MULTIPLE SCLEROSIS BEST EVIDENCE-BASED STRATEGIES AND TREATMENT/THERAPIES FOR REHABILITATION

Cognitive Impairment: Non-pharmacological Rehabilitation Interventions

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Acknowledgements: Thank you Magdalena Mirkowski, Jaclyn Morken, Julia Rybkina and Dr. Aman Saini for editorial and research support and to the Ralph M. Barford Foundation, University of Saskatchewan College of Medicine, Saskatchewan Health Authority and Saskatchewan Health Research Foundation for research funding for this module.

Dedicated to Devon Ireland and family

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Author Disclosures

Dr. Sarah Donkers has received research funding from the Canadian Institutes of Health Research, Multiple Sclerosis Society of Canada, Branch Out Neurological Foundation, Praxis Spinal Cord Institute, Craig Neilson Foundation, Saskatchewan Health Research Foundation, Saskatchewan Centre for Patient-Oriented Research, College of Medicine University of Saskatchewan, Saskatchewan Ministry of Health, Heart and Stroke Saskatchewan, Spinal Cord Injury Saskatchewan and Saskatoon City Hospital Foundation. She has received investigator-initiated research funds from Helius Medical Technologies, and program funding from the Multiple Sclerosis Society of Canada for the NeuroSask Active and Connected Program.

Dr. Katherine Knox has received research funding from the Multiple Sclerosis Society of Canada, Saskatchewan Health Research Foundation, Saskatchewan Centre for Patient-oriented Research, Saskatchewan Ministry of Health Drug Plan and Extended Benefits Branch, College of Medicine University of Saskatchewan, and Saskatoon City Hospital foundation. She is the director for the Saskatchewan MS Drugs Research Program Quality of Life and Health Outcomes Study, is a member of the Saskatchewan MS Drugs Program Panel, was involved in a Roche sponsored clinical trial as a site investigator and received program funding from the Multiple Sclerosis Society of Canada for the NeuroSask Active and Connected Program.

Dr. Sarah Morrow has served on advisory boards for Biogen Idec, Celgene, EMD Serono, Novartis, Roche, Sanofi Genzyme, and Teva Neurosciences. She has received investigator-initiated grant funds from Biogen Idec, Novartis, Roche, and Sanofi Genzyme and has acted as site primary investigator for multicenter trials funded by AbbVie, Celgene, EMD Serono, Novartis, Roche, and Sanofi Genzyme. She has received research funding from the Multiple Sclerosis Society of Canada, National Multiple Sclerosis Society, and Canadian Institutes of Health Research.

Dr. Robert Simpson has received funding from the Canadian Institutes for Health Research for an integrated knowledge translation grant studying mindfulness for people with multiple sclerosis.

Eman Abdulhadi, Devon Ireland and Dr. Emma Le have no disclosures.

Lay Summary of Evidence

Interventions favouring a benefit for one or more cognitive outcomes
Rehabilitation approaches targeting memory improve memory in persons with MS with minimum to moderate cognitive impairment compared to no treatment. Restitution approaches may increase self-reported stress levels compared to compensatory approaches. Non-specific or multi-modal rehabilitation approaches delivered individually, in a group, or remotely may improve memory in persons with MS compared to no treatment. The Modified Story Memory Technique improves verbal learning and memory but does not improve other forms of memory in persons with MS. Rehabilitation approaches targeting executive function improve executive function outcomes in persons with MS with minimum cognitive impairment Computer cognitive training in memory improves memory in persons with MS with mild cognitive impairment compared to no treatment Computer cognitive training in processing speed improves processing speed in persons with MS with mild cognitive impairment compared to no treatment Computer cognitive training in executive function improves executive function in persons with MS with mild cognitive impairment compared to no treatment Computer cognitive training in attention may improve attention in persons with MS with mild cognitive impairment compared to no treatment Nintendo's Braining Training video games may improve executive function and information processing speed, and the Space Fortress video game may improve spatial memory and visuospatial memory in persons with MS. Cognitive rehabilitation carried out in a virtual reality environment may improve information processing and memory in persons with MS. Strobic visual training may improve processing speed, but not other cognitive domains in persons with MS.

Interventions favouring a benefit for one or more cognitive outcomes

Neurofeedback training may improve long-term memory and executive function in persons with MS.

Spaced learning improves memory more than mass learning.

Retrieval practice learning improves memory more than spaced or mass learning in persons with MS with mild or severe cognitive impairment at baseline.

Preliminary evidence suggests that cue salience may improve prospective memory in persons with MS.

Selective reminding tasks may improve memory in persons with MS.

Teaching the Self-Generation Technique may improve recall on memory tasks where the technique is applied.

Mental visual imagery training may improve memory in patients with relapsing remitting MS on an autobiographical memory interview assessment; other objective memory and cognitive outcomes were not reported.

Preliminary evidence supports that mindfulness-based cognitive therapies may improve attention and verbal skills in persons with MS.

Preliminary evidence supports that meditation may improve information processing speed in persons with relapsing-remitting MS.

Preliminary evidence supports that psychotherapy may improve memory but not attention in persons with MS.

Preliminary evidence suggests that psychotherapy may improve auditory information processing speed but not visual information processing speed in persons with MS.

Music therapy may be beneficial for improving memory in persons with MS.

There is preliminary evidence that action observation training added to an upper limb rehabilitation program may improve auditory processing speed in persons with MS.

An exercise program with a cooling garment may improve verbal fluency in persons with MS.

Interventions favouring a benefit for one or more cognitive outcomes

Preliminary evidence suggests that team-based artistic therapy may improve visual information processing speed and memory but may not improve auditory information processing speed in persons with relapsing-remitting MS.

Preliminary evidence suggests that a modified paleolithic diet combined with electrical stimulation, exercise, and stress management may improve executive functioning in persons with MS.

Preliminary evidence supports that running may improve spatial memory but not verbal learning and memory or information processing speed in persons with MS.

High intensity aerobic training may improve verbal memory compared to moderate intensity aerobic training but may not improve cognition in other cognitive domains.

Balance training coupled with dual task training may improve general cognition and executive function compared to no intervention in persons with MS.

Preliminary evidence supports that Pilates may improve information processing speed and memory for persons with MS.

Preliminary evidence supports that yoga may improve attention in persons with MS.

Functional electrical stimulation cycling may improve visual processing speed compared to passive cycling in persons with MS with mobility impairments.

Transcranial Direct Current Stimulation over the left dorsolateral prefrontal cortex may improve executive function when combined with cognitive training tasks.

Interventions with inconclusive or conflicting findings

There is conflicting evidence whether computer-based cognitive rehabilitation improves verbal language skills in persons with MS with minimal cognitive impairment compared to no treatment.

There is conflicting evidence whether the combination of computer based cognitive rehabilitation with compensatory rehabilitation approaches provides added benefit for improving attention, information processing speed, executive function, spatial skills, verbal language skills or memory in persons with MS.

Compensatory approaches targeting memory in persons with MS may not be superior to restitution approaches, self-management coaching, or access to MS occupational therapy and nursing services for improving memory.

Non-specific cognitive rehabilitation approaches may not improve outcomes in other cognitive domains besides memory compared to no treatment.

There is conflicting evidence whether mindfulness-based cognitive therapies improve memory in persons with MS.

There is conflicting evidence whether meditation improves memory in persons with relapsing-remitting MS.

There is conflicting evidence whether music mnemonics improves memory in persons with MS.

There is conflicting evidence whether cooling garments improve information processing in persons with MS.

There is conflicting evidence whether cycling improves cognition in persons with MS, with positive results for improving memory in persons with progressive MS.

There is conflicting evidence whether walking programs improve information processing speed or executive function in persons with MS.

There is conflicting evidence whether yoga improves executive function in persons with MS.

Social Cognitive Education combined with exercise may improve information processing speed, but not more than Attention Control Education combined with exercise.

Interventions with no observed benefit on cognitive outcomes

The Space Fortress video game may not improve verbal learning and memory in persons with MS.

Robot-assisted gait training in a virtual reality environment may not improve information processing speed, memory, or verbal language skills more than standard robot-assisted gait training.

Robotic-assisted gait training may not improve cognitive impairment more than gait training alone in persons with MS.

Cognitive Occupation-Based Programme for People with Multiple Sclerosis (COB-MS) may not improve processing speed or executive function, but self-reported performance on ADLs, IADLs and occupational competence may improve.

Preliminary evidence suggests that cooling below the resting normal temperature may worsen memory in persons with MS.

Dual Task Training combined with gait training may not improve attention, memory, or information processing speed more than gait training alone in persons with MS.

Dual Task Training may not improve executive function more than strength training in persons with MS.

Aerobic and strength training combined may not improve information processing speed, attention, or memory after short- term follow up in MS.
Long-term effects and response heterogeneity warrant further study.

Preliminary evidence from small studies supports that circuit training may not improve memory, verbal fluency, or processing speed more than relaxation exercises in persons with MS

Walking Programs may not improve verbal learning and memory in persons with MS.

Preliminary evidence from small studies supports that stepping exercises may not improve cognitive outcomes in persons with MS compared to usual activity or light physical activity.

Prelimnary evidence from small studies supports that high frequency repetitive transcranial magnetic stimulation may not improve working memory in persons with MS.

Interventions with no observed benefit on cognitive outcomes

Transcranial random noise stimulation may not improve attention in persons with MS.

Preliminary evidence supports that non-invasive tongue stimulation may not improve memory, executive function, or information processing speed in persons with MS.

Colour Coding

Colour	Meaning
(light blue)	Interventions favouring a benefit for one or more cognitive outcomes
(light grey)	Interventions with inconclusive or conflicting findings
(light orange)	Interventions with no observed benefit on cognitive outcomes

Abbreviations

ACT	Adaptive Cognitive Training
AI-EFT	Autobiographical Interview for Episodic Future Thought
AM	Autobiographical Memory
AMI	Autobiographical Memory Interview
AQ	Awareness Questionnaire
AVLT	Auditory Verbal Learning Test
BDI	Beck Depression Index
CBT	Cognitive Behavioural Therapy
CCR	Conventional Cognitive Rehab
CHART-R	Craig Handicap Assessment and Rating Technique-Revised
CI	Cognitive Impairment
COB-MS	Cognitive Occupation-Based Programme for People with Multiple Sclerosis
COPM	Canadian occupational performance measure
CR	Cognitive Rehabilitation
CST	Cognitive Screening Test
CSI	Cognitive Stability Index
DBT	Dialectical Behaviour Therapy
DCAQ	Daily Cognitive Activities Questionnaire
DKBT	Dr. Kawashima's Brain Training video game
EMQ	Everyday Memory Questionnaire
FAMS	Functional Assessment of MS
GAS	Goal Attainment Scale
GE	Generation Effect Task (GE): recall and recognition of generated or provided stimuli
HC	Healthy Control
HVT	Hybrid-Variable priority Training
MBCT	Mindfulness-based cognitive therapy
MBI	Mindfulness-based interventions
MBSR	Mindfulness-based stress reduction
MBT	Mindfulness-Based Training
MFIS	Modified Fatigue Impact Scale
MFQ	Memory Functioning Questionnaire
MR	Massed Restudy
MS	Multiple Sclerosis
MS-MILD	MS-Mildly Impaired
MS-MOD	MS-Moderately Impaired
MS-UN	MS-Unimpaired
mSMT	modified Story Memory Technique
MSNQ	Multiple Sclerosis Neuropsychological Questionnaire
MVI	Mental Visual Imagery
NMT	neurologic music therapy
OSA-DLS	Occupational Self-Asessment-Daily Living Scales
PCT	Prospective Controlled Trial
PS-TTC, -RT	Preference shifting (PS): trials to criterion (TTC), reaction time (RT)
PSAI	Pythagorean Self-Awareness Intervention
PwMS	Persons with Multiple Sclerosis
RCT	Randomized Controlled Trial

Self-GEN	Self-generation learning program
SR	Spaced Restudy
ST	Spaced Testing
STEM	Strategy-based Training to Enhance Memory
SMT	Story Memory Technique
SVT	Stroboscopic Visual Training
TBI	Traumatic Brain Injury
VPA	Verbal Paired Associates
WRAT-3	Wide Range Achievement Test-3 (WRAT-3) reading subtest
WTAR	Wechsler Test of Adult Reading

Cognitive Impairment: Non-pharmacological Rehabilitation Interventions

1.0 Introduction

Non-pharmacological approaches addressing cognitive impairment (CI) in MS include a large variety of interventions. In persons with MS (PwMS), there is individual variability in the severity of CI and the cognitive domains affected. Over the disease course, most PwMS experience a change in cognitive function, with processing speed being the most predominantly affected (Van Schependom et al. 2015). Objective loss of grey matter and functional neural network changes are associated with CI in MS. Functional network alterations may also occur with cognitive training in PwMS (Bonavita et al. 2015; A. Ernst et al. 2018; O. Boukrina et al. 2019). CI negatively affects the quality of life of PwMS and caregivers (Labiano-Fontcuberta et al. 2014), and is associated with increased risk for future institutionalized care (Thorpe et al. 2015).

In the management of dementia, stroke, and acquired brain injury, non-pharmacological approaches addressing CI are routine care. Cognitive rehabilitation strategies are divided broadly into compensatory (i.e., external memory aids) or restorative (i.e., re-organization of information and internal encoding for enhanced retrieval). Traumatic brain injury involves different mechanisms of injury in comparison to MS, with some common molecular pathways (Macrez et al. 2016). Traumatic Brain Injury and MS both may affect younger adults where the potential for neuroplasticity may be greater in comparison to older adults. International guidelines by INCOG for cognitive rehabilitation following traumatic brain injury provide guiding principles for clinicians (Bayley et al. 2014). Cognitive rehabilitation may include restorative and compensatory strategies, caregiver training, functional adaptation and environmental manipulation, and education about the consequences of CI. Rehabilitation should be tailored to the "patient's neuropsychological profile, including considering premorbid cognitive characteristics and goals for life activities and participation" (Bayley et al. 2014 p.301).

Guidelines from The National Institute for Health and Care Excellence (NICE) for the management of MS and Consensus recommendations for CI in MS both help to raise awareness about the existence of CI in MS. The Consensus recommendations are endorsed by the Consortium of Multiple Sclerosis Centers and the International Multiple Sclerosis Cognition Society (*Multiple Sclerosis in Adults: Management* 2019; R. Kalb et al. 2018), and emphasize screening, assessment, and referral to a specialist for remediation management (i.e., a neuropsychologist, speech language therapist, or occupational therapist). However, the NICE guidelines and the Consensus recommendations do not provide specific advice about the selection of interventions most appropriate for PwMS. Similar to acquired brain injury, the success of an intervention may depend in part on individualizing the approach to the person's neuropsychological profile and goals of treatment. For example, if insight is markedly impaired, caregiver training may be appropriate—yet there is limited research on how to best support caregivers in the management of CI in MS (Rajachandrakumar and Finlayson 2021; Clare et al. 2019).

In research settings, there may be recruitment bias towards the inclusion of more activated PwMS. Activation, motivation, and practice are key ingredients for learning. In clinical practice, mood and fatigue symptoms and cognitive fatigability (the inability to maintain performance throughout a sustained cognitive task (Walker, Berard, and Walker 2021)) are common. For these reasons, interventions demanding sustained attention may be less feasible for PwMS. The 2018 Consensus recommendations (R. Kalb et al. 2018) list promising interventions for CI from positive MS pivotal trials, including remediation techniques such as spaced learning and retrieval practice (Sumowski, Chiaravalloti, and DeLuca 2010), supervised computer-based attention training (Bonavita et al. 2015), and the use of context and imagery (story memory technique) (N. D. Chiaravalloti et al. 2013). Prior to recommending comprehensive neuropsychological testing in PwMS, how testing may inform management and what resources are available after testing to support PwMS requires consideration. One of the earliest and largest randomized controlled trials investigating CI in PwMS found that comprehensive neuropsychological testing was associated with worsening quality of life and mood symptoms (Lincoln 2002). There is a need for more research to guide evidence-based recommendations appropriate for the neuropsychological profiles of PwMS with respect to both CI assessment and treatment.

There are patient and family resources aimed to help with managing CI in MS (Multiple Sclerosis Society of Canada, n.d.; LaRocca and King 2016).[1,2] These resources have similarities to patient resources developed for acquired brain injury, stroke, and dementia, in that compensatory strategies, mental health and health behaviour suggestions are frequently included (Heart and Stroke Canada, n.d.; Ontario Neurotrauma Foundation 2020; Saskatchewan Health ABI, n.d.; Alzheimer Society, n.d.). A patient resource from the Multiple Sclerosis International Federation conveniently combines recommendations for cognitive and mood symptoms into one resource for PwMS (MS International Federation, n.d.).[3] Patient resources importantly help to dispel the myth that cognition is spared in MS, yet additional measures are needed to help address the challenge of CI in MS.

A lack of rigour in controlling for confounders or moderators of cognitive function, including baseline CI, mood, fatigue, and fatigability in PwMS, is a limitation of the research. The literature search date for the first edition of this module has an end date of July of 2020. Despite these limitations, there exists a large variety of non-pharmacological interventions reporting improvement on objective cognitive outcomes in PwMS. For a review of the pharmacological interventions for cognition in MS and further information on the prevalence, measurement, and impact of CI in MS, please visit the module on ***Cognitive Pharmacological.*** The present module provides a review of the non-pharmacological interventions trialed in MS.

[1] https://mssociety.ca/library/document/LrvdiAzUK01SbsCcafFt938eQhNP2IJ7/original.pdf

[2] https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Brochure-Managing-Cognitive-Problems_1.pdf

[3] https://www.msif.org/about-ms/symptoms-of-ms/cognition-and-emotional-changes/

2.0 Cognitive Outcome Measures and Defining Cognitive Impairment

Please refer to the module on *Cognitive Impairment: Pharmacological Interventions* for an introductory text summary on outcome measures.

Table 1. Cognitive Outcome Measures Utilized in the Reviewed Literature for non-pharmacological interventions

Cognitive Domain		Outcome measure
Attention		Attention Network Test (ANT) Brickenkamp d2 Test (Bd2T) Brief Test of Attention (BTA) Cogstate Brief Battery (CBB) Conner's Continuous Performance Test (CCPT) Continuous Performance Test (CPT) Integrated Auditory Visual-2 (IVA-2) Leiter-3: attention Stroop Attention Scale (SAS) Stroop Test/Stroop Color-Word Test (SCWT) Test of Attentional Performance (TAP) Urban Daily Cog
Executive function		Behavior Rating Inventory of Executive Function-Adult (BRIEF-A) Delis-Kaplan Executive Function System (D-KEFS)[2] Dysexecutive Syndrome Questionnaire (DEQ): clinician rated Frontal Assessment Battery (FAB) Frontal Systems Behavior Scale (FrSBe) Hayling and Brixton Test (HBT) Self-Regulation Skill (SRSI) Tower of London-II (TOL-II/TOW-II)
	Cognitive interference & mental flexibility	Flanker Task (FT) Stroop Test/Stroop Color-Word Test (SCWT) Trail Making Test - B (TMT -B)
	Cognitive reasoning	Raven's Advanced Progressive Matrices (RAPM) Raven's Colored Progressive Matrices (RCPM) Wisconsin Card Sorting Test (WCST)
Information processing speed		Paced Visual Serial Addition Test (PVSAT) Paced Visual Serial Addition Test-III (PVSAT-III) Trail Making Test - A (TMT -A)
	Auditory processing speed	Paced Auditory Serial Addition Test (PASAT)[2,3]
	Visual processing speed	Digit Symbol Substitution (DSST) Faces Symbol Test (FST) Salthouse Perceptual Comparison Test (PCT) Symbol Digit Modalities Test (SDMT)[1,2,3] Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol
Visuospatial skills		
	Spatial processing	WAIS-R: Block design subtest
	Visual perception	Judgment of Line Orientation (JLO)
Memory		
	Spatial memory	10/36 Spatial Recall Test (10/36;10/36-SPART; SPART)[3] 7/24 Spatial Recall Test

		Location Learning Task (LLT)
		Rivermead Behavioural Memory Test – Third Edition (RBMT-3) The Novel Task
	Visuospatial memory	Brief Visuospatial Memory Test-Revised (BVMT-R)[1,2]
		Brief Visuospatial Memory Test (BVMT)
		Door and People Test (DPT)
		Rey-Osterrieth Complex Figure Test (ROCF or CFT)
	Visual memory	Contextual Memory Text (CMT)
		Doors and People
		Wechsler Memory Scale (WMS)
	Verbal learning & memory	California Verbal Learning Test (CVLT) [1,2]
		California Verbal Learning Test II (CVLT-II)[1,2]
		Greek Verbal Learning Test (GVLT)
		Hopkins Verbal Learning Test (HVLT)
		Hopkins Verbal Learning Test-Revised (HVLT-R)
		Regensburger Verbal Fluency Test (RVFT)
		Selective Reminding Test (SRT)[3]
		Verbal Learning and Memory Test (VLMT)
		Word List Generation Test (WLGT)[3]
	Verbal memory	Rey Auditory Verbal Learning Test (RAVLT)
		Wechsler Memory Scale (WMS)
		Wechsler Memory Scale-III (WMS-III)
		Wechsler Memory Scale-Revised (WMS-R)
		Rivermead Behavioural Memory Test (RBMT) – Story Memory
	Working memory	2-back
		Cogstate Brief Battery (CBB)
		Corsi block-tapping Test (CT/CORSI)
		Memory Assessment Scale (MAS)
		Memory for Intentions Test (MIST)
		National Adult Reading Test (NART)
		N-back
		Selective Reminding Prospective Memory paradigm (SRPM)
		Wechsler Adult Intelligence Scale-III (WAIS-III) digit span
		Wechsler Adult Intelligence Scale-Revised (WAIS-R) digit span
		Wechsler Adult Intelligence Scale-III (WAIS-III) letter-number sequencing
	Autobiography memory	Autobiographical Interview (AI)
		Cue-word Modified Crovtiz Test (MCT)
		Galton-Crovitz Cue-word Test-Modified (GCCW-M)
Verbal language skills		
	Word retrieval	Boston Naming Test (BNT)
		Controlled Oral Word Association Test (COWAT)
	Verbal fluency	Animal Fluency (AF)
		Bilan Informatisé d’Aphasie (BIA)
		Calibrated Ideational Fluency Assessment (CIFA)
		Gottschalk and Gleser Measure
		Isaacs Set Test (IST)
		Phonemic Fluency Test (PFT)

General Cognition	Addenbrooke's Cognitive Examination (ACE) Cambridge Neuropsychological Test Automated Battery (CANTAB) Mindstream Computerized Cognitive Test (MCCT) Neuropsychological assessment battery (NAB) Shipley Institute of Living Scales (SILS) Wechsler Adult Intelligence Scale-Revised (WAIS-R) Wechsler Adult Intelligence Scale-IV (WAIS-IV) Woodcock Johnson Test-Revised (WJ-R) Abbreviated Mental Test (AMT) Montreal Cognitive Assessment (MoCA) Mini-Mental State Examination (MMSE) Global Intelligence Efficiency Test (GIET) Multiple Sclerosis Inventory for Cognition (MUSIC) Brief International Cognitive Assessment for Multiple Sclerosis (BiCAMS) Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) Rao's Brief Repeatable (BRB)

[1]Components of the BiCAMS battery
[2]Components of the MACFIMS battery
[3]Components of Rao's Brief Repeatable Battery

3.0 Non-pharmacological Interventions

3.1 Cognitive Rehabilitation Mixed Non-Computer Approaches

This section includes a collection of studies where authors include mixed strategies or compare broadly different cognitive rehabilitation approaches. Studies targeting or aiming to test a specific cognitive rehabilitation strategy (i.e., self-generation, spaced learning, music mnemonics, etc…) are described separately in each applicable section of this module.

