision were ±4.47

p. MIDs used to assess imprecision were ±4.53

q. MIDs used to assess imprecision were ±2.06

r. Downgraded by 1 increment as general Fatigue Severity Scale reported rather than cognitive fatigue specifically

s. MIDs used to assess imprecision were ±0.88

Table 24: Clinical evidence profile: Attention/working memory: computer-aided training for attention/working memory vs. control, 18 weeks – 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: computer-aided training of attention/working memory	control, 18 weeks - 6 months	Relative (95% CI)	Absolute (95% CI)		
SDMT - 18 weeks - 6 months (mix of final values and change from baseline) (follow up: 18 weeks - 6 months)												
2	randomised trials	serious [a]	not serious	not serious	serious [b,c]	none	28	25	-	MD **1.14 lower** (4.82 lower to 2.54 higher)	⨁⨁◯◯ LOW	CRITICAL
PASAT - 6 months (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,d]	none	11	11	-	MD **1.27 higher** (8.32 lower to 10.86 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: computer-aided training of attention/working memory	control, 18 weeks - 6 months	Relative (95% CI)	Absolute (95% CI)		
California Verbal Learning Test-II (CVLT-II) Total Immediate Recall - 18-weeks - 6 months (follow up: 18 weeks - 6 months)												
2	randomised trials	serious [a]	not serious	not serious	serious [b,e]	none	28	25	-	MD **0.12 lower** (5.19 lower to 4.95 higher)	⨁⨁◯◯ LOW	CRITICAL
Brief Visuospatial Memory Test – Revised (BVMT-R) Total Immediate Recall - 18 weeks - 6 months (follow up: 18 weeks - 6 months)												
2	randomised trials	serious [a]	not serious	not serious	serious [b,f]	none	28	25	-	MD **2.88 higher** (0.46 lower to 6.22 higher)	⨁⨁◯◯ LOW	CRITICAL
Wechsler Memory Scale-III Spatial Span - 6 months - Forward (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,g]	none	11	11	-	MD **0.73 lower** (1.86 lower to 0.4 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Memory Scale-III Spatial Span - 6 months - Backward (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,h]	none	11	11	-	MD **0.27 lower** (1.6 lower to 1.06 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Adult Intelligence Scale-III - 6 months - Arithmetic (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	11	11	-	MD **1 higher** (1.35 lower to 3.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: computer-aided training of attention/working memory	control, 18 weeks - 6 months	Relative (95% CI)	Absolute (95% CI)		
Wechsler Adult Intelligence Scale-III - 6 months - Letter-Number Sequencing (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,j]	none	11	11	-	MD **0.63 higher** (1.84 lower to 3.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Adult Intelligence Scale-III - 6 months - Digit span forward (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,k]	none	11	11	-	MD **0.36 higher** (1.33 lower to 2.05 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wechsler Adult Intelligence Scale-III - 6 months - Digit span backward (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,l]	none	11	11	-	MD **0.73 higher** (0.61 lower to 2.07 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Delis-Kaplan Executive Function System (DKEFS) - Color-Word Interference - 6 months (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,m]	none	11	11	-	MD **1.46 lower** (8.37 lower to 5.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
N-back test errors - 18 weeks - 0-back errors (follow up: 18 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: computer-aided training of attention/working memory	control, 18 weeks - 6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,n]	none	17	14	-	MD **0.11 lower** (2.28 lower to 2.06 higher)	⨁⨁◯◯ LOW	CRITICAL
N-back test errors - 18 weeks - 1-back errors (follow up: 18 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [o]	none	17	14	-	MD **0.92 higher** (0.95 lower to 2.79 higher)	⨁⨁◯◯ LOW	CRITICAL
N-back test errors - 18 weeks - 2-back errors (follow up: 18 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,p]	none	17	14	-	MD **0.53 lower** (3.92 lower to 2.86 higher)	⨁⨁◯◯ LOW	CRITICAL
Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ; scale usually 0-60) - 18 weeks - 6 months (follow up: 18 weeks - 6 months; Scale from: 0 to 60)												
2	randomised trials	very serious [a]	not serious	not serious	very serious [b,q]	none	28	25	-	MD **0.47 lower** (7.86 lower to 6.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive Failure Questionnaire (CFQ; scale usually 0-100) - 6 months (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,r]	none	11	11	-	MD **6.81 higher** (11.97 lower to 25.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Dysexecutive questionnaire (DEX; scale usually 0-80) - 6 months (follow up: 6 months; Scale from: 0 to 80)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: computer-aided training of attention/working memory	control, 18 weeks - 6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,s]	none	11	11	-	MD **2.54 higher** (9.71 lower to 14.79 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Perceived Deficits Questionnaire (PDQ; scale usually 0-80) - 6 months (follow up: 6 months; Scale from: 0 to 80)

1	randomised trials	very serious [a]	not serious	not serious	very serious [b,t]	none	11	11	-	MD **7.09 higher** (9.96 lower to 24.14 higher)	⨁◯◯◯ VERY LOW	CRITICAL

SF-36 quality of life (unclear which subscale or composite of physical and mental health) - 6 months (follow up: 6 months; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,u]	none	11	11	-	MD **11.9 higher** (4.06 lower to 27.86 higher)	⨁◯◯◯ VERY LOW	CRITICAL

EQ-5D (scale 0-1) - 18 weeks (follow up: 18 weeks; Scale from: 0 to 1)

1	randomised trials	very serious [a]	not serious	not serious	very serious [b,v]	none	17	14	-	MD **0.04 lower** (0.21 lower to 0.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Functional Assessment of MS (FAMS; scale usually 0-176) - 18 weeks (follow up: 18 weeks; Scale from: 0 to 176)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,w]	none	17	14	-	MD **12 lower** (34.47 lower to 10.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: computer-aided training of attention/working memory	control, 18 weeks - 6 months	Relative (95% CI)	Absolute (95% CI)		
Beck Depression Inventory-Fast Screen (scale usually 0-21) - 6 months (follow up: 6 months; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,x]	none	11	11	-	MD **0.09 lower** (2.93 lower to 2.75 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Hospital Anxiety and Depression Scale (HADS; scale usually 0-21) - 18 weeks - 6 months - Anxiety (follow up: 18 weeks - 6 months; Scale from: 0 to 21)												
2	randomised trials	very serious [a]	not serious	not serious	serious [b,y]	none	28	25	-	MD **1.39 higher** (1.14 lower to 3.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Hospital Anxiety and Depression Scale (HADS; scale usually 0-21) - 18 weeks - 6 months - Depression (follow up: 18 weeks - 6 months; Scale from: 0 to 21)												
2	randomised trials	very serious [a]	not serious	not serious	very serious [b,z]	none	28	25	-	MD **0.25 higher** (1.72 lower to 2.21 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (FSS; scale likely 1-7) - 6 months (follow up: 6 months; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	serious [aa]	very serious [ab,b]	none	11	11	-	MD **0.29 lower** (1.82 lower to 1.24 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (9-63 scale) - 18 weeks (follow up: 18 weeks; Scale from: 9 to 63)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: computer-aided training of attention/working memory	control, 18 weeks - 6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [aa]	very serious [ac,b]	none	17	14	-	MD **3.24 higher** (6.54 lower to 13.02 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Patient Activation Measure-13 (PAM-13; measures engagement in health; scale usually 0-100) - 18 weeks (follow up: 18 weeks; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	not serious	serious [ad,b]	none	17	14	-	MD **3.31 lower** (14.44 lower to 7.82 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Unidimensional Self-Efficacy scale for MS (USE-MS; scale unclear) - 18 weeks (follow up: 18 weeks)

1	randomised trials	very serious [a]	not serious	not serious	serious [ae,b]	none	17	14	-	MD **2.84 lower** (8.14 lower to 2.46 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±4.38

d. MIDs used to assess imprecision were ±6.77

e. MIDs used to assess imprecision were ±4.95

f. MIDs used to assess imprecision were ±3.61

g. MIDs used to assess imprecision were ±0.85

h. MIDs used to assess imprecision were ±1.01

i. MIDs used to assess imprecision were ±1.66

j. MIDs used to assess imprecision were ±1.45

k. MIDs used to assess imprecision were ±0.92

l. MIDs used to assess imprecision were ±0.64

m. MIDs used to assess imprecision were ±3.86

n. MIDs used to assess imprecision were ±2.09

o. MIDs used to assess imprecision were ±2.98

p. MIDs used to assess imprecision were ±3.66

q. MIDs used to assess imprecision were ±6.20

r. MIDs used to assess imprecision were ±8.43

s. MIDs used to assess imprecision were ±6.98

t. MIDs used to assess imprecision were ±6.71

u. MIDs used to assess imprecision were ±9.12

v. MIDs used to assess imprecision were ±0.09

w. MIDs used to assess imprecision were ±14.42

x. MIDs used to assess imprecision were ±1.42

y. MIDs used to assess imprecision were ±1.84

z. MIDs used to assess imprecision were ±1.69

aa. Downgraded by 1 increment as general Fatigue Severity Scale reported rather than specifically cognitive fatigue

ab. MIDs used to assess imprecision were ±0.73

ac. MIDs used to assess imprecision were ±6.27

ad. MIDs used to assess imprecision were ±7.95

ae. MIDs used to assess imprecision were ±3.14

Table 25: Clinical evidence profile: Attention/working memory: high-intensity working memory training vs. distributed working memory training, 4-8 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: high-intensity working memory training	distributed working memory training, 4-8 weeks	Relative (95% CI)	Absolute (95% CI)		
SDMT - 4-8 weeks (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	15	15	-	MD **8.35 lower** (19.45 lower to 2.75 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 4-8 weeks (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	15	15	-	MD **3.2 lower** (8.13 lower to 1.73 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Corsi blocks - 4-8 weeks - Backward (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,f]	none	15	15	-	MD **0.46 lower** (1.76 lower to 0.84 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Corsi blocks - 4-8 weeks - Forward (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,g]	none	15	15	-	MD **0.53 lower** (1.94 lower to 0.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Digit Span - 4-8 weeks - Backward (follow up: 4-8 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: high-intensity working memory training	distributed working memory training, 4-8 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,h]	none	15	15	-	MD **0.46 higher** (1.03 lower to 1.95 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Digit Span - 4-8 weeks - Forward (follow up: 4-8 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,i]	none	15	15	-	MD **0.46 lower** (1.76 lower to 0.84 higher)	⨁◯◯◯ VERY LOW	CRITICAL

2-back number correct - 4-8 weeks (follow up: 4-8 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,j]	none	15	15	-	MD **2.26 lower** (5.15 lower to 0.63 higher)	⨁◯◯◯ VERY LOW	CRITICAL

2-back omissions - 4-8 weeks (follow up: 4-8 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	not serious [k]	none	15	15	-	MD **0.34 higher** (0.05 lower to 0.73 higher)	⨁◯◯◯ VERY LOW	CRITICAL

2-back reaction time - 4-8 weeks (follow up: 4-8 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,l]	none	15	15	-	MD **101.26 higher** (67.23 lower to 269.75 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Faces Symbol Test - 4-8 weeks (follow up: 4-8 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: high-intensity working memory training	distributed working memory training, 4-8 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,m]	none	15	15	-	MD **0.41 higher** (0.11 lower to 0.93 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional Assessment of MS (FAMS; scale usually 0-176) - 4-8 weeks (follow up: 4-8 weeks; Scale from: 0 to 176)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,n]	none	15	15	-	MD **15.59 lower** (35.23 lower to 4.05 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Allgemeine Depressionsskala (scale unclear) - 4-8 weeks (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,o]	none	15	15	-	MD **1.95 higher** (5.25 lower to 9.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Scale for Motor and Cognitive Functions (FSMC; scale usually 20-100) - 4-8 weeks (follow up: 4-8 weeks; Scale from: 20 to 100)												
1	randomised trials	very serious [a]	not serious	very serious [b,p]	very serious [c,q]	none	15	15	-	MD **3.73 higher** (11.04 lower to 18.5 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale (MFIS; scale usually 0-84) - 4-8 weeks (follow up: 4-8 weeks; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	very serious [b,r]	very serious [c,s]	none	15	15	-	MD **0.1 lower** (13.37 lower to 13.17 higher)	⨁◯◯◯ VERY LOW	CRITICAL

1 a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence comes from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±6.13

e. MIDs used to assess imprecision were ±4.05

f. MIDs used to assess imprecision were ±0.69

g. MIDs used to assess imprecision were ±0.81

h. MIDs used to assess imprecision were ±1.04

i. MIDs used to assess imprecision were ±0.74

j. MIDs used to assess imprecision were ±1.68

k. MIDs used to assess imprecision were ±0.92

l. MIDs used to assess imprecision were ±142.13

m. MIDs used to assess imprecision were ±0.41

n. MIDs used to assess imprecision were ±13.11

o. MIDs used to assess imprecision were ±4.20

p. Downgraded by 1 increment as reported general FSMC score and not specifically the cognitive subdomain

q. MIDs used to assess imprecision were ±10.43

r. Downgraded by 1 increment as reported general MFIS score and not specifically the cognitive subdomain

s. MIDs used to assess imprecision were ±8.65

1 **Table 26: Clinical evidence profile: Attention/working memory: high-intensity working memory training vs. control (no training), 4 weeks**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: high-intensity working memory training	control (no training), 4 weeks	Relative (95% CI)	Absolute (95% CI)		
SDMT - 4 weeks (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	15	15	-	MD **4.8 lower** (17.06 lower to 7.46 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 4 weeks (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	15	15	-	MD **1.88 higher** (5.02 lower to 8.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Corsi blocks - 4 weeks - Backward (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,f]	none	15	15	-	MD **0.74 higher** (0.62 lower to 2.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Corsi blocks - 4 weeks - Forward (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,g]	none	15	15	-	MD **1.6 lower** (2.88 lower to 0.32 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Digit Span - 4 weeks - Backward (follow up: 4 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: high-intensity working memory training	control (no training), 4 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,h]	none	15	15	-	MD **1.47 higher** (0.1 lower to 3.04 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Digit Span - 4 weeks - Forward (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [i]	none	15	15	-	MD **2.14 higher** (0.83 higher to 3.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back number correct - 4 weeks (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,j]	none	15	15	-	MD **0.2 lower** (3.04 lower to 2.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back omissions - 4 weeks (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,k]	none	15	15	-	MD **0.13 lower** (0.81 lower to 0.55 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back reaction time - 4 weeks (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,l]	none	15	15	-	MD **5.59 higher** (184.07 lower to 195.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Faces Symbol Test - 4 weeks (follow up: 4 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: high-intensity working memory training	control (no training), 4 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,m]	none	15	15	-	MD **0.05 higher** (0.54 lower to 0.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Functional Assessment of MS (FAMS; scale usually 0-176) - 4 weeks (follow up: 4 weeks; Scale from: 0 to 176)

1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,n]	none	15	15	-	MD **4.32 lower** (28.25 lower to 19.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Allgemeine Depressionsskala (scale unclear) - 4 weeks (follow up: 4 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,o]	none	15	15	-	MD **0.65 lower** (8.96 lower to 7.66 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Fatigue Scale for Motor and Cognitive Functions (FSMC; scale usually 20-100) - 4 weeks (follow up: 4 weeks; Scale from: 20 to 100)

1	randomised trials	very serious [a]	not serious	very serious [b,p]	very serious [c,q]	none	15	15	-	MD **3.33 lower** (16.16 lower to 9.5 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Modified Fatigue Impact Scale (MFIS; scale usually 0-84) - 4 weeks (follow up: 4 weeks; Scale from: 0 to 84)

1	randomised trials	very serious [a]	not serious	very serious [b,r]	serious [c,s]	none	15	15	-	MD **3.4 lower** (12.92 lower to 6.12 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence came from studies that reported the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±7.59

e. MIDs used to assess imprecision were ±5.07

f. MIDs used to assess imprecision were ±0.77

g. MIDs used to assess imprecision were ±1.00

h. MIDs used to assess imprecision were ±0.82

i. MIDs used to assess imprecision were ±0.68

j. MIDs used to assess imprecision were ±1.74

k. MIDs used to assess imprecision were ±0.61

l. MIDs used to assess imprecision were ±130.20

m. MIDs used to assess imprecision were ±0.46

n. MIDs used to assess imprecision were ±15.49

o. MIDs used to assess imprecision were ±5.11

p. Downgraded by 1 increment as general FSMC score reported rather than the cognitive subdomain

q. MIDs used to assess imprecision were ±8.85

r. Downgraded by 1 increment as general MFIS score reported rather than the cognitive subdomain

s. MIDs used to assess imprecision were ±8.34

Table 27: Clinical evidence profile: Attention/working memory: distributed working memory training vs. control (no training), 4-8 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: distributed working memory training	control (no training), 4-8 weeks	Relative (95% CI)	Absolute (95% CI)		
SDMT - 4-8 weeks (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,d]	none	15	15	-	MD **3.55 higher** (9.17 lower to 16.27 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 4-8 weeks (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	15	15	-	MD **5.08 higher** (1.23 lower to 11.39 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Corsi blocks - 4-8 weeks - Backward (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,f]	none	15	15	-	MD **1.2 higher** (0 to 2.4 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Corsi blocks - 4-8 weeks - Forward (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,g]	none	15	15	-	MD **0.4 lower** (1.39 lower to 0.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Digit Span - 4-8 weeks - Backward (follow up: 4-8 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: distributed working memory training	control (no training), 4-8 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,h]	none	15	15	-	MD **1.01 higher** (0.32 lower to 2.34 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Digit Span - 4-8 weeks - Forward (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,i]	none	15	15	-	MD **1 higher** (0.28 lower to 2.28 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back number correct - 4-8 weeks (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,j]	none	15	15	-	MD **2.06 higher** (0.8 lower to 4.92 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back omissions - 4-8 weeks (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,k]	none	15	15	-	MD **0.47 lower** (1.05 lower to 0.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back reaction time - 4-8 weeks (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,l]	none	15	15	-	MD **95.67 lower** (258.27 lower to 66.93 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Faces Symbol Test - 4-8 weeks (follow up: 4-8 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: distributed working memory training	control (no training), 4-8 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,m]	none	15	15	-	MD **0.36 lower** (0.95 lower to 0.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional Assessment of MS (FAMS; scale usually 0-176) - 4-8 weeks (follow up: 4-8 weeks; Scale from: 0 to 176)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,n]	none	15	15	-	MD **11.27 higher** (7.79 lower to 30.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Allgemeine Depressionsskala (scale unclear) - 4-8 weeks (follow up: 4-8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,o]	none	15	15	-	MD **2.6 lower** (9.28 lower to 4.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Scale for Motor and Cognitive Functions (FSMC; scale usually 20-100) - 4-8 weeks (follow up: 4-8 weeks; Scale from: 20 to 100)												
1	randomised trials	very serious [a]	not serious	very serious [b,p]	serious [c,q]	none	15	15	-	MD **7.06 lower** (21.06 lower to 6.94 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale (MFIS; scale usually 0-84) - 4-8 weeks (follow up: 4-8 weeks; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	very serious [b,r]	serious [c,s]	none	15	15	-	MD **3.3 lower** (13.91 lower to 7.31 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence comes from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±6.95

e. MIDs used to assess imprecision were ±4.61

f. MIDs used to assess imprecision were ±0.67

g. MIDs used to assess imprecision were ±0.81

h. MIDs used to assess imprecision were ±0.92

i. MIDs used to assess imprecision were ±0.66

j. MIDs used to assess imprecision were ±2.12

k. MIDs used to assess imprecision were ±0.77

l. MIDs used to assess imprecision were ±124.28

m. MIDs used to assess imprecision were ±0.40

n. MIDs used to assess imprecision were ±13.90

o. MIDs used to assess imprecision were ±4.26

p. Downgraded by 1 increment as general FSMC score reported rather than the cognitive subdomain

q. MIDs used to assess imprecision were ±9.98

r. Downgraded by 1 increment as general MFIS score reported rather than the cognitive subdomain

s. MIDs used to assess imprecision were ±9.52

Table 28: Clinical evidence profile: Attention/working memory: Attention Processing Training (APT) + multidisciplinary rehabilitation vs. multidisciplinary rehabilitation only, 3-6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: Attention Processing Training (APT) + multidisciplinary rehabilitation	multidisciplinary rehabilitation only, 3-6 months	Relative (95% CI)	Absolute (95% CI)		
SDMT - 6 months (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,c]	none	17	17	-	MD **0.8 lower** (5.51 lower to 3.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 6 months - 2 seconds (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,d]	none	17	17	-	MD **0.8 lower** (5.17 lower to 3.57 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT - 6 months - 3 seconds (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,e]	none	17	17	-	MD **0.6 higher** (5.41 lower to 6.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test (SRT) - 6 months - Long-term storage (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,f]	none	17	17	-	MD **0.4 higher** (4.35 lower to 5.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Selective Reminding Test (SRT) - 6 months - Delayed recall (follow up: 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: Attention Processing Training (APT) + multidisciplinary rehabilitation	multidisciplinary rehabilitation only, 3-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,g]	none	17	17	-	MD **1 higher** (1.11 lower to 3.11 higher)	⨁⨁◯◯ LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 6 months - Immediate (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,h]	none	17	17	-	MD **1 lower** (5.64 lower to 3.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 6 months - Delayed (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,i]	none	17	17	-	MD **0.1 higher** (3.23 lower to 3.43 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Word List Generation - 6 months (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,j]	none	17	17	-	MD **1.6 lower** (7.65 lower to 4.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Stroop Test - 6 months (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,k]	none	17	17	-	MD **9 lower** (16.21 lower to 1.79 lower)	⨁⨁◯◯ LOW	CRITICAL
Montgomery and Asberg Depression Rating Scale (scale possibly 0-60) - 3 months (follow up: 3 months; Scale from: 0 to 60)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: Attention Processing Training (APT) + multidisciplinary rehabilitation	multidisciplinary rehabilitation only, 3-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,l]	none	17	17	-	MD **3.71 lower** (9.46 lower to 2.04 higher)	⨁⨁◯◯ LOW	CRITICAL