Table 2. Studies Examining Cognitive Rehabilitation for Cognitive Impairment in Multiple Sclerosis (non-computer-based approaches)

Author Year Title Country Research Design PEDro Sample Size	**Methods**	**Results**
Brissart et al. 2020 *Memory improvement in multiple sclerosis after an extensive cognitive rehabilitation program in groups with a multicenter double-blind randomized trial* France **RCT** PEDro=8 $N_{Initial}$=128, N_{Final}=94	**Population:** *Intervention group (n=52)*: Mean age=47.2yr; Sex: males=14, females=38; Disease course: RRMS=9; Mean EDSS=3.5; Mean disease duration=11.3yr. *Control group (n=49)*: Mean age=44.9yr; Sex: males=9, females=40; Disease course: RRMS=13; Mean EDSS=3.4; Mean disease duration=12.4yr **Intervention:** Following randomization, both groups completed 13, 2-hr sessions over 6mos. The intervention group completed an extended cognitive rehabilitation program, ProCog-SEP, which uses facilitation and reorganization strategies. Facilitation aims to improve cognitive abilities through exercises that target episodic memory, working memory, executive function, and language. Reorganization aims to identify cognitive treatments the patient has not used or only infrequently used and then begin using those treatments. The control group completed non-cognitive exercises with discussion. Outcome measures were collected at baseline and at the end of the intervention. **Cognitive Outcome Measures:** Selective Reminding Test (SRT)[1]; 10/36 Spatial Recall Test (SPART); Test of Attentional Performance (TAP)[2]; Wechsler Adult Intelligence Scale (WAIS-III): Digit Symbol and Digit Span[2]; Bilan Informatisé d'Aphasie (BIA): Letter M and Animals.[2]	1. Between-group comparisons showed statistically significant improvements in the intervention group on the learning index of the SRT (intervention mean baseline: 53.8; mean f/u: 60.7; control mean baseline: 55.6; mean f/u: 54.0; p=0.02), digit span backward (intervention mean baseline: 4.2; mean f/u: 4.8; control mean baseline: 4.4; mean f/u: 4.5; p=0.01), working memory subset of the TAP (intervention mean baseline: 4.2; mean f/u: 2.8; control mean baseline: 3.0; mean f/u: 2.9; p=0.04). 2. No between-group differences were observed on the digit symbol, BIA, or SPART. 3. At baseline, the intervention group exhibited more omissions than the placebo group on the working memory subset of the TAP (p<0.02). 4. Inclusion criteria required participants to have CI.
Martin et al. 2014 *Group-based memory rehabilitation for people*	**Population:** *Compensation group (n=12):* Mean age=48.3yr; Gender: males=3, females=9; Disease course: unspecified; Disease severity: unspecified; Mean disease duration=131.5mo.	1. No significant differences between groups were observed on memory-related outcomes. 2. Inclusion criteria required patients have memory impairments at baseline.

with multiple sclerosis: subgroup analysis of the ReMiND trial UK **RCT** PEDro=8 $N_{Initial}$=39, N_{Final}=39	*Restitution group (n=17):* Mean age=45.2yr; Gender: males=4, females=13; Disease course: unspecified; Disease severity: unspecified; Mean disease duration=100.8mo. *Control group (n=17):* Mean age=47.7yr; Gender: males=3, females=7; Disease course: unspecified; Disease severity: unspecified; Mean disease duration=95.7mo. **Intervention:** MS participants were randomized to receive group-based memory rehabilitation, either compensation-based or restitution-based, or to the self-help control condition. The compensation group were taught to use external memory aids while the restitution group completed exercises related to attention, encoding, and retrieval. The self-help control group learned relaxation techniques and coping mechanisms to deal with their condition. Each rehabilitation programme consisted of 10 weekly sessions of 1.5hrs each for 10wks. Assessments were performed at baseline and at 5- and 7-mo follow-up. **Cognitive Outcome Measures:** Everyday Memory Questionnaire (EMQ)[1]; Rivermead Behavioural Memory Test (RBMT)[2]; Internal and External Memory Aids questionnaires.[2]	3. MS participants were part of a larger trial inclusive of participants with stroke and TBI (das Nair and Lincoln 2012).
Lamargue et al. 2020 *Effect of cognitive rehabilitation on neuropsychological and semiecological testing and on daily cognitive functioning in multiple sclerosis: The REACTIV randomized controlled study* France **RCT** PEDro=7 $N_{Initial}$=35, N_{Final}=35	**Population:** *Specific Cognitive Rehabilitation group (n=18)*: Mean age=43.8yr; Sex: males=6, females=12; Disease course: RRMS=14, PPMS=1, SPMS=3; Median EDSS=3; Mean disease duration=6.7yr. *Nonspecific intervention group (n=17)*: Mean age=38.3yr; Sex: males=3, females=14; Disease course: RRMS=15, PPMS=1, SPMS=1; Median EDSS=2; Mean disease duration=6.5yr. *Healthy subjects' group (n=21)*: Mean age=39.7yr; Sex: males=4, females=17. **Intervention:** Following randomization, both groups completed 50 individual sessions, 3x/wk for 17wks. The specific cognitive rehabilitation group completed the REACTIV program which focused on fundamental cognitive processes including attention and reaction time. Visual and auditory modalities were used throughout the intervention. The program was progressive and adjusted its level of difficulty based on performance. The nonspecific intervention group received information on MS, coaching on physical activity, and global cognitive stimulation on semantic memory, autobiographical memory, and verbal and visual episodic memory. The healthy subjects group received no intervention. Outcome measures were collected at baseline, 4mos post-treatment,	1. The specific cognitive rehabilitation group improved significantly more than the nonspecific group on four outcomes or subtests at 4mos: a) reaction times for TAP phasic alertness (p<0.05) and TAP auditory attention (p<0.05) b) On 1 of 7 subtests of the CVLT-immediate cued recall (p<0.05) c) On 2 out of 3 Urban Daily Cog tasks (p<0.05) with a trend noticed on the third task (p=0.06) d) Rey's Complex Figure (p<0.01) 2. There were no significant between-group differences on the other 39 neuropsychological outcomes, including N-back, SCWT, TMT-A/B, CVLT, and ROCF. 3. Both groups improved on the SDMT, TAP, SCWT, and TMT (p<0.05), but there were no significant between group differences. 4. Inclusion criteria required patients have mild CI defined as $\geq$ 3 scores 1 SD below normative values on information processing speed, working memory, attention, or executive function. 5. Number of correct answers on task 3 of the virtual reality Urban Daily Cog

	and at 8-mo f/u. MRI measures were collected at baseline. **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT); Test of Attentional Performance (TAP); California Verbal-Learning Test (CVLT); Stroop Test (SCWT); Trail Making Test (TMT); Rey-Osterrieth Complex Figure Test (ROCF); Baddley's Dual Task; Daily Cognitive Activities Questionnaire (DCAQ); Urban Daily Cog.[3]	significantly improved in the SCR group (p<0.01). 6. Statistically significant improvements were observed on 8/12 questions of the DCAQ in the specific cognitive rehabilitation group but no between-group differences existed. 7. Healthy subjects improved in visual scanning scores with and without a target (p<0.01 and p<0.05 respectively) and SCWT task naming and reading times (p<0.01). 8. At baseline, all DCAQ scores differed between PwMS and healthy subjects (p<0.01).
Mani et al. 2018 *Efficacy of group cognitive rehabilitation therapy in Multiple Sclerosis* Iran **RCT** PEDro=7 $N_{Initial}$=34, N_{Final}=30	**Population:** *Intervention group (n=17)*: Mean age=35.29yr; Sex: males=0, females=17; Disease course: RRMS, Severity: unspecified; Disease duration: unspecified. *Control group (n=17)*: Mean age=35.82yr; Sex: males=0, females=17; Disease course: RRMS, Severity: unspecified; Disease duration: unspecified. **Intervention:** Following randomization, both groups received 2, 2-hr sessions/wk for 4 wks. The intervention group received the cognitive rehabilitation intervention in a group setting. The first session focused on education of the impact of MS on cognitive performance, taught the information processing model, and assigned homework with the direction to write about the impact of MS on their daily cognitive function. The second session focused on the effect of MS on mood and cognition with a homework assignment on documenting daily activities for the week. The third session focused on compensatory attention rehabilitation. Sessions four to seven focused on memory rehabilitation. The eighth session focused on executive function. The control group received a psycho-education intervention as a sham intervention in comparison to the cognition-targeted program of the intervention group. Outcome measures were collected at baseline, at the end of the intervention and at 3-mo f/u. **Cognitive Outcome Measures:** Addenbrooke's Cognitive Examination (ACE); Continuous Performance Test (CPT); Wisconsin Card Sorting Test (WCST); Behavior Rating Inventory of Executive Function-Adult (BRIEF-A); Memory Functioning Questionnaire (MFQ); Wechsler Memory Scale-Revised (WMS-R).[3]	1. Between-group comparison was statistically significant on the ACE (p=0.01), WMS-R visual memory (p=0.029), WMS-R verbal memory (p=0.006), MFQ general rating (p=0.04), MFQ frequency of forgetting (p=0.06), and MFQ mnemonics usage (p=0.01) for the intervention group. 2. Statistically significant within-group improvements were observed on the ACE (p=0.01), WMS-R visual (p=0.018) and verbal memory (p=0.001) subscales, and MFQ general rating (p=0.01), MFQ frequency of forgetting (p=0.01), and MFQ mnemonics usage (p=0.001) for participants in the intervention group. 3. No statistical between-group differences or within-group differences were noted on the CPT. 4. Between-group comparison was statistically significant on the WCST Perseverative errors (p=0.01), category completed (p=0.01), non-perseverative errors (p=0.04), total time consumed (p=0.01), BRIEF-A behaviour regulation index (p=0.01), metacognition index (p=0.01), and global executive composite (p=0.01) for the intervention group. 5. Statistically significant within-group improvements were noted on the perspective errors (p=0.01), category completed (p=0.01), non-preservative errors (p=0.03), and total time consumed (p=0.01) domains of the WSCT in the intervention group. 6. Statistically significant improvements were noted on the behavioral

		regulation index (p=0.01), metacognition index (p=0.01), and global executive composite (p=0.03) domains of the BRIEF-A. 7. Inclusion criteria required mild CI.
Mousavi et al. 2018 *Memory rehabilitation for the working memory of patients with multiple sclerosis (MS)* Iran **RCT** PEDro=7 $N_{Initial}$=60, N_{Final}=60	**Population:** *Intervention group (n=20)*: Mean age=40.55yr; Disease course: not specified; EDSS=<4; Mean disease duration=6.2yr. *Placebo (relaxation) group (n=20)*: Mean age=41.25yr; Disease course: not specified; EDSS=<4; Mean disease duration=7.55yr. *Control group (n=20)*: Mean age=40.65yr; Disease course: not specified; EDSS=<4; Mean disease duration=6.8yr. **Intervention:** Following randomization, the intervention group completed weekly, 1-hr sessions for 8wks. Each session consisted of introduction of the memory aids, compensatory strategies, mental review methods, error-free learning, focused attention and concentration, and coping mechanisms for memory problems. A homework assignment was assigned at the end of each session. The placebo group completed a relaxation technique at the same frequency. The control group had no intervention. Outcome measures were collected at baseline, after the intervention and 5wks post-intervention. **Cognitive Outcome Measures:** Wechsler Memory Scale-III (WMS-III).[3]	1. Pairwise comparisons revealed statistically significant improvements in the experimental group on working memory in comparison to the placebo (mean difference=2.939, p=0.007) and the control group (mean difference= 4.087, p=0.000) at post-test. 2. Pairwise comparisons revealed statistically significant improvements in the experimental group in comparison to the placebo (mean difference=2.536, p=0.010) and the control group (mean difference=2.321, p=0.019) at 5-wk f/u. 3. Statistically significant improvements on working memory were observed in the intervention group at post-test (n^2=0.224, p=0.001) and at 5-wk f/u (n^2= 0.134, p0.018). 4. All participants reported memory deficits at baseline.
Lincoln et al. 2020 *Cognitive rehabilitation for attention and memory in people with multiple sclerosis: a randomized controlled trial (CRAMMS)* UK **RCT** PEDro=6 $N_{Initial}$=449, N_{Final}=387	**Population:** *Intervention group (n=245)*: Mean age=49.9yr; Sex: males=67, females=178; Disease course: RRMS=159, PPMS=22, SPMS=64; Severity: unspecified; Mean disease duration=12.1yr. *Control group (n=204)*: Mean age=48.9yr; Sex: males=56, females=148; Disease course: RRMS=132, PPMS=24, SPMS=48; Severity: unspecified; Mean disease duration=11.1yr. **Intervention:** The intervention group received cognitive rehabilitation in a group setting weekly for 10 sessions. The intervention included attention and memory restitution and encoding and retrieval strategies. Homework assignments were assigned to encourage individualization of care and incorporation of cognitive strategies to daily life. The control group received usual care protocol. This included general advice on MS management from a nurse and cognitive deficits management from an occupational therapist. They were also notified of services available through MS charities. Participants nominated a relative or friend to complete the Everyday Memory Questionnaire-relative	1. There were no between-group differences for six of the eight sub-scores/tests of the BRBN. On the selective reminding test, total recall was higher at 6mos in the intervention group and delayed recall was higher in the intervention group at 12mos. On the Doors and People test, combined verbal scores where higher in the intervention group at 6 and 12mos. No other differences were observed on the cognitive tests. 2. Participants were included if they were impaired on at least one BRB-N test. 3. Improvements were greater in the intervention group on the Everyday Memory Questionnaires (self-reported) for the participant (intervention mean 6mos: 37.6, mean 12mos: 37.9; control mean 6mo: 44.5, mean 12mos: 43.1) and the relative (intervention mean 6mos: 31.3, mean 12mos: 30.5; control mean 6mos: 38.6, mean

	version for them. Outcome measures were collected at baseline, 6-mo f/u and 12-mo f/u. **Cognitive Outcome Measures:** Brief Repeatable Battery of Neuropsychological Tests (BRB-N)[2] (Selective Reminding Test (SRT); 10/36 Spatial Recall Test (SPART); Paced Auditory Serial Addition Test-3 (PASAT-3); Symbol Digit Modalities (SDMT)); Word Fluency; Doors and People Test[2]; Trail Making Test (TMT)[2]; Everyday Memory Questionnaire.[2]	12mos: 38.5) versions at 6 and 12mos.
Kahraman et al. 2020 *Physical, cognitive, and psychosocial effects of telerehabilitation-based motor imagery training in people with multiple sclerosis: A randomized controlled pilot trial* Turkey **RCT** PEDro=5 $N_{Initial}$=50, N_{Final}=33	**Population:** *Intervention group (n=20)*: Median age=34.5yr; Sex: males=4, females=16; Disease course: unspecified; Median EDSS=1; Mean disease duration=4yr. *Control group (n=15)*: Median age=36yr; Sex: males=1, females=14; Disease course: unspecified; Median EDSS=2; Mean disease duration=4yr. *Healthy control group (n=20)*: Median age=31yr; Sex: males=6, females=14. **Intervention:** Following randomization, the intervention group received 2 individualized, physiotherapist-run sessions/wk for 8wks of the telerehabilitation-based motor imaging training (Tele-MIT) intervention. During the training, they used the Physical Environment, Task, Timing, Learning, Emotion, Perspective model which encourages motor imagery to maximize function equivalence. The sessions include relaxation exercises, multisensory environment information, and MIT training. Sessions were progressed as participants improved. A waitlist control group was used in this study. Outcome measures were collected at baseline and following the intervention. The healthy controls only completed the outcome measures once. **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT)[2]; Selective Reminding (SRT)[2]; 10/36 Spatial Recall Test (SPART).[2]	1. Statistically significant between-group differences were observed on SDMT scores (p=0.014). 2. Statistically significant improvements were observed on the SDMT (p=0.012), SRT short- (p=0.024) and long-term (p=0.005), and SPART short-term (p<0.001) in the intervention group with a large effect size (d=>0.80). 3. Healthy participants had significantly higher scores on the SRT short- and long-term and SPART short and long-term scores in comparison to the intervention group (p<0.05). 4. Healthy controls had significantly better scores on the SDMT and SPART short-term in comparison to the MS control group (p<0.05).
Aguirre et al. 2019 *Repeated Working Memory Training Improves Task Performance and Neural Efficiency in Multiple Sclerosis Patients and Healthy Controls* Spain **RCT** PEDro=5 $N_{Initial}$=58, N_{Final}=27	**Population:** *MS untrained group (n=14)*: Mean age=36.14yr; Sex: males=3, females=11; Disease course: RRMS; Mean EDSS=1.8; Mean disease duration=7.54yr. *MS trained group (n=15)*: Mean age=35.8yr; Sex: males=7, females=8; Disease course: RRMS; Mean EDSS=1.67; Mean disease duration=8.33yr. *Healthy control untrained group (n=xx)*: Mean age=34.13yr; Sex: males=9, females=6. *Healthy control trained group (n=xx)*: Mean age=31.21yr; Sex: males=6, females=8. **Intervention:** Participants were randomized into four groups. The trained groups received the N-back training protocol and completed 4, 60-min sessions over the course of 1wk. The first phase included working memory training	1. Repeated measures analysis revealed statistically significant improvements on correct responses of training sessions (n^2=0.114, p<0.05) but not group (n^2=0.002, p=0.831) or first-order interaction (n^2=0.047, p=0.273) on the 2-back task. 2. There were more correct responses at training session 4 vs. session 1 on the 2-back task (t=2.479, p<0.05). 3. Repeated measures analysis revealed statistically significant improvements on response times for correct responses of training sessions (n^2=0.284, p<0.001) but not for group (n^2=0.001, p=0.883) or the

	exercises over eight blocks that varied in load (1-back, 2-back, 3-back). Participants were asked to respond with only their right hand, using the thumb to respond to targets and the forefinger to nontargets. At the end of the block participants were given information on their correct responses and reaction times. During the test phase, the participants completed 8 blocks of the 2-back and 3-back tasks but were not provided feedback. The non-trained group did nothing during the intervention. fMRI data was collected at baseline, post-intervention, and 42d later. **Cognitive Outcome Measures:** N-back task.[3]	first-order interaction (n^2=0.037, p=0.378) on the 2-back task. 4. There were shorter response times at training session 4 vs. session 1 on the 2-back task (t= -4.33, p<0.001). 5. Repeated measures analysis revealed statistically significant improvements on correct responses of training sessions (n^2=0.271, p<0.001) but not group (n^2=0.003, p=0.770) or the first-order interaction (n^2=0.027, p=0.528) on the 3-back task. 6. There were more correct responses at training session 4 vs. session 1 on the 3-back task (t=3.89, p<0.001). 7. Repeated measures analysis revealed statistically significant improvements on response times for correct responses of training sessions (n^2=0.209, p<0.001) but not group (n^2=0.01, p=0.608) or the first-order interaction (n^2=0.037, p=0.377) on the 3-back task. 8. There were shorter response times at training session 4 vs. session 1 on the 2-back task (t= -3.48, p<0.01).
Shahpouri et al. 2019 *Evaluation of cognitive rehabilitation on the cognitive performance in multiple sclerosis: A randomized controlled trial.* Iran **RCT** PEDro=5 $N_{Initial}$=66, N_{Final}=56	**Population:** *Intervention group (n=28)*: Mean age=32.21yr; Sex: males=8, females=20; Disease course: RRMS=19, PPMS=3, SPMS=6; Mean EDSS=2.28; Mean disease duration=7.46yr. *Control group (n=28)*: Mean age=30.46yr; Sex: males=9, females=19; Disease course: RRMS=20, PPMS=3, SPMS=5; Mean EDSS=1.87; Mean disease duration=7.07yr. **Intervention:** Following randomization, the intervention group completed 10, 2-hr sessions of cognitive rehabilitation over 8wks. The program targeted attention, concentration, visual memory, auditory memory, and autobiographical memory. A mnemonic approach that included visual imagery, theological organization, and relational strategies was used during the session. Autobiographical memory training and effects on daily memory disturbances were also discussed. Outcome measures were collected at baseline and within 3mos following the intervention. **Cognitive Outcome Measures:** Abbreviated Mental Test (AMT); Prospective and Retrospective Memory Questionnaire (PRMQ); Everyday Memory Questionnaire (EMQ); Digit Span.[3]	1. Participants in the intervention group showed statistically significant improvements on everyday memory (baseline mean: 126.86; f/u mean: 92.93, p<0.001), prospective and retrospective memory (baseline mean: 49.07; f/u mean: 36.11, p<0.001), and digit span test (baseline mean: 10.14, f/u mean: 12, p<0.001) at f/u measures. 2. Both groups were similar at baseline with regards to the EMQ (p=0.994), PRMQ (p=0.568) and digit span test (p=0.062), but not with respect to physical or mental health assessments. 3. Inclusion criteria required moderate CI as reported by the EMQ.
Rilo et al. 2018	**Population:** *Intervention group (n=21)*: Mean age=43.9yr; Sex: males=8, females=13; Disease course: RRMS=15, PPMS=1, SPMS=5;	1. Group x Time interactions showed a significant improvement for the intervention in processing speed (n_p^2=0.16, p=0.011), working

Integrative group-based cognitive rehabilitation efficacy in multiple sclerosis: a randomized clinical trial Spain **RCT** PEDro=5 $N_{Initial}$=44, N_{Final}=42	Mean EDSS=3.52; Mean disease duration=9.95yr. *Control group (n=21)*: Mean age=43.67yr; Sex: males=7, females=14; Disease course: RRMS=17, SPMS=4; Mean EDSS=2.5; Mean disease duration=10.67yr. **Intervention:** Following randomization, the intervention group completed 3, 1-hr sessions/wk over 3mos and received homework to be completed 3x/wk. The intervention group completed the group-based REHACOP protocol. The REHACOP protocol trains attention, processing speed, working memory, language, executive function, and social cognition. REHACOP has been used to treat CI in Parkinson's disease and schizophrenia. The study used a waitlist control group. Outcome measures were collected at baseline and following the intervention. **Cognitive Outcome Measures:** Brief Test of Attention (BTA); Symbol Digit Modalities Test (SDMT); Trail Making Test-A (TMT-A); Salthouse Perceptual Comparison Test (PCT); Wecshler Adult Intelligence Scale-III (WAIS-III): Digit Span Backwards; Hopkins Verbal Learning Test-Revised (HVLT-R); Calibrated Ideational Fluency Assessment (CIFA); Stroop Color-Word Test (SCWT).[3]	memory (n_p^2= 0.15, p=0.014), verbal memory (n_p^2= 0.13, p=0.025), and executive functioning (n_p^2= 0.13, 0.024) compared to the control group. 2. The intervention group had significantly more improvements on processing speed, working memory, verbal memory, and executive function in comparison to the control group. Processing speed and working memory showed large effect sizes while medium effect sizes were observed on verbal memory and executive function. There was a positive trend on attention and verbal fluency but non-significant results. 3. Group x Time interactions showed that participants in the intervention group who had completed private cognitive rehabilitation had significantly greater improvements on processing speed (n_p^2=0.18, p=0.014), working memory (n_p^2= 0.16, p=0.019), verbal memory (n_p^2=0.17, p=0.017), and executive functioning (n_p^2=0.13, p=0.04). 4. The intervention group performed significantly poorer than the control group on measures of attention (p=0.022), working memory (p=0.040), processing speed (p=0.010) and verbal memory (p=0.005) at baseline.
Carr et al. 2014 *Group memory rehabilitation for people with multiple sclerosis: a feasibility randomized controlled trial* UK **RCT** PEDro=5 $N_{Initial}$=48, N_{Final}=31	**Population:** *Treatment group (n=24):* Mean age=55.8yr; Gender: males=7, females=17; Disease course: RRMS=7, PPMS=6, SPMS=4, benign=2, unknown=5; Mean EDSS: unspecified; Mean disease duration=16.3yr. *Control group (n=24):* Mean age=52.9yr; Gender: males=8, females=16; Disease course: RRMS=9, PPMS=10, SPMS=4, unknown=1; Mean EDSS: Unspecified; Mean disease duration=12.3yr. **Intervention:** MS participants with reported memory difficulties received a group memory rehabilitation programme of ten 1.5-hr sessions for 10wks. The programme focused on attention training, internal memory strategies, and external memory aids with a combination of compensatory techniques and restitution. The control group received no treatment. Assessments were administered 4 and 8mos after randomization. **Cognitive Outcome Measures:** Everyday Memory Questionnaire (EMQ): self report, carer report.[1]	1. There was no significant difference observed between the groups at 4 and 8mos on the EMQ.

Jønsson et al. 1993 *Effects of neuropsychological treatment in patients with multiple sclerosis* Denmark **RCT** PEDro=5 $N_{Initial}$=40, N_{Final}=40	**Population:** *Total population:* Disease course: RRMS=6, SPMS=25, PPMS=9. *Group 1 - Specific Cognitive Training and Psychotherapy (n=20):* Mean age=46.1yr; Gender: males=11, females=9; Disease course: Unspecified; Mean EDSS=5.6; Mean disease duration=15.0yr. *Group 2 - Non-specific Mental Stimulation 2 (n=20):* Mean age=43.0yr; Gender: males=10, females=10; Disease course: Unspecified; Mean EDSS=5.6; Mean disease duration=15.1yr. **Intervention:** MS patients were randomized to receive either specific cognitive training and psychotherapy or to non-specific mental stimulation. The specific cognitive training and psychotherapy group received traditional cognitive therapy aimed at restoring concentration, memory, and spatial skills and learning compensatory skills. They also received psychotherapy to improve their coping skills. The non-specific mental stimulation group played games and watched/read and discussed films, literature, and newspaper articles. Both groups were treated for 1 to 1.5hrs 3x/wk for an average duration of 46d. Assessments were performed at baseline, immediately after, and 6mos after treatment. **Cognitive Outcome Measures:** Wechsler Adult Intelligence Scale (WAIS): Similarities, Picture Arrangement, Digit Span, and Block Design; Trail Making Test-A and B (TMT); Symbol Digit Modalities (SDMT); STREET incomplete pictures; Paced Auditory Serial Addition Test (PASAT); Verbal Fluency (Animals and Words); 50 words and 50 Faces; Visual Gestalts Test.[3]	1. A significant improvement was observed in group 1 compared with group 2 immediately after treatment in visual perception test score on the STREET incomplete pictures test ($p<0.05$). There were no other significant between-group differences immediately after treatment. 2. A significant difference was observed in group 1 compared with group 2 6mos after treatment in visuo-spatial memory test score ($p<0.05$). There were no other significant between group differences at the 6-mo f/u. 3. Group 1 was impaired on all cognitive factors at baseline while group 2 was impaired on all cognitive factors except visual perception at baseline. 4. Group 1 was more impaired in spatial memory and visual perception compared to group 2 at baseline.
Hanssen et al. 2016 *Cognitive rehabilitation in multiple sclerosis: A randomized controlled trial* Norway **RCT** PEDro=4 $N_{Initial}$=120, N_{Final}=101	**Population:** *Intervention group (n=60):* Mean age=53.9yr; Gender: males=20, females=40; Disease course: RRMS=27, PPMS=18, SPMS=15; Mean EDSS=4.4; Mean disease duration=10.6yr. *Control group (n=60):* Mean age=52.5yr; Gender: males=12, females=48; Disease course: RRMS=32, PPMS=10, SPMS=18; Mean EDSS=4.2; Mean disease duration=12.0yr. **Intervention:** MS patients were randomized to receive a cognitive rehabilitation intervention group or a control group. Both groups received ordinary MS inpatient rehabilitation for 4wks, which consisted of education and physical activities. The intervention group also participated in group and individual rehabilitation sessions for 4mos for a total of about 15hrs of total therapy, which focused on compensatory techniques aimed at executive functioning.	1. No significant differences in cognitive outcomes between groups were observed at any time point. 2. Both intervention and control groups showed significant improvements on the BRIEF-A: MI and GEC subscales at 4 and 7mos ($p<0.01$ for all).

	The intervention group also received psychotherapy. Assessments were performed at baseline, and at 4 and 7mos from the start of the study. **Cognitive Outcome Measures:** Behavior Rating Inventory of Executive Function-Adult (BRIEF-A): Global executive composite score (GEC), Intelligence quotient Global executive composite score (GEC IQ), Metacognitive index (MI); General executive composite (GEC BRIEF-A).[1]	
Zuber et al. 2020 *Efficacy of inpatient personalized multidisciplinary rehabilitation in multiple sclerosis: behavioural and functional imaging results* Switzerland **PCT** $N_{Initial}$=48, N_{Final}=48	**Population:** *MS Participants (n=24)*: Mean age=47.7yr; Sex: males=8, females=16; Disease course: Relapse onset MS; Median EDSS=5; Mean disease duration=15.2yr. *Non-MS Control group (n=24)*: Mean age=45yr; Sex: males=8, females=16. **Intervention:** The participants with MS took part in a personalized 4-wk inpatient multidisciplinary rehabilitation program. They received an average 16.6d of rehabilitation lasting an average of 46.1hrs. The interdisciplinary approach was based on the International Classification of Functioning, Disability and Health and included the development of personalized goals. Both individual and group therapy settings were utilized in the study. The non-MS control group received no intervention. Outcome and MRI measures for both groups were collected at baseline and following the intervention, and the intervention group had one more session at 4-wk f/u. During the fMRI session, participants had to complete a motor sequence learning task. **Cognitive Outcome Measures:** Paced Auditory Serial Addition Task (PASAT); oral version of Symbol Digit Modalities Test (SDMT); Wechsler Adult Intelligence Scale-IV (WAIS-IV): Digit Span; Corsi Block-Tapping Test (CORSI). [3]	1. Statistically significant improvements were seen on the PASAT (F(1,40)=4.9, p<0.05) and the Digit Span (F(1,40)=6.7, p<0.05) among the MS participants. 2. No significant changes were observed on the CORSI or the SDMT among the MS participants. 3. Outcomes on a motor sequence task demonstrated improved accuracy, and on fMRI during this task there was a decrease in brain activity in the left cerebellum and right frontal lobe post-rehabilitation only in the MS participants, which was maintained at f/u.
Brissart et al. 2013 *Cognitive rehabilitation in multiple sclerosis* France **PCT** $N_{Initial}$=20, N_{Final}=20	**Population:** *Treatment Group (n=10):* Mean age=42.5yr; Gender unspecified; Disease course: RRMS=10; Mean EDSS=2.9; Mean disease duration=5yr. *Control Group (n=10):* Mean age=41.3yr; Gender unspecified; Disease course: RRMS=10; Mean EDSS=2.85; Mean disease duration=7.2yr. **Intervention:** The treatment group underwent the ProCogSEP cognitive rehabilitation program consisting of 2 hrs/session for 13 sessions over 6mos. ProCogSEP has 13 modules, which focus on semantic memory, visual memory, verbal memory, working memory, and executive function. The control group followed 13, 2-hr sessions of neutral discussion and non-	1. Between-group comparison showed the intervention group had a significant improvement compared to the control group on the SPART Delayed Recall (p=0.03) and Fluencies "M" (p=0.01). No other between-group comparisons were significant. 2. Within-group comparison showed the intervention group significantly improved on the SRT Free Recall (pre: 10.62, post: 11.61, p=0.29), SRT learning percent (pre: 56.45, post: 71.63, p=0.002), SPART Free Recall (pre: 12.50, post: 13.40, p=0.046), TAP (p=0.031), Fluencies "M" (p=0.05), and BNT (p=0.015).

	cognitive exercises. All patients received assessments at baseline and 3mos after treatment. **Cognitive Outcome Measures:** Selective Reminding Test (SRT): free mean recall, learning percent, delayed free recall; 10/36 Spatial Recall Test (SPART): free recall, delayed Recall; Test of Attentional Performance (TAP): correct responses, working memory omissions, flexibility errors, incompatibility correct responses; Verbal Fluencies and Semantic Fluencies (Fluencies "M" and Fluencies animals); Wechsler Adult Intelligence Scale-III (WAIS-III): Digit Span; Boston Naming Test (BNT).[3]	
Fink et al. 2010 *Efficacy of an executive function intervention programme in MS: a placebo-controlled and pseudo-randomized trial* Germany **PCT** $N_{Initial}$=50, N_{Final}=20	**Population:** Mean age=44.8yr; Gender: males=9, females=41; Disease course: RRMS=50; Severity: Unspecified; Mean disease duration=92.4mo. *Cognitive intervention group (CIG, n=11).* *Placebo group (PG, n=14).* *Untreated group (UG, n=15).* **Intervention:** RRMS patients were divided into either a cognitive intervention group (CIG), a placebo group (PG), or an untreated group (UG). Subjects in the CIG and PG completed 6-wk interventions. Patients in the CIG completed 30-min sessions, 4x/wk, on textbook exercises for executive functioning. They also met with a psychologist for 1.5hrs weekly for feedback. Subjects in the PG completed five 40-min sessions/wk of reaction capacity testing using RehaCom software. The UG received no training. Assessments were performed at baseline (t1), after intervention (t2), and 1yr after enrollment (t3). **Cognitive Outcome Measures:** Preference Shifting (PS): trials to criterion (TTC), reaction time (RT); Response Shifting (RS): trials to criterion (TTC), reaction time (RT); 2-back: commissions, omissions; California Verbal Learning Test (CVLT): learning; Wechsler Adult Intelligence Scale: short form (WAIS).[3]	1. Between-group comparison showed that the cognitive intervention group improved significantly compared to the placebo group (p=0.04) and the untreated control group (p=0.01) in RS immediately after intervention. This improvement was not maintained at the 1-yr f/u. 2. Between-group comparison showed the cognitive intervention group significantly improved compared to the placebo (p=0.01) and untreated control group (p=0.001) on CVLT learning immediately after intervention. This improvement was maintained at 1yr compared to the placebo group (p=0.03) but not the untreated control group (p=0.001). 3. No other between-group differences existed for the other cognitive outcomes. 4. A significant improvement was observed in CVLT scores of the CIG at t2 and t3 with respect to baseline (t1) (p=0.02, p=0.02 respectively). 5. There were significant improvements from t1 to t2 in RS and RT for the CIG group (p=0.02).
Brenk, Laun, and Haase 2008 *Short-term cognitive training improves mental efficiency and mood in patients with multiple sclerosis* Germany **Pre-Post** $N_{Initial}$=41, N_{Final}=41	**Population:** *MS Participants (n=27):* Mean age=43.5yr; Gender: males=12, females=15; Disease course: RRMS=27; Severity: Unspecified; Disease duration=3-10yr. *Healthy control group (n=14):* Mean age=39.6yr; Gender: males=7, females=7. **Intervention:** Participants received home-based non-specific cognitive training for 6wks. The training consisted of 90 small 5-min tasks/wk from Brain Gymnastics (Gripsgymnastik) books, which include crosswords, comparisons, recall of images, and word definitions. These exercises may be completed in approximately 5min.	1. MS participants had a significant improvement on the VLMT tonic alertness (p=0.002), VLMT phasic alertness (p=0.028), CFT delay (p=0.001), and TAP (mistakes in change of reaction) (p=0.039) compared to baseline. 2. No significant differences between T1 and T2 were observed for VLMT interference, VLMT recognition, TAP go/no-go, TAP shared, or RWT.

	Participants were free to complete the 90 5-min tasks in a single day or over the course of each week. Assessments were performed at baseline (T1) and after treatment (T2) at 6wks. **Cognitive Outcome Measures:** Wechsler Memory Scale (WMS): Digit Span; Verbal Learning and Memory Test (VLMT); Rey-Osterrieth Complex Figure Test (CFT): delayed; Test of Attentional Performance (TAP): tonic and phasic alertness, go/no-go, shared attention; Regensburger Test of Word Fluency (RWT).[3]	
Gentry 2008 *PDAs as cognitive aids for people with multiple sclerosis* USA **Pre-Post** $N_{Initial}$=21, N_{Final}=20	**Population:** Median age=50yr; Gender: males=4, females=16; Disease course: RRMS=13, PPMS=3, SPMS=3, other=1; Severity: unspecified; Median disease duration=14yr. **Intervention:** Participants were trained to use Personal Digital Assistants (PDAs) to investigate functional performance which was assessed at the start of the 8-wk pre-treatment period, at the beginning and end of the training, and at 8wks after the conclusion of the training. **Cognitive Outcome Measures:** Rivermead Behavioral Memory Test-Extended (RBMT-E); Canadian Occupational Performance Measure (COPM); Craig Handicap Assessment and Rating Technique-Revised (CHART-R).[3]	1. No significant change from pre- to post test was found in the RBMT-E scores. 2. Functional performance as measured by COPM did not significantly change during the 8-wk baseline period, but a significant improvement was noted during the treatment period ($p<0.001$). 3. Performance dropped during the posttreatment period but remained significantly higher than the initial scores ($p<0.01$). 4. A significant change was observed in the Mobility, Cognitive, and Social subscales of CHART-R over time ($p=0.003$, $p=0.000$, $p=0.015$). However, with the Bonferroni adjustment, only the cognitive and the mobility subscales remained significant. 5. Improvement in cognitive and mobility handicap occurred only during the treatment period ($p<0.001$, $p<0.01$).
Kardiasmenos et al. 2008 *Prospective memory and the efficacy of a memory strategy in multiple sclerosis* USA **Pre-Post** $N_{Initial}$=24, N_{Final}=24	**Population:** *MS participants (n=24):* Mean age=44.4yr; Gender: males=13, females=11; Disease course: RRMS=18, SPMS=6; Median EDSS=3.75; Mean disease duration=7.9yr. *Healthy control (n=24):* Mean age=42.8yr; Gender: males=12, females=12. **Intervention:** MS participants received training in implementation intentions, which is a mnemonic strategy. Participants played a board game ("Virtual Week") that mimics everyday life and requires the use of prospective memory by requiring players to complete future tasks at specific times. Participants were given two types of instructions. When given the rote-rehearsal instructions, participants were told a task to complete, asked to repeat it aloud for 10s, and then told to stop. When given implementation-intentions instructions, participants were told that whenever a task	1. MS participants performed significantly better on prospective memory tasks under the implementation-intentions condition compared with the rote-rehearsal condition ($\eta_p^2=0.124$, $p=0.018$). 2. A significant difference was observed on card-cued task performance between highly associated tasks and non-associated tasks ($p<0.001$).

	was assigned, they should close their eyes, visualize completing the task, and then state aloud their future intentions. **Cognitive Outcome Measures:** Mean Correct Proportion of Memory Tasks.[3]	
Rodgers et al. 1996 *Cognitive therapy for multiple sclerosis: a preliminary study* US **PCT** $N_{Initial}$=27, N_{Final}=22	**Population:** *Therapy group (n=12)*: Mean age=49.9yr; Gender: males=5, females=7. No further information provided. *Control group (n=10)*: Mean age=37.8yr; Gender: males=6, females=4. No further information provided. **Intervention:** Participants in the therapy group received a multimodal educational program consisting of psychotherapy, expressive therapy (art and music), and mind-body approaches using training in self-regulation, visualization techniques, guided imagery, meditation, relaxation, and mental and physical exercises. Participants received therapy across 24 3-hr sessions, occurring once per week. Homework was assigned for 1-1.5hr/d. Participants in the control group received no therapy. Assessments were performed at baseline, 12wks, and 24wks. **Cognitive Outcome Measures:** Word List Learning and Memory; Symbol Digit Modalities Test (SDMT); Shipley Institute of Living Scales (SILS): vocabulary and abstraction.[1]	1. The treatment group showed significantly greater improvement in word list learning and memory and SILS verbal abstraction (p<0.05) compared to the control group. Differences were not significant for the SDMT.