Barthel Index (measure of activities of daily living; scale 0-100) - 3 months (follow up: 3 months; Scale from: 0 to 100)

1	randomised trials	serious [a]	not serious	not serious	serious [b,m]	none	17	17	-	MD **5.22 lower** (18.81 lower to 8.37 higher)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±2.98

d. MIDs used to assess imprecision were ±3.00

e. MIDs used to assess imprecision were ±3.13

f. MIDs used to assess imprecision were ±3.85

g. MIDs used to assess imprecision were ±2.43

h. MIDs used to assess imprecision were ±2.85

i. MIDs used to assess imprecision were ±1.80

j. MIDs used to assess imprecision were ±3.70

k. MIDs used to assess imprecision were ±3.88

l. MIDs used to assess imprecision were ±4.80

m. MIDs used to assess imprecision were ±9.35

Table 29: Clinical evidence profile: Attention/working memory: reaction time tasks + usual rehabilitation vs. active control (cognitive software with no time component), 2 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention/working memory: reaction time tasks + usual rehab	active control (cognitive software with no time component), 2 weeks	Relative (95% CI)	Absolute (95% CI)		
Alertness - T-value indicating normal results (≥40), 2 weeks (follow up: 2 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	9/14 (64.3%)	37.5%	**OR 3.00** (0.68 to 13.31)	**268 more per 1,000** (from 85 fewer to 514 more)	⨁◯◯◯ VERY LOW	CRITICAL
WEIMuS score indicating fatigue (≥32), 2 weeks (follow up: 2 weeks)												
1	randomised trials	very serious [a]	not serious	very serious [b,d]	very serious [c]	none	6/14 (42.9%)	68.8%	**OR 0.34** (0.08 to 1.52)	**260 fewer per 1,000** (from 538 fewer to 82 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence - completed training sessions of 10 h total, 2 weeks (follow up: 2 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [c]	none	10/14 (71.4%)	50.0%	**OR 2.50** (0.55 to 11.41)	**214 more per 1,000** (from 145 fewer to 419 more)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence comes from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Downgraded by 1 increment as a general fatigue scale used rather than one specific to cognitive fatigue

Table 30: Clinical evidence profile: Memory: computer-aided training for memory (with or without attention components) vs. control (no training), 6-14 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: computer-aided training for memory (with or without attention)	control (no training), 6-14 weeks	Relative (95% CI)	Absolute (95% CI)		
California Verbal Learning Test (CVLT) - 6 weeks - Learning trials (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	17	25	-	MD **0.99 higher** (0.27 lower to 2.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test (CVLT) - 6 weeks - Short delay free recall (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	17	25	-	MD **1.86 higher** (0.12 lower to 3.84 higher)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test (CVLT) - 6 weeks - Short delay cued recall (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,f]	none	17	25	-	MD **0.99 higher** (0.85 lower to 2.83 higher)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test (CVLT) - 6 weeks - Long delay free recall (follow up: 6 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: computer-aided training for memory (with or without attention)	control (no training), 6-14 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	17	25	-	MD **1.08 higher** (0.95 lower to 3.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test (CVLT) - 6 weeks - Long delay cued recall (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,g]	none	17	25	-	MD **0.35 higher** (1.49 lower to 2.19 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PASAT (MSFC) - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,h]	none	17	25	-	MD **0.01 higher** (0.57 lower to 0.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Object alternation reaction time - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,i]	none	17	25	-	MD **76 higher** (102.65 lower to 254.65 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Object alternation errors - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,j]	none	17	25	-	MD **0.98 lower** (2.42 lower to 0.46 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: computer-aided training for memory (with or without attention)	control (no training), 6-14 weeks	Relative (95% CI)	Absolute (95% CI)		
Alertness - 6 weeks - Without cueing (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,k]	none	17	25	-	MD **15 higher** (29.09 lower to 59.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Alertness - 6 weeks - With cueing (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,l]	none	17	25	-	MD **11 higher** (32.91 lower to 54.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Spatial span (Corsi) % change - ~14 weeks (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [m]	none	20	20	-	MD **26.5 higher** (14.88 higher to 38.12 higher)	⨁⨁◯◯ LOW	CRITICAL
Paired associates % change - ~14 weeks - Easy (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,n]	none	20	20	-	MD **9.2 higher** (0.87 lower to 19.27 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Paired associates % change - ~14 weeks - Hard (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,o]	none	20	20	-	MD **56.79 higher** (9.25 higher to 104.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: computer-aided training for memory (with or without attention)	control (no training), 6-14 weeks	Relative (95% CI)	Absolute (95% CI)		
Short story recall % change - ~14 weeks (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,p]	none	20	20	-	MD **14.7 higher** (8.16 lower to 37.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Visual reproduction % change - ~14 weeks (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [q]	none	20	20	-	MD **49.8 higher** (26.52 higher to 73.08 higher)	⨁⨁◯◯ LOW	CRITICAL
Luria-Nebraska neuropsychological battery memory scale % change - ~14 weeks (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [r]	none	20	20	-	MD **3.1 higher** (1.47 higher to 4.73 higher)	⨁⨁◯◯ LOW	CRITICAL
Signal detection hits % change - ~14 weeks (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,s]	none	20	20	-	MD **2.1 higher** (8.08 lower to 12.28 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Signal detection reaction time % change - ~14 weeks (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,t]	none	20	20	-	MD **7.7 higher** (1.5 higher to 13.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: computer-aided training for memory (with or without attention)	control (no training), 6-14 weeks	Relative (95% CI)	Absolute (95% CI)		
Recognition memory % change - ~14 weeks (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,u]	none	20	20	-	MD **5.9 higher** (1 higher to 10.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Digit Span % change - ~14 weeks - Forward (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,v]	none	20	20	-	MD **24.15 higher** (10.5 higher to 37.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Digit Span % change - ~14 weeks - Backward (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,w]	none	20	20	-	MD **16.55 higher** (1.3 lower to 34.4 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-12 quality of life (scale usually 0-100) - 6 weeks - Bodily score (follow up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,x]	none	17	25	-	MD **2.5 lower** (9.91 lower to 4.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-12 quality of life (scale usually 0-100) - 6 weeks - Mental score (follow up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,y]	none	17	25	-	MD **0.7 higher** (6.68 lower to 8.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: computer-aided training for memory (with or without attention)	control (no training), 6-14 weeks	Relative (95% CI)	Absolute (95% CI)		
Beck Depression Inventory (scale usually 0-63) - 6 weeks (follow up: 6 weeks; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,z]	none	17	25	-	MD **0.7 lower** (5.79 lower to 4.39 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (FSS; scale usually 9-63) - 6 weeks (follow up: 6 weeks; Scale from: 9 to 63)												
1	randomised trials	very serious [a]	not serious	very serious [aa,b]	very serious [ab,c]	none	17	25	-	MD **0.7 higher** (8.42 lower to 9.82 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence came from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±1.05

e. MIDs used to assess imprecision were ±1.65

f. MIDs used to assess imprecision were ±1.54

g. MIDs used to assess imprecision were ±1.70

h. MIDs used to assess imprecision were ±0.55

i. MIDs used to assess imprecision were ±196.00

j. MIDs used to assess imprecision were ±2.13

k. MIDs used to assess imprecision were ±42.50

l. MIDs used to assess imprecision were ±36.00

m. MIDs used to assess imprecision were ±7.75 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

n. MIDs used to assess imprecision were ±5.20 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

o. MIDs used to assess imprecision were ±32.4 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

p. MIDs used to assess imprecision were ±20.2 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

q. MIDs used to assess imprecision were ±10.50 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

r. MIDs used to assess imprecision were ±1.10 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

s. MIDs used to assess imprecision were ±7.40 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

t. MIDs used to assess imprecision were ±4.85 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

u. MIDs used to assess imprecision were ±4.90 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

v. MIDs used to assess imprecision were ±10.55 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

w. MIDs used to assess imprecision were ±14.10 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

x. MIDs used to assess imprecision were ±5.20

y. MIDs used to assess imprecision were ±5.40

z. MIDs used to assess imprecision were ±3.08

aa. Downgraded by 1 increment as general Fatigue Severity Scale reported rather than cognitive fatigue specifically

ab. MIDs used to assess imprecision were ±7.93

Table 31: Clinical evidence profile: Memory: computer-aided RehaCom memory (and attention) training vs. active control, 14-16 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: computer-aided RehaCom memory (and attention) training	active control, 14-16 weeks	Relative (95% CI)	Absolute (95% CI)		
SDMT - % change from baseline - 16 weeks (follow up: 16 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious [b]	none	40	37	-	MD **1.5 lower** (15.78 lower to 12.78 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
PASAT 2 seconds - % change from baseline - 16 weeks (follow up: 16 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [c,d]	none	40	37	-	MD **22.1 lower** (58.09 lower to 13.89 higher)	⨁⨁◯◯ LOW	CRITICAL
Selective reminding test (SRT) - 16 weeks - Consistent long-term retrieval, % change from baseline (follow up: 16 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [c,e]	none	40	37	-	MD **16.8 higher** (116.77 lower to 150.37 higher)	⨁⨁◯◯ LOW	CRITICAL
Selective reminding test (SRT) - 16 weeks - Delayed recall, % change from baseline (follow up: 16 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [c,f]	none	40	37	-	MD **34.5 lower** (68.41 lower to 0.59 lower)	⨁⨁◯◯ LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 16 weeks - Immediate, % change from baseline (follow up: 16 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: computer-aided RehaCom memory (and attention) training	active control, 14-16 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [c,g]	none	40	37	-	MD **9.2 lower** (36.48 lower to 18.08 higher)	⨁⨁◯◯ LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 16 weeks - Delayed, % change from baseline (follow up: 16 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [c,h]	none	40	37	-	MD **65.1 lower** (117.2 lower to 13 lower)	⨁⨁◯◯ LOW	CRITICAL
Word List Generation - 16 weeks - % change from baseline (follow up: 16 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [c,i]	none	40	37	-	MD **31.7 higher** (13.7 higher to 49.7 higher)	⨁⨁◯◯ LOW	CRITICAL
Spatial span (Corsi) % change - ~14 weeks (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,j]	none	20	20	-	MD **10.7 higher** (3.13 lower to 24.53 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Digit span % change - ~14 weeks - Forward (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,k]	none	20	20	-	MD **17.8 higher** (5.17 higher to 30.43 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Digit span % change - ~14 weeks - Backward (follow up: 14 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: computer-aided RehaCom memory (and attention) training	active control, 14-16 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [c,l]	none	20	20	-	MD **23.3 higher** (7.72 higher to 38.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Paired associates % change - ~14 weeks - Easy (follow up: 14 weeks)

1	randomised trials	very serious [a]	not serious	not serious	serious [c,m]	none	20	20	-	MD **8.4 higher** (1.82 lower to 18.62 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Paired associates % change - ~14 weeks - Hard (follow up: 14 weeks)

1	randomised trials	very serious [a]	not serious	not serious	serious [c,n]	none	20	20	-	MD **37.4 higher** (5.83 lower to 80.63 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Short story recall % change - ~14 weeks (follow up: 14 weeks)

1	randomised trials	very serious [a]	not serious	not serious	not serious [o]	none	20	20	-	MD **36.05 higher** (18.27 higher to 53.83 higher)	⨁⨁◯◯ LOW	CRITICAL

Visual reproduction % change - ~14 weeks (follow up: 14 weeks)

1	randomised trials	very serious [a]	not serious	not serious	serious [c,p]	none	20	20	-	MD **2.2 higher** (37.79 lower to 42.19 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Luria-Nebraska neuropsychological battery memory scale % change - ~14 weeks (follow up: 14 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: computer-aided RehaCom memory (and attention) training	active control, 14-16 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [c,q]	none	20	20	-	MD **2.1 higher** (0.3 higher to 3.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Recognition memory % change - ~14 weeks (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,r]	none	20	20	-	MD **1.3 lower** (7.59 lower to 4.99 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Signal detection hits % change - ~14 weeks (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,s]	none	20	20	-	MD **4.7 higher** (4.87 lower to 14.27 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Signal detection reaction time % change - ~14 weeks (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,t]	none	20	20	-	MD **4.9 higher** (1.04 lower to 10.84 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Improvement >20% in at least 5 of Brief Repeatable Battery of Neuropsychological Tests (BRBNT) - 16 weeks (follow up: 16 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	19/40 (47.5%)	54.0%	**OR 0.77** (0.31 to 1.88)	**65 fewer per 1,000** (from 273 fewer to 148 more)	⨁◯◯◯ VERY LOW	CRITICAL
MSQoL-54 (scale usually 0-100)- 16 weeks - Physical composite (follow up: 16 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: computer-aided RehaCom memory (and attention) training	active control, 14-16 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [c,u]	none	40	37	-	MD **7.1 lower** (33.74 lower to 19.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL

MSQoL-54 (scale usually 0-100)- 16 weeks - Mental health composite (follow up: 16 weeks; Scale from: 0 to 100)

1	randomised trials	serious [a]	not serious	not serious	very serious [c,v]	none	40	37	-	MD **13.2 lower** (72.94 lower to 46.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Chicago Mood Depression Inventory (scale unclear) % change - 16 weeks (follow up: 16 weeks)

1	randomised trials	serious [a]	not serious	not serious	serious [c,w]	none	40	37	-	MD **0.3 lower** (1.74 lower to 1.14 higher)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. MIDs used to assess imprecision were ±18.00 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±50.54 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

e. MIDs used to assess imprecision were ±142.01 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

f. MIDs used to assess imprecision were ±49.04 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

g. MIDs used to assess imprecision were ±33.74 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

h. MIDs used to assess imprecision were ±74.98 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

i. MIDs used to assess imprecision were ±14.70 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

j. MIDs used to assess imprecision were ±11.55 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

k. MIDs used to assess imprecision were ±8.75 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

l. MIDs used to assess imprecision were ±10.00 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

m. MIDs used to assess imprecision were ±5.50 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

n. MIDs used to assess imprecision were ±23.25 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

o. MIDs used to assess imprecision were ±11.80 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

p. MIDs used to assess imprecision were ±38.55 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

q. MIDs used to assess imprecision were ±1.40 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

r. MIDs used to assess imprecision were ±6.65 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

s. MIDs used to assess imprecision were ±6.25 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

t. MIDs used to assess imprecision were ±4.40 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

u. MIDs used to assess imprecision were ±8.78

v. MIDs used to assess imprecision were ±9.15

w. MIDs used to assess imprecision were ±1.70 (based on 0.5 multiplied by the SD in the control group as results were reported as % change from baseline)