[1]Primary Outcome Measure; [2]Secondary Outcome Measure; [3]Outcome Measure Not Specified

Summary

Table 3. Summary Table of Studies Examining Cognitive Rehabilitation (non-computer-based approaches)

	Improve	No statistical sig. difference
General Cognition	• Andrews et al. 2018 (FIMS)	
Attention	• **Lamargue et al. 2020** (TAP) • *Brenk et al. 2008 (TAP)*	• **Mani et al. 2018** (CPT) • Rilo et al. 2018
Executive Function	• **Mani et al. 2018** (WCST and BRIEF-A) • Hanssen et al. 2016[W] (BRIEF-A) • Rilo et al. 2018 • *Fink et al. 2010 (Proprietary tests)* • *Brenk et al. 2008 (CFT)*	• **Lamargue et al. 2020** (STROOP, TMT-B) • Hanssen et al. 2016 (BRIEF-A)
Information Processing	• Kahraman et al. 2020 (SDMT) • Rilo et al. 2018 • *Zuber et al. 2020* (PASAT)	• **Brissart et al. 2020** (Digit Symbol) • **Lincoln et al. 2020** (PASAT, SDMT, TMT) • **Lamargue et al. 2020 (TMT-A)** • *Zuber et al. 2020* (SDMT) • Rodgers et al. 1996 (SDMT)
Memory	• **Brissart et al. 2020** (SRT, Digit Span, TAP: working memory) • **Mani et al. 2018** (WMS-R: visual and verbal) • **Mousavi et al. 2018** (WMS-III) • **Lamargue et al. 2020** (CVLT) • Aguirre et al. 2019 (n-back) • Rilo et al. 2018	• **Martin et al. 2014** (RBMT) • Kahraman et al. 2020 (SRT, SPART) • **Lincoln et al. 2020** (SPART, SRT, Doors and People) • **Lamargue et al. 2020** (n-back, ROCF) • Carr et al. 2014 (EMQ) • *Zuber et al. 2020* (CORSI)

	• Jonsson et al. 1993 (spatial memory) • Dobryakova et al. 2014 (CVLT) • Shahpouri et al. 2019[W] • *Zuber et al. 2020 (Digit Span)* • *Brissart et al. 2013 (SPART)* • *Sumowski et al. 2013 (VPA)* • *Fink et al. 2010 (CVLT)* • *Sumowski et al. 2010 (VPA)* • *Goverover et al. 2009* • *Brenk et al. 2008 (VLMT, Digit Span)* • *Kardiasmenos et al. 2008 (correct responses)* • Rodgers et al. 1996 (Word List learning and memory)	• *Fink et al. 2010 (2-back)* • *Gentry 2008 (RBMT-E)* • *Brissart et al. 2013 (Digit Span, SPART subtests)*
Verbal Fluency	• *Brissart et al. 2013 (Fluencies "M")*	• **Brissart et al. 2020** (BIA) • Rilo et al. 2018 • *Brissart et al. 2013 (Animals)*

W	RCT with within-group comparison only
Bold	PEDro ≥ 6
Regular	PEDro < 6
Italic	Non-RCT

Discussion

Six high-quality RCTs (Brissart et al. 2020; Martin et al. 2014; Lamargue et al. 2020; Mani et al. 2018; Mousavi et al. 2018; Lincoln et al. 2020) investigated various cognitive rehabilitation approaches. Four of these studies included at least some compensatory memory approaches delivered in a group setting (Martin et al. 2014; Mani et al. 2018; Mousavi et al. 2018; Lincoln et al. 2020). Significant improvement on objective memory testing occurred in comparison to the control groups for two RCTs delivering group-based interventions (Mani et al. 2018; Mousavi et al. 2018) and two RCTs delivering individual programs (Brissart et al. 2020; Lamargue et al. 2020). Lower quality studies report mixed results; however, a greater proportion of the lower quality studies also report positive findings for objective memory outcomes. There remain unanswered questions about the most appropriate patient selection for which approaches, the duration and intensity of treatment, and the longer-term benefit. All six of the higher quality RCTs included PwMS with minimum to moderate cognitive impairment in one or more cognitive domain. In one study, the positive results on objective memory testing occurred after only 8 hours of a group-based intervention over four weeks (Mousavi et al. 2018). The focus of the intervention in this study was on coping and compensatory strategies (Mousavi et al. 2018).

From a service delivery perspective, lower cost group-based interventions are feasible and acceptable for many PwMS. Patient self-reported cognitive functioning may improve significantly with group-based memory restitution and encoding strategy training, even when improvement on the objective cognitive outcomes may not reach statistical significance (Lincoln et al. 2020). A multimodal approach involving physiotherapy, psychotherapy, and an imagery intervention compared to no intervention improved objective memory outcomes when this type of multi-modal intervention was delivered in person (Rodgers et al. 1996) or by tele-rehabilitation (Kahraman et al. 2020).

When interpreting the results of the MS cognitive rehabilitation research, heterogeneity across studies, effect sizes within groups, and other design issues warrant consideration. In the Lincoln et al. (2020) high-quality RCT, the intervention group (receiving focused memory training) performed significantly better than the control group on only two of the eight objective cognitive subtests. However, the control group received "usual care", including access to MS nursing support and occupational therapy. Objective cognitive test scores still improved over the course of the study in both the intervention and the usual care control groups. Control groups where participants may access health professionals with expertise in cognitive rehabilitation may diminish the power to detect between-group differences on cognitive outcomes.

Martin et al. (2014) was also a high-quality RCT with negative results for between-group differences on objective cognitive outcomes. Martin et al. (2014) report the MS participant results from the ReMIND trial (das Nair and Lincoln 2012), which is a large trial including people with stroke, acquired brain injury, and MS. The primary objective of the ReMIND trial was to compare compensatory versus restitution approaches in cognitive rehabilitation. The trial included three arms: one group received compensatory approaches; one group received restitution exercises related to attention, encoding, and retrieval; and the control group learned relaxation techniques and coping mechanisms. Importantly, all three groups improved on objective memory outcomes. The restitution group also demonstrated increased self-reported use of internal memory aids, and more symptoms of emotional distress at the five- and seven-month follow-up. The possible positive confounding effects of self-help and relaxation in the control group for improving cognitive performance and the increased emotional distress in the restitution group are of clinical relevance. The ReMIND trial does not provide evidence that one cognitive rehabilitation approach over another is more effective at improving objective cognitive outcomes. However, the results do suggest that stressors and response to stress may be important when choosing strategies to optimize self-reported functioning and objective memory.

The results are more conflicting for objective cognitive outcomes in cognitive domains beyond memory. This may be because cognitive rehabilitation may not be as effective for improving cognition in other cognitive domains in PwMS, active control groups diminish the power to detect between-group differences, and studies may differently emphasize cognitive rehabilitation techniques known to influence learning. For example, spaced practice is more effective at improving learning than mass practice (Sumowski, Chiaravalloti, and DeLuca 2010; Sumowski et al. 2013; Yael Goverover et al. 2009) (see section 3.8 of this module).

Task-specific training or cognitive domain-specific training may be more likely to improve testing in the trained domain. Lamargue et al. (2020) targeted attention training using the REACTIV program for the intervention group while the control group received non-specific cognitive and physical activity coaching. Attention improved in the REACTIV intervention group compared to the control group, yet executive function did not (Lamargue et al. 2020). Fink et al. (2010) compared a group receiving targeted executive function training to a control group receiving only reaction time training. Greater improvement in executive function occurred in the group receiving targeted executive function training. In future research and clinical practice, individualizing and aligning the cognitive rehabilitation training with the goals of treatment is more likely to lead to best outcomes.

The focus of this module is on objective cognitive outcomes as the gold standard for assessing cognition. The mechanisms resulting in improved objective cognitive function are also of interest. Zuber et. al. (2020) completed a pre-post study examining the effects of an individualized cognitive and physical rehabilitation program among PwMS on fMRI and a battery of cognitive outcomes. Improvements on the cognitive outcomes occurred after 4 weeks of rehabilitation for some of the objective cognitive outcomes (i.e., the Paced Auditory Serial Addition Test and Digit Span), but not all (i.e., Symbol Digit Modalities Test and Corsi Block-Tapping Test). Post rehabilitation, PwMS demonstrated improved accuracy on a cognitive motor learning sequence task whereby at the same time, on fMRI a decrease in brain activity was observed in the left cerebellum and right frontal lobe. Self-reported fatigue symptoms and walking speed also improved over the four weeks of inpatient rehabilitation. Authors suggest that inpatient rehabilitation training may improve the efficiency by which PwMS complete cognitive motor tasks. Similar improved efficiencies on fMRI are described with purely cognitive tasks after cognitive rehabilitation training in PwMS (Olga Boukrina et al. 2020; A. Ernst et al. 2018) (see also section 3.13, Mental Visual Imagery).

No other studies with strictly inpatient rehabilitation settings met the inclusion criteria for this module, with the exception the above-mentioned Zuber et al. (2020) study. However, information about the effectiveness of inpatient rehabilitation services on cognition in PwMS may be helpful for setting realistic expectations and developing best practices. An inpatient case series by Andrews and Middleton (2018) from Australia included over 1400 PwMS. They reported on the Functional Independence Measure (FIM) cognitive sub-score changes from admission to discharge (Andrews and Middleton 2018). Mean FIM cognitive sub-scores for PwMS improved by 37.5%, which was comparable to the improvement observed for acute stroke patients. To calculate the FIM cognitive sub-score, the clinician evaluates the patient's level of assistance required for comprehension, expression, social interaction, problem solving, and memory (Zeltzer, Korner-Bitensky, and Sitcoff, n.d.). The FIM is not a direct objective measure of cognition, and therefore the case series by Andrews and Middleton (2018) did not meet the inclusion criteria for the MSBEST module. The FIM provides an estimate of the demands on the caregiver. Inpatient rehabilitation services may vary considerably for PwMS, especially since MS best practice inpatient rehabilitation guidelines are not established. Appropriate selection for inpatient services may be critical, as is the case for stroke rehabilitation (Canadian Stroke Best Practices 2019). However, it is encouraging that PwMS improved on the FIM cognitive sub-scores in this large case series study (Andrews and Middleton 2018).

Testing in different paradigms may help to understand the real-world implications of cognitive rehabilitation. Lamargue et al. (2020) included a virtual reality cognitive testing paradigm using the Urban Daily Cog. The virtual Urban Daily Cog task in this study involved viewing a screen with roads and responding to traffic lights. The intervention group (receiving specific attention and reaction time training) improved in their accuracy on this virtual task in comparison to an active control group—despite the fact that the two groups performed similarly on the majority of the other objective cognitive outcomes (Lamargue et al. 2020).

Virtual reality training or testing paradigms may not yet be readily accessible for PwMS, yet may show promise for improving cognitive functioning and outcomes (see section 3.4 Virtual Reality). Digital technology is widely accessed by a large portion of the MS population, especially among those with lower levels of disability (Remy et al. 2018). In a study by Gentry et al. (2008), PwMS with memory impairment at baseline were trained to use a Personal Digital Assistant (PDA) to help with everyday tasks. There was no improvement on the objective cognitive outcomes, yet there was significant improvement on measures of patient- and clinician-rated functional performance.

The interventions for cognitive rehabilitation are heterogeneous and the results of objective cognitive outcomes may not correlate with the patient or caregiver experience. Interventions in which both objective measures as well as patient- and caregiver-reported outcomes improve are of particular interest. There is high-level evidence from four high-quality RCTs and from lower quality studies supporting that mixed cognitive rehabilitation approaches incorporating various strategies improve objective memory outcomes in PwMS.

Conclusion

Attention

There is conflicting evidence whether cognitive rehabilitation improves attention (three randomized controlled trials and one pre-post study; Brenk et al. 2008, Lamargue et al. 2020, Mani et al. 2018, and Rilo et al. 2018).

There is level 1b evidence that the REACTIV program, which targets attention, may improve attention more than non-specific cognitive exercises persons with MS (one randomized controlled trial; Lamargue et al. 2020).

There is level 2 evidence that the REHACOP protocol may not improve attention more than no treatment (one randomized controlled trial; Rilo et al. 2018).

There is level 1b evidence that memory and attention rehabilitation using education and compensatory strategies may not improve attention more than sham psychoeducation in persons with MS with cognitive impairment (one randomized controlled trial; Mani et al. 2018).

Memory

There is level 1b evidence that the French ProCog-SEP involving facilitation and reorganization training improves memory in persons with MS with cognitive impairment more than non-cognitive training and discussion (one randomized controlled trial and one prospective controlled trial; Brissart et al. 2020 and Brissart et al. 2013).

There is level 2 evidence that n-back training over the course of 1 week may improve working memory in persons with MS with cognitive impairment compared to no treatment (one randomized controlled trial; Aguirre et al. 2019).

There is level 2 evidence that memory improves more with the REHACOP protocol compared to no treatment (one randomized controlled trial; Rilo et al. 2013).

There is level 1b evidence that the REACTIV protocol may improve verbal learning and memory but not other aspects of memory persons with MS with cognitive impairment (one randomized controlled trial; Lamargue et al. 2020).

There is level 1b evidence that compensatory strategies targeting attention and memory may improve memory more than no treatment in persons with MS (Mousavi et al. 2018 and Mousavi et al. 2018b).

There is level 1b evidence that compensatory memory strategies may not improve memory more than restitution in persons with MS with cognitively impaired (one randomized controlled trial; Martin et al. 2014).

There is level 4 evidence that practicing mental imagery with mnemonic memory techniques together may improve prospective memory when playing a board game in minimally cognitive-impaired persons with MS more than in healthy controls (one pre-post study; Kardiasmenos et al. 2008).

There is conflicting evidence whether cognitive rehabilitation improves memory in persons with MS among studies with different rehabilitation interventions, comparator groups, and memory outcomes (twelve randomized controlled trials, four prospective controlled trials, and one pre-post study; Aguirre et al. 2019, Brenk et al. 2008, Brissart et al. 2013, Brissart et al. 2020, Carr et al. 2014, Fink et al. 2010, Goverover et al. 2009, Jonsson et al. 1993, Kahraman et al. 2020, Lamargue et al. 2020, Lincoln et al. 2020, Mani et al. 2018, Martin et al. 2014, Mousavi et al. 2018, Rilo et al. 2018, Rodgers et al., 1996, and Shahpouri et al. 2019).

Executive Function

There is conflicting evidence whether cognitive rehabilitation improves executive function in persons with MS (four randomized controlled trials, one prospective controlled trial, and one pre-post study; Brenk et al. 2008, Fink et al. 2010, Hanssen et al. 2016, Lincoln et al. 2002, Mani et al. 2018, and Rilo et al., 2018).

There is conflicting evidence whether memory and attention cognitive rehabilitation combined with compensatory strategies improves executive function in persons with MS (two randomized controlled trials; Lincoln et al. 2002 and Mani et al. 2018).

There is level 2 evidence that cognitive rehabilitation targeting executive function may not improve executive function more than normal MS rehab and physiotherapy (one randomized controlled trial; Hanssen et al. 2016).

There is level 2 evidence that the REHACOP protocol may improve executive function more than no treatment persons with MS (one randomized controlled trial; Rilo et al. 2018).

There is level 2 evidence that executive functioning training using executive function textbook exercises may improve executive function in relapsing-remitting MS more than RehaCom reaction time training or no treatment (one prospective controlled trial; Fink et al. 2010).

Information Processing

There is conflicting evidence whether cognitive rehabilitation improves information processing speed persons with MS (five randomized controlled trials, one prospective trial study, and one pre-post study; Brissart et al. 2020, Kahraman et al. 2020, Lamargue et al. 2020, Lincoln et al. 2020, Rilo et al. 2018, Rodgers et al., 1996, and Zuber et al. 2020).

There is level 1b evidence that the French ProCog-SEP program involving facilitation and reorganization training may not improve information processing speed more than non-cognitive exercises and discussion in relapsing-remitting MS (one randomized controlled trial, Brissart et al. 2020).

There is level 1b evidence that the REACTIV program may not improve information processing more than non-specific cognitive training and physical activity (one randomized controlled trial; Lamargue et al. 2020).

There is level 1b evidence that group cognitive training that focuses on compensatory strategies and restitution for memory and attention may not improve information processing speed compared to usual care (defined as advice from nursing and OT) in persons with MS (one randomized controlled trial; Lincoln et al. 2020).

There is level 2 evidence that the REHACOP protocol may improve information processing more than no treatment persons with MS (one randomized controlled trial; Rilo et al. 2018).

There is level 2 evidence that Tele-MIT may improve information processing more than no treatment in persons with MS (one randomized controlled trial; Kahraman et al. 2020).

Verbal Language

There is conflicting evidence whether cognitive rehabilitation improves verbal language skills persons with MS (one randomized controlled trial and one prospective controlled trial; Brissart et al. 2013 and Rilo et al. 2013).

Lay Summary

Rehabilitation approaches targeting memory improve memory in persons with MS with minimum to moderate cognitive impairment compared to no treatment.

Restitution approaches may increase self-reported stress levels compared to compensatory approaches.

Non-specific or multi-modal rehabilitation approaches delivered individually, in a group, or remotely may improve memory in persons with MS compared to no treatment.

Rehabilitation approaches targeting executive function improve executive function outcomes in persons with MS with minimum cognitive impairment.

Compensatory approaches targeting memory in persons with MS may not be superior to restitution approaches, self-management coaching, or access to MS occupational therapy and nursing services for improving memory.

Non-specific cognitive rehabilitation approaches may not improve outcomes in other cognitive domains besides memory compared to no treatment.

3.2 Computer-Based Cognitive Rehabilitation Approaches

This section includes research studies evaluating the potential benefit of a computer-based cognitive intervention, either in comparison to no treatment, to another computer-based intervention, or to other non-computer-based cognitive rehabilitation approaches.

The distinction between cognitive computer training and gaming is not always obvious in the literature. Several studies clearly set out to examine the effects of gaming. We include these few gaming studies in a separate extraction table following the computer training studies (See section 3.3, Video Games, table 6).

Table 4. Studies Examining Computer-based Training for Cognitive Impairment in Multiple Sclerosis

Author Year **Title** **Country** **Research Design** **PEDro** **Sample Size**	**Methods**	**Results**
Chiaravalloti et al. 2018 *A Pilot Study Examining Speed of Processing Training (SPT) to Improve Processing Speed in Persons With Multiple Sclerosis* USA **RCT**	**Population:** *Intervention group (n=12)*: Mean age=46.42yr; Sex: males=3, females=9; Disease course: RRMS; Severity: unspecified; Mean disease duration=12.7yr. *Control group (n=9)*: Mean age=52.11yr; Sex: males=3, females=6; Disease course: RRMS; Severity: unspecified; Mean disease duration=3.4yr. **Intervention:** Following randomization, the intervention group completed 10 computerized sessions of Speed of Processing Training (SPT) over a 5-wk period. The intervention involved three levels. Level 1	1. Participants in the treatment group improved on the WAIS-III coding task following the intervention ($F(1,21)=2.72$, $p=0.05$, $\eta_p^2=0.133$, large effect). 2. Of the participants in the intervention group who had impaired coding scores at baseline, 25% had improved their scores to the unimpaired range. 3. A non-significant, medium-large effect size was shown from baseline to f/u on the PC in the intervention group ($F(1,21)=2.16$, $p=0.08$, $\eta_p^2=0.107$, medium-large effect size).

PEDro=9 $N_{Initial}$=21, N_{Final}=21	involved a single discrimination task that was to be completed at a progressively faster speed. Level 2 involved a discrimination task to be completed while locating a peripheral target. Level 3 involved the same tasks as level 2, but the peripheral target was hidden among distractors. Each level continued until the participants got 75% correct. The control group received no treatment. Outcome measures were collected at baseline and within 1wk following the intervention. **Cognitive Outcome Measures:** Wechsler Adult Intelligence Scale-III (WAIS-III): Digit Symbol[1]; Letter Comparison (LC)[2]; Pattern Comparison (PC)[2]; California Learning Verbal Test II (CVLT-II).[2]	4. No significant differences from baseline to f/u existed on LC (η_p^2=0.025, small effect). 5. Statistically significant improvements were seen from baseline to f/u on the CVLT-II short delay free recall in the intervention group (F(1,21)=4.93, p=0.015, ηp^2=0.215, large effect). 6. No significant differences from baseline to f/u existed on CVLT-II learning slope (ηp^2=0.029, small effect). 7. Inclusion criteria required impaired processing speed at least 1.5 standard deviations below normative data for SDMT.
De Luca et al. 2019 *Do people with multiple sclerosis benefit from PC based neurorehabilitation? A pilot study.* Italy **RCT** PEDro=8 $N_{Initial}$=40, N_{Final}=40	**Population:** *Intervention group (n=20)*: Mean age=52.7yr; Sex: males=12, females=8; Disease course: RRMS; Mean EDSS=5.1; Mean disease duration=8.3yr. *Control group (n=20)*: Mean age=57.0yr; Sex: males=11, females=9; Disease course: RRMS; Mean EDSS=5.1; Mean disease duration=8.9yr. **Intervention:** Following randomization, both groups received 3, 45-min sessions/wk for 8wks. Participants in the computer-based intervention used the ERICA platform. Sessions focused on specific cognitive domains including attention, verbal memory, visuospatial memory, and executive function. Difficulty was adjusted to the patient's performance. The control group completed traditional face-to-face cognitive therapy which was individualized to each patient. Outcome measures were collected at baseline and following the intervention. **Cognitive Outcome Measures:** Montreal Cognitive Assessment (MoCA); Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Selective Reminding (SRT), 10/36 Spatial Recall Test (SPART), Paced Auditory Serial Addition Test-3 (PASAT-3), Symbol Digit Modalities (SDMT), Word List Generation Test (WLGT)).[3]	1. Statistically significant improvements were observed on MoCA (R^2=0.77, p<0.001), SDMT (R^2=0.58, p<0.001), SRT-LTS (R^2=0.79, p<0.001), and SRT-delayed recall (R^2=0.79, p<0.001) in the intervention group compared to the control group. 2. Intervention group scores improved by 0.91 points on the MoCA, 5.25 points on the SRT-long term storage, 0.88 points on the SRT-delayed recall and 0.31 points on the SDMT in comparison to the control group. 3. No significant between-group differences were observed for the SPART, PASAT, or WLGT). 4. Participants were only included if they had a mild to moderate CI.
Stuifbergen et al. 2018 *Computer-assisted cognitive rehabilitation in persons with multiple sclerosis: Results of a multi-site randomized controlled trial with six month follow-up* USA	**Population:** *Intervention group (n=93)*: Mean age=49.8yr; Sex: males=13, females=80; Disease course: RRMS=64, PPMS=3, SPMS=14, PRMS=1; Mean EDSS=5.1; Mean disease duration=13.9yr. *Control group (n=90)*: Mean age=49.4yr; Sex: males=10, females=80; Disease course: RRMS=61, PPMS=5, SPMS=10, PRMS=1; Mean EDSS=5.3; Mean disease duration=12.1yr. **Intervention:** Following randomization, the intervention group received the MAPSS-MS program. This included weekly, 2-hr group sessions and 3 daily, 45-min home-based	1. Both groups showed significant change over time on all measures (p<0.01). 2. There were no significant group x time effects for any of the cognitive outcomes. 3. ANOCVA analysis revealed that after the intervention, the intervention group had significant improvements on the CVLT delayed score (F=6.47, p=0.012) and PASAT-3 (F=7.72, p=0.006) in comparison to the control group. 4. At 3-mo f/u, the intervention group had statistically significant improvements on

RCT PEDro=8 $N_{Initial}$=183, N_{Final}=163	computer training sessions for 6wks. The first four group sessions focused on common cognitive deficits in MS and compensatory strategies. The final four group sessions focused on lifestyle behaviours to support cognitive functioning. The computer protocol used the Lumosity software, which addressed attention, memory, flexibility, and problem solving. The complexity of the tasks adjusted to the participant's performance. The control group underwent usual care and had access to the public computer games "MyBrainGames" on multiplesclerosis.com, which target information processing, attention, and executive function. Outcome measures were collected at baseline, after the intervention (6wks) and at 3- and 6-mo f/u. **Cognitive Outcome Measures:** Minimal Assessment of Cognitive Function in MS (MACFIMS) (Controlled Oral Word Association Test (COWAT), California Verbal Learning Test-II (CVLT-II), Brief Visuospatial Memory Test-Revised (BVMT-R), Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT)); PROMIS Applied Cognition Abilities Short Form.[3]	the PROMIS cognitive abilities (F=5.33, p<0.05), PASAT-3 (F=3.92, p<0.05), and PASAT-2 (F=5.78, p<0.05) in comparison to the control group. 5. At 6-mo f/u, the intervention group had statistically significant improvements on the PROMIS cognitive abilities (F=6.62, p<0.05), SDMT (F=4.09, p<0.05), and COWAT (F=4.42, p<0.05) in comparison to the control group.
Charvet et al. 2017 *Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial* USA **RCT** PEDro=8 $N_{Initial}$=135, N_{Final}=135	**Population:** *Adaptive Cognitive Rehabilitation (ACR) group (n=74):* Mean age=48yr; Gender: males=24, females=50; Disease course: RRMS=51, PPMS=3, SPMS=20; Mean EDSS=3.5; Mean disease duration=11.9yr. *Active Control group (n=61):* Mean age=52; Gender: males=7, females=54; Disease course: RRMS=39, PPMS=4, SPMS=15; Mean EDSS=3.5; Mean disease duration=13.5yr. **Intervention:** MS patients were randomized to receive either Adaptive Cognitive Remediation (ACR) or active control of computer games for 60hr over 12wks. The ACR program was adapted from BrainHQ, an online brain-training service, and included 15 exercises targeting attention, working memory, executive function, and information processing speed. The active control played "Hoyle puzzles and board games," which included card games such as bridge and board games such as backgammon. Assessments were performed at baseline and after treatment. **Cognitive Outcome Measures:** Neuropsychological composite score (Paced Auditory Serial Addition Test (PASAT); Wechsler Adult Intelligence Scale-IV (WAIS-IV): letter number sequence, digit span backwards; Selective Reminding Test (SRT); Brief Visuospatial Memory Test-Revised	1. The ACR group was observed to have significantly improved scores on the Neuropsychological Composite Score compared to the control group (estimated difference=0.16, p=0.0286). 2. No significant differences between groups were observed for any of the individual constituent measures. 3. Inclusion criteria required participants to score one or more standard deviations below baseline for SDMT.

	(BVMT-R); Delis-Kaplan Executive Function System (D-KEFS) trails).[1]	
Charvet et al. 2015 *Remotely-delivered cognitive remediation in multiple sclerosis (MS): protocol and results from a pilot study* USA **RCT** PEDro=8 $N_{Initial}$=20, N_{Final}=20	**Population:** *Intervention group (n=11):* Mean age=38yr; Gender: males=4, females=7; Disease course: RRMS=11; Median EDSS=2; Mean disease duration Unspecified. *Control group (n=9):* Mean age=42yr; Gender: males=2, females=7; Disease course: RRMS=9; Median EDSS=2.5; Mean disease duration Unspecified. **Intervention:** RRMS patients were randomized to either a home-based, remotely supervised, active cognitive remediation (ACR) program group, or a control group consisting of ordinary video games. The ACR program used Lumosity, an online platform with brain training games. The control played "Hoyle puzzles and board games," which included card games such as bridge and board games such as backgammon. Both groups completed 5d of treatment/wk for 12wks in 30-min sessions. Assessments were performed at baseline and after treatment. **Cognitive Outcome Measures:** A Cognitive Composite score (Wechsler Adult Intelligence Scale-IV: letter number sequencing, Selective Reminding Test (SRT), Brief Visuospatial Memory Test-Revised (BVMT-R), Corsi Block Visual Sequence (CORSI)).[2]	1. The intervention group (mean change=0.46) significantly improved on the cognitive composite measure compared to the control group (mean change=0.014) (d=1.11, p=0.02). 2. The groups did not significantly differ at baseline or f/u in any individual cognitive outcome measures.
Mäntynen 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* Finland **RCT** PEDro=8 $N_{Initial}$=102, N_{Final}=98	**Population:** *Treatment group (n=58):* Mean age=43.5yr; Gender: males=13, females=45; Disease course: RRMS; Mean EDSS=2.2; Mean disease duration=9.2yr. *Control group (n=40):* Mean age=44.1yr; Gender: males=9, females=31; Disease course: RRMS; Mean EDSS=2.2; Mean disease duration=10.1yr **Intervention:** MS patients were randomized to receive either neuropsychological rehabilitation or the control condition. Before intervention, patients set three goals related to attentional problems. These goals were reviewed at the end of rehabilitation. The computer-based neuropsychological rehabilitation consisted of weekly 60-min sessions for 13wks on attention retraining and working memory. In addition, they received compensatory strategies for managing perceived cognitive, mood, and fatigue deficits. Assessments were performed at baseline (T0), 3mos (T1) and 6mos (T2) after initiation. **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT)[1]; Perceived Deficits Questionnaire (PDQ)[1]; Goal Attainment Scaling (GAS)[1]; Buschkle selective reminding test: long-term storage (BSRT/LTS),	1. No significant difference was observed between the treatment and control groups on the SDMT at any time point. 2. The intervention group reported significantly fewer cognitive deficits on the PDQ at T1 and T2 compared with the control group (η_p^2=0.077, p<0.001 for both). 3. A significant difference was observed between groups at T1 but not at T2 on the TMT-A scores. 4. Significant differences were observed between the groups on the 10/36 total correct (p=0.011) and the 10/36 delayed recall (p=0.032). 5. All objective cognitive performance measures, except TMT-B, showed significant improvements over time in both groups (10/36 total correct p=0.022; p<0.001 for all others). However, between-group differences were not significant except where noted. 6. Inclusion criteria required total scores on SDMT < 50 but no overall CI (defined as scoring <-1.5 SD on the Brief Repeatable Battery of Neuropsychological Tests).

	consistent long-term retrieval (BSRT/CLTR), Delayed recall (BSRT)[2]; 10/36 total correct, delayed recall (SPART)[2]; Paced Auditory Serial Addition Test 2,3 seconds (PASAT-2, -3)[2]; Controlled Oral Word Association Test (COWAT)[2]; Stroop: colour naming time, colour/word interference time[2]; Trail Making Test A and B (TMT-A, -B)[2].	
Cerasa et al. 2013 *Computer-assisted cognitive rehabilitation of attention deficits for multiple sclerosis: a randomized trial with fMRI correlates* Italy **RCT** PEDro=8 $N_{Initial}$=26, N_{Final}=23	**Population:** *Experimental Group (n=12):* Mean age=31.7yr; Gender: males=3, females=9; Disease course: RRMS=12; Median EDSS=3; Mean disease duration=51.2mos. *Control Group (n=11):* Mean age=33.7yr; Gender: males=3, females=8; Disease course: RRMS=11; Median EDSS=2; Mean disease duration=61.6mos. **Intervention:** RRMS patients were randomized to receive cognitive rehabilitation or placebo intervention. The computer-based cognitive rehabilitation used the RehaCom software, which has modules dedicated to different cognitive domains. This study used the "divided attention," "attention and concentration," and "vigilance" modules. Patients met 2x/wk for 1h for 6wks. The control group performed visuomotor computer-based exercises. Outcome measures were collected at baseline and 6wks following the end of the intervention. **Cognitive Outcome Measures:** Selective Reminding Test: long-term storage (SRT-LTS), consistent long-term storage (SRT-CLTR), delayed (SRT-D); Spatial recall test: immediate (SPART-I), delayed (SPART-D); Word List Generation Test (WLGT); Symbol Digit Modality Test (SDMT); Trial Making Test A, B (TMT-A, TMT-B); Paced Auditory Serial Addition Test-3 second (PASAT-3); Stroop Color-Word-Test (SCWT).[3]	1. The experimental group performed statistically better on the ST than the control group at 6wks (d=0.88, p<0.007). 2. No other between-group differences were statistically significant.
Stuifbergen et al. 2012 *A randomized controlled trial of a cognitive rehabilitation intervention for persons with multiple sclerosis* USA **RCT** PEDro=8 $N_{Initial}$=63, N_{Final}=61	**Population:** *Total population (n=61):* Mean age=47.95yr; Gender: males=7, females=54; Disease course: Unspecified; Mean EDSS=5.2; Mean disease duration=12.2yr. *Treatment group (n=34):* Gender: males=5, females=29. *Control group (n=27):* Gender: males=2, females=25. **Intervention:** MS patients were randomized to the cognitive rehabilitation treatment group (Memory, Attention, and Problem-Solving Skills for persons with Multiple Sclerosis (MAPSS-MS)) or to the waitlist control group for 8wks of intervention. The intervention consisted of 8 weekly group sessions focused on building efficacy for use of cognitive compensatory strategies and computer-assisted cognitive rehabilitation with home-based training. The cognitive	1. Significant improvements were seen between groups at T3 on the CVLT-II total score (p=0.005). 2. There were no other significant between-group differences.

	rehabilitation exercises were found on www.neuropsychonline.com and focused on attention, executive function, memory, and problem solving. Assessments were performed at baseline, after 8wks of intervention, and 5mos after randomization. **Cognitive Outcome Measures:** Minimal Assessment of Cognitive Function in MS (MACFIMS) (Controlled Oral Word Association Test (COWAT); Judgment of line orientation test (JLO); California Verbal Learning Test II (CVLT-II); Brief Visuospatial Memory Test-Revised (BVMT-R); Paced Auditory Serial Addition Test (PASAT); Symbol Digit Modalities Test (SDMT); Delis-Kaplan Executive Function System (DKEFS)).[3]	
Mattioli et al. 2010 *Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis* Italy **RCT** PEDro=8 $N_{Initial}$=20, N_{Final}=20	**Population:** *Study group (n=10):* Median age=44.00yr; Gender: females=10; Disease course: RRMS; Mean EDSS=2.5; Mean disease duration=16.50yr. *Control group (n=10):* Median age=42.00yr; Gender: females=10; Disease course: RRMS; Mean EDSS=1.5; Mean disease duration=18.50yr. **Intervention:** MS patients were randomized to receive a computer-based intensive training program or a control condition. The training program used RehaCom software's "Plan a Day" and "Divided Attention" modules and consisted of 1-hr sessions, 3x/wk for 3mos focusing on attention, information processing, and executive function. The control group did not receive any rehabilitation. Assessments were performed at baseline (T0) and after 3mos of rehabilitation (T1). **Cognitive Outcome Measures:** Paced Auditory Serial Addition Test 2, 3 seconds (PASAT-2, -3); Wisconsin Card Sorting Task (WCST) total errors (te), perseverative errors (pe), perseverative responses (pr); Controlled Oral Word Association Test with phonemic (COWA/P) and semantic (COWA/S) cues; Divided attention of test of everyday attention (TEA); Selective Reminding Test: consistent long-term retrieval (SRT-CLTR), delayed recall (SRT-DR); 10/36 Spatial Recall Test: long term retrieval (10/36 SRT LTR), delayed recall (10/36 SRT LTR); Symbol Digit Modalities Test (SDMT).[3]	1. Improvements were observed at T1 between the intervention and control groups on the PASAT-2 (p=0.004), WCSTte (p=0.037), and WCSTpe (p=0.051). 2. The change scores between T1 and T0 showed improvement in the intervention group compared to the control group on the PASAT-3 (p=0.023), PASAT-2 (p=0.004), and WCSTte (p=0.037). 3. Comparisons adjusted for confounding variables (EDSS, age, and T0 score) through linear regression showed significant differences between the control and intervention groups on the TEAar (p=0.031), TEAte (p=0.004) and COWA/P (p=0.009).
Solari et al. 2004 *Computer-aided retraining of memory and attention in people with multiple sclerosis: A randomized,*	**Population:** *Intervention group (n=40):* Mean age=46.2yr; Gender: males=14, females=26; Disease course: RRMS=17, RPMS=20, CPMS=3; Mean EDSS=3.0; Mean disease duration=15.2yr. *Control group (n=37):* Mean age=41.2yr; Gender: males=14, females=23; Disease	1. Differences were observed between the intervention group and the control group in favour of the intervention group at 8wks on the SRT: consistent long-term retrieval (p<0.001), SDMT (p=0.047), WLGT (p=0.002), and SPART immediate (p<0.001) and delayed recall (p=0.006).

double-blind controlled trial Italy **RCT** PEDro=8 $N_{Initial}$=82, N_{Final}=77	course: RRMS=22, RPMS=15; Mean EDSS=4.0; Mean disease duration=13.5yr. **Intervention:** MS patients were randomized to one of two computer-assisted retraining interventions using RehaCom software. The intervention consisted of memory and attention training, and the control condition consisted of visuo-motor coordination. Both groups received 16 training sessions over 8wks. Assessments were performed before and after 8 and 16wks. **Cognitive Outcome Measures:** Brief Repeatable Battery of Neuropsychological Tests (Selective Reminding Test (SRT): consistent long-term retrieval, delayed recall; Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test-2 (PASAT-2); Word List Generation Test (WLGT); 10/36 Spatial Recall Test (SPART): immediate recall, delayed recall).[3]	2. Differences were observed between the intervention group and the control group in favor of the intervention group at 16wks on the SRT: consistent long-term retrieval (p=0.003) and delayed recall (p<0.001), WLGT (p=0.002), SPART immediate (p<0.003) and delayed recall (p=0.002).
Messinis et al. 2020 *Do Secondary Progressive Multiple Sclerosis patients benefit from Computer-based cognitive neurorehabilitation? A randomized sham controlled trial* Greece **RCT** PEDro=7 $N_{Initial}$=36, N_{Final}=36	**Population:** *Intervention group (n=19)*: Mean age=46.47yr; Sex: males=7, females=12; Disease course: SPMS; Median EDSS=5.5; Mean disease duration=21.15yr. *Control group (n=17)*: Mean age=45.29yr; Sex: males=5, females=12; Disease course: SPMS; Median EDSS=6.0; Mean disease duration=20.76yr. **Intervention:** Following randomization, both groups completed 3, 45-min sessions/wk for 8wks. The intervention was conducted using the home-based RehaCom software, which included 24 individual domain and task-specific sessions. The control group completed a computer-based sham intervention along with their standard clinical therapy. The sham included computer-based brain teasers, newspaper articles, shopping games, etc. Outcome measures were collected at baseline and following the intervention. **Cognitive Outcome Measures:** Brief International Cognitive Assessment for Multiple Sclerosis (BiCAMS)[1] (Symbol Digits Modalities Test (SDMT), Greek Verbal Learning Test (GVLT), Brief Visuospatial Memory Test-Revised (BVMT-R)).	1. Statistically significant between-group differences were observed on the SDMT (g=2.980, p<0.005), GVLT (g=2.898, p<0.0005), and BVMT-R (g=1.699, p<0.0005). 2. Statistically significant within-group improvements were noted on the SDMT (z= -3.843, p=0.000), GVLT (t(18)=6.723, p=0.000), and BVMT-R (t (18)= -6.131, p=0.000). 3. No significant within-group effects of treatment were observed in the control group on the SDMT (t(16)=2.242, p=0.040), GVLT (t(16)=1.423, p=0.174), or BVMT-R (t(16)=0.599, p=0.599). 4. No statistically significant differences existed between the intervention and control groups at baseline. 5. Inclusion criteria required CI on at least one domain of the Central Nervous System Vital Sign neuropsychological screening battery. CI was defined as scoring between the 2nd and 8th percentile compared to normative data.
Campbell et al. 2016 *A randomised controlled trial of efficacy of cognitive rehabilitation in multiple sclerosis: A cognitive, behavioural, and MRI study*	**Population:** *Treatment group (n=19):* Mean age=46.21yr; Gender: males=6, females=13; Disease course: RRMS=14, SPMS=5; Mean EDSS=4.42; Mean disease duration=10.53yr. *Control group (n=19):* Mean age=48.53yr; Gender: males=5, females=14; Disease course: RRMS=13, SPMS=6; Mean EDSS=4.45; Mean disease duration=12.68yr. **Intervention:** Participants with MS and CI were randomized to undergo 45min of computerized cognitive rehabilitation using	1. Between-group comparison showed the intervention group had a significant improvement (mean change score=3.94) on the SDMT compared to the control group (mean change score=-0.63) immediately following treatment (p=0.005). This was not maintained at the 12-wk f/u. 2. No other significant between-group differences existed at any time point.