Table 32: Clinical evidence profile: Memory: Story Memory Technique vs. control, 5-11 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Story Memory Technique	control, 5-11 weeks	Relative (95% CI)	Absolute (95% CI)		
SDMT z-score - processing speed - 5 weeks (follow up: 5 weeks; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	45	41	-	MD **0.15 lower** (0.73 lower to 0.43 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Story Memory Technique	control, 5-11 weeks	Relative (95% CI)	Absolute (95% CI)		
Hopkins Verbal Learning Test-Revised (HVLT-R) - 5-11 weeks (mix of change from baseline and final values) (follow up: 5-11 weeks)												
2	randomised trials	serious [a]	not serious	serious [b]	serious [c,e]	none	24	24	-	MD **2.99 higher** (0.55 higher to 5.43 higher)	⨁◯◯◯ VERY LOW	CRITICAL
% with improvement on HVLT-R - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	8/14 (57.1%)	35.7%	**RR 1.60** (0.69 to 3.69)	**214 more per 1,000** (from 111 fewer to 960 more)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test (CVLT) learning slope - 5 weeks (follow up: 5 weeks)												
2	randomised trials	very serious [a]	not serious	serious [b]	serious [c,f]	none	60	54	-	MD **0.27 higher** (0.03 lower to 0.57 higher)	⨁◯◯◯ VERY LOW	CRITICAL
CVLT total learning (T-score) - 5 weeks (follow up: 5 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [g]	none	45	41	-	MD **4.89 higher** (0.51 lower to 10.29 higher)	⨁◯◯◯ VERY LOW	CRITICAL
>10% improvement on California Verbal Learning Test (CVLT) - 5 weeks - Short-delay recall (follow up: 5 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	6/8 (75.0%)	25.0%	**OR 9.00** (0.94 to 86.52)	**500 more per 1,000** (from 11 fewer to 716 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Story Memory Technique	control, 5-11 weeks	Relative (95% CI)	Absolute (95% CI)		
>10% improvement on California Verbal Learning Test (CVLT) - 5 weeks - Learning slope (follow up: 5 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	28/45 (62.2%)	36.6%	**OR 2.85** (1.19 to 6.85)	**256 more per 1,000** (from 41 more to 432 more)	⨁◯◯◯ VERY LOW	CRITICAL
Objective everyday memory (Rivermead Behavioural Memory Test Story Memory) - 5 weeks (follow up: 5 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,h]	none	45	41	-	MD **0.32 higher** (0.05 higher to 0.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Working memory - Letter-Number Sequencing scaled score - 5 weeks (follow up: 5 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,i]	none	45	41	-	MD **0.73 higher** (0.63 lower to 2.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Attention - Digit Span scale score - 5 weeks (follow up: 5 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [j]	none	45	41	-	MD **0.24 higher** (0.87 lower to 1.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Memory Functioning Questionnaire Spanish version- 5 weeks (follow up: 5 weeks; Scale from: 31 to 217)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,k]	none	10	10	-	MD **4.9 lower** (12.91 lower to 3.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Story Memory Technique	control, 5-11 weeks	Relative (95% CI)	Absolute (95% CI)		
Awareness of Cognitive Deficits Questionnaire (AQ; scale possibly 17-85) - 5 weeks (follow up: 5 weeks; Scale from: 17 to 85)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,l]	none	15	13	-	MD **4.26 higher** (0.41 higher to 8.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional Assessment of Multiple Sclerosis - General Contentment (FAMS; scale usually 0-28, subjective everyday cognition and emotional functioning) - 5 weeks (follow up: 5 weeks; Scale from: 0 to 28)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,m]	none	45	41	-	MD **4.45 higher** (0.33 lower to 9.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Frontal Systems Behavior Scale (FrSBe; reported by significant others) - 5 weeks - Apathy (scale unclear, possibly 14-70) (follow up: 5 weeks; Scale from: 14 to 70)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,n]	none	45	41	-	MD **4.02 higher** (0.59 lower to 8.63 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Frontal Systems Behavior Scale (FrSBe; reported by significant others) - 5 weeks - Executive dysfunction (scale unclear, possibly 17-85) (follow up: 5 weeks; Scale from: 17 to 85)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,o]	none	45	41	-	MD **4.13 higher** (0.92 lower to 9.19 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Frontal Systems Behavior Scale (FrSBe; reported by significant others) - 5 weeks - Disinhibition after illness (scale unclear, possibly 15-75) (follow up: 5 weeks; Scale from: 15 to 75)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,p]	none	15	13	-	MD **2.65 higher** (0.4 higher to 4.89 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Story Memory Technique	control, 5-11 weeks	Relative (95% CI)	Absolute (95% CI)		
State-Trait Anxiety Inventory (STAI) T-score - 5 weeks - State score (follow up: 5 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,q]	none	45	41	-	MD **3.01 lower** (9.66 lower to 3.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
State-Trait Anxiety Inventory (STAI) T-score - 5 weeks - Trait score (follow up: 5 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,r]	none	45	41	-	MD **4.29 lower** (10.86 lower to 2.28 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Chicago Multidimensional Depression Inventory T-score - 5 weeks (follow up: 5 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,s]	none	45	41	-	MD **1.34 lower** (7.4 lower to 4.72 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Satisfaction with Life Scale (scale usually 5-35) - 5 weeks (follow up: 5 weeks; Scale from: 5 to 35)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,t]	none	10	10	-	MD **3.28 higher** (0.16 higher to 6.4 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Patient Competency Rating Scale (PCRS; scale usually 30-150) - 5 weeks - Patient-reported (follow up: 5 weeks; Scale from: 30 to 150)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c,u]	none	10	10	-	MD **0.67 higher** (6.92 lower to 8.26 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Patient Competency Rating Scale (PCRS; scale usually 30-150) - 5 weeks - Family-reported (follow up: 5 weeks; Scale from: 30 to 150)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Story Memory Technique	control, 5-11 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	not serious [v]	none	10	10	-	MD **2.38 lower** (5.19 lower to 0.43 higher)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence came from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±0.71 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

e. MIDs used to assess imprecision were ±2.28

f. MIDs used to assess imprecision were ±0.28

g. MIDs used to assess imprecision were ±6.72 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

h. MIDs used to assess imprecision were ±0.33

i. MIDs used to assess imprecision were ±1.61 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

j. MIDs used to assess imprecision were ±1.43 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

k. MIDs used to assess imprecision were ±8.78

l. MIDs used to assess imprecision were ±2.66 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

m. MIDs used to assess imprecision were ±5.51 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

n. MIDs used to assess imprecision were ±4.93 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

o. MIDs used to assess imprecision were ±5.42 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

p. MIDs used to assess imprecision were ±1.45 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

q. MIDs used to assess imprecision were ±7.74 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

r. MIDs used to assess imprecision were ±7.25 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

s. MIDs used to assess imprecision were ±6.46 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

t. MIDs used to assess imprecision were ±2.84

u. MIDs used to assess imprecision were ±4.87

v. MIDs used to assess imprecision were ±5.74

Table 33: Clinical evidence profile: Memory: Story Memory Technique vs. control, 7 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Story Memory Technique	control, ~7 months	Relative (95% CI)	Absolute (95% CI)		
SDMT z-score - processing speed - ~7 months (follow up: 7 months; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	40	38	-	MD **1.97 lower** (2.58 lower to 1.36 lower)	⨁⨁◯◯ LOW	CRITICAL
California Verbal Learning Test (CVLT) learning slope z-score - ~7 months (follow up: 7 months; Scale from: -5 to 5)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,d]	none	40	38	-	MD **0.11 higher** (0.15 lower to 0.37 higher)	⨁◯◯◯ VERY LOW	CRITICAL
CVLT total learning (T-score) - ~7 months (follow up: 7 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,e]	none	40	38	-	MD **6.85 higher** (0.31 lower to 14.01 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Objective everyday memory (Rivermead Behavioural Memory Test Story Memory) - ~7 months - Immediate Profile Score (follow up: 7 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Story Memory Technique	control, ~7 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [c,f]	none	40	38	-	MD **0.09 lower** (0.47 lower to 0.29 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Objective everyday memory (Rivermead Behavioural Memory Test Story Memory) - ~7 months - Delayed Profile Score (follow up: 7 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [g]	none	40	38	-	MD **0.03 higher** (0.29 lower to 0.35 higher)	⨁⨁◯◯ LOW	CRITICAL
Working memory - Letter-Number Sequencing scaled score - ~7 months (follow up: 7 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [h]	none	40	38	-	MD **0** (1.35 lower to 1.35 higher)	⨁⨁◯◯ LOW	CRITICAL
Attention - Digit Span scale score - ~7 months (follow up: 7 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,i]	none	40	38	-	MD **0.23 higher** (1.01 lower to 1.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL
FAMS General Contentment (scale usually 0-28, subjective everyday cognition and emotional functioning) - ~7 months (follow up: 7 months; Scale from: 0 to 28)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,j]	none	40	38	-	MD **2.69 higher** (0.22 lower to 5.6 higher)	⨁◯◯◯ VERY LOW	CRITICAL
FrSBe T-score (reported by significant others) - ~7 months - Apathy (follow up: 7 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Story Memory Technique	control, ~7 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [c,k]	none	40	38	-	MD **3.93 higher** (6.13 lower to 13.99 higher)	⨁◯◯◯ VERY LOW	CRITICAL
FrSBe T-score (reported by significant others) - ~7 months - Executive dysfunction (follow up: 7 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [l]	none	40	38	-	MD **1.06 lower** (8.43 lower to 6.31 higher)	⨁⨁◯◯ LOW	CRITICAL
State-Trait Anxiety Inventory (STAI) T-score - ~7 months - State score (follow up: 7 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,m]	none	40	38	-	MD **3.61 lower** (9.53 lower to 2.31 higher)	⨁◯◯◯ VERY LOW	CRITICAL
State-Trait Anxiety Inventory (STAI) T-score - ~7 months - Trait score (follow up: 7 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,n]	none	40	38	-	MD **1.5 lower** (8.13 lower to 5.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Chicago Multidimensional Depression Inventory T-score - ~7 months (follow up: 7 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,o]	none	40	38	-	MD **2.04 lower** (8.1 lower to 4.02 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. MIDs used to assess imprecision were ±0.70 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±0.28 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

e. MIDs used to assess imprecision were ±8.24 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

f. MIDs used to assess imprecision were ±0.33

g. MIDs used to assess imprecision were ±0.35 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

h. MIDs used to assess imprecision were ±1.53 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

i. MIDs used to assess imprecision were ±1.43 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

j. MIDs used to assess imprecision were ±3.16 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

k. MIDs used to assess imprecision were ±10.48 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

l. MIDs used to assess imprecision were ±8.56 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

m. MIDs used to assess imprecision were ±6.94 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

n. MIDs used to assess imprecision were ±8.09 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

o. MIDs used to assess imprecision were ±5.73 (based on 0.5 multiplied by the SD for the control group value as no baseline values were reported)

Table 34: Clinical evidence profile: Memory: group memory programme (various learning techniques) vs. control, 3-6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Group memory programme (various learning techniques)	control, 3-6 months	Relative (95% CI)	Absolute (95% CI)		
SDMT - 6 months - SDMT - 6 months (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	220	181	-	MD **1.3 higher** (0.6 lower to 3.2 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Group memory programme (various learning techniques)	control, 3-6 months	Relative (95% CI)	Absolute (95% CI)		
Selective Reminding Test (SRT) - 6 months - Total (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [c]	none	220	182	-	MD **1.6 higher** (0.1 higher to 3.1 higher)	⨁⨁◯◯ LOW	CRITICAL
Selective Reminding Test (SRT) - 6 months - Delay (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [d]	none	220	182	-	MD **0.2 higher** (0.2 lower to 0.6 higher)	⨁⨁◯◯ LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 6 months - Total (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [e]	none	217	182	-	MD **0.6 lower** (1.5 lower to 0.3 higher)	⨁⨁◯◯ LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 6 months - Delay (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [f]	none	217	182	-	MD **0** (0.4 lower to 0.4 higher)	⨁⨁◯◯ LOW	CRITICAL
PASAT - 6 months - Easy (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [g]	none	217	178	-	MD **0** (2.4 lower to 2.4 higher)	⨁⨁◯◯ LOW	CRITICAL
PASAT - 6 months - Hard (follow up: 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Group memory programme (various learning techniques)	control, 3-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious [h]	none	217	178	-	MD **0.3 lower** (2.9 lower to 2.3 higher)	⨁⨁◯◯ LOW	CRITICAL
Trail Making Test (B-A) - 6 months - Trail Making Test (B-A) - 6 months (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [i]	none	218	179	-	MD **0.3 lower** (6.8 lower to 6.2 higher)	⨁⨁◯◯ LOW	CRITICAL
Word fluency - 6 months - Word fluency - 6 months (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [j]	none	219	182	-	MD **0** (1.3 lower to 1.3 higher)	⨁⨁◯◯ LOW	CRITICAL
Working memory (possibly Wechsler Memory Scale–III) - 13 weeks (follow up: 13 weeks)												
1	randomised trials	not serious	not serious	not serious	serious [k,l]	none	20	40	-	MD **2.2 higher** (0.5 higher to 3.9 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Doors and people (overall age-scaled score) - 6 months - Doors and people (overall age-scaled score) - 6 months (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [m]	none	221	181	-	MD **0.4 higher** (0.1 lower to 0.9 higher)	⨁⨁◯◯ LOW	CRITICAL
Digit Span Test for attention assessment - 3 months (follow up: 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Group memory programme (various learning techniques)	control, 3-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [l,n]	none	28	28	-	MD **0.46 higher** (0.95 lower to 1.87 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Everyday Memory Questionnaire (EMQ; scale 0-140) - 3-6 months - Self-report (follow up: 3-6 months; Scale from: 0 to 140)												
3	randomised trials	very serious [a]	not serious	not serious	not serious [o]	none	259	230	-	MD **5.48 lower** (8.69 lower to 2.28 lower)	⨁⨁◯◯ LOW	CRITICAL
Everyday Memory Questionnaire (EMQ; scale 0-140) - 4-6 months - Carer-report (follow up: 4-6 months; Scale from: 0 to 140)												
2	randomised trials	very serious [a]	not serious	not serious	not serious [p]	none	201	173	-	MD **4.02 lower** (7.3 lower to 0.75 lower)	⨁⨁◯◯ LOW	CRITICAL
Everyday Memory Questionnaire (scale 0-175) - 13 weeks (follow up: 13 weeks; Scale from: 0 to 175)												
1	randomised trials	not serious	not serious	not serious	serious [l,q]	none	20	40	-	MD **0.3 higher** (0.52 lower to 1.12 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Prospective and Retrospective Memory Questionnaire (scale 16-80?) - 3 months (follow up: 3 months; Scale from: 16 to 80)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [r]	none	28	28	-	MD **9.46 lower** (14.07 lower to 4.85 lower)	⨁⨁◯◯ LOW	CRITICAL
MSIS-29 quality of life (scale 0-100) - 6 months - Psychological (follow up: 6 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Group memory programme (various learning techniques)	control, 3-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious [s]	none	217	187	-	MD **0.9 lower** (1.7 lower to 0.1 lower)	⨁⨁◯◯ LOW	CRITICAL
MSIS-29 quality of life (scale 0-100) - 6 months - Physical (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [t]	none	215	187	-	MD **0.6 lower** (2.2 lower to 1 higher)	⨁⨁◯◯ LOW	CRITICAL
MSIS-29 quality of life (scale 29-145) - 4 months (follow up: 4 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [t,u]	none	16	21	-	MD **8.2 higher** (9.92 lower to 26.32 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQoL-54 - 3 months - Physical health (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [t,v]	none	28	28	-	MD **10.28 higher** (2.97 higher to 17.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQoL-54 - 3 months - Mental health (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [w]	none	28	28	-	MD **16.87 higher** (8.9 higher to 24.84 higher)	⨁⨁◯◯ LOW	CRITICAL
EQ-5D visual analogue (scale 0-100) - 6 months - EQ-5D visual analogue (scale 0-100) - 6 months (follow up: 6 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Group memory programme (various learning techniques)	control, 3-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious [x]	none	224	187	-	MD **2.6 higher** (0.9 lower to 6.1 higher)	⨁⨁◯◯ LOW	CRITICAL
General Health Questionnaire (GHQ-28; scale 0-84) - 4 months (follow up: 4 months; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [y]	none	16	21	-	MD **1 higher** (5.82 lower to 7.82 higher)	⨁⨁◯◯ LOW	CRITICAL
GHQ-30 (scale 0-90) - 6 months - GHQ-30 (scale 0-90) - 6 months (follow up: 6 months; Scale from: 0 to 90)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [z]	none	212	183	-	MD **3.4 lower** (5.9 lower to 0.9 lower)	⨁⨁◯◯ LOW	CRITICAL
Beck Depression Inventory (scale usually 0-63) - 3 months (follow up: 3 months; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [aa]	none	28	28	-	MD **9.64 lower** (12.94 lower to 6.34 lower)	⨁⨁◯◯ LOW	CRITICAL
Fatigue Severity Scale (FSS; scale likely 1-7) - 6 months - Fatigue Severity Scale (FSS; scale likely 1-7) - 6 months (follow up: 6 months; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	serious [ab]	not serious [ac]	none	214	185	-	MD **0.1 lower** (0.3 lower to 0.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Carer Strain Index (scale possibly 0-13) - 6 months - Carer Strain Index (scale possibly 0-13) - 6 months (follow up: 6 months; Scale from: 0 to 13)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Group memory programme (various learning techniques)	control, 3-6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious [ad]	none	173	154	-	MD **0.9 lower** (2.2 lower to 0.4 higher)	⨁⨁◯◯ LOW	CRITICAL

Any employment - 6 months - Any employment - 6 months (follow up: 6 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [l]	none	0/224 (0.0%)	57/187 (30.5%)	**OR 0.88** (0.55 to 1.41)	**26 fewer per 1,000** (from 111 fewer to 77 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. MIDs used to assess imprecision were ±5.90

c. MIDs used to assess imprecision were ±5.38

d. MIDs used to assess imprecision were ±1.40

e. MIDs used to assess imprecision were ±2.35

f. MIDs used to assess imprecision were ±1.08

g. MIDs used to assess imprecision were ±8.15

h. MIDs used to assess imprecision were ±8.08

i. MIDs used to assess imprecision were ±20.60

j. MIDs used to assess imprecision were ±4.43

k. MIDs used to assess imprecision were ±1.14

l. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

m. MIDs used to assess imprecision were ±1.90

n. MIDs used to assess imprecision were ±1.54

o. MIDs used to assess imprecision were ±11.50

p. MIDs used to assess imprecision were ±10.73

q. MIDs used to assess imprecision were ±0.63

r. MIDs used to assess imprecision were ±4.70

s. MIDs used to assess imprecision were ±2.95

t. MIDs used to assess imprecision were ±6.68

u. MIDs used to assess imprecision were ±12.08

v. MIDs used to assess imprecision were ±7.08

w. MIDs used to assess imprecision were ±7.45

x. MIDs used to assess imprecision were ±10.38

y. MIDs used to assess imprecision were ±9.40

z. MIDs used to assess imprecision were ±7.50

aa. MIDs used to assess imprecision were ±3.30

ab. Downgraded by 1 increment as general Fatigue Severity Scale reported rather than cognitive fatigue specifically

ac. MIDs used to assess imprecision were ±0.68

ad. MIDs used to assess imprecision were ±3.10 (based on 0.5 multiplied by the SD for the control group as no baseline values were reported)