UK **RCT** PEDro=7 $N_{Initial}$=38, N_{Final}=38	RehaCom software 3x/wk for 6wks, or to the control condition in which patients watched natural history DVDs. The intervention group trained in three RehaCom modules: divided attention, working memory, and topological memory. Assessments were conducted at baseline (T1), after treatment (T2), and at a 12-wk post-treatment f/u (T3). **Cognitive Outcome Measures:** Brief International Cognitive Assessment for MS (BiCAMS) (Symbol Digit Modalities Test (SDMT); California Verbal Learning Test (CVLT); Brief Visuospatial Memory Test (BVMT)).[3]	
Amato et al. 2014 *Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial* Italy **RCT** PEDro=7 $N_{Initial}$=102, N_{Final}=88	**Population:** *Specific Computer Training (ST) (n=55):* Mean age=40.1yr; Gender: males=11, females=44; Disease course: RRMS=55; Mean EDSS=2.5; Mean disease duration=12.0yr. *Non-Specific Computer Training (n-ST) (n=33):* Mean age=42.4yr; Gender: males=8, females=25; Disease course: RRMS=33; Mean EDSS=3.0; Mean disease duration=14.7yr. **Intervention:** Patients were randomized to receive either specific or non-specific computer training in 1-hr sessions, 2x/wk for 3mos. The specific training was home-based Attention Processing Training (APT) that targets selective, sustained, focused, alternating, and divided attention. The non-specific training included reading comprehension exercises and descriptions of pictures. Assessments were made at baseline, after 3mos of treatment, and at 6mos since the beginning of treatment. **Cognitive Outcome Measures:** Rao's Brief Repeatable Battery (Selective Reminding Test (SRT); 10/36 Spatial Recall Test (SPART); Paced Auditory Serial Addition Test 2 and 3 (PASAT-2, PASAT-3); Symbol Digit Modalities Test (SDMT); Word List Generation Test (WLGT)); Stroop Color-Word Test (SCWT); Trail Making Test A and B (TMT-A, TMT-B); The Visual Search: selective attention (VAS).[3]	1. A significant improvement was observed on the PASAT-3 and -2 in both groups at both time points (p<0.001). The effect was significantly better in the ST group (PASAT-2 p=0.001, PASAT-3 p=0.002). 2. Both groups showed significant improvement (p<0.001) on the SDMT at both time points with a larger improvement in mean scores for the specific training group. However, the difference between the groups did not reach significance. 3. No significant improvement was found for other tested outcomes. 4. There was a significant improvement in VAS-attention in both groups after therapy (p=0.003) at both time points (unspecified) without any significant difference between the groups. 5. At baseline, the non-specific training group were more impaired compared to the specific training group on the PASAT and SDMT, although this did not reach statistical significance (i.e., baseline n-ST mean SDMT 33.5 ±12.3; ST 37.4±11.8).
Hildebrandt et al. 2007 *Cognitive training in MS: Effects and relation to brain atrophy* Germany **RCT** PEDro=7 $N_{Initial}$=42, N_{Final}=42	**Population:** *Intervention group (n=17):* Mean age=42.4yr; Gender: males=5, females=12 Disease course: RRMS=17; Mean EDSS=2.9; Mean disease duration=5.4yr. *Control group (n=25):* Mean age=36.5yr; Gender: males=12, females=13; Disease course: RRMS=25; Mean EDSS=2.7; Mean disease duration=4.5yr. **Intervention:** RRMS participants were randomized to either an intervention group or a control group. The intervention group underwent home-based computer cognitive therapy for 6wks. The treatment group used VILAT-G to perform memory and working memory tasks. Cognitive therapy was started	1. Improvement was observed in the intervention compared to the control group on the CVLT learning trials (p=0.03), CVLT long delay free recall, and PASAT (p=0.049). 2. No other significant differences between groups were observed after treatment.

	at least 4wks after methylprednisolone treatment was discontinued. The control group received no treatment. Assessments were performed before and 2wks after treatment. **Cognitive Outcome Measures:** Wechsler Abbreviated Intelligence Scale (WAIS): similarities, information; Block design; Picture completion; California Verbal Learning Test (CVLT): short delay free recall, short delay cued recall, long delay free recall, long delay cued recall; Paced Auditory Serial Addition Test: 3 second (PASAT); Test of Attentional Performance (TAP): object alternation (OA); TAP: alertness task.[3]	
Naeeni Davarani et al. 2020 *RehaCom rehabilitation training improves a wide range of cognitive functions in multiple sclerosis patients* Iran **RCT** PEDro=6 $N_{Initial}$=60, N_{Final}=54	**Population:** *Intervention group (n=28)*: Mean age=39.3yr; Sex: males=5, females=23; Disease course: unspecified; Severity: unspecified; Disease duration: unspecified. *Control group (n=26)*: Mean age=37.55yr; Sex: males=5, females=21; Disease course: unspecified; Severity: unspecified; Disease duration: unspecified. **Intervention:** Following randomization, the intervention group received 2, 60-min sessions/wk for 5wks. The intervention group was assigned the RehaCom software-based intervention. The modules selected for this study were the responsiveness, divided attention 2, attention and concentration, logical reasoning, and spatial operations 3D modules to target working memory, attention, processing speed, executive function, and spatial awareness. The control group received no intervention. Outcome measures were collected at baseline, following the intervention, and at 5-wk and 10-wk f/u. **Cognitive Outcome Measures:** Integrated Auditory Visual-2 (IVA-2); Paced Auditory Serial Addition Test (PASAT); Symbol Digit Modalities Test (SDMT); Judgement of Line Orientation (JLO); Delis-Kaplan Executive Function System (D-KEFS).[3]	1. Time-treatment analyses revealed statistically significant differences between groups on all the scales of the IVA-2, with the intervention group performing better (p<0.001). 2. Between-subject analyses revealed significant improvements in all attention and response control scales (p<0.001). 3. Effect of treatment on outcome measures revealed that the intervention group improved on different attention and response control scales at post-test (p<0.05). 4. Between-group analyses revealed that the intervention group improved more than the control group at post-test. 5. At 5-wk f/u, only auditory attention, visual response control, auditory response control, auditory persistence attention, and visual sensory-motor attention maintained the improved scores (p=0.05). 6. Time-treatment and between-subject analyses revealed statistically significant differences between groups on the SDMT, D-KEFS, PASAT, and the JLO (p<0.001), with the intervention group performing better. 7. Effect of treatment on outcome measures revealed that the intervention group improved on visuospatial skills (JLO), working memory (PASAT), and processing speed (SDMT) at post-test and f/u (p<0.05). The D-KEFS only improved at post-test (p<0.01).
Arsoy, Tuzun, and Turkoglu 2018 *Effects of computer-assisted cognitive*	**Population:** *Benign MS group (n=21 of which n=10 received the intervention and n=11 constituted the Benign MS control group)*: Mean age=37.0yr; Sex: males=6, females=15; Mean EDSS=2.2; Mean disease duration=13.2yr. *Non-Benign MS control group (n=22)*: Mean age=39.3yr; Sex: males=10, females=12;	1. Benign MS patients completing the intervention showed statistically significant higher (better) scores on the SDMT (p=0.016), COWAT (p=0.036) and SCWT (p=0.023) compared to benign MS patients in the control group. 2. Statistically significant improvements in the Benign MS intervention group were

rehabilitation in benign multiple sclerosis Turkey **RCT** PEDro=6 $N_{Initial}$=81, N_{Final}=81	Mean EDSS=4.2; Disease course: RRMS=14, SPMS=8; Mean disease duration=14.8yr. *Healthy Control group (n=38)*: Mean age=36.0yr; Sex: males=10, females=28. **Intervention:** Benign MS participants (EDSS <3 with disease duration >10yrs) where randomized to the intervention group (n=10) or a Benign MS control group (n=11). Benign MS participants in the intervention group received the computer-assisted cognitive rehabilitation (CCR), which was based on the NOROSOFT Mental Exercise Software and contained five modules. The modules focused on attention, memory, reasoning, visual, and verbal tasks. Participants practiced 5d/wk for 50-min sessions The control group Benign MS participants and other control groups received no intervention. Outcome measures were collected at baseline and at 6mos. **Cognitive Outcome Measures:** Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Selective Reminding Test (SRT), 10/36 Spatial Recall Test (SPART), Paced Auditory Serial Addition Test-3 (PASAT-3), Symbol Digit Modalities Test (SDMT), Controlled Oral Word Association Test (COWAT)); Stroop Color-Word Test (SCWT).[3]	observed on the PASAT (baseline mean: 40.3, post mean: 46.3, p=0.008). 3. SDMT and SCWT test scores significantly deteriorated in the benign MS control group at the 6-mo f/u evaluation (SDMT scores pre: 42.1 ± 14.1 vs. post: 36.0 ± 10.7, P = 0.031; SCWT scores pre: 47.7 ± 37.6 vs. post: 63.7 ± 49.3, P = 0.043). 4. No significant between-group improvements were reported for the SRT, SPART, or PASAT for the intervention Benign MS group vs. the control Benign MS control compared to baseline. 5. Participants with MS had significantly lower baseline scores on the SRT, SPART, PASAT, SDMT, SCWT, and COWAT when compared to the healthy controls.
Flachenecker et al. 2017 *Neuropsychological Training of Attention Improves MS-Related Fatigue: Results of a Randomized, Placebo-Controlled, Double-Blind Pilot Study* Germany **RCT** PEDro=6 $N_{Initial}$=32, N_{Final}=30	**Population**: *Intervention group (n=14)*: Mean age=43.3yr; Sex: males=6, females=8; Disease course: unspecified; Mean EDSS=3.8; Mean disease duration=6.5yr. *Active control group (n=16)*: Mean age=45.2yr; Sex: males=2, females=14; Disease course: unspecified; Mean EDSS=4.7; Mean disease duration=9.4yr. **Intervention**: Following randomization, both groups participated in 2, 30-min training sessions/day for over 5 sessions/wk for 2wks of supervised computerized neuropsychological training in addition to their regular rehabilitation program. The intervention group received computer training with reaction time-based tasks (Reaktion and Jeton software) in which the difficulty of the reaction time-based tasks were individualized to the patient. The active control group received non-reaction time-based computer training with software designed to improve selective attention, cognitive flexibility, and working memory (Bilder, Garten, Mosaik, Partino, and Vario). Outcome measures were collected at baseline and following the intervention at 2wks. **Cognitive Outcome Measures**: Test of Attentional Performance (TAP).[1]	1. Between-group comparison of reaction times showed significantly faster reaction times in the intervention group compared to the active control group after 2wks (p<0.05). 2. Improvements with a large effect size were observed in the treatment group on the subtest alertness after 2wks (d_c=1.71); this did not reach statistical significance. 3. The percentage of patients with normal results on the alertness subtest was higher in the intervention group (64%) compared to the active control group (38%) after 2wks, but this did not reach statistical significance (p=0.27). 4. Inclusion criteria required patients to have impaired reaction times at baseline.

Grasso et al. 2017 *Evaluation of the Impact of Cognitive Training on Quality of Life in Patients with Multiple Sclerosis* Italy **RCT** PEDro=6 $N_{Initial}$=34, N_{Final}=34	**Population:** *Intervention group (n=17)*: Mean age=59.5yr; Sex: males=6, females=11; Disease course: RRMS=8, PPMS=2, SPMS=7; Mean EDSS=7.54; Mean disease duration=21.64yr. *Control group (n=17)*: Mean age=58.67yr; Sex: males=6, females=11; Disease course: RRMS=8, PPMS=1, SPMS=8; Mean EDSS=7.5; Mean disease duration=21.9yr. **Intervention:** Following randomization, all participants received 2 daily physiotherapy sessions for 5d/wk. This treatment was focused on improving movements of paretic upper limb and improving balance and transfers. Both groups also received their respective intervention for 3x/wk for 3mos. The intervention group underwent computer-assisted cognitive rehabilitation. This program was based on the Attention Processing Training (APT) program. The tasks were focused on increasing demands on complex attention and working memory. The control group underwent standard occupational therapy instead of the computer-based therapy. Outcome measures were collected 3d after admission, after the 3-mo intervention. and 6mos after the end of treatment **Cognitive Outcome Measures:** Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Selective Reminding Test (SRT), 10/36 Spatial Recall Test (SPART), Paced Auditory Serial Addition Test-3 (PASAT-3), Word List Generation Test (WLGT)); Stroop Color-Word Interference Test (SCWT)[3].	1. The intervention group had statistically significant improvements on the SCWT following the 3-mo intervention (p=0.024). 2. In patients who had improved following the intervention, neuropsychological improvements were significantly linked to depression (p=0.042) and persisted at 6-mo f/u (p=0.036). 3. Improvements on the SCWT were correlated with improvements in general health (p=0.047) following the intervention. 4. There were no between-group differences on outcomes following the intervention (with the exception of improved mood in favor of the intervention group).
Messinis et al. 2017 *Efficacy of a Computer-Assisted Cognitive Rehabilitation Intervention in Relapsing-Remitting Multiple Sclerosis Patients: A Multicenter Randomized Controlled Trial* Greece **RCT** PEDro=6 $N_{Initial}$=58, N_{Final}=58	**Population:** *Intervention group (n=32)*: Mean age=46.03yr; Sex: males=10, females=22; Disease course: RRMS; Median EDSS=3; Mean disease duration=13.31yr. *Control group (n=26)*: Mean age=45.15yr; Sex: males=8, females=18; Disease course: RRMS; Median EDSS=3.5; Mean disease duration=11.27yr. **Intervention:** Following randomization, participants in both groups received 2, 60-min sessions/wk for 10wks. The RehaCom software was used for the intervention delivery. The RehaCom program includes 20 modules and adapts the level of difficulty based on the participant's performance. These modules target attention, executive function, information processing, and memory. The control group received their usual clinical care. Outcome measures were collected at baseline and following the intervention, with one more f/u for the intervention group at 6mos.	1. Group by time interactions showed a significant improvement in the composite cognitive domains of verbal episodic memory, processing speed, verbal fluency, and attention for the intervention group compared to the control group. 2. Within-group comparison showed the intervention group had significant improvements post intervention on the SDMT (r=0.522, p=0.000), SRT verbal memory and long term storage (p=0.00, large effect size, r=0.481), SRT verbal memory and delay recall (p=0.000, medium effect size, r=0.481), BVMT-R visuospatial memory and total recall (p=0.00, medium effect size, r=0.469), TMT-A attention and processing speed (p=0.00, large effect size, r=0.573), TMT-B executive function and set shifting (p=0.00, large effect size, r=0.506), and SCWT executive function and response inhibition (p=0.00, medium effect size,

	Cognitive Outcome Measures: Brief Visuospatial Memory Test-Revised (BVMT-R); Selective Reminding Test (SRT); Symbol Digit Modalities Test (SDMT); Trail Making Test Part A (TMT-A); Verbal Fluency Test (VFT); Stroop Colour-Word Task (SCWT); Trail Making Test Part B (TMT-B).[3]	r=0.460). These remained significant at 6-mo f/u except for the SDMT. 3. Within-group comparison showed the control group had significant improvements for TMT-A (r=0.294, p=0.034) and VLT (r=0.328, p=0.018) but no other cognitive outcome. 4. Inclusion criteria required CI on at least one domain of the Central Nervous System Vital Sign neuropsychological screening battery. CI was defined as scoring between the 2nd and 8th percentile compared to normative data.
Perez-Martin et al. 2017 *Efficacy of a short cognitive training program in patients with multiple sclerosis* Spain **RCT** PEDro=6 $N_{Initial}$=62, N_{Final}=62	**Population:** *Treatment group (n=30):* Mean age=44.93yr; Gender: males=12, females=18; Disease course: RRMS=27, SPMS=2, PPMS=1; Mean EDSS=2.78; Mean disease duration=11.50yr. *Control group* (n=32): Mean age=40.88yr; Gender: males=18, females=14; Disease course: RRMS=30, PPMS=2; Mean EDSS=2.11; Mean disease duration=9.59yr. **Intervention:** MS patients were randomized to receive a neuropsychological training program and compensatory strategies or no intervention. The intervention group participated in weekly cognitive training sessions lasting 60-75min each. The exercises focused on attention, processing speed, memory, and executive function, and used a mixture of computer-based exercises and traditional pen-and-paper exercises. Patients were given booklets with exercises and compensatory strategies to complete at home. Assessments were performed at baseline and after 3mos of therapy. **Cognitive Outcome Measures:** Brief Repeatable Battery of Neuropsychological Test (BRB-N)[1] (Selective Reminding Test (SRT): long-term storage (SRT-LTS), consistent long-term retrieval (SRT-CLTR), delayed recall (SRT-DR); 10/36 Spatial Recall Test (SPART): total, delayed recall (SPART-DR); Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test 3 seconds (PASAT); Controlled Oral Word Association Test (COWAT): Verbal Fluency FAS Test, animals)); MS neuropsychological questionnaire (MSNQ).[2]	1. The treatment group scored significantly better than the control group on the SRT-LTS (p<0.05), SRT-CLTR (p<0.001), SRT-DR (p<0.001), SPART-DR (p<0.05), SDMT (p<0.05), PASAT-3 (p<0.001) and COWAT FAS (p<0.05). 2. The treatment group showed significant improvements after treatment in SRT-LTS (p<0.05), SRT-CLTR (p<0.001), SRT-DR (p<0.001), PASAT (p≤0.05), COWAT FAS (p<0.05), and MSNQ (p<0.05). 3. The control group showed no significant change on any cognitive outcome measure. 4. Inclusion criteria required CI defined as scores 1.5 SD or lower on at least two cognitive tests.
Pusswald et al. 2014 *A neuropsychological rehabilitation program for patients with Multiple Sclerosis based on the model of the ICF*	**Population:** *Total population* (n=40): Disease course: RRMS=33, SPMS=6, PPMS=1. *Intervention group (n=20):* Mean age=42.6yr; Gender: males=5, females=15; Disease course: unspecified; Mean EDSS=3; Mean disease duration=15.1yr. *Control group (n=20):* Mean age=45.3yr; Gender: males=4, females=16; Disease course: unspecified; Mean EDSS=4; Mean disease duration=12.6yr.	1. Significant differences were observed between the intervention and control groups in terms of the TAP alertness RT simple (p=0.036), TAP alertness RT cued (p=0.017), and TAP Divided Attention RT acoustic (p=0.049) at 5wks. 2. 3-mo f/u showed no significant changes in terms of reaction time or divided attention tasks from post-treatment 5-

Austria **RCT** PEDro=6 $N_{Initial}$=40, N_{Final}=40	**Intervention:** MS patients were randomized to an intervention group or a control group. The intervention group received 30-min sessions 3x/wk of computer-based home training of attention, and 90-min/wk of group psychological counselling, which focused on compensatory strategies, for 5wks. The computer-based training used Fresh minder 2 software. The control group received no training. Assessments were performed at baseline, after 5wks, and after 3mos. **Cognitive Outcome Measures:** Test of Attentional Performance (TAP): Alertness and Divided Attention; Multiple Sclerosis Inventory for Cognition (MUSIC): verbal memory, verbal retrieval, verbal fluency, interferences.[3]	wk follow-up, indicating stable treatment effects. 3. Significant differences were observed in the intervention group before and after training in terms of TAP Alertness RT simple (p=0.002) and RT cued (p=0.001), TAP Divided Attention RT acoustic (p=0.039) and RT visual (p=0.032), variance acoustic (p=0.013), and MUSIC verbal memory (p=0.007) scores. 4. No significant between-group differences were observed for the MUSIC test.
Mattioli et al. 2012 *Persistence of the effects of attention and executive functions intensive rehabilitation in relapsing remitting multiple sclerosis* Italy **RCT** PEDro=6 $N_{Initial}$=24, N_{Final}=24	**Population:** *Intervention group (n=13):* Mean age=45.46yr; Gender: Unspecified; Disease course: RRMS; Mean EDSS=2.34; Mean disease duration=16.69yr. *Control group (n=11):* Mean age=46.90yr; Gender: Unspecified; Disease course: RRMS; Mean EDSS=2.40; Mean disease duration=20.00yr. **Intervention:** MS patients were randomized to the intervention group that received neuropsychological treatment for 3mos or to the control group that received no treatment. Neuropsychological training used the RehaCom software modules for attention, information processing, and executive function exercises. The training consisted of 1-hr sessions 3x/wk for 3 consecutive mos. Assessments were performed at baseline (T0), 3mos (T1), and 9mos after baseline (T2). **Cognitive Outcome Measures:** Paced Auditory Serial Addition Test 2, 3 seconds (PASAT-2, -3); Wisconsin Card Sorting Task (WCST) total errors (te), perseverative errors (pe), perseverative responses (pr); Controlled Oral Word Association Test with phonemic (COWA/P) and semantic (COWA/S) cues; Divided attention of Test of Everyday Attention (TEA); Selective Reminding Test (SRT): consistent long-term retrieval (SRT-CLTR), delayed recall (SRT-DR); 10/36 Spatial Recall Test: long term retrieval (10/36 SPART LTR), delayed recall (10/36 SPART LTR); Symbol Digit Modalities Test (SDMT).[3]	1. Change in scores from T0 to T1 was greater in the intervention group compared to the control group on the PASAT-2, PASAT-3, WCSTte, WCSTpe, and COWA/P (all p<0.05). This was maintained at T2. 2. Within-group change in scores in the intervention group from T0 to T2 was observed on the PASAT-2, PASAT-3, WCSTte, WCSTpr, WCSTpe, COWA/S, COWA/P, TEAto, TEAte, and SRT/DR (all p<0.05). 3. Within-group change in scores in the control group from T0 to T2 on the WCSTpr, WCSTpe, TEAvm, TEAte, and SRT/DR (all p<0.05). 4. The change scores from T0 to T2 was greater in the intervention group compared to the control group on the PASAT-3, WCSTpe, and COWA/S (all p<0.05).
Arian Darestani et al. 2020 *The therapeutic effect of treatment with RehaCom software on verbal*	**Population:** *Intervention group (n=27)*: Mean age=37.11yr; Sex: males=6, females=21; Disease course: unspecified; Mean/Median Severity: unspecified; Disease duration: unspecified. *Control group (n=26)*: Mean age=39.23yr; Sex: males=4, females=22; Disease course:	1. Differences between the two groups in favor of the intervention group were observed on the CVLT-II (F=904.05, df=1, p<0.001) and COWAT (F=590.99, df=1, p<0.001). 2. At week 5, the intervention improved on the CVLT-II (change score: -9.42, p<0.05) and COWAT (change score: -6.73,