Table 35: Clinical evidence profile: Memory: group memory programme (various learning techniques) vs. control, 8-12 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Group memory programme (various learning techniques)	control, 8-12 months	Relative (95% CI)	Absolute (95% CI)		
SDMT - 12 months - SDMT - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	205	170	-	MD **0.4 higher** (1.7 lower to 2.5 higher)	⨁⨁◯◯ LOW	CRITICAL
Selective Reminding Test (SRT) - 12 months - Total (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [c]	none	206	170	-	MD **0.6 higher** (0.9 lower to 2.1 higher)	⨁⨁◯◯ LOW	CRITICAL
Selective Reminding Test (SRT) - 12 months - Delay (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [d]	none	206	170	-	MD **0.4 higher** (0.1 higher to 0.7 higher)	⨁⨁◯◯ LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 12 months - Total (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [e]	none	206	170	-	MD **0.1 lower** (1 lower to 0.8 higher)	⨁⨁◯◯ LOW	CRITICAL
10/36 SPART (Spatial Recall Test) - 12 months - Delay (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [f]	none	206	170	-	MD **0.1 lower** (0.5 lower to 0.3 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Group memory programme (various learning techniques)	control, 8-12 months	Relative (95% CI)	Absolute (95% CI)		
PASAT - 12 months - Easy (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [g]	none	205	169	-	MD **0.6 lower** (3.1 lower to 1.9 higher)	⨁⨁◯◯ LOW	CRITICAL
PASAT - 12 months - Hard (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [h]	none	205	169	-	MD **1.9 lower** (4.8 lower to 1 higher)	⨁⨁◯◯ LOW	CRITICAL
Trail Making Test (B-A) - 12 months - Trail Making Test (B-A) - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [i]	none	205	165	-	MD **3.2 lower** (10 lower to 3.6 higher)	⨁⨁◯◯ LOW	CRITICAL
Word fluency - 12 months - Word fluency - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [j]	none	206	169	-	MD **0.2 lower** (1.5 lower to 1.1 higher)	⨁⨁◯◯ LOW	CRITICAL
Doors and people (overall age-scaled score) - 12 months - Doors and people (overall age-scaled score) - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [k]	none	206	168	-	MD **0.6 higher** (0 to 1.2 higher)	⨁⨁◯◯ LOW	CRITICAL
Everyday Memory Questionnaire (EMQ; scale 0-140) - 8-12 months - Self-report (follow up: 8-12 months; Scale from: 0 to 140)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Group memory programme (various learning techniques)	control, 8-12 months	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	not serious [l]	none	225	184	-	MD **4.85 lower** (8.1 lower to 1.6 lower)	⨁⨁◯◯ LOW	CRITICAL
Everyday Memory Questionnaire (EMQ; scale 0-140) - 8-12 months - Carer-report (follow up: 8-12 months; Scale from: 0 to 140)												
2	randomised trials	very serious [a]	not serious	not serious	not serious [m]	none	179	157	-	MD **5.13 lower** (9.1 lower to 1.16 lower)	⨁⨁◯◯ LOW	CRITICAL
General Health Questionnaire (GHQ; scale 0-84) - 8 months (follow up: 8 months; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	serious [n,o]	none	17	16	-	MD **6.9 lower** (13.19 lower to 0.61 lower)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 quality of life (scale 29-145) - 8 months (follow up: 8 months; Scale from: 29 to 145)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [n,p]	none	15	16	-	MD **6.3 lower** (25.16 lower to 12.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 quality of life (scale 0-100) - 12 months - Psychological (follow up: 12 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [q]	none	214	173	-	MD **0.6 lower** (1.5 lower to 0.3 higher)	⨁⨁◯◯ LOW	CRITICAL
MSIS-29 quality of life (scale 0-100) - 12 months - Physical (follow up: 12 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Group memory programme (various learning techniques)	control, 8-12 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious [r]	none	214	173	-	MD **0.1 lower** (1.8 lower to 1.6 higher)	⨁⨁◯◯ LOW	CRITICAL
EQ-5D visual analogue (scale 0-100) - 12 months - EQ-5D visual analogue scale (0-100) - 12 months (follow up: 12 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [s]	none	209	173	-	MD **2.6 higher** (0.9 lower to 6.1 higher)	⨁⨁◯◯ LOW	CRITICAL
GHQ-30 (scale 0-90) - 12 months - GHQ-30 (scale 0-90) - 12 months (follow up: 12 months; Scale from: 0 to 90)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [t]	none	209	167	-	MD **3.4 lower** (6.2 lower to 0.6 lower)	⨁⨁◯◯ LOW	CRITICAL
Fatigue Severity Scale (FSS; scale likely 1-7) - 12 months - Fatigue Severity Scale (FSS; scale likely 1-7) - 12 months (follow up: 12 months; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	serious [u]	not serious [v]	none	210	168	-	MD **0.3 lower** (0.5 lower to 0.1 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Carer Strain Index (scale possibly 0-13) - 12 months - Carer Strain Index (scale possibly 0-13) - 12 months (follow up: 12 months; Scale from: 0 to 13)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [w]	none	159	141	-	MD **0.4 lower** (1.6 lower to 0.8 higher)	⨁⨁◯◯ LOW	CRITICAL
Any employment - 12 months - Any employment - 12 months (follow up: 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: Group memory programme (various learning techniques)	control, 8-12 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [n]	none	0/209 (0.0%)	50/173 (28.9%)	**OR 0.99** (0.60 to 1.63)	**2 fewer per 1,000** (from 93 fewer to 110 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. MIDs used to assess imprecision were ±5.90

c. MIDs used to assess imprecision were ±5.38

d. MIDs used to assess imprecision were ±1.40

e. MIDs used to assess imprecision were ±2.35

f. MIDs used to assess imprecision were ±1.08

g. MIDs used to assess imprecision were ±8.15

h. MIDs used to assess imprecision were ±8.08

i. MIDs used to assess imprecision were ±20.60

j. MIDs used to assess imprecision were ±4.43

k. MIDs used to assess imprecision were ±1.90

l. MIDs used to assess imprecision were ±11.35

m. MIDs used to assess imprecision were ±10.73

n. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

o. MIDs used to assess imprecision were ±4.70

p. MIDs used to assess imprecision were ±12.08

q. MIDs used to assess imprecision were ±2.95

r. MIDs used to assess imprecision were ±6.68

s. MIDs used to assess imprecision were ±10.38

t. MIDs used to assess imprecision were ±7.50

u. Downgraded by 1 increment as general Fatigue Severity Scale reported rather than cognitive fatigue specifically

v. MIDs used to assess imprecision were ±0.68

w. MIDs used to assess imprecision were ±3.00 (based on 0.5 multiplied by the SD in the control group as no baseline values were reported)

Table 36: Clinical evidence profile: Memory: behaviour intervention (self-generated learning) vs. control (memory tasks with no self-generated learning taught), 3-4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: behaviour intervention (self-generated learning)	control (memory tasks with no self-generated learning taught), 3-4 weeks	Relative (95% CI)	Absolute (95% CI)		
California Verbal Learning Test-II (CVLT-II) - 3-4 weeks - Five trials sum (follow up: 3-4 weeks)												
1	randomised trials	not serious	not serious	serious [a]	very serious [b,c]	none	19	16	-	MD **1.4 higher** (5.62 lower to 8.42 higher)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test-II (CVLT-II) - 3-4 weeks - Long delay (follow up: 3-4 weeks)												
1	randomised trials	not serious	not serious	serious [a]	serious [b,d]	none	19	16	-	MD **1.1 higher** (1.39 lower to 3.59 higher)	⨁⨁◯◯ LOW	CRITICAL
Contextual Memory Test (CMT) - 3-4 weeks - Immediate (follow up: 3-4 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: behaviour intervention (self-generated learning)	control (memory tasks with no self-generated learning taught), 3-4 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a]	not serious [e]	none	19	16	-	MD **4 higher** (2.23 higher to 5.77 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Contextual Memory Test (CMT) - 3-4 weeks - Delay (follow up: 3-4 weeks)												
1	randomised trials	not serious	not serious	serious [a]	serious [b,f]	none	19	16	-	MD **3.62 higher** (1.43 higher to 5.81 higher)	⨁⨁◯◯ LOW	CRITICAL
Memory for Intentions Test (MIST) - 3-4 weeks (follow up: 3-4 weeks)												
1	randomised trials	not serious	not serious	serious [a]	serious [b,g]	none	19	16	-	MD **14.6 higher** (2.77 lower to 31.97 higher)	⨁⨁◯◯ LOW	CRITICAL
Verbal fluency test (total across three letters) - 3-4 weeks (follow up: 3-4 weeks)												
1	randomised trials	not serious	not serious	serious [a]	serious [b,h]	none	19	16	-	MD **4.55 higher** (4.97 lower to 14.07 higher)	⨁⨁◯◯ LOW	CRITICAL
Actual Reality™ Task (AR) - 3-4 weeks - Total errors (follow up: 3-4 weeks)												
1	randomised trials	not serious	not serious	serious [a]	serious [b,i]	none	19	16	-	MD **2.4 lower** (5.09 lower to 0.29 higher)	⨁⨁◯◯ LOW	CRITICAL
Actual Reality™ Task (AR) - 3-4 weeks - Cognitive score (scale usually 0-20) (follow up: 3-4 weeks; Scale from: 0 to 20)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: behaviour intervention (self-generated learning)	control (memory tasks with no self-generated learning taught), 3-4 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a]	very serious [b,j]	none	19	16	-	MD **0.9 lower** (2.99 lower to 1.19 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Memory Functioning Questionnaire (MFQ; scale usually 64-448) - 3-4 weeks (follow up: 3-4 weeks; Scale from: 64 to 448)

1	randomised trials	not serious	not serious	serious [a]	serious [b,k]	none	19	16	-	MD **40.8 higher** (6.05 higher to 75.55 higher)	⨁⨁◯◯ LOW	CRITICAL

Functional Behavioural Profile (FBP; scale possibly 0-108) - 3-4 weeks (follow up: 3-4 weeks; Scale from: 0 to 108)

1	randomised trials	not serious	not serious	serious [a]	serious [b,l]	none	19	16	-	MD **12.6 higher** (3.32 higher to 21.88 higher)	⨁⨁◯◯ LOW	CRITICAL

Functional Assessment of MS (FAMS; scale usually 0-176) - 3-4 weeks (follow up: 3-4 weeks; Scale from: 0 to 176)

1	randomised trials	not serious	not serious	serious [a]	serious [b,m]	none	19	16	-	MD **4.2 higher** (15.58 lower to 23.98 higher)	⨁⨁◯◯ LOW	CRITICAL

Self-awareness of cognitive deficits questionnaire (AQ; scale usually 17-85) - 3-4 weeks (follow up: 3-4 weeks; Scale from: 17 to 85)

1	randomised trials	not serious	not serious	serious [a]	serious [b,n]	none	19	16	-	MD **3.8 higher** (0.54 lower to 8.14 higher)	⨁⨁◯◯ LOW	CRITICAL

Self-regulation skills interview (self-awareness and strategy use; scale unclear) - 3-4 weeks (follow up: 3-4 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memory: behaviour intervention (self-generated learning)	control (memory tasks with no self-generated learning taught), 3-4 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a]	serious [b,o]	none	19	16	-	MD **2.5 lower** (6.94 lower to 1.94 higher)	⨁⨁◯◯ LOW	CRITICAL
State-Trait Anxiety Inventory (STAI) - Trait score (scale usually 20-80) - 3-4 weeks (follow up: 3-4 weeks; Scale from: 20 to 80)												
1	randomised trials	not serious	not serious	serious [a]	serious [b,p]	none	19	16	-	MD **2 lower** (9.65 lower to 5.65 higher)	⨁⨁◯◯ LOW	CRITICAL
Chicago Multiscale Depression Inventory (CDMI; scale possibly 42-210) - 3-4 weeks (follow up: 3-4 weeks; Scale from: 42 to 210)												
1	randomised trials	not serious	not serious	serious [a]	serious [b,q]	none	19	16	-	MD **10.1 lower** (20.46 lower to 0.26 higher)	⨁⨁◯◯ LOW	CRITICAL
Satisfaction with Life Scale (scale usually 5-35) - 3-4 weeks (follow up: 3-4 weeks; Scale from: 5 to 35)												
1	randomised trials	not serious	not serious	serious [a]	very serious [b,r]	none	19	16	-	MD **0.89 higher** (8.29 lower to 10.07 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment as the majority of the evidence came from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±5.43

d. MIDs used to assess imprecision were ±1.90

e. MIDs used to assess imprecision were ±1.38

f. MIDs used to assess imprecision were ±1.53

g. MIDs used to assess imprecision were ±15.25

h. MIDs used to assess imprecision were ±7.08

i. MIDs used to assess imprecision were ±1.25

j. MIDs used to assess imprecision were ±0.88

k. MIDs used to assess imprecision were ±25.03

l. MIDs used to assess imprecision were ±8.40

m. MIDs used to assess imprecision were ±15.80

n. MIDs used to assess imprecision were ±2.68

o. MIDs used to assess imprecision were ±4.18

p. MIDs used to assess imprecision were ±6.30

q. MIDs used to assess imprecision were ±9.25

r. MIDs used to assess imprecision were ±3.63

Table 37: Clinical evidence profile: Executive function: executive function-specific training vs. control (no training), 6 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: executive function specific training	control (no training), 6 weeks	Relative (95% CI)	Absolute (95% CI)		
California Verbal Learning Test (CVLT) - Learning - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,d]	none	11	15	-	MD **0.6 higher** (1.03 lower to 2.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wisconsin Card Sorting Test (WCST) - Number of categories - 6 weeks (follow up: 6 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: executive function specific training	control (no training), 6 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	10	10	-	MD **1.3 higher** (0.48 higher to 2.12 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Wisconsin Card Sorting Test (WCST) - Total errors - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [f]	none	10	10	-	MD **21.7 lower** (24.82 lower to 18.58 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Preference Shifting trials to criterion - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,g]	none	11	15	-	MD **7.8 lower** (23.86 lower to 8.26 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Preference Shifting reaction time - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,h]	none	11	15	-	MD **59 lower** (190.39 lower to 72.39 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Response Shifting trials to criterion - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,i]	none	11	15	-	MD **9.5 higher** (9.41 lower to 28.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Response Shifting reaction time - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,j]	none	11	15	-	MD **71 lower** (227.25 lower to 85.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: executive function specific training	control (no training), 6 weeks	Relative (95% CI)	Absolute (95% CI)		
2-back commissions - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,k]	none	11	15	-	MD **1.2 higher** (3.6 lower to 6 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back omissions - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,l]	none	11	15	-	MD **1 lower** (2.24 lower to 0.24 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back reaction time - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,m]	none	11	15	-	MD **15 lower** (143.81 lower to 113.81 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence comes from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±0.98

e. MIDs used to assess imprecision were ±0.60

f. MIDs used to assess imprecision were ±2.81

g. MIDs used to assess imprecision were ±12.95

h. MIDs used to assess imprecision were ±60.00

i. MIDs used to assess imprecision were ±12.08

j. MIDs used to assess imprecision were ±84.75

k. MIDs used to assess imprecision were ±2.20

l. MIDs used to assess imprecision were ±0.80

m. MIDs used to assess imprecision were ±92.50

Table 38: Clinical evidence profile: Executive function: executive function-specific training vs. control (no training), 6 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: executive function specific training	control (no training), 12 months	Relative (95% CI)	Absolute (95% CI)		
California Verbal Learning Test (CVLT) - Learning - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,c]	none	6	6	-	MD **0.8 lower** (3.01 lower to 1.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Preference Shifting trials to criterion - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	6	6	-	MD **21.4 higher** (5.04 lower to 47.84 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Preference Shifting reaction time - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,e]	none	6	6	-	MD **85 higher** (113.88 lower to 283.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: executive function specific training	control (no training), 12 months	Relative (95% CI)	Absolute (95% CI)		
Response Shifting trials to criterion - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,f]	none	6	6	-	MD **11.5 lower** (44.35 lower to 21.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Response Shifting reaction time - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,g]	none	6	6	-	MD **9 higher** (254.11 lower to 272.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back commissions - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,h]	none	6	6	-	MD **0.1 lower** (4.75 lower to 4.55 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back omissions - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,i]	none	6	6	-	MD **0.1 lower** (1.34 lower to 1.14 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back reaction time - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,j]	none	6	6	-	MD **103 higher** (105.78 lower to 311.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL

1 a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±0.98

d. MIDs used to assess imprecision were ±12.95

e. MIDs used to assess imprecision were ±60.00

f. MIDs used to assess imprecision were ±12.08

g. MIDs used to assess imprecision were ±84.75

h. MIDs used to assess imprecision were ±2.20

i. MIDs used to assess imprecision were ±0.80

j. MIDs used to assess imprecision were ±92.50

Table 39: Clinical evidence profile: Executive function: executive function-specific training vs. active control (responding quickly to visual stimuli), 6 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: executive function specific training	active control (responding quickly to visual stimuli), 6 weeks	Relative (95% CI)	Absolute (95% CI)		
California Verbal Learning Test (CVLT) - Learning - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	11	14	-	MD **0.6 higher** (0.79 lower to 1.99 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Preference Shifting trials to criterion - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	11	14	-	MD **5.8 lower** (20.7 lower to 9.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: executive function specific training	active control (responding quickly to visual stimuli), 6 weeks	Relative (95% CI)	Absolute (95% CI)		
Preference Shifting reaction time - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,f]	none	11	14	-	MD **40 higher** (87.17 lower to 167.17 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Response Shifting trials to criterion - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,g]	none	11	14	-	MD **0.6 lower** (20.5 lower to 19.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Response Shifting reaction time - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,h]	none	11	14	-	MD **20 lower** (177.1 lower to 137.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back commissions - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,i]	none	11	14	-	MD **1.1 higher** (2.83 lower to 5.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back omissions - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [j]	none	11	14	-	MD **0.1 higher** (0.65 lower to 0.85 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back reaction time - 6 weeks (follow up: 6 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: executive function specific training	active control (responding quickly to visual stimuli), 6 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,k]	none	11	14	-	MD **91 lower** (243.91 lower to 61.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence came from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±0.90

e. MIDs used to assess imprecision were ±12.23

f. MIDs used to assess imprecision were ±72.50

g. MIDs used to assess imprecision were ±11.25

h. MIDs used to assess imprecision were ±84.75

i. MIDs used to assess imprecision were ±1.60

j. MIDs used to assess imprecision were ±1.10

k. MIDs used to assess imprecision were ±86.25

Table 40: Clinical evidence profile: Executive function: executive function-specific training vs. active control (responding quickly to visual stimuli), 12 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: executive function specific training	active control (responding quickly to visual stimuli), 12 months	Relative (95% CI)	Absolute (95% CI)		
California Verbal Learning Test (CVLT) - Learning - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,c]	none	6	8	-	MD **0** (1.85 lower to 1.85 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Preference Shifting trials to criterion - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	6	8	-	MD **13.5 higher** (9.26 lower to 36.26 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Preference Shifting reaction time - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,e]	none	6	8	-	MD **49 lower** (226.08 lower to 128.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Response Shifting trials to criterion - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,f]	none	6	8	-	MD **9.5 lower** (40.23 lower to 21.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Response Shifting reaction time - 12 months (follow up: 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: executive function specific training	active control (responding quickly to visual stimuli), 12 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,g]	none	6	8	-	MD **63 lower** (306.46 lower to 180.46 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back commissions - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,h]	none	6	8	-	MD **2 higher** (2.29 lower to 6.29 higher)	⨁◯◯◯ VERY LOW	CRITICAL
2-back omissions - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	6	8	-	MD **1.9 lower** (3.26 lower to 0.54 lower)	⨁◯◯◯ VERY LOW	CRITICAL
2-back reaction time - 12 months (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,j]	none	6	8	-	MD **98 higher** (105.15 lower to 301.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±0.90

d. MIDs used to assess imprecision were ±12.23

e. MIDs used to assess imprecision were ±72.50

f. MIDs used to assess imprecision were ±11.25

g. MIDs used to assess imprecision were ±84.75

h. MIDs used to assess imprecision were ±1.60

i. MIDs used to assess imprecision were ±1.10

j. MIDs used to assess imprecision were ±86.25

Table 41: Clinical evidence profile: Executive function: goal management programme vs. psychoeducation, 9 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: Goal management programme	psychoeducation, 9 weeks	Relative (95% CI)	Absolute (95% CI)		
Sustained Attention to Response Task (SART) errors - 9 weeks - Commission errors (% of no-go trials) (follow up: 9 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	13	14	-	MD **11.1 higher** (8.69 lower to 30.89 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Sustained Attention to Response Task (SART) errors - 9 weeks - Omission errors (% of go trials) (follow up: 9 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c,e]	none	13	14	-	MD **0.2 higher** (3.46 lower to 3.86 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SART reaction time across go trials - 9 weeks (follow up: 9 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,f]	none	13	14	-	MD **6.2 lower** (78.81 lower to 66.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Test of Everyday Attention (TEA) - 9 weeks - Elevator counting with distraction (follow up: 9 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: Goal management programme	psychoeducation, 9 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,g]	none	13	14	-	MD **1.9 higher** (0.36 lower to 4.16 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Test of Everyday Attention (TEA) - 9 weeks - Visual elevator (follow up: 9 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c,h]	none	13	14	-	MD **0.4 higher** (1.38 lower to 2.18 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Test of Everyday Attention (TEA) - 9 weeks - Elevator counting with reversal (follow up: 9 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,i]	none	13	14	-	MD **1.2 higher** (1.18 lower to 3.58 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Delis-Kaplan Executive Function Scale (DKEFS) Tower Test achievement score - 9 weeks (follow up: 9 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,j]	none	13	14	-	MD **1.3 lower** (3.53 lower to 0.93 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Hotel Test - tasks attempted - 9 weeks (follow up: 9 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,k]	none	13	14	-	MD **0.4 higher** (0.19 lower to 0.99 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Hotel Test - deviation from optimal task time - 9 weeks (follow up: 9 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,l]	none	13	14	-	MD **54.7 lower** (162.87 lower to 53.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: Goal management programme	psychoeducation, 9 weeks	Relative (95% CI)	Absolute (95% CI)		
Cognitive Failures Questionnaire (CFQ; scale 0-100) - 9 weeks (follow up: 9 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,m]	none	13	14	-	MD **5 higher** (4.33 lower to 14.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Dysexecutive Questionnaire (DEX; scale usually 0-80) - 9 weeks - Self-reported (follow up: 9 weeks; Scale from: 0 to 80)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,n]	none	13	14	-	MD **1.8 higher** (5.18 lower to 8.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Dysexecutive Questionnaire (DEX; scale usually 0-80) - 9 weeks - Informant-reported (follow up: 9 weeks; Scale from: 0 to 80)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c,o]	none	13	14	-	MD **1 lower** (14.8 lower to 12.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Profile of Mood States (POMS) - Total Mood Disturbance (scale usually 0-200) - 9 weeks (follow up: 9 weeks; Scale from: 0 to 200)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,p]	none	13	14	-	MD **11.9 higher** (3.64 lower to 27.44 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pittsburgh Sleep Quality Index (PSQI) - Global Sleep Disturbance (scale usually 0-21) - 9 weeks (follow up: 9 weeks; Scale from: 0 to 21)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c,q]	none	13	14	-	MD **0.2 lower** (3.48 lower to 3.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Goal attainment post-intervention - proportion achieving or exceeding target goal - 9 weeks (follow up: 9 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: Goal management programme	psychoeducation, 9 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	7/13 (53.8%)	21.4%	**RR 2.51** (0.82 to 7.72)	**323 more per 1,000** (from 39 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence came from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±13.25

e. MIDs used to assess imprecision were ±2.78

f. MIDs used to assess imprecision were ±48.20

g. MIDs used to assess imprecision were ±1.63

h. MIDs used to assess imprecision were ±0.95

i. MIDs used to assess imprecision were ±1.43

j. MIDs used to assess imprecision were ±1.75

k. MIDs used to assess imprecision were ±0.58

l. MIDs used to assess imprecision were ±137.80

m. MIDs used to assess imprecision were ±7.75

n. MIDs used to assess imprecision were ±6.38

o. MIDs used to assess imprecision were ±8.53

p. MIDs used to assess imprecision were ±15.55

q. MIDs used to assess imprecision were ±2.23

1

2 **Table 42: Clinical evidence profile: Executive function: goal management programme vs. psychoeducation, 8 months**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: Goal management programme	psychoeducation, 8 months	Relative (95% CI)	Absolute (95% CI)		
Sustained Attention to Response Task (SART) errors - 8 months - Commission errors (% of no-go trials) (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	11	12	-	MD **10 higher** (10.47 lower to 30.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Sustained Attention to Response Task (SART) errors - 8 months - Omission errors (% of go trials) (follow up: 8 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,d]	none	11	12	-	MD **0.7 higher** (2 lower to 3.4 higher)	⨁⨁◯◯ LOW	CRITICAL
SART reaction time across go trials - 8 months (follow up: 8 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,e]	none	11	12	-	MD **10.8 lower** (92.78 lower to 71.18 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Test of Everyday Attention (TEA) - 8 months - Elevator counting with distraction (follow up: 8 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,f]	none	11	12	-	MD **0.9 higher** (1.21 lower to 3.01 higher)	⨁⨁◯◯ LOW	CRITICAL
Test of Everyday Attention (TEA) - 8 months - Visual elevator (follow up: 8 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,g]	none	11	12	-	MD **0.5 lower** (1.6 lower to 0.6 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: Goal management programme	psychoeducation, 8 months	Relative (95% CI)	Absolute (95% CI)		
Test of Everyday Attention (TEA) - 8 months - Elevator counting with reversal (follow up: 8 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,h]	none	11	12	-	MD **1.1 higher** (1.35 lower to 3.55 higher)	⨁⨁◯◯ LOW	CRITICAL
Delis-Kaplan Executive Function Scale (DKEFS) Tower Test achievement score - 8 months (follow up: 8 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,i]	none	11	12	-	MD **0.5 lower** (2.35 lower to 1.35 higher)	⨁⨁◯◯ LOW	CRITICAL
Hotel Test - tasks attempted - 8 months (follow up: 8 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,j]	none	11	12	-	MD **0.3 higher** (0.13 lower to 0.73 higher)	⨁⨁◯◯ LOW	CRITICAL
Hotel Test - deviation from optimal task time - 8 months (follow up: 8 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,k]	none	11	12	-	MD **60.9 lower** (167.46 lower to 45.66 higher)	⨁⨁◯◯ LOW	CRITICAL
Cognitive Failures Questionnaire (CFQ; scale 0-100) - 8 months (follow up: 8 months; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,l]	none	11	12	-	MD **5.9 higher** (5.54 lower to 17.34 higher)	⨁⨁◯◯ LOW	CRITICAL
Dysexecutive Questionnaire (DEX; scale usually 0-80) - 8 months - Self-reported (follow up: 8 months; Scale from: 0 to 80)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Executive function: Goal management programme	psychoeducation, 8 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,m]	none	11	12	-	MD **3.2 higher** (4.91 lower to 11.31 higher)	⨁⨁◯◯ LOW	CRITICAL
Dysexecutive Questionnaire (DEX; scale usually 0-80) - 8 months - Informant-reported (follow up: 8 months; Scale from: 0 to 80)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,n]	none	11	12	-	MD **2.7 lower** (12.37 lower to 6.97 higher)	⨁⨁◯◯ LOW	CRITICAL
Profile of Mood States (POMS) - Total Mood Disturbance (scale usually 0-200) - 8 months (follow up: 8 months; Scale from: 0 to 200)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,o]	none	11	12	-	MD **15.8 higher** (2.6 lower to 34.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pittsburgh Sleep Quality Index (PSQI) - Global Sleep Disturbance (scale usually 0-21) - 8 months (follow up: 8 months; Scale from: 0 to 21)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,p]	none	11	12	-	MD **1.3 higher** (1.6 lower to 4.2 higher)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±13.25

d. MIDs used to assess imprecision were ±2.78

e. MIDs used to assess imprecision were ±48.20

f. MIDs used to assess imprecision were ±1.63

g. MIDs used to assess imprecision were ±0.95

h. MIDs used to assess imprecision were ±1.43

i. MIDs used to assess imprecision were ±1.75

j. MIDs used to assess imprecision were ±0.58

k. MIDs used to assess imprecision were ±137.80

l. MIDs used to assess imprecision were ±7.75

m. MIDs used to assess imprecision were ±6.38

n. MIDs used to assess imprecision were ±8.53

o. MIDs used to assess imprecision were ±15.55

p. MIDs used to assess imprecision were ±2.23

Table 43: Clinical evidence profile: Improving language: RehaCom verbal fluency training vs. control (no intervention), 5-10 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Improving language: RehaCom verbal fluency training	control (no intervention), 10 weeks	Relative (95% CI)	Absolute (95% CI)		
California Verbal Learning Test-II (CVLT-II) - 10 weeks (follow up: 10 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	27	26	-	MD **7.38 higher** (0.77 higher to 13.99 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Controlled Oral Word Association Test (COWAT) - 10 weeks (follow up: 10 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Improving language: RehaCom verbal fluency training	control (no intervention), 10 weeks	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	27	26	-	MD **4.89 higher** (0.65 higher to 9.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Adherence - optional dropout of treatment - 5 weeks (follow up: 5 weeks)

1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	3/30 (10.0%)	13.3%	**RR 0.75** (0.18 to 3.07)	**33 fewer per 1,000** (from 109 fewer to 275 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence came from studies reporting the outcome at a time-point <3-month minimum specified in the protocol

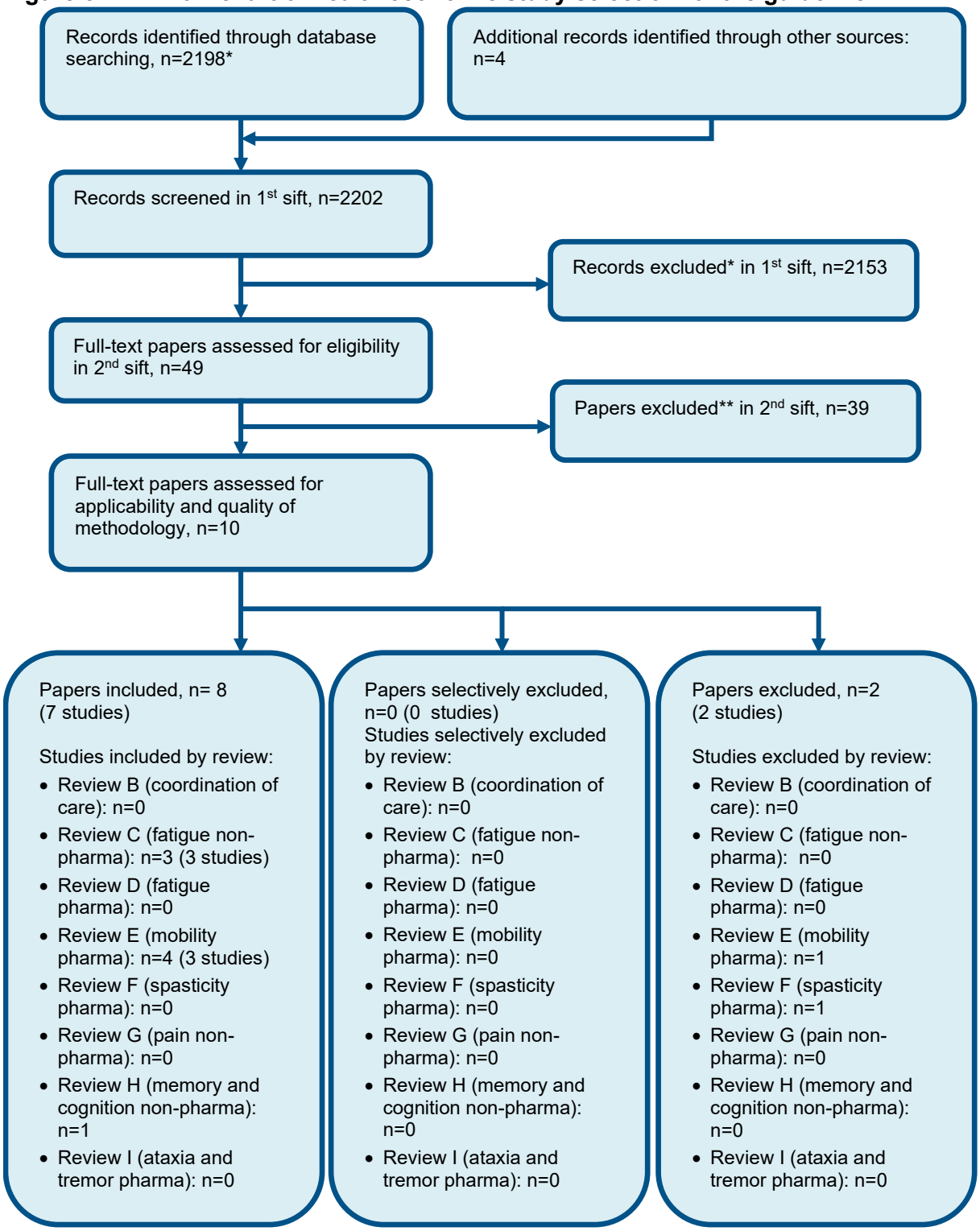
c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MIDs used to assess imprecision were ±6.16

e. MIDs used to assess imprecision were ±3.97

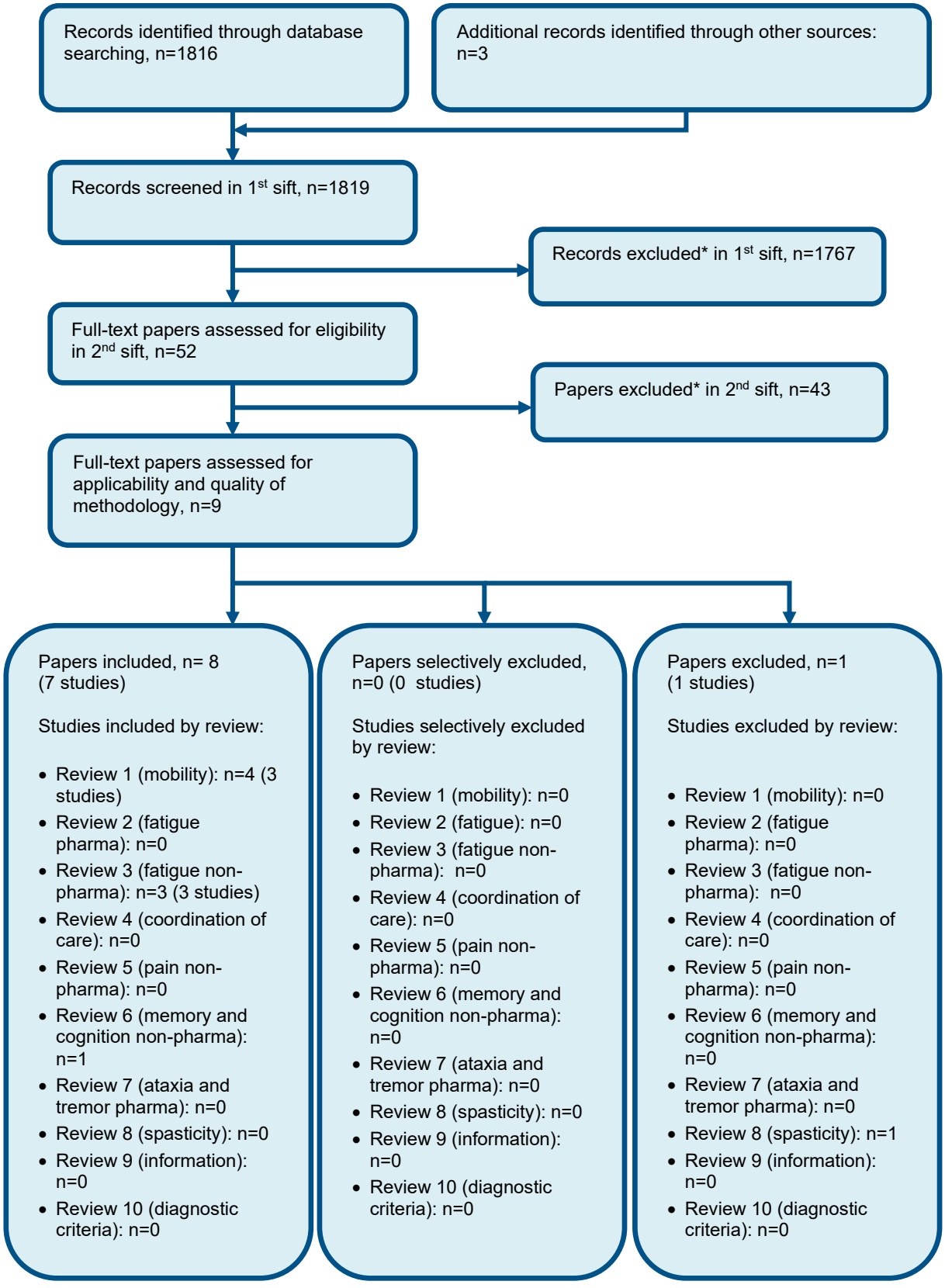
Appendix G – Economic evidence study selection

Figure 542: Flow chart of health economic study selection for the guideline



* Excluding conference abstracts.
**Non-relevant population, intervention, comparison, design or setting; non-English language

Figure 543: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

Study	Lincoln 2020[1]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Within-RCT analysis (CRAMMS RCT, same paper) **Approach to analysis:** Analysis of individual level data for EQ5D and resource use using regression to account for baseline differences. Multiple imputation for missing inputs. Unit costs applied. Incremental cost per improvement in MSIS-Psy score (primary trial outcome) at 12 months also presented. **Perspective:** UK NHS **Follow-up:** 12 months	**Population:** Adults with MS who have cognitive problems **Cohort settings:** Start age: 1. 48.9 (n=204) 2. 49.9 (n=245) Male: 27% **Intervention 1:** Usual care **Intervention 2:** Cognitive rehabilitation for attention and memory problems (10-week intervention, once weekly 1.5-hour group session) and usual care.	**Total costs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): saves £575 (95% CI: saves £1,879 to £729; p=0.39) **Currency & cost year:** 2017 UK pounds **Cost components incorporated:** CRAMMS intervention (including training, implementation and delivery costs) (£209) and healthcare and personal social service resource use, and medication.	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.00 (95% CI:-0.02 to 0.02; p=0.91)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominant Probability Intervention 2 cost effective (£20/£30K threshold): 84.8%/85.7% **Alternative analyses:** Cost per QALY using MSIS-8D to derive QALYs. Incremental QALYs at 12 months were 0.01 (95% CI: -0.01 to 0.03; p=0.19). Intervention 2 remains dominant. Cost per improvement in MSIS-Psy score presented as a sensitivity analysis. Incremental effect -0.5 (95%CI: -1.5 to 0.5). Intervention 2 remains dominant. Across all scenarios, the CIs for both incremental costs and incremental effects span zero, and for the costs, CIs are wide. Given this, caution should be applied in interpreting these results.