performance in patients with multiple sclerosis Iran **RCT** PEDro=5 $N_{Initial}$=60, N_{Final}=53	unspecified; Severity: unspecified; Disease duration: unspecified. **Intervention:** Following randomization, participants in the intervention group completed the RehaCom intervention. The intervention included 10, 1-hr sessions over 5wks. RehaCom cognitive rehabilitation software includes 20 modules and adapts the level of difficulty based on the participant's performance. These modules offer attention, memory, executive function, visual field, and visuo-motor training. The control group received no treatment. Outcome measures were collected at baseline, after completion (5wks), and 5wks after completion (10wks). **Cognitive Outcome Measures:** Controlled Oral Word Association Test (COWAT); California Verbal Learning Test- II (CVLT-II).[3]	p<0.01). This was maintained at f/u (CVLT-II: 95% CI: -7.38, -14.51 to -0.25, p<0.05; COWAT: 95% CI: -4.89, -8.7 to -1.07, p<0.05). 3. For the entire study population, improvement was observed on the CVLT-II (F=45.11, df=1.26, p<0.001) and COWAT (F=65.27, df=1.29, p<0.001). 4. A time-treatment interaction was observed on the CVLT-II (F=84.55, df=1.26, p<0.001) and COWAT (F=62.5, df=1.29, p<0.001) in the intervention group.
Rahmani et al. 2020 *Comparing the Effectiveness of Computer-Based, Manual-based, and Combined Cognitive Rehabilitation on Cognitive Functions in Relapsing-Remitting Multiple Sclerosis Patients* Iran **RCT** PEDro=5 $N_{Initial}$=60, N_{Final}=60	**Population:** *Computer-Based Intervention group (n=12)*: Mean age=30.16yr; Sex: female=12; Disease course: RRMS; Severity: unspecified; Disease duration range=2-7yr. *Manual Cognitive Training group (n=12):* Mean age= 29.41y; Sex: females=12; Disease course: RRMS; Severity: unspecified; Disease duration range=2-7yr. *Combined Computer and Manual Intervention group (n=12)*: Mean age=27.83yr; Sex: females=12; Disease course: RRMS; Severity: unspecified; Disease duration range=2-7yr. *Placebo Physical Therapy group (n=12)*: Mean age=31.16yr; Sex: females=12; Disease course: RRMS; Severity: unspecified; Disease duration range=2-7yr. *Control No Intervention group (n=12)*: Mean age=29.7yr; Sex: females=12; Disease course: RRMS; Severity: unspecified; Disease duration range=2-7yr. **Intervention**: The intervention was split up into 3 groups, including the computer-based intervention, the manual intervention, and a combined intervention. The other two groups included the placebo group, which received physical therapy intervention, and the control group, which received no intervention. A total of 21 sessions over 5mos were conducted for the intervention groups using the Pars Cognitive Rehabilitation Package and Captain's Log Computerized Cognitive Training System. This program has exercises for improving attention and working memory. Difficulty of the tasks changed based on the participant's responses. The outcome measures were collected at baseline, end of the intervention, and at 2-mo f/u. **Cognitive Outcome Measures:** Stroop Colour-Word Test (SCWT); Paced Auditory Serial	1. Statistically significant improvements on all comparisons between the 3 experimental groups and the control and placebo groups at post-test were observed for attention, working memory, executive function, and information processing sped (p<0.05), and most were maintained at f/u. Mean test score results and test change scores are not provided. 2. There was no significant difference in outcome between the 3 intervention groups. 3. Effect of time was found to be statistically significant (n_p^2=0.259, p<0.001), while effect of group factor was found to be non-significant (n_p^2=0.129, p>0.001).

	Addition Test (PASAT); Wisconsin Card Sorting Test (WCST).[3]	
Gich et al. 2015 *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* Spain **RCT** PEDro=5 $N_{Initial}$=43, N_{Final}=41	**Population:** *Experimental group (n=22):* Mean age=45.5yr; Gender: males=6, females=16; Disease course: RRMS=21, SPMS=1; Mean EDSS=2.6; Mean disease duration=9.8yr. *Control group (n=22):* Mean age=44.0yr; Gender: males=9, females=13; Disease course: RRMS=17, SPMS=4; Mean EDSS=2.8; Mean disease duration=10.7yr. **Intervention:** MS participants with mild CI were randomized to receive cognitive rehabilitation (experimental group), or to the control condition for 6mos. Participants in the experimental group received 2, 75-min sessions/wk of MS-Line! cognitive rehabilitation for 6mos. MS-Line! consists of written, computer-based, and manipulative (spatial) material. The experimental group also performed short daily cognitive exercises at home lasting no more than 5min. Participants in the control group received no treatment. Assessments were performed at baseline and after 6mos of treatment. Inclusion criteria required CI defined as < -1.5 SD below normative values on cognitive tests. **Cognitive Outcome Measures:** 10/36 Spatial Recall Test (10/36 SPART): total (T), delayed recall (DR)[1]; Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT); Word List Generation Test (WLGT); Phonemic Fluency Test (FAS); Wechsler Adult Intelligence Scale-third edition (WAIS-III): digit span, block design, and letter number sequencing (LNS)[1]; Boston Naming Test (BNT); Trail Making Test-A, -B (TMT-A, -B); Selective Reminding Test (SRT): total (T), long-term storage (LTS), consistent long-term retrieval (CLTR), delayed recall (DR).[1]	1. Significant differences were found between the experimental and control groups in terms of the 10/36 SPART-T (p=0.0002), 10/36 SPART-DR (p=0.0021), WLG (p=0.0123), letter number sequencing (p=0.043), BNT (p=0.0007), and TMT-A (p=0.010). 2. No significant between-group differences were observed for the SRT, SDMT, PASAT, FAS, Digit Span, Block Design, or TMT-B. 3. Significant differences were found within groups for final vs. baseline scores on the SRT-DR (p=0.0491), 10/36 SPART-T (p<0.0001), 10/36 SPART-DR (p=0.0001), WLGT (p<0.0001), FAS test (p=0.0002), WAIS-III Digit Span: total (p=0.0001), TMT-A (p=0.0003), and TMT-B (p=0.0437).
Hancock et al. 2015 *Processing speed and working memory training in multiple sclerosis: a double-blind randomized controlled pilot study* USA **RCT** PEDro=5 $N_{Initial}$=71, N_{Final}=40	**Population: Total population:** Gender: males=6, females=24; Disease course: RRMS=21, PPMS=4, SPMS=5. *Cognitive training (n=15):* Mean age=50.65yr; Gender: Unspecified; Disease course: RRMS=10; Severity: Unspecified; Mean disease duration=128mos. *Sham (n=15):* Mean age=49.13yr; Gender: unspecified; Disease course: RRMS=10; Severity: unspecified; Mean disease duration=180mos. **Intervention:** MS participants were randomized to receive either active or sham computerized cognitive training focused on improving memory speed and working memory. The active group used Posit Science Insight and Brain Twister visual n-back programs in their homes for 30min 6x/wk for 6wks to target working memory and	1. A significant difference was observed in PASAT scores of the treatment group after therapy (η_p^2=0.30, p=0.007), while no significant difference was observed in the sham group over the same time frame. 2. No other significant differences between groups were observed after treatment.

	information processing speed. The sham group used the same software on introductory difficulty mode. Outcomes were assessed at baseline and after intervention. **Cognitive Outcome Measures:** Paced Auditory Serial Addition Test (PASAT); Symbol Digit Modalities Test (SDMT); Letter-number sequencing (LNS); Brief Visuospatial Memory Test (BVMT) Trials 1-3; Controlled Oral Word Association Test (COWAT); Conner's Continuous T-score (CPT); Auditory Verbal Learning Task (AVLT) Trials 1-5.[3]	
Filippi et al. 2012 *Multiple sclerosis: effects of cognitive rehabilitation on structural and functional MR Imaging measures—an explorative study* Italy **RCT** PEDro=5 $N_{Initial}$=20, N_{Final}=20	**Population:** *Intervention group (n=10):* Mean age=46.7yr; Gender: Female=10; Disease course: RRMS=10; Mean EDSS=2; Mean disease duration=13.5yr. *Control group (n=10):* Mean age=44.8yr; Gender: Female=10; Disease course: RRMS=10; Mean EDSS=2.5; Mean disease duration=15.5yr. **Intervention:** RRMS patients were randomized to receive either the intervention or control condition. The intervention group received computer-assisted individual cognitive rehabilitation of attention, information processing, and executive functions in 1-hr sessions, 3x/wk for 12wks using RehaCom software. The RehaCom modules used were "Plan a Day" and "Divided Attention." The control group received no rehabilitation. Assessments were performed before and 3mos later. **Cognitive Outcome Measures:** Paced Auditory Serial Addition Test: 2 second, 3 seconds (PASAT-2, -3); Wisconsin Card Sorting Test (WCST): total errors, perseverative responses; Controlled Oral Word Association Test with phonemic cues (COWAT/P); Controlled Oral Word Association Test with semantic cues (COWAT/S); Test of everyday attention (TEA): auditory stimulus, visual stimulus, total omitted stimuli, total errors; Selective Reminding Test for verbal learning/delayed recall (SRT-DR); Selective Reminding Test for verbal learning/consistent long-term retrieval (SRT-CLTR); 10/36 Spatial Recall Test long-term retrieval (10/36 SPART LTR); 10/36 Spatial Recall Test delayed recall (10/36 SPART DR).[3]	1. Differences between the control group and intervention group in favor of the intervention group was observed on the PASAT-2 (p=0.03), PASAT-3 (p=0.001), the WCST total errors (p=0.02), the WCST perseverative responses (p=0.01), the WCST perseverative errors (p=0.03) and the COWAT/P (p=0.006). 2. No other outcome measures showed significant between-group differences. 3. The inclusion criteria required participants to have CI defined as z-scores < -1.5 for the PASAT and WCST.
Tesar, Bandion, and Baumhackl 2005 *Efficacy of a neuropsychological training programme for patients with multiple*	**Population:** *Treatment group (n=10):* Mean age=45.3yr; Gender: males=3, females=7; Disease course: RRMS=7, CPMS=3; Mean EDSS=4.5; Mean disease duration=8yr. *Control group (n=10):* Mean age=46.9yr; Gender: males=4, females=5; Disease course: RRMS=6, CPMS=3; Mean EDSS=4.4; Mean disease duration=10.4yr.	1. Group*time differences were seen in the intervention group but not the control group on the CKV correct, CKV incorrect, and HAWIE-R (p<0.05 for all). 2. No group*time differences were observed for the VLT, NVLT, or sustained attention. 3. The intervention group improved significantly on the CKV correct and

sclerosis -- a randomised controlled trial Austria **RCT** PEDro=5 $N_{Initial}$=19, N_{Final}=19	**Intervention:** MS participants were randomized into the Rehacom-based neuropsychological training treatment group, or to the control group. The training programme consisted of RehaCom training targeting the two weakest cognitive areas individualized to each patient, as well as the teaching of compensation and relaxation strategies. The compensatory strategies targeted memory and attention and planning. Neuropsychological training consisted of 12, 1-hr sessions over 4wks. Assessments were performed at baseline, immediately after the training programme at 4wks, and at a f/u 3mos later. Patients had mild to moderate CI at baseline. **Cognitive Outcome Measures:** Computer-aided card-sorting procedure (CKV); Verbal learning test (VLT); Non-verbal learning test (NVLT); Sustained attention test (DAUF): correct, incorrect, reaction time, variation reaction time; Mosaic Test from Hamburg Wechsler Intelligence Test (HAWIE-R).[3]	incorrect, VLT, and NVLT between baseline and 3-mo f/u (p<0.05) while the control group did not improve. 4. The control group significantly improved in sustained attention: correct (p=0.02), incorrect (p=0.01), reaction time (p=0.01), and variation reaction time (p=0.01) between baseline and 3-mo f/u, 5. The intervention group did not improve on sustained attention: correct and incorrect, and improved on sustained attention: reaction time (p=0.02) and variation reaction time (p=0.02). 6. Both intervention and treatment groups improved on the HAWIE-R from baseline to post-intervention (p=0.04 for both) but did not improve from baseline to 3-mo f/u (p>0.05).
Mattioli et al. 2016 *Two years follow up of domain specific cognitive training in relapsing remitting multiple sclerosis: A randomized clinical trial* Italy **RCT** PEDro=4 $N_{Initial}$=41, N_{Final}=32	**Population:** *Aspecific group (n=17):* Mean age=44.88yr; Gender: unspecified; Disease course: RRMS; Mean EDSS=2.97; Mean disease duration=87.18mos. *Specific group (n=15):* Mean age=44.80yr; Gender: unspecified; Disease course: RRMS; Mean EDSS=1.63; Mean disease duration=67.20mos. **Intervention:** MS participants were randomized to receive either specific cognitive rehabilitation or to aspecific psychological intervention for 1yr or 2yr if still cognitively impaired. Assessments were performed at baseline (T0), and after 12 and 24mos of treatment (T12 and T24). **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test 3, 2 seconds (PASAT-3, -2); 10/36 Spatial Recall Test (10/36, 10/36-SPART, SPART): delayed recall (SPART-DR); Selective Reminding Test: Long-term storage (SRT-LTS), Consistent long-term retrieval (SRT-CLTR), Delayed recall (SRT-DR); Controlled Oral Word Association Test (COWAT): Phoneme (P), Category (C); Stroop Color-Word Test (SCWT).[3]	1. The number of pathological tests in the specific group were significantly reduced from T0 to T24 (p<0.001), while that of the aspecific group was not. 2. The number of impaired tests at T24 was significantly less than in the specific group compared with the aspecific group (p=0.02). This finding was not significant if EDSS was considered as a covariate. 3. The specific training group performed significantly better than the aspecific group on the SDMT (p=0.02) and COWAT (p=0.006) at T24. 4. Subjects in the specific group showed significantly improved scores on nearly all neuropsychological tests at T12 and T24 compared with T0 (significance not reported). The aspecific training group did not show significant improvements on any test.
Olga 2014 *Training of attention in patients with remitting-relapsing multiple sclerosis* Ukraine	**Population:** *Intervention group (n=13)*: Disease course: RRMS. No further information provided. *Control group (n=7)*: Disease course: RRMS. No further information provided **Intervention:** Participants were randomized to either the intervention group, who used the computer-based cognitive rehabilitation program ERICA, or to the control group, who	1. Both the experimental and control groups showed a significant improvement between baseline and post-intervention assessment. 2. Comparisons between the two groups revealed significant differences in terms of level of attention at 3wks. The experimental group improved significantly more than the control group

RCT PEDro=4 $N_{Initial}$=20, N_{Final}=19	were asked to complete paper and pencil tasks (e.g., “find 10 differences”). The ERICA modules targeted focused and selective attention. The groups trained for 40min/d for 3wks. Assessment was performed at baseline and at 3wks. **Cognitive Outcome Measures:** Leiter-3 test: concentration, attention, Stroop Test (SCWT).[3]	in terms of level of attention, as per the subtests of the Leiter-3 Test (concentration, divided attention, Stroop congruent, Stroop incongruent; p<0.05 for all). 3. Inclusion criteria required patients to have moderate attention impairments.
Shatil et al. 2010 *Home-based personalized cognitive training in MS patients: a study of adherence and cognitive performance* Israel **RCT** PEDro=3 $N_{Initial}$=107, N_{Final}=46	**Population:** *Training group (n=59):* Mean age=43.78yr; Gender: males=15, females=44; Disease course: RRMS, PRMS; Mean EDSS=3.06; Disease duration: Unspecified. *Control group (n=48):* Mean age=41.35yr; Gender: males=9, females=39; Disease course: RRMS, PRMS; Mean EDSS=2.66; Disease duration: Unspecified. **Intervention:** MS participants were randomized to a cognitive training program or to a control condition. The training group was instructed to train 3x/ wk for 12wks with the CogniFit Personal Coach program. This program has 21 different training tasks that target 17 cognitive abilities, but the study did not specify what these tasks or targets were. The control group received no training. Outcomes were collected at baseline and following the intervention. **Cognitive Outcome Measures:** Neuropsychological Examination – CogniFit Personal Coach (N-CPC): Auditory working memory, Awareness, Divided attention, Avoiding distractions, Hand-eye coordination, General memory, Inhibition, Naming, Planning, Response time, Shifting attention, Spatial perception, Time estimation, Visual working memory, Visual perception, Visual scanning, and Verbal auditory working memory; Memory tasks: Flowers and numbers: visuo-spatial working memory, digit forward, digit backward; Letters: naming speed, naming accuracy; Pictures and words: working memory reaction time, working memory accuracy; Television: working memory accuracy; Objects seen or heard before: recall speed, recall accuracy.[3]	1. Between-group comparison showed an improvement for general memory (η_p^2=0.207, p=0.002) for the training group compared to the control group. 2. No other between-group improvements were significant. 3. Significant improvement was observed in the control group in seven cognitive abilities: divided attention (p=0.007), avoiding distractions (p=0.011), naming (p=0.004), response time (p=0.014), shifting attention (p=0.004), spatial perception (p=0.024), and time estimation (p=0.013). 4. Significant improvement was observed in the training group in 11 cognitive abilities: divided attention (p=0.011), hand-eye coordination (p<0.0001), general memory (p<0.0001), naming (p=0.029), response time (p=0.001), spatial perception (p<0.0001), time estimation (p=0.014), visual working memory (p<0.0001), visual perception (p=0.006), visual scanning (p=0.029), and verbal-auditory working memory (p=0.001). 5. Improvements were observed in the training group in all speed scores (Letters naming speed p=0.016, pictures and words reaction time p=0.010, objects seen or heard before recall speed p=0.004), and most working memory scores (flowers and numbers working memory p=0.001, digit forward p=0.002, digit backward p=0.023, objects seen or heard before recall accuracy p=0.05, television p=0.028). 6. In the control group, no improvements were seen on any of the memory tasks except the accuracy of recall on the Objects Seen or Heard Before task (p=0.005). 7. No improvement was seen in the training group in terms of naming accuracy.
Hubacher et al. 2015	**Population:** *Treatment group (n=6):* Mean age=47.5yr; Gender: males=2, females=4; Disease course: RRMS=6; Mean EDSS=2.42; Mean disease duration=2.5yr.	1. No significant differences were observed between groups after treatment.

Case-based fMRI analysis after cognitive rehabilitation in MS: A novel approach Switzerland **RCT** PEDro=1 $N_{Initial}$=16, N_{Final}=10	*Control group (n=4):* Mean age=44.75yr; Gender: males=3, females=1; Disease course: RRMS=4; Mean EDSS=1.63; Mean disease duration=2.25yr. **Intervention:** RRMS participants were randomized to the training or control groups. The treatment group received a 4-wk computerized working memory training, consisting of 16 sessions, 45min/session. The control group received no intervention. **Cognitive Outcome Measures:** Corsi block backwards task; Digit span backwards test; Symbol Digit Modalities Test (SDMT); Test of Attentional Performance (TAP): alertness task (tonic and phasic).[3]	
Barbarulo et al. 2018 *Integrated Cognitive and Neuromotor Rehabilitation in Multiple Sclerosis: A Pragmatic Study* Italy **PCT** $N_{Initial}$=63, N_{Final}=63	**Population:** *Intervention group (n=32)*: Mean age=50.22yr; Sex: males=12, females=20; Disease course: RRMS=4, Progressive MS=28; Mean EDSS=5.76; Mean disease duration=17.7yr. *Control group (n=31)*: Mean age=46.2yr; Sex: males=13, females=18; Disease course: RRMS=5, Progressive MS: 26; Mean EDSS=5.16; Mean disease duration=17.2yr. **Intervention:** Participants were assigned to either the intervention group, who completed both neuropsychological treatment and conventional neuromotor rehabilitation, or the control group, who received only neuromotor rehabilitation. Both groups received 2, 60-min sessions/wk for 24wks. The treatment group completed the ERICA software and paper-pencil task, complemented by conventional therapy. The focus was on exercises for attention, spatial cognition, memory, and verbal and non-verbal executive function. Exercise complexity was individualized to each patient. The neuromotor rehabilitation included individualized balance and gait exercises and was progressed based on the individual participant's needs. Pelvic floor dysfunction exercises were also prescribed. All participants were cognitively impaired, defined as 1.5 SD below normative values. Outcome measures were collected at baseline and following the intervention at 24wks. **Cognitive Outcome Measures:** Rao's Brief Repeatable Battery of Neuropsychological Tests (BRB) (Selective Reminding (SRT), 10/36 Spatial Recall Test (SPART), Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Controlled Oral Word Association Test (COWAT), Word List Generation Test (WLGT)); Stroop Color-Word Test (SCWT); Forward and Backward Verbal Span; Spatial Span; Frontal Assessment Battery (FAB); Raven's Coloured Metrics	1. The intervention group improved significantly more than the control group on 3 of the 9 cognitive tests (SPART, SPART-D and PASAT-3) (p=0.027). For the other 6 cognitive tests, the intervention group trended to improve more than the control group. 2. Statistically significant improvements were observed in the intervention group on all parts of the BRB including SRT-LTS (p=0.009), SRT-CLTR (p=0.007), SRT-D (p=0.001), SPART (p=0.001), SPART-D (p=0.001), WLGT (p=0.002), SDMT (p=0.018), PASAT-3 (p=0.001) and PASAT-2 (p=0.024). The only test with no significant pre-post improvement was the SCWT. 3. Statistically significant improvements were observed in the intervention group on the spatial span (p=0.003), forward verbal span (p=0.032), backward verbal span (p=0.027), phonological fluency (p<0.001), and FAB (p=0.009). The control group showed no significant improvements on any of these tests. Participants exhibited moderate CI across both groups at baseline.