Treatment effect duration:[(a)] NA **Discounting:** Costs: NA; Outcomes: NA				**Analysis of uncertainty:** Deterministic one-way sensitivity analyses conducted as well as a threshold analysis and bootstrapping undertaken. In the one-way sensitivity analyses they found that at 12 months, using the lower bound for cost and the upper bound for effect, intervention 2 dominance is observed to be consistent with the base-case analysis, whereas when using the upper bound for cost and the lower bound for effects, intervention 1 is dominant. Using the upper bound for both incremental costs and incremental effects produces an ICER of £31,055 per QALY gained for intervention 2 compared to intervention 1, whereas using the lower bound for both incremental costs and incremental effects produces an ICER of £89,306 per QALY gained for intervention 1 compared to intervention 2. These analysis highlight uncertainty in base-case analysis. Including cognitive assessment in the cost of intervention 2, intervention 2 was no longer cost effective, with an ICER of £39,826 per QALY gained. An available-case analysis was conducted on both outcomes and costs

				as part of a sensitivity analysis. The results of this were similar to the base case and conclusions did not change. Extrapolation beyond 1 year considered but authors deemed that the data inputs would yield an extrapolation of the within-trial results and not produce plausible, reliable, or informative estimates of the longer-term costs and consequences of cognitive rehabilitation.
Data sources				
Health outcomes: QALYs calculated using the area under the curve approach (assuming linear interpolation). Other health outcomes measure included Multiple Sclerosis Impact Scale (MSIS-29) to derive the MSIS-8D and MSIS-Psy, the former was used to estimate QALYs as an alternative QoL outcome measure and the latter health outcomes was presented in a cost-consequence analysis in the paper. No mortality or serious adverse events reported and therefore not included in health economic analysis. **Quality-of-life weights:** EQ5D-5L measured at baseline, 6 and 12 months. EQ5D-5L mapped to EQ5D-3L in base case. Mapping function not reported. **Cost sources:** Intervention resource use from interviews and direct communication with clinical staff involved in trial and trial staff. Some resource use based on assumption (duration of additional catch-up sessions), but these were explored in sensitivity analyses. Healthcare and personal social service resource use from a health and social service questionnaire (UHSSQ) at baseline, 6 and 12 months, completed by participants. Medication resource use based on patient recall. Published unit costs used (PSSRU, NHS reference costs and BNF).				
Comments				
Source of funding: NIHR. **Limitations:** EQ5D-5L mapped to EQ5D-3L but mapping function used was not reported. Does not include all comparators in the review protocol. Based on a single RCT and so may not reflect full body of clinical evidence. RCT and HE analysis based on follow up of only 12 months and many not capture long term costs. **Other:** For the base-case analysis, the costs of the cognitive assessment to determine eligibility for the CRAMMS trial were excluded as these were assumed to be part of usual care. The impact of including the cognitive assessment as part of the CRAMMS trial intervention was tested in a sensitivity analysis.				
Overall applicability: Partially applicable[(b)] **Overall quality: Minor limitations**[(c)]				

Abbreviations: 95% CI= 95% confidence interval; CRAMMS = Cognitive Rehabilitation for Attention and Memory in people with Multiple Sclerosis; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; MSIS 8D= Multiple Sclerosis Impact Scale 8 dimensions; MSIS Psy= Multiple Sclerosis Impact Scale – psychological subscale; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

1 *(b) Directly applicable / Partially applicable / Not applicable*
2 *(c) Minor limitations / Potentially serious limitations / Very serious limitations*

Appendix I – Health economic model

No original economic modelling was undertaken.

Appendix J – Excluded studies

Clinical studies

Table 44: Studies excluded from the clinical review

Study	Code [Reason]
(2019) Impact of an adaptive program for cognitive and emotional deficits (ADACOG program) in multiple sclerosis patients with cognitive impairments. Revue neurologique	- Study design not relevant to this review protocol. *Nonrandomised study.*
Abdolghaderi, M., Narimani, M., Atadokht, A. et al. (2019) Comparing the effect of positive psychotherapy and dialectical behavior therapy on memory and attention in multiple sclerosis patients. NeuroQuantology 17(12): 1-8	- Study design not relevant to this review protocol
Aguirre, N., Cruz-Gomez, A. J., Esbri, S. F. et al. (2021) Enhanced frontoparietal connectivity in multiple sclerosis patients and healthy controls in response to an intensive computerized training focused on working memory. Multiple Sclerosis and Related Disorders 52: 102976	- Population was limited to those without cognitive impairment
Aguirre, N., Cruz-Gomez, A. J., Miro-Padilla, A. et al. (2019) Repeated Working Memory Training Improves Task Performance and Neural Efficiency in Multiple Sclerosis Patients and Healthy Controls. Multiple Sclerosis International 2019: 2657902	- Results reported for MS and healthy control groups combined
Alschuler, K. N., Arewasikporn, A., Nelson, I. K. et al. (2018) Promoting resilience in individuals aging with multiple sclerosis: Results from a pilot randomized controlled trial. Rehabilitation Psychology 63(3): 338-348	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Amato, M. P., Goretti, B., Viterbo, R. G. et al. (2014) Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial. Multiple Sclerosis 20(1): 91-8	- Data not reported in an extractable format or a format that can be analysed
Amatya, B.; Khan, F.; Galea, M. (2019) Rehabilitation for people with multiple sclerosis: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Amiri, M. , Rabiei, M. and Donyavi V (2016) Effectiveness of Mindfulness Training in Enhancing Executive Function and Decreasing Symptoms of Depression and Anxiety in	- Memory and cognition not the focus of the intervention

Study	Code [Reason]
Patients with Multiple Sclerosis (MS). Journal of Behavioral and Brain Science 6(8): 329-336	
Anonymous (2018) Correction: Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial(PLoS ONE (2017) 12:5 e0177177 DOI: 10.1371/journal.pone.0177177). PLoS ONE 13 (1)	- Full text paper not available *ref for correction of results only*
Askari, M., Radmehr, H., Mohammadi, H. et al. (2017) The effectiveness of mindfulness-based cognitive therapy on increasing the quality of life and reducing psychological symptoms in patients with multiple sclerosis. Journal of isfahan medical school 34(410): 1487-1495	- Study not reported in English
Askey-Jones, S., David, A. S., Silber, E. et al. (2013) Cognitive behaviour therapy for common mental disorders in people with Multiple Sclerosis: A bench marking study. Behaviour Research & Therapy 51(10): 648-55	- Study design not relevant to this review protocol
Bahrani, S., Zargar, F., Yousefipour, G. et al. (2017) The effectiveness of mindfulness-integrated cognitive behavior therapy on depression, anxiety, and stress in females with multiple sclerosis: A single blind randomized controlled trial. Iranian Red Crescent Medical Journal 19 (4)	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Barbarulo, A. M., Lus, G., Signoriello, E. et al. (2018) Integrated cognitive and neuromotor rehabilitation in multiple sclerosis: A pragmatic study. Frontiers in Behavioral Neuroscience 12:196	- Study design not relevant to this review protocol
Beckerman, H., Blikman, L. J., Heine, M. et al. (2013) The effectiveness of aerobic training, cognitive behavioural therapy, and energy conservation management in treating MS-related fatigue: the design of the TREFAMS-ACE programme. Trials 14: 250	- Study design not relevant to this review protocol
Benedict, R. H., Shapiro, A., Priore, R. et al. (2000) Neuropsychological counselling improves social behavior in cognitively-impaired multiple sclerosis patients. Multiple Sclerosis 6(6): 391-6	- Insufficient reporting of outcomes
Benedict, Ralph H., Amato, Maria Pia, DeLuca, John et al. (2020) Cognitive impairment in	- Review article but not a systematic review

Study	Code [Reason]
multiple sclerosis: Clinical management, MRI, and therapeutic avenues. The Lancet Neurology 19(10): 860-871	
Bogosian, A., Chadwick, P., Windgassen, S. et al. (2015) Distress improves after mindfulness training for progressive MS: A pilot randomised trial. Multiple Sclerosis 21(9): 1184-94	- Memory and cognition not the focus of the intervention
Bombardier, C. H., Cunniffe, M., Wadhwani, R. et al. (2008) The efficacy of telephone counselling for health promotion in people with multiple sclerosis: a randomized controlled trial. Archives of Physical Medicine & Rehabilitation 89(10): 1849-56	- Memory and cognition not the focus of the intervention
Bonavita, S., Sacco, R., Della Corte, M. et al. (2015) Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study. Journal of Neurology. 262(1):91-100	- Study design not relevant to this review protocol
Boukrina, O., Dobryakova, E., Schneider, V. et al. (2020) Brain activation patterns associated with paragraph learning in persons with multiple sclerosis: The MEMREHAB trial. International Journal of Psychophysiology 154: 37-45	- Insufficient reporting of outcomes
Bovend'Eerdt, T. J., Dawes, H., Sackley, C. et al. (2010) An integrated motor imagery program to improve functional task performance in neurorehabilitation: a single-blind randomized controlled trial. Archives of Physical Medicine & Rehabilitation 91(6): 939-46	- Population not relevant to this review protocol
Brissart H, Leroy M, Morele E et al. (2013) Cognitive rehabilitation in multiple sclerosis. Neurocase 19(6): 553-565	- Study design not relevant to this review protocol
Carletto, S., Borghi, M., Francone, D. et al. (2016) The efficacy of a Mindfulness Based Intervention for depressive symptoms in patients with Multiple Sclerosis and their caregivers: study protocol for a randomized controlled clinical trial. BMC Neurology 16: 7	- Protocol only
Chiaravalloti, N. D. and DeLuca, J. (2008) Cognitive impairment in multiple sclerosis. The Lancet Neurology 7(12): 1139-1151	- Review article but not a systematic review

Study	Code [Reason]
Chiaravalloti, N. D. and DeLuca, J. (2015) The influence of cognitive dysfunction on benefit from learning and memory rehabilitation in MS: A sub-analysis of the MEMREHAB trial. Multiple Sclerosis 21(12): 1575-82	- Secondary publication of an included study that does not provide any additional relevant information
Chiaravalloti, N. D., Moore, N. B., Weber, E. et al. (2021) The application of Strategy-based Training to Enhance Memory (STEM) in multiple sclerosis: A pilot RCT. Neuropsychological Rehabilitation 31(2): 231-254	- Insufficient reporting of outcomes
Clare, L., Teale, J. C., Toms, G. et al. (2018) Cognitive rehabilitation, self-management, psychotherapeutic and caregiver support interventions in progressive neurodegenerative conditions: A scoping review. Neurorehabilitation 43(4): 443-471	- Systematic review used as source of primary studies
Coote, S., Gallagher, S., Msetfi, R. et al. (2014) A randomised controlled trial of an exercise plus behaviour change intervention in people with multiple sclerosis: the step it up study protocol. BMC Neurology 14: 241	- Study design not relevant to this review protocol
Coote, S., Uszynski, M., Herring, M. P. et al. (2017) Effect of exercising at minimum recommendations of the multiple sclerosis exercise guideline combined with structured education or attention control education - secondary results of the step it up randomised controlled trial. BMC Neurology 17(1): 119	- Memory and cognition not the focus of the intervention
Cosio, D., Jin, L., Siddique, J. et al. (2011) The effect of telephone-administered cognitive-behavioural therapy on quality of life among patients with multiple sclerosis. Annals of Behavioral Medicine 41(2): 227-34	- Study does not contain an intervention relevant to this review protocol
Craig, J., Young, C. A., Ennis, M. et al. (2003) A randomised controlled trial comparing rehabilitation against standard therapy in multiple sclerosis patients receiving intravenous steroid treatment. Journal of neurology, neurosurgery, and psychiatry 74(9): 1225-1230	- Study does not contain an intervention relevant to this review protocol
Crawford, J. D. and McIvor, G. P. (1985) Group psychotherapy: Benefits in multiple sclerosis. Archives of Physical Medicine and Rehabilitation 66(12): 810-813	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
Dana, A.; Rafiee, S.; Gholami, A. (2019) Motor reaction time and accuracy in patients with multiple sclerosis: effects of an active computerized training program. Neurological Sciences 40(9): 1849-1854	- Follow-up <1 month
Dardiotis, E., Nousia, A., Siokas, V. et al. (2018) Efficacy of computer-based cognitive training in neuropsychological performance of patients with multiple sclerosis: A systematic review and meta-analysis. Multiple Sclerosis and Related Disorders 20: 58-66	- Systematic review used as source of primary studies
das Nair, R. and Lincoln, N. B. (2012) Evaluation of rehabilitation of memory in neurological disabilities (ReMiND): a randomized controlled trial. Clinical Rehabilitation 26(10): 894-903	- Population not relevant to this review protocol
das Nair, R.; Martin, K. J.; Lincoln, N. B. (2016) Memory rehabilitation for people with multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
dasNair, R., Griffiths, H., Clarke, S. et al. (2019) Everyday memory measures in multiple sclerosis: a systematic review. Neuropsychological Rehabilitation 29(10): 1543-1568	- Systematic review used as source of primary studies
De Keersmaecker, E., Beckwee, D., Denissen, S. et al. (2021) Virtual reality for multiple sclerosis rehabilitation. Cochrane Database of Systematic Reviews	- Protocol only
de Lima, M. F. R., Cavendish, B. A., de Deus, J. S. et al. (2020) Retrieval Practice in Memory- and Language-Impaired Populations: A Systematic Review. Archives of Clinical Neuropsychology 09: 09	- Systematic review used as source of primary studies
De Luca, R., Russo, M., Gasparini, S. et al. (2021) Do people with multiple sclerosis benefit from PC-based neurorehabilitation? A pilot study. Applied Neuropsychology Adult: 28(4):427-435	- Comparator in study does not match that specified in this review protocol
De-Bernardi-Ojuel, L.; Torres-Collado, L.; Garcia-de-la-Hera, M. (2021) Occupational Therapy Interventions in Adults with Multiple Sclerosis or Amyotrophic Lateral Sclerosis: A	- Systematic review used as source of primary studies

Study	Code [Reason]
Scoping Review. International Journal of Environmental Research & Public Health [Electronic Resource] 18(4): 03	
Di Fabio, R. P., Soderberg, J., Choi, T. et al. (1998) Extended outpatient rehabilitation: its influence on symptom frequency, fatigue, and functional status for persons with progressive multiple sclerosis. Archives of Physical Medicine & Rehabilitation 79(2): 141-6	- Study design not relevant to this review protocol
Di Tella, S., Pagliari, C., Blasi, V. et al. (2020) Integrated telerehabilitation approach in multiple sclerosis: A systematic review and meta-analysis. Journal of Telemedicine & Telecare 26(78): 385-399	- Systematic review used as source of primary studies
Dobryakova, E., Wylie, G. R., DeLuca, J. et al. (2014) A pilot study examining functional brain activity 6 months after memory retraining in MS: the MEMREHAB trial. Brain Imaging & Behavior 8(3): 403-6	- Insufficient reporting of outcomes
Dunne, J., Chih, H. J., Begley, A. et al. (2021) A randomised controlled trial to test the feasibility of online mindfulness programs for people with multiple sclerosis. Multiple Sclerosis and Related Disorders 48: 102728	- Study does not contain an intervention relevant to this review protocol
Dwyer, C. P., Alvarez-Iglesias, A., Joyce, R. et al. (2020) Evaluating the feasibility and preliminary efficacy of a Cognitive Occupation-Based programme for people with Multiple Sclerosis (COB-MS): protocol for a feasibility cluster-randomised controlled trial. Trials [Electronic Resource] 21(1): 269	- Study design not relevant to this review protocol
Elwishy, A., Ebraheim, A. M., Ashour, A. S. et al. (2020) Influences of Dual-Task Training on Walking and Cognitive Performance of People With Relapsing Remitting Multiple Sclerosis: Randomized Controlled Trial. Journal of Chiropractic Medicine 19(1): 1-8	- Study does not contain an intervention relevant to this review protocol
Ernst, A., Blanc, F., De Seze, J. et al. (2015) Using mental visual imagery to improve autobiographical memory and episodic future thinking in relapsing-remitting multiple sclerosis patients: A randomised-controlled trial study. Restorative Neurology & Neuroscience 33(5): 621-38	- Insufficient reporting of outcomes

Study	Code [Reason]
Ernst, A., Sourty, M., Roquet, D. et al. (2018) Benefits from an autobiographical memory facilitation programme in relapsing-remitting multiple sclerosis patients: a clinical and neuroimaging study. Neuropsychological Rehabilitation 28(7): 1110-1130	- Secondary publication of an included study that does not provide any additional relevant information
Eyssen, I. C., Steultjens, M. P., de Groot, V. et al. (2013) A cluster randomised controlled trial on the efficacy of client-centred occupational therapy in multiple sclerosis: good process, poor outcome. Disability and rehabilitation 35(19): 1636-1646	- Study does not contain an intervention relevant to this review protocol
Feinstein, A., Amato, M. P., Brichetto, G. et al. (2020) Study protocol: improving cognition in people with progressive multiple sclerosis: a multi-arm, randomized, blinded, sham-controlled trial of cognitive rehabilitation and aerobic exercise (COGEx). BMC Neurology 20(1): 204	- Protocol only
Feys, P., Moumdjian, L., Van Halewyck, F. et al. (2019) Effects of an individual 12-week community-located "start-to-run" program on physical capacity, walking, fatigue, cognitive function, brain volumes, and structures in persons with multiple sclerosis. Multiple Sclerosis 25(1): 92-103	- Study does not contain an intervention relevant to this review protocol
Freeman, J. A., Langdon, D. W., Hobart, J. C. et al. (1997) The impact of inpatient rehabilitation on progressive multiple sclerosis. Annals of Neurology 42(2): 236-44	- Study does not contain an intervention relevant to this review protocol
Gandy, M., Karin, E., McDonald, S. et al. (2020) A feasibility trial of an internet-delivered psychological intervention to manage mental health and functional outcomes in neurological disorders. Journal of Psychosomatic Research 136: 110173	- Population not relevant to this review protocol
Ghielen, I., Rutten, S., Boeschoten, R. E. et al. (2019) The effects of cognitive behavioural and mindfulness-based therapies on psychological distress in patients with multiple sclerosis, Parkinson's disease and Huntington's disease: Two meta-analyses. Journal of Psychosomatic Research 122: 43-51	- Systematic review used as source of primary studies
Gholami, M., Nami, M., Shamsi, F. et al. (2021) Effects of transcranial direct current stimulation	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
on cognitive dysfunction in multiple sclerosis. Neurophysiologie Clinique 51(4):319-328	
Gich J, Freixenet J, Garcia R et al. (2015) A new cognitive rehabilitation programme for patients with multiple sclerosis: the 'MS-line! Project'. Multiple sclerosis 21(10): 1344-1348	- Study design not relevant to this review protocol
Gomez-Gastiasoro, A., Pena, J., Ibarretxe-Bilbao, N. et al. (2019) A Neuropsychological Rehabilitation Program for Cognitive Impairment in Psychiatric and Neurological Conditions: A Review That Supports Its Efficacy. Behavioural Neurology 2019 :4647134	- Review article but not a systematic review
Goodwin, R. A., Lincoln, N. B., das Nair, R. et al. (2020) Evaluation of NeuroPage as a memory aid for people with multiple sclerosis: A randomised controlled trial. Neuropsychological Rehabilitation 30(1): 15-31	- Study design not relevant to this review protocol
Goodwin, R., Lincoln, N., das Nair, R. et al. (2017) External memory aids for memory problems in people with multiple sclerosis: A systematic review. Neuropsychological Rehabilitation 27(8): 1081-1102	- Systematic review used as source of primary studies
Goverover, Y., Chiaravalloti, N. D., O'Brien, A. R. et al. (2018) Evidenced-Based Cognitive Rehabilitation for Persons With Multiple Sclerosis: An Updated Review of the Literature From 2007 to 2016. Archives of Physical Medicine & Rehabilitation 99(2): 390-407	- Systematic review used as source of primary studies
Graziano, F., Calandri, E., Borghi, M. et al. (2014) The effects of a group-based cognitive behavioural therapy on people with multiple sclerosis: a randomized controlled trial. Clinical Rehabilitation 28(3): 264-74	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Gromisch, E. S.; Fiszdon, J. M.; Kurtz, M. M. (2020) The effects of cognitive-focused interventions on cognition and psychological well-being in persons with multiple sclerosis: A meta-analysis. Neuropsychological Rehabilitation 30(4): 767-786	- Systematic review used as source of primary studies
Grossman, P., Kappos, L., Gensicke, H. et al. (2010) MS quality of life, depression, and fatigue improve after mindfulness training: A randomized trial. Neurology 75(13): 1141-1149	- Focus is not on memory or cognition as no memory or cognition outcomes reported

Study	Code [Reason]
Guijarro-Castro, C., Aladro-Benito, Y., Sanchez-Musulim, A. et al. (2017) Face-to-Face or Telematic Cognitive Stimulation in Patients with Multiple Sclerosis and Cognitive Impairment: Why Not Both?. Behavioural Neurology 2017: 5713934	- Protocol only
Gutierrez-Cruz, C., Rojas-Ruiz, F. J., De la Cruz-Marquez, J. C. et al. (2020) Effect of a Combined Program of Strength and Dual Cognitive-Motor Tasks in Multiple Sclerosis Subjects. International Journal of Environmental Research & Public Health 17(17): 02	- Study does not contain an intervention relevant to this review protocol
Hajibabaei, M., Kajbaf, B., Esmaeili, M. et al. (2020) Impact of an Existential-Spiritual Intervention Compared with a Cognitive-Behavioral Therapy on Quality of Life and Meaning in Life among Women with Multiple Sclerosis. Iranian Journal of Psychiatry 15(4): 322-330	- Study does not contain an intervention relevant to this review protocol
Hamalainen, P. and Rosti-Otajarvi, E. (2014) Is neuropsychological rehabilitation effective in multiple sclerosis?. Neurodegenerative Disease Management 4(2): 147-54	- Review article but not a systematic review
Han, A. (2021) Effects of mindfulness-and acceptance-based interventions on quality of life, coping, cognition, and mindfulness of people with multiple sclerosis: a systematic review and meta-analysis. Psychology Health & Medicine: 1-18	- Systematic review used as source of primary studies
Han, A. (2021) Mindfulness-and acceptance-based interventions for symptom reduction of people with multiple sclerosis: A systematic review and meta-analysis. Archives of physical medicine and rehabilitation. 102(10): 2022-2031.e4	- Systematic review used as source of primary studies
Harand, C., Daniel, F., Mondou, A. et al. (2019) Neuropsychological management of multiple sclerosis: evaluation of a supervised and customized cognitive rehabilitation program for self-used at home (SEPIA): protocol for a randomized controlled trial. Trials 20(1): 614	- Protocol only
Hayes, S., Uszynski, M. K., Motl, R. W. et al. (2017) Randomised controlled pilot trial of an exercise plus behaviour change intervention in	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
people with multiple sclerosis: the Step it Up study. BMJ Open 7(10): e016336	
Heine, M., Beckerman, H., Hamalainen, P. et al. (2020) Evidence-Based Rehabilitation for Multiple Sclerosis Made Easy: The Online Applying Evidence with Confidence (APPECO) Platform. International Journal of Ms Care 22(6): 263-269	- Review article but not a systematic review
Hoang, P., Schoene, D., Gandevia, S. et al. (2016) Effects of a home-based step training programme on balance, stepping, cognition and functional performance in people with multiple sclerosis - A randomized controlled trial. Multiple Sclerosis 22(1): 94-103	- Study does not contain an intervention relevant to this review protocol
Hubacher, M., Kappos, L., Weier, K. et al. (2015) Case-based fMRI analysis after cognitive rehabilitation in MS: A novel approach. Frontiers in Neurology 6: 78	- Study design not relevant to this review protocol
Huiskamp, M., Dobryakova, E., Wylie, G. D. et al. (2016) A pilot study of changes in functional brain activity during a working memory task after mSMT treatment: The MEMREHAB trial. Multiple Sclerosis and Related Disorders 7: 76-82	- Secondary publication of an included study that does not provide any additional relevant information
Impellizzeri, F., Leonardi, S., Latella, D. et al. (2020) An integrative cognitive rehabilitation using neurologic music therapy in multiple sclerosis: A pilot study. Medicine 99(4): e18866	- Comparator in study does not match that specified in this review protocol
Jimenez-Morales, R. M., Herrera-Jimenez, L. F., Macias-Delgado, Y. et al. (2017) Cognitive training combined with aerobic exercises in multiple sclerosis patients: a pilot study. Revista de neurologia 64(11): 489-495	- Study not reported in English
Jongen, P. J., Heerings, M., Ruimschotel, R. et al. (2016) An intensive social cognitive program (can do treatment) in people with relapsing remitting multiple sclerosis and low disability: a randomized controlled trial protocol. BMC Neurology 16: 81	- Protocol only
Jongen, P. J., van Mastrigt, G. A., Heerings, M. et al. (2019) Effect of an intensive 3-day social cognitive treatment (can do treatment) on control self-efficacy in patients with relapsing remitting multiple sclerosis and low disability: A	- Focus is not on memory or cognition as no memory or cognition outcomes reported

Study	Code [Reason]
single-centre randomized controlled trial. PLoS ONE [Electronic Resource] 14(10): e0223482	
Jonsdottir, J., Gervasoni, E., Bowman, T. et al. (2018) Intensive Multimodal Training to Improve Gait Resistance, Mobility, Balance and Cognitive Function in Persons With Multiple Sclerosis: A Pilot Randomized Controlled Trial. Frontiers in neurology. 9: 800	- Study does not contain an intervention relevant to this review protocol
Kahraman, T., Savci, S., Ozdogar, A. T. et al. (2020) Physical, cognitive and psychosocial effects of telerehabilitation-based motor imagery training in people with multiple sclerosis: A randomized controlled pilot trial. Journal of Telemedicine & Telecare 26(5): 251-260	- Study does not contain an intervention relevant to this review protocol
Kalina, J. T., Hinojosa, J., Strober, L. et al. (2018) Randomized Controlled Trial to Improve Self-Efficacy in People With Multiple Sclerosis: The Community Reintegration for Socially Isolated Patients (CRISP) Program. The American journal of occupational therapy : official publication of the American Occupational Therapy Association 72(5): 7205205030p1-7205205030p8	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Kardiasmenos KS, Clawson DM, Wilken JA et al. (2008) Prospective memory and the efficacy of a memory strategy in multiple sclerosis. Neuropsychology 22(6): 746-754	- Study design not relevant to this review protocol
Kermani, L. S., Fazilat-Pour, M., Hossein Mousavi Nasab, S. M. et al. (2020) Effectiveness of mindfulness integrated cognitive behavioural therapy on the emotional states and quality of life of patients with multiple sclerosis: a clinical trial study. Koomesh 22(3): 446-451	- Study not reported in English
Khan, F. and Amatya, B. (2017) Rehabilitation in Multiple Sclerosis: A Systematic Review of Systematic Reviews. Archives of Physical Medicine & Rehabilitation 98(2): 353-367	- Systematic review used as source of primary studies
Khan, F., Amatya, B., Kesselring, J. et al. (2015) Telerehabilitation for persons with multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Khan, F.; Ng, L.; Turner-Stokes, L. (2009) Effectiveness of vocational rehabilitation	- Systematic review used as source of primary studies

Study	Code [Reason]
intervention on the return to work and employment of persons with multiple sclerosis. Cochrane Database of Systematic Reviews	
Khan, F., Pallant, J. F., Brand, C. et al. (2008) Effectiveness of rehabilitation intervention in persons with multiple sclerosis: a randomised controlled trial. Journal of Neurology, Neurosurgery & Psychiatry 79(11): 1230-5	- Study does not contain an intervention relevant to this review protocol
Khan, F., Turner-Stokes, L., Ng, L. et al. (2007) Multidisciplinary rehabilitation for adults with multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Kiropoulos, L., Kilpatrick, T., Kalincik, T. et al. (2020) Comparison of the effectiveness of a tailored cognitive behavioural therapy with a supportive listening intervention for depression in those newly diagnosed with multiple sclerosis (the ACTION-MS trial): protocol of an assessor-blinded, active comparator, randomised controlled trial. Trials 21(1): 100	- Protocol only
Kopke, S., Kasper, J., Muhlhauser, I. et al. (2009) Patient education program to enhance decision autonomy in multiple sclerosis relapse management: A randomized-controlled trial. Multiple Sclerosis 15(1): 96-104	- Study does not contain an intervention relevant to this review protocol
Korakas, Nikolaos and Tsolaki, Magda (2016) Cognitive impairment in multiple sclerosis: A review of neuropsychological assessments. Cognitive and Behavioral Neurology 29(2): 55-67	- Study design not relevant to this review protocol
Krause, N., Riemann-Lorenz, K., Steffen, T. et al. (2021) Study protocol for a randomised controlled trial of a web-based behavioural lifestyle programme for emPOWERment in early Multiple Sclerosis (POWER@MS1). BMJ Open 11(2): e041720	- Protocol only
Lampit, A., Heine, J., Finke, C. et al. (2019) Computerized Cognitive Training in Multiple Sclerosis: A Systematic Review and Meta-analysis. Neurorehabilitation & Neural Repair 33(9): 695-706	- Systematic review used as source of primary studies
Lannin, N. and Longley, W. A. (2006) The evidence for the effectiveness of psychological interventions to assist people with cognitive	- Systematic review used as source of primary studies

Study	Code [Reason]
impairments with multiple sclerosis was found to be inconclusive. Australian Occupational Therapy Journal 53(4): 341-343	
Latorraca, C. O. C., Martimbianco, A. L. C., Pachito, D. V. et al. (2019) Palliative care interventions for people with multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Leavitt, V. M., Wylie, G. R., Girgis, P. A. et al. (2014) Increased functional connectivity within memory networks following memory rehabilitation in multiple sclerosis. Brain Imaging & Behavior 8(3): 394-402	- Secondary publication of an included study that does not provide any additional relevant information
Leonardi, S., Maggio, M. G., Russo, M. et al. (2021) Cognitive recovery in people with relapsing/remitting multiple sclerosis: A randomized clinical trial on virtual reality-based neurorehabilitation. Clinical Neurology & Neurosurgery 208: 106828	- Comparator in study does not match that specified in this review protocol
Lin, W. S.; Lin, S. J.; Hsu, T. R. (2020) Cognitive Assessment and Rehabilitation for Pediatric-Onset Multiple Sclerosis: A Scoping Review. Children 7(10): 15	- Population not relevant to this review protocol
Lincoln, N. B., das Nair, R., Bradshaw, L. et al. (2015) Cognitive Rehabilitation for Attention and Memory in people with Multiple Sclerosis: study protocol for a randomised controlled trial (CRAMMS). Trials 16: 556	- Protocol only
Liu, Y. (2017) A hope-based group therapy program to women with multiple sclerosis: Quality of life. NeuroQuantology 15(4): 127-132	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Longley, W. A.; Tate, R. L.; Brown, R. F. (2012) A protocol for measuring the direct psychological benefit of neuropsychological assessment with feedback in multiple sclerosis. Brain Impairment 13(2): 238-255	- Protocol only
Maggio, M. G., De Luca, R., Manuli, A. et al. (2020) Do patients with multiple sclerosis benefit from semi-immersive virtual reality? A randomized clinical trial on cognitive and motor outcomes. Applied Neuropsychology adult: 1-7	- Comparator in study does not match that specified in this review protocol
Maggio, M. G., Russo, M., Cuzzola, M. F. et al. (2019) Virtual reality in multiple sclerosis	- Systematic review used as source of primary studies

Study	Code [Reason]
rehabilitation: A review on cognitive and motor outcomes. Journal of Clinical Neuroscience 65: 106-111	
Malekzadeh, M., Hashemi Mohammadabad, N., Kharamin, S. et al. (2020) The Effectiveness of Group-based Cognitive Hypnotherapy on the Psychological Well-being of Patients with Multiple Sclerosis: A Randomized Clinical Trial. American Journal of Clinical Hypnosis 62(4): 364-379	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Mattioli, F., Bellomi, F., Stampatori, C. et al. (2016) Neuroenhancement through cognitive training and anodal tDCS in multiple sclerosis. Multiple Sclerosis 22(2): 222-30	- Study does not contain an intervention relevant to this review protocol
Mattioli, Flavia, Stampatori, Chiara, Zanotti, Deborah et al. (2011) "Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis": Erratum. Journal of the Neurological Sciences 303(12): 151	- Secondary publication of an included study that does not provide any additional relevant information
McKeever, J. D., Schultheis, M. T., Sim, T. et al. (2019) Selective reminding of prospective memory in Multiple Sclerosis. Neuropsychological Rehabilitation 29(5): 675-690	- Study design not relevant to this review protocol
Mendoza, R. J.; Pittenger, D. J.; Weinstein, C. S. (2001) Unit management of depression of patients with multiple sclerosis using cognitive remediation strategies: a preliminary study. Neurorehabilitation & Neural Repair 15(1): 9-14	- Insufficient reporting of outcomes
Mhizha-Murira, J. R., Drummond, A., Klein, O. A. et al. (2018) Reporting interventions in trials evaluating cognitive rehabilitation in people with multiple sclerosis: a systematic review. Clinical Rehabilitation 32(2): 243-254	- Systematic review used as source of primary studies
Miller, E., Morel, A., Redlicka, J. et al. (2018) Pharmacological and Non-pharmacological Therapies of Cognitive Impairment in Multiple Sclerosis. Current Neuropharmacology 16(4): 475-483	- Review article but not a systematic review
Mitolo, M., Venneri, A., Wilkinson, I. D. et al. (2015) Cognitive rehabilitation in multiple sclerosis: A systematic review. Journal of the Neurological Sciences 354(12): 1-9	- Systematic review used as source of primary studies

Study	Code [Reason]
Mohr, D. C.; Hart, S.; Vella, L. (2007) Reduction in disability in a randomized controlled trial of telephone-administered cognitive-behavioural therapy. Health Psychology 26(5): 554-63	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Momenabadi, V., Kaveh, M. H., Nakhaee, N. et al. (2019) Effect of educational intervention based on health-promoting self-care behaviors model on quality of life, resilience, and sense of coherence in patients with multiple sclerosis: A randomized controlled trial. Iranian Red Crescent Medical Journal 21 (12)	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Momsen, A. H.; Ortenblad, L.; Maribo, T. (2021) Effective rehabilitation interventions and participation among people with multiple sclerosis: an overview of reviews. Annals of Physical & Rehabilitation Medicine: 101529	- Full text paper not available
Moore, K. S., Peterson, D. A., O'Shea, G. et al. (2008) The effectiveness of music as a mnemonic device on recognition memory for people with multiple sclerosis. Journal of Music Therapy 45(3): 307-29	- Comparator in study does not match that specified in this review protocol
Morrow, S. A., Riccio, P., Vording, N. et al. (2021) A mindfulness group intervention in newly diagnosed persons with multiple sclerosis: A pilot study. Multiple Sclerosis and Related Disorders 52: 103016	- Memory and cognition not the focus of the intervention
Moss-Morris, R., Dennison, L., Landau, S. et al. (2013) A randomized controlled trial of cognitive behavioural therapy (CBT) for adjusting to multiple sclerosis (the saMS trial): does CBT work and for whom does it work? Journal of Consulting & Clinical Psychology 81(2): 251-62	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Mosweu, I., Moss-Morris, R., Dennison, L. et al. (2017) Cost-effectiveness of nurse-delivered cognitive behavioural therapy (CBT) compared to supportive listening (SL) for adjustment to multiple sclerosis. Health Economics Review 7(1): 36	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Motl, R. W., Sandroff, B. M., Wingo, B. C. et al. (2018) Phase-III, randomized controlled trial of the behavioural intervention for increasing physical activity in multiple sclerosis: Project BIPAMS. Contemporary Clinical Trials 71: 154-161	- Protocol only

Study	Code [Reason]
Nauta, I. M., Speckens, A. E. M., Kessels, R. P. C. et al. (2017) Cognitive rehabilitation and mindfulness in multiple sclerosis (REMIND-MS): a study protocol for a randomised controlled trial. BMC Neurology 17(1): 201	- Protocol only
Nedeljkovic, U., Raspopovic, E. D., Ilic, N. et al. (2016) Effectiveness of rehabilitation in multiple sclerosis relapse on fatigue, self-efficacy and physical activity. Acta Neurologica Belgica 116(3): 309-315	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Nordin, L. and Rorsman, I. (2011) Brief cognitive behavioural therapy in outpatient groups with multiple sclerosis. A randomised controlled pilot study on acceptance and commitment therapy and relaxation training. Multiple sclerosis [abstracts of the 5th joint triennial congress of the european and americas committees for treatment and research in multiple sclerosis; 2011 oct 19-22 ; amsterdam netherlands] 17(10suppl1): 249	- Conference abstract
Nordin, L. and Rorsman, Ia (2012) Cognitive behavioural therapy in multiple sclerosis: a randomized controlled pilot study of acceptance and commitment therapy. Journal of Rehabilitation Medicine 44(1): 87-90	- Focus is not on memory or cognition as no memory or cognition outcomes reported
O'Brien, A. R., Chiaravalloti, N., Goverover, Y. et al. (2008) Evidenced-based cognitive rehabilitation for persons with multiple sclerosis: a review of the literature. Archives of Physical Medicine & Rehabilitation 89(4): 761-9	- Systematic review used as source of primary studies
Omrani, S., Mirzaeian, B., Aghabagheri, H. et al. (2012) Investigating effectuality of cognitive-behavioural therapy (CBT) as group method on the basis of hope rate in patients suffering from multiple sclerosis (M.S). Journal of mazandaran university of medical sciences 22(93): 57-65	- Study not reported in English
Orel, Olga (2014) Training of attention in patients with remitting-relapsing multiple sclerosis. Applied Psychology Bulletin 270(62): 59-64	- Comparator in study does not match that specified in this review protocol
Oz, H. S. and Oz, F. (2020) A psychoeducation program for stress management and psychosocial problems in multiple sclerosis. Nigerian Journal of Clinical Practice 23(11): 1598-1606	- Focus is not on memory or cognition as no memory or cognition outcomes reported

Study	Code [Reason]
Ozdogar, A. T., Ertekin, O., Kahraman, T. et al. (2020) Effect of video-based exergaming on arm and cognitive function in persons with multiple sclerosis: A randomized controlled trial. Multiple Sclerosis and Related Disorders 40: 101966	- Study does not contain an intervention relevant to this review protocol
Ozkul, C., Guclu-Gunduz, A., Eldemir, K. et al. (2020) Effect of task-oriented circuit training on motor and cognitive performance in patients with multiple sclerosis: A single-blinded randomized controlled trial. Neurorehabilitation 46(3): 343-353	- Study does not contain an intervention relevant to this review protocol
Ozkul, C., Guclu-Gunduz, A., Eldemir, K. et al. (2020) Combined exercise training improves cognitive functions in multiple sclerosis patients with cognitive impairment: A single-blinded randomized controlled trial. Multiple Sclerosis and Related Disorders 45: 102419	- Study does not contain an intervention relevant to this review protocol
Ozkul, C., Guclu-Gunduz, A., Yazici, G. et al. (2020) Effect of immersive virtual reality on balance, mobility, and fatigue in patients with multiple sclerosis: A single-blinded randomized controlled trial. European Journal of Integrative Medicine 35: 101092	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Panagopoulou, Z., Artemiadis, A. K., Chrousos, G. P. et al. (2021) Pythagorean Self-Awareness Intervention for Multiple Sclerosis Patients: A Quasi-Experimental Pragmatic Trial. Archives of Clinical Neuropsychology 15: 15	- Study design not relevant to this review protocol
Patti, F., Ciancio, M. R., Cacopardo, M. et al. (2003) Effects of a short outpatient rehabilitation treatment on disability of multiple sclerosis patients--a randomised controlled trial. Journal of Neurology 250(7): 861-6	- Study does not contain an intervention relevant to this review protocol
Pedulla, L., Brichetto, G., Tacchino, A. et al. (2016) Adaptive vs. non-adaptive cognitive training by means of a personalized App: a randomized trial in people with multiple sclerosis. Journal of Neuroengineering & Rehabilitation 13(1): 88	- Comparator in study does not match that specified in this review protocol
Penner, Iris-Katharina and Kappos, Ludwig (2006) Retraining attention in MS. Journal of the Neurological Sciences 245(12): 147-151	- Review article but not a systematic review