	(RCMPs); Phonological Verbal Fluency Task (PFV).[3]	
Bonavita 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* Italy **PCT reporting pre-post results** $N_{Initial}$=32, N_{Final}=32	**Population:** *Computer-based Cognitive Therapy (cCR) (n=18):* Mean age=49yr; Gender: males=0, females=18; Disease course: RRMS=18, Mean EDSS=5; Mean disease duration=22yr. *aspecific Cognitive Therapy (aCR) (n=14);* Mean age=46yr; Gender: males=1, females=13; Disease course: RRMS=14, Mean EDSS=4; Mean disease duration=21yr. **Intervention:** The cCR group received computer-based cognitive rehabilitation 2x/wk for 8wks using RehaCom software. The RehaCom modules used were attention and concentration, plan a day, divided attention, reaction behavior, and logical thinking. These modules intend to target attention, information processing, and executive function. The aCR group received aspecific cognitive rehabilitation consisting of reading a newspaper for about 30min, 2x/wk for 8wks, and subsequently explaining the content read to a resident in neurology. Assessments were measured at baseline and after treatment (8wks). To avoid training effects, version A of the Brief Repeatable Battery (BRB) was used at baseline and version B was used after aCR or cCR. **Cognitive Outcome Measures:** Brief Repeatable Battery (BRB) (Selective Reminding Test (SRT); SRT-delayed recall (SRT-D); 10/36 Spatial Recall Test (SPART); 10/36 SPART-delayed recall (SPART-D)); Paced Auditory Serial Addition Test (PASAT-3, PASAT-2); Symbol Digit Modalities Test (SDMT); Word List Generation Test (WLGT); Stroop Color-Word Interference Test (SCWIT).[3]	1. No between-group results were reported. 2. Significant improvements were measured after cCR treatment on the SDMT (p<0.01), PASAT-3 (p<0.00), PASAT-2 (p<0.03), SRT-D (p<0.02), and 10/36 SPART-D (p<0.04) compared to baseline scores. 3. No significant differences for the cCR group were measured for WLGT and SCWT. 4. No significant differences were measured following aCR. 5. Inclusion criteria required participants to be cognitively impaired.
Vogt et al. 2009 *Working memory training in patients with multiple sclerosis - comparison of two different training schedules* Switzerland **PCT** $N_{Initial}$=45, N_{Final}=45	**Population:** *High-Intensity group (n=15):* Mean age=43.20yr; Gender: males=4, females=11; Mean EDSS=3.23; Mean disease duration=9.13yr. *Distributed group (n=15):* Mean age=43.40yr; Gender: males=6, females=9; Mean EDSS=2.3; Mean disease duration=8.13yr. *Control group (n=15):* Mean age=46.27yr; Gender: males=5, females=10; Mean EDSS=3.20; Mean disease duration=12.06yr. **Intervention:** MS patients were allocated to two different computer-based working memory training groups (using BrainStim) and a control group without training. The High-Intensity training group received 16 training sessions 4x/wk for 4wks. The Distributed training group trained 2x/wk for 8wks. Assessments were performed at baseline and after training.	1. Significant improvements from baseline to post-training were observed in the High-Intensity group vs. the control group in the Digit Span backward (η_p^2=0.11, p=0.01), 2-back task omissions (η_p^2=0.06, p=0.05), PASAT (η_p^2=0.10, p=0.02), and FST (η_p^2=0.11, p=0.01) scores. 2. Significant improvements from baseline to post training were observed in the Distributed group vs. the control group in the Corsi Blocks backward (η_p^2=0.08, p=0.03), Digit Span backwards (η_p^2=0.11, p=0.01), 2-back task omissions (η_p^2=0.06, p=0.04), PASAT (η_p^2=0.10, p=0.02), and FST (η_p^2=0.14, p=0.01). 3. No significant differences from pre to post training were observed between

	Cognitive Outcome Measures: Corsi Blocks forward and backward; Wechsler Memory Scale revised (WMS-R): Digit span forward and backward; Test of Attentional Performance (TAP): 2-back numbers correct, omissions, reaction time; Paced Auditory Serial Addition Test (PASAT); Faces Symbol Test (FST); Symbol Digit Modalities Test (SDMT).[3]	the High Intensity and Distributed training groups.
Mendozzi et al. 1998 *Computer-assisted memory retraining of patients with multiple sclerosis* Italy **PCT** $N_{Initial}$=60, N_{Final}=59	**Population:** *Specific group (n=20):* Mean age=47.92yr; Gender: males=9, females=11; Disease course: RRMS, SPMS; Mean EDSS=3.65; Mean disease duration=12.00yr. *Non-specific group (n=20):* Mean age=45.92yr; Gender: males=8, females=12; Disease course: RRMS, SPMS; Mean EDSS=4.00; Mean disease duration=10.70yr. *Control group (n=20):* Mean age=45.38yr; Gender: males=10, females=10; Disease course: RRMS; Mean EDSS=3.30; Mean disease duration=10.15yr. **Intervention:** MS participants received either a specific computer-assisted memory retraining (SCRP) programme, a non-specific computer-based cognitive rehabilitation programme (NCRP), or no treatment. Cognitive training for the specific and non-specific groups consisted of 15, ~45-min sessions 2x/wk for an average duration of 8wks, and employed Rehacom procedures for cognitive rehabilitation. The SCRP group focused on attention and memory while the NCRP group focused on reaction time and visual tracking. **Cognitive Outcome Measures:** Wechsler Memory Scale (WMS): story recall, digit span, visual production, verbal paired associates; Corsi test: spatial span (CORSI); Luria-Nebraska Neuropsychological Battery (LNNB): memory scale; Signal Detection Task: number of hits, reaction time.[3]	1. The specific group improved significantly more at retest than the control group on the spatial span (p<0.01), paired associates hard (p=0.008), LNNB memory scale (p=0.002), and digit span forward (p=0.001) scores. 2. The specific group improved significantly more at retest than the non-specific group on the digit span forward (p=0.001), and short story recall (p=0.01). 3. The non-specific group improved significantly more at retest than the control group on the digit span forward task (p=0.001) and the visual reproduction task (p<0.001). 4. No other significant treatment or group effects were observed.
Plohmann, Kappos, and Brunnschweiler 1994 *Evaluation of a computer-based attention retraining program for patients with multiple sclerosis* Switzerland **PCT** $N_{Initial}$=10, N_{Final}=10	**Population:** Mean age=39.7yr; Gender: males=2, females=8; Disease course: SPMS=5, RRMS=5; Mean EDSS=3.95; Mean disease duration=9.5yr. **Intervention:** Participants were divided into pairs. Half of the participants (one of each pair) were matched to the waitlist control and the other participants began the computer-based attention-retraining program. The program constituted 16 training sessions, 4x/wk, 45-60min/session. Comprehensive neuropsychological testing including the attention test battery (TAP) were administered prior to and following the training program. TAP testing was also repeated at 3mos post training. When the	1. During the training, a decrease in reaction time and errors was reported (no quantitative scores provided with results). The difficulty of exercises was also increased. 2. Participants showed a more homogeneous performance and a lower number of errors and omissions during TAP testing. 3. An improvement in performance on the PASAT is reported (quantitative data not reported). 4. An accelerated learning in the 7/24 Spatial Recall Test was observed, as well as a reduced pro- or retroactive inhibition.

	first half of participants completed training, the second half began the training program. **Cognitive Outcome Measures**: Attention Test Battery (TAP); Paced Auditory Serial Addition Test (PASAT); 7/24 Spatial Recall Test.	
Sharifi, Yazdanbakhsh, and Momeni 2019 *The Effectiveness of Computer-Based Cognitive Rehabilitation in Executive Functions in Patients with Multiple Sclerosis* Iran **Controlled Quasi Experimental** $N_{Initial}$=20, N_{Final}=not reported	**Population:** *Intervention group (n=10)*: Mean age=38.10yr; Sex: males=4, females=6; Disease course: unspecified; Severity: unspecified; Disease duration: unspecified. *Control group (n=10)*: Mean age=36yr; Sex: males=5, females=5; Disease course: unspecified; Severity: unspecified; Disease duration: unspecified. **Intervention:** Twenty of 60 participants with less-impaired executive function on the computerized executive function perseverative test (score ≤20) were randomized to the experimental or control groups. The intervention group completed 12, 50-min sessions over 6wks. The intervention used the Captain's Log software and specifically focused on the executive functions module. This module included stimulus reaction/inhibition and scanning reaction/inhibition training. As the participants progressed through the 15 stages, the tasks would become more difficult. The control group did not receive any treatment. Outcome measures were collected at baseline and following the intervention. **Cognitive Outcome Measures:** Wisconsin Card Sorting Test (WCST)[1].	1. The intervention group revealed statistically significant benefits on all components of executive function including number of categories (n_p^2=0.48, p=0.003), perseverative error (n_p^2=0.52, p=0.002), total error (n_p^2=0.88, p=0.001), and other errors (n_p^2=0.30, p=0.03). 2. Covariance analysis between groups revealed that the intervention and control group differed significantly on at least one dependent variable (n_p^2=0.90).
Bonzano et al. 2020 *Brain activity pattern changes after adaptive working memory training in multiple sclerosis* Italy **Pre-post** $N_{Initial}$=36, N_{Final}=36	**Population**: *MS group (n=18)*: Mean age=45.3yr; Sex: males=6, females=12; Disease course: RRMS=12, SPMS=6; Median EDSS=3.5; Mean disease duration=14.3yr. *Healthy subjects (n=18)*: Mean age=41.6yr; Sex: males=8, females=10. **Intervention**: Participants with MS completed 5, 30-min sessions/wk for 8ks of the self-administered, at-home, computer-based rehabilitation protocol. Each session included three types of working memory training: a visuospatial task, an operation N-back task and a dual N-back task. Task difficulty was adjusted based on the number of correct and incorrect responses. Outcome and fMRI measures were completed at baseline and following the intervention. **Cognitive Outcome Measures**: Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Selective Reminding Test (SRT), 10/36 Spatial Recall Test (SPART), Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Word List Generation Test (WLGT)).[3]	1. All test scores significantly improved (p<0.00) post intervention and had medium, large or very large effect sizes: SDMT (pre: 39.96, post: 48.24, d=0.76), SRT-LTS (pre: 24.74, post: 41.35, d=1.64), SRT-CLTR (pre: 16.18, post: 33.03, d=1.31), SPART (pre: 14.46, post: 19.27, d=1.03), PASAT-3 (pre: 27.70, post: 44.32, d=1.34), PASAT-2 (pre: 18.97, post: 33.02, d=1.48), SRT-D (pre: 5.43, post: 8.97, d=1.84), SPART-D (pre: 4.56, post: 6.31, d=1.03), and WLGT (pre: 38.94, post: 46.89, d=0.99). Improvements on the PASAT-3 and the SDMT were clinically meaningful. 2. The blood-oxygenation-level dependent (BOLD) fMRI signal in the right hemisphere inferior parietal lobe correlated with performance on the PASAT-3 pre and post intervention (Pre: r=0.51, p=0.02, Post: r=0.46, p=0.03). 3. At baseline, the median number of failed BRB-N tests was 4 tests (range 2-8). The most failed test was the SRT-LTS by 72% of participants.

		4. Inclusion criteria required patients present with complaint of cognitive disturbance and score 1.5 standard deviations below normative values on at least two tests of the BRB-N.
Fuchs et al. 2020 *Functional Connectivity and Structural Disruption in the Default-Mode Network Predicts Cognitive Rehabilitation Outcomes in Multiple Sclerosis* USA **Pre-post** $N_{Initial}$=25, N_{Final}=X	**Population:** Mean age=54.7yr; Sex: males=4, females=21; Disease course: RRMS=19, PMS=6; Median EDSS=4; Mean disease duration=23.5yr. **Intervention:** Participants completed 60, 45-60-min sessions over 12wks. The participants are a subgroup of the Fuchs et al. (2019) study. The participants used the BrainHQ program for their intervention and the training focused on improving cognitive processing speed. Baseline MRI testing was completed between 1.6-2.8 years prior to baseline neuropsychological testing. Outcome measures were collected at baseline and following the intervention. **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT).[1]	1. Participants had a significant 7% mean improvement on the SDMT following the intervention relative to baseline (p=0.005, t=3.02). This was 600% over the expected practice effect seen in PwMS (~0.5points/replication). 2. When using a regression model to predict post-intervention SDMT improvements (R^2=0.385, p=0.017) a statistically significant interaction existed between white matter tract disruption and deviation in functional connectivity with associated network (p=0.023). 3. There was a statistically significant correlation between baseline functional connectivity of multiple clusters of grey matter with default-mode network and post-intervention SDMT improvements (mean p=0.04, t-stat=2.37, 137 voxels).
Barker et al. 2019 *A Pilot Study to Assess At-Home Speed of Processing Training for Individuals with Multiple Sclerosis* USA **Pre-post** $N_{Initial}$=15, N_{Final}=12	**Population:** Mean age=47.0yr; Sex: males=3, females=12; Disease course: unspecified; Median EDSS=1.75; Mean disease duration=14.4yr. **Intervention:** Participants were enrolled in an at-home computerized Speed of Processing (SOP) training intervention using the Visual Rehabilitation package of BrainHQ. The intervention included 10 sessions, 2x/wk for 15wks. The intervention involved five major tasks. While the tasks changed slightly, they all shared the same visual-based speed component. Task difficulty was automatically adjusted once the user maintained an 85% correct rate. Outcome measures were completed at baseline and following the intervention. **Cognitive Outcome Measures:** Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Selective Reminding (SRT), 10/36 Spatial Recall Test (SPART), Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Controlled Oral Word Association Test (COWAT)); Stroop Test (SCWT).[3]	1. Participants who completed the intervention showed significant improvements on SRT long term storage (8.75, 95% CI: 2.21, 15.29, p=0.013), SRT consistent long-term retrieval (10, 95% CI: 2.96, 17.04, p=0.01), PASAT-2 (5.08, 95% CI: 1.95, 8.21, p=0.004), Stroop word (4, 95% CI: 0.18, 7.82, p=0.042) and Stroop color-word (4, 95% CI: 0.32, 7.68, p=0.036). 2. All participants involved in the intervention showed significant improvements on SRT long term storage (9.45, 95% CI: 2.85, 16.06, p=0.009), SRT consistent long-term retrieval (10.43, 95% CI: 3.38, 17.48, p=0.008), PASAT-2 (5.04, 95% CI: 1.92, 8.15, p=0.004) and Stroop word (3.95, 95% CI: 0.19, 7.72, p=0.041).
Fuchs et al. 2019 *Response heterogeneity to home-based restorative cognitive rehabilitation*	**Population:** Mean age=56.1yr; Sex: males=15, females=36; Disease course: RRMS=35, PPMS=4, SPMS=12; Median EDSS=4.0; Mean disease duration=21.6yr. **Intervention:** Participants completed 60, 45-60-min sessions over 12wks. The participants used the BrainHQ program for their intervention and the training focused on	1. A statistically significant improvement (d=0.55, t=3.91, p<0.001) was noted on the SDMT pre- (mean: 49.6) to post-test (mean: 52.6). 2. Statistically significant post-intervention improvements were observed on the SDMT for participants who were cognitively impaired at baseline (mean

in multiple sclerosis: An exploratory study USA **Pre-post** $N_{Initial}$=54, N_{Final}=51	improving cognitive processing speed. Participants were contacted 1x/wk for technical support and mild encouragement. Baseline MRI was completed 2yr before baseline testing. Outcome measures were collected at baseline and following the intervention. **Cognitive Outcome Measures:** Brief International Cognitive Assessment for Multiple Sclerosis (BiCAMS) (Symbol Digit Modalities Test (SDMT)[1], California Verbal Learning Test II (CVLT-II)[2], Brief Visuospatial Memory Test-Revised (BVMT-R)[2]; Delis-Kaplan Executive Functions System (D-KEFS).[2]	change: 3.4, d=0.74, t=2.75, p=0.016) and those who were not (mean change=3.0, d=0.48, t=2.96, p=0.005). 3. Participants with RRMS improved by a clinically meaningful average of 4.4 points on the SDMT which exceeded the practice effect in PwMS by over 800%. Over the total participants, 22 showed improvements above the 4 raw score points. 4. Participants with PMS only improved an average of 0.25 points. 5. Non-significant improvements were seen on the BVMT-R (d=0,22, t=1.58, p=0.119) and the CVLT-II (d=0.26, t=1.86, p=0.069). 6. Higher baseline gray matter volume was predictive of improved post-intervention SDMT score (p=0.03).
Covey et al. 2018 *Improved cognitive performance and event-related potential changes following working memory training in patients with multiple sclerosis* USA **Pre-post** $N_{Initial}$=24, N_{Final}=24	**Population:** *Intervention group (n=12)*: Mean age=32.83yr; Sex: males=4, females=8; Disease course: RRMS; Median EDSS=2; Mean disease duration=9.17yr. *Healthy Control group (n=12)*: Mean age=26.25yr; Sex: males=3, females=9. **Intervention:** Participants completed 20, 25-30-min sessions, 5d/wk for 4wks. The sessions targeted working memory by using n-back training, during which a series of letters were presented on the screen and the participants had to actively recall if a certain letter was presented n trials back. Difficulty was adjusted based on performance of each trial. An average of 10 blocks per session was used to obtain an index of performance for the session, which was then used as a measure of improvement on the training task. Outcome measures and electrophysiology recordings were completed at baseline and following the intervention. **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT); Raven's Advanced Progressive Metrices (RAPM) shortened version; Analysis Synthesis and Concept Formation WJ-R Tests; Letter Series.[3]	1. Statically significant session effects were observed on the SDMT and n-back in both groups. 2. Participants with MS had lower accuracy on the concept formation test in comparison to the control group (p=0.019). 3. No statistically significant differences existed between the intervention and control group on the baseline SDMT (MS pretest: 62.75, HC pretest: 64.42).
Altun et al. 2015 *The effects of cognitive rehabilitation on relapsing remitting multiple sclerosis patients* Turkey **Pre-Post** $N_{Initial}$=32, N_{Final}=32	**Population:** Mean age=36.09yr; Gender: males=8, females=24; Disease course: RRMS; Mean EDSS=2.08; Mean disease duration=9.31yr. **Intervention:** RRMS participants received computer-assisted cognitive rehabilitation programs for developing coping strategies and improving attention, visual and verbal memory, and information processing speed 1x/wk for 8wks. Assessments were performed at baseline and after 4 and 8wks of treatment.	1. A significant difference was observed in the scores of PASAT, SRT I, SRT II, SDMT, and WLG tests between baseline and f/u 1 and f/u 2 (p=0.0001 for all). 2. SPART I, SPART II, and SPART III tests did not show significant differences between baseline, f/u 1 or f/u 2.

	Cognitive Outcome Measures: Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Paced Auditory Serial Addition Test (PASAT); Selective Reminding Test-total learning (SRT-TL); Selective Reminding Test-long-term memory (SRT-DR); Spatial recall test-total learning (SPART-TL); Spatial recall test-long-term memory (SPART-DR); Symbol Digit Modalities Test (SDMT); Word List Generation (WLG)); MS neuropsychological screening questionnaire (MSNQ).[3]	
Sastre-Garriga et al. 2011 *A functional magnetic resonance proof of concept pilot trial of cognitive rehabilitation in multiple sclerosis* Spain **Pre-Post** $N_{Initial}$=15, N_{Final}=15	**Population:** *MS participants (n=15):* Mean age=50.73yr; Gender: males=5, females=10; Disease course: RRMS=3, PPMS=2, SPMS=10; Mean EDSS=6.0; Mean disease duration=14.43yr. *Healthy participants (n=5).* **Intervention:** Participants underwent a 5-wk cognitive rehabilitation program, using computer and non-computer exercises aimed at speed of information processing, attention, executive functions, memory, and high-level language functions. Participants completed 3 weekly sessions. Outcome measures were collected 5wks prior to start of the program, at the beginning of the program, and following the program. **Cognitive Outcome Measures:** Digit span (DS) forward; Digit span (DS) backward; Digit span (sum); Trail Making Test A, B (TMT-A, -B); Symbol Digit Modalities Test (SDMT).[3]	1. Significant improvements were observed on the DS backward (p=0.007), DS sum (p=0.01), and composite score (p=0.009). 2. No significant changes were observed in TMT-A, TMT-B and SDMT scores. 3. Inclusion criteria required CI defined as scoring below the 5th percentile on the TAP, TMT-A/-B, SDMT, RALT, or DS.
Allen et al