Study	Code [Reason]
Perez, T. O., Hernandez, M. B., Perez, M. A. H. et al. (2018) A randomized trial of cognitive behavioural therapy for improving psychological distress and cognitive impairments in multiple sclerosis. Multiple sclerosis journal 24: 238-239	- Conference abstract
Plohmann, A. M., Kappos, L., Ammann, W. et al. (1998) Computer assisted retraining of attentional impairments in patients with multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry 64(4): 455-62	- Study design not relevant to this review protocol
Rahn, A. C., Wenzel, L., Icks, A. et al. (2021) Development and evaluation of an interactive web-based decision-making programme on relapse management for people with multiple sclerosis (POWER@MS2)-study protocol for a randomised controlled trial. Trials 22 (1)	- Protocol only
Rigby, S. A.; Thornton, E. W.; Young, C. A. (2008) A randomized group intervention trial to enhance mood and self-efficacy in people with multiple sclerosis. British Journal of Health Psychology 13(pt4): 619-31	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Rodgers, D., Khoo, K., MacEachen, M. et al. (1996) Cognitive therapy for multiple sclerosis: a preliminary study. Alternative Therapies in Health & Medicine 2(5): 70-4	- Study design not relevant to this review protocol
Rooney, S.; Ozkul, C.; Paul, L. (2020) Correlates of dual-task performance in people with multiple sclerosis: A systematic review. Gait & Posture 81: 172-182	- Study design not relevant to this review protocol
Rosti-Otajärvi, E. M. and Hämäläinen, P. I. (2014) Neuropsychological rehabilitation for multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Saeedi, H., Nasab, S. M. H. M., Zadeh, A. M. et al. (2015) The effectiveness of positive psychology interventions with Islamic approach on quality of life in females with Multiple Sclerosis. Biomedical and Pharmacology Journal 8(2): 965-970	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Schirda, Brittney Leigh (2021) Mindfulness training and impact on emotion dysregulation and strategy use in multiple sclerosis: A pilot, placebo-controlled, randomized controlled trial.	- Full text paper not available

Study	Code [Reason]
Dissertation Abstracts International: Section B: The Sciences and Engineering 82(7b):	
Senders, A., Hanes, D., Bourdette, D. et al. (2019) Impact of mindfulness-based stress reduction for people with multiple sclerosis at 8 weeks and 12 months: A randomized clinical trial. Multiple Sclerosis 25(8): 1178-1188	- Memory and cognition not the focus of the intervention
Sesel, A. L., Sharpe, L., Beadnall, H. N. et al. (2019) The evaluation of an online mindfulness program for people with multiple sclerosis: study protocol. BMC Neurology 19(1): 129	- Protocol only
Sesel, A. L.; Sharpe, L.; Naismith, S. L. (2018) Efficacy of Psychosocial Interventions for People with Multiple Sclerosis: A Meta-Analysis of Specific Treatment Effects. Psychotherapy & Psychosomatics 87(2): 105-111	- Systematic review used as source of primary studies
Shahpouri, M. M., Barekatain, M., Tavakoli, M. et al. (2020) Comparison of Cognitive Rehabilitation versus Donepezil Therapy on Memory Performance, Attention, Quality of Life, and Depression among Multiple Sclerosis Patients. Neurology Research International 2020: 8874424	- Study design not relevant to this review protocol
Shinto, L., Calabrese, C., Morris, C. et al. (2008) A randomized pilot study of naturopathic medicine in multiple sclerosis. Journal of Alternative & Complementary Medicine 14(5): 489-96	- Study does not contain an intervention relevant to this review protocol
Sigmundsdottir, L.; Longley, W. A.; Tate, R. L. (2016) Computerised cognitive training in acquired brain injury: A systematic review of outcomes using the International Classification of Functioning (ICF). Neuropsychological Rehabilitation 26(56): 673-741	- Systematic review used as source of primary studies
Silveira, S. L., McCroskey, J., Wingo, B. C. et al. (2019) eHealth-Based Behavioral Intervention for Increasing Physical Activity in Persons With Multiple Sclerosis: Fidelity Protocol for a Randomized Controlled Trial. JMIR Research Protocols 8(3): e12319	- Protocol only
Simpson, R., Booth, J., Lawrence, M. et al. (2014) Mindfulness based interventions in multiple sclerosis--a systematic review. BMC Neurology 14: 15	- Systematic review used as source of primary studies

Study	Code [Reason]
Simpson, R.; Mair, F. S.; Mercer, S. W. (2017) Mindfulness-based stress reduction for people with multiple sclerosis - a feasibility randomised controlled trial. BMC Neurology 17(1): 94	- Memory and cognition not the focus of the intervention
Simpson, R., Simpson, S., Ramparsad, N. et al. (2019) Mindfulness-based interventions for mental well-being among people with multiple sclerosis: a systematic review and meta-analysis of randomised controlled trials. Journal of Neurology, Neurosurgery & Psychiatry 90(9): 1051-1058	- Systematic review used as source of primary studies
Sokolov, A. A.; Grivaz, P.; Bove, R. (2018) Cognitive Deficits in Multiple Sclerosis: Recent Advances in Treatment and Neurorehabilitation. Current Treatment Options in Neurology 20(12): 53	- Review article but not a systematic review
Solari, A., Giordano, A., Grasso, M. G. et al. (2015) Home-based palliative approach for people with severe multiple sclerosis and their carers: study protocol for a randomized controlled trial. Trials 16: 184	- Study does not contain an intervention relevant to this review protocol
Solari, A., Giordano, A., Patti, F. et al. (2018) Randomized controlled trial of a home-based palliative approach for people with severe multiple sclerosis. Multiple Sclerosis 24(5): 663-674	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Solari, A., Motta, A., Mendozzi, L. et al. (2004) Erratum: Computer-aided retraining of memory and attention in people with multiple sclerosis: A randomized, double-blind controlled trial. Journal of the Neurological Sciences 224(12): 113	- Study design not relevant to this review protocol
Sorensen, J., Lee, A., Lovendahl, B. et al. (2012) Study protocol: to investigate effects of highly specialized rehabilitation for patients with multiple sclerosis. A randomized controlled trial of a personalized, multidisciplinary intervention. BMC Health Services Research 12: 306	- Protocol only
Sosnoff, J. J., Wajda, D. A., Sandroff, B. M. et al. (2017) Dual task training in persons with Multiple Sclerosis: a feasability randomized controlled trial. Clinical Rehabilitation 31(10): 1322-1331	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
Steultjens, Eemj, Dekker, J. J., Bouter, L. M. et al. (2003) Occupational therapy for multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Stimmel, M. B., Cohen, J. N., Schneider, S. J. et al. (2020) A neuropsychologically-based intervention with increased follow-up support for employed women with multiple sclerosis: a pilot randomized controlled trial. Clinical Rehabilitation 34(10): 1292-1302	- Study does not contain an intervention relevant to this review protocol
Suh, Y., Motl, R. W., Olsen, C. et al. (2015) Pilot Trial of a Social Cognitive Theory-Based Physical Activity Intervention Delivered by Nonsupervised Technology in Persons With Multiple Sclerosis. Journal of Physical Activity & Health 12(7): 924-30	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Tesar, N., Baumhackl, U., Kopp, M. et al. (2003) Effects of psychological group therapy in patients with multiple sclerosis. Acta Neurologica Scandinavica 107(6): 394-399	- Study design not relevant to this review protocol
Thaut, M. H., Peterson, D. A., McIntosh, G. C. et al. (2014) Music mnemonics aid Verbal Memory and Induce Learning - Related Brain Plasticity in Multiple Sclerosis. Frontiers in Human Neuroscience 8: 395	- Study does not contain an intervention relevant to this review protocol - Insufficient reporting of outcomes
Thomas, P. W., Thomas, S., Hillier, C. et al. (2006) Psychological interventions for multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Thomas, P. W., Thomas, S., Kersten, P. et al. (2014) One year follow-up of a pragmatic multi-centre randomised controlled trial of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. BMC Neurology 14: 109	- Study does not contain an intervention relevant to this review protocol
van Kessel, K.; Wouldes, T.; Moss-Morris, R. (2016) A New Zealand pilot randomized controlled trial of a web-based interactive self-management programme (MSInvigor8) with and without email support for the treatment of multiple sclerosis fatigue. Clinical Rehabilitation 30(5): 454-62	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
van Mastrigt, G. A., Evers, S. M., Heerings, M. et al. (2019) An economic evaluation attached to a single-centre, parallel group, unmasked, randomized controlled trial of a 3-day intensive social cognitive treatment (can do treatment) in patients with relapsing remitting multiple sclerosis and low disability. Journal of Medical Economics 22(10): 967-980	- Focus is not on memory or cognition as no memory or cognition outcomes reported
Veldkamp, R., Baert, I., Kalron, A. et al. (2019) Structured Cognitive-Motor Dual Task Training Compared to Single Mobility Training in Persons with Multiple Sclerosis, a Multicenter RCT. Journal of Clinical Medicine 8(12): 10	- Study does not contain an intervention relevant to this review protocol
Vogt, A., Kappos, L., Stocklin, M. et al. (2008) BrainStim - Evaluation of a new computerised working memory training tool for MS-patients. Neurologie und rehabilitation 14(2): 93-101	- Study not reported in English
Wajda, D. A. and Sosnoff, J. J. (2015) Cognitive-motor interference in multiple sclerosis: a systematic review of evidence, correlates, and consequences. BioMed Research International 2015: 720856	- Study design not relevant to this review protocol
Woo, Charlene, Borg, Lara, Isaac, Shantel et al. (2016) Clinically Meaningful Cognitive Interventions for People With Multiple Sclerosis: A Systematic Review With a Functional Perspective. American Journal of Occupational Therapy 70(4_Suppl_1): 7011515276p1	- Conference abstract
Yu, C. H. and Mathiowetz, V. (2014) Systematic review of occupational therapy-related interventions for people with multiple sclerosis: part 2. Impairment. American Journal of Occupational Therapy 68(1): 33-8	- Systematic review used as source of primary studies
Yu, C. H. and Mathiowetz, V. (2014) Systematic review of occupational therapy-related interventions for people with multiple sclerosis: part 1. Activity and participation. American Journal of Occupational Therapy 68(1): 27-32	- Systematic review used as source of primary studies
Zare, H. (2019) The effect of computerized cognitive rehabilitation on everyday memory function in Multiple Sclerosis patients. Advances in cognitive science 20(4): 1-9	- Study not reported in English

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Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 45: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix K – Research recommendations – full details

K.1 Research recommendation

For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of non-pharmacological interventions for memory and cognitive problems?

This might include individual or group interventions for people with MS and also in person, holistic or computerised rehabilitation programmes.

Research should aim to include outcome measures looking at:

- Direct measures of cognitive function
- Experience, engagement and acceptability of cognitive rehabilitation
- Functional outcomes including engagement in meaningful activities

Long-term follow up to consider the longer-term benefits and maintenance of change to support evidence of cost effectiveness of intervention.

K.1.1 Why this is important

Cognitive impairment affects 43–70% of people with MS often affecting speed of information processing, working memory and memory and executive function. Cognitive impairment can affect ability to carry out everyday activities and engage in social and vocational activities, employment and carrying out routine household tasks. Cognition can also impact on someone's ability to independently manage medication regimes and make complex decisions about their MS related care.

Cognitive impairment has a complex interplay with other symptoms of MS such as fatigue and psychological distress, low mood and anxiety. Furthermore, cognitive impairment can also impact on family and social roles including parenting and can affect these relationships with others. Caring for a person with MS is also likely to be more difficult if they have cognitive impairment and outcomes from research should include effect on caregivers.

K.1.2 Rationale for research recommendation

Importance to 'patients' or the population	If non-pharmacological Interventions are shown to offer clinically important benefits to the management of memory and cognition for people with MS, at a reasonable cost threshold, then it may be an important modality to improve current practice and enhance clinical outcomes in this patient group. If specific interventions are identified to be effective, this can support people with MS to choose effective interventions while an increased understanding of optimal strategies can help standardise care and improve patient outcomes.
Relevance to NICE guidance	This research can reduce the existing uncertainty regarding the clinical and cost-effectiveness of non-pharmacological interventions for memory and cognition and support decision making in the development of future recommendations.

Relevance to the NHS	A clear recommendation for the non-pharmacological interventions for memory and cognition will offer clinicians clearer guidance on best care for people with MS. Increased knowledge of non-pharmacological interventions would improve and standardise care.
National priorities	The national service framework for long term conditions supports the early management of symptoms
Current evidence base	The current research base is limited. Limitations in the evidence included most outcomes within each comparison being based on one or two very small studies, as there was limited opportunity for pooling, there was uncertainty in the direction and/or size of the effect for most outcomes reported.
Equality considerations	Trials are unlikely to impact on equality issues.

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K.123 Modified PICO table

Population	Inclusion: Adults (≥18 years) with MS, including people receiving palliative care. Exclusion: Children and young people (≤18 years).
Intervention	**Multi-domain cognitive/neuropsychological rehabilitation, for example (list not exhaustive),** • Individualised neuropsychological rehabilitation, for example, external compensatory training • Brain Training Apps such as luminosity • Neuropsychological intervention for example neuropsychological • Computer aided 'Cognifit Personal Coach' for cognition • MS-Rehab computerised tool • Insight and awareness (typically termed as 'metacognitve training or metacognitive strategies') **Speed of information processing** • Individualised neuropsychological rehabilitation, for example, external compensatory training Time Pressure Management Training (TPM) **Attention and Working Memory** • Individualised neuropsychological rehabilitation, for example, external compensatory training • CogMed Working Memory Training • Attention Process Training (APT)

	• Computer aided RehaCom module 'Divided Attention' for attention **Memory** • Individualised neuropsychological rehabilitation, for example, external compensatory training • External compensatory strategies • Errorless Learning Techniques • Personal assistant apps • Computer aided RehaCom module 'memory and Attention' • Computer aided (VILAT-G 1.0) training for memory • Story memory technique (SMT) • Computer aided memory retraining programme (SCRP) **Executive Function** • Individualised neuropsychological rehabilitation, for example, external compensatory training • Goal Management Training (GMT) • Problem Solving Training • Computer aided RehaCom module 'Plan a Day' for organization and planning • Interventions for apathy **Social Cognition** • Individualised neuropsychological rehabilitation, for example, external compensatory training • Social Cognition Training **Language** • Individualised speech and language therapy and rehabilitation, for example, external compensatory training • Retraining type approaches • Compensatory type approaches (for example, use of communication aids) **Perception** • Psychoeducation • Retraining type approaches (repeated practice on identifying specific objects/patterns) • Compensatory type approaches (for example, labelling objects)
Comparator	• Interventions will be compared to each other, placebo/sham, or usual care. • Waiting list control • Supportive therapy (dedicated time with a supportive clinician)

Outcome	All outcomes are considered equally important for decision making and therefore have all been rated as critical.
	• Objective Measures
	  ○ Cognitive functions, such as memory, attention, executive functions, processing speed, for example, symbol digit modality test (SMDT)
	• Subjective Measures
	  ○ Health-related Quality of Life, for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale.
	  ○ Patient-reported outcomes, for example symptoms,(for example Canadian Occupational Performance measure, Cognitive failure questionnaire, perceived deficits questionnaire
	  ○ Self-efficacy/self-management (MS self-efficacy scale
	• Functional Measures
	  ○ Medication management/ adherence to medication
	  ○ Mood
	  ○ Fatigue (MS fatigue scale includes cognition)
	  ○ Activities of daily living (ADL).
	• Vocational Measures
	  ○ Employment
	  ○ Training
	  ○ Social engagement
	  ○ Relationship satisfaction
	  ○ Impact on carers.
	• Engagement Measures
	  ○ Completion/adherence rates
	  ○ Acceptability
	  ○ Satisfaction
	
	Validated measures should be used where possible
	
	Follow up:
	Looking at long-term follow up is helpful to establish long-term cost-effectiveness

	• 3-6 months • >6 months – 1 year
Study design	RCT or cohort study adjusted for key confounders
Timeframe	Long term
Additional information	The studies should be adequately powered for the main outcomes

K.2 Research recommendation

The development of a set of core outcomes measures for trials assessing memory and cognition in people with multiple sclerosis

K.2.1 Why this is important

There are a large number of outcomes measures used to assess memory and cognition in people with multiple sclerosis. Inconsistency in outcomes used and concerns over the validity of some outcomes measures make it difficult to combine and compare results from different trials, limiting the ability to draw overall conclusions on the clinical and cost effectiveness of interventions. The development of a core outcome set will allow direct comparisons of interventions for multiple sclerosis and symptoms management. A standard dataset should include outcome measure in both objective, subjective and functional tools. This should be considered as a minimum dataset and research studies may want to add specific measures to the intervention they are investigating.

K.2.2 Rationale for research recommendation

Importance to 'patients' or the population	At present there is no agreed core outcome set for MS for use in trials in the clinical effectiveness of treatments for memory and cognition. With a standardised set of validated outcome measures trials can be combined in meta-analysis and treatments can be directly compared to allow clinicians to evaluate their effectiveness.
Relevance to NICE guidance	High quality research in this area will reduce the heterogeneity of the evidence base and will inform the evidence base to support decision making for NICE recommendations in the area of the management of memory and cognition in people with MS
Relevance to the NHS	Stronger recommendations for interventions for memory and cognition will offer clinicians clearer guidance in providing care for people with MS.
National priorities	None
Current evidence base	Throughout the development of the guideline the heterogeneity of the outcomes in the evidence base was noted.

Equality considerations	The recommendation is unlikely to impact on equality issues.

K.2.13 Modified PICO table

Population	Specialist MS healthcare professionals and researchers People with multiple sclerosis
Intervention	For use in all trials of interventions to treat or manage memory and cognition in people with MS
Study design	Phase 1: Systematic search to identify existing or ongoing studies on developing a core outcome set using COMENT online database and studies reporting on Patient Reported Outcome Measures (PROMS). Phase 2: Systematic review to evaluate current outcome measures used in trials, identifying the frequency of use of each outcome and validation data. In line with the four-step process for developing core outcome sets outlined in the COMET handbook, this is to initially identify and agree on potential outcomes, to define and determine how they will be measured. These should include family reported outcome measures as well as patient reported outcome measures Phase 3: To reach consensus on which outcomes should be included in the core outcome set, their definition and measurement, a Delphi consensus technique of multiple rounds, involving specialists, research experts and people with lived experience of ME/CFS in the UK will be used.
Timeframe	Medium
Additional information	

2

3

References

1. Lincoln NB, Bradshaw LE, Constantinescu CS, Day F, Drummond AE, Fitzsimmons D et al. Group cognitive rehabilitation to reduce the psychological impact of multiple sclerosis on quality of life: The CRAMMS RCT. Health Technology Assessment. 2020; 24(4)

2. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated 2020]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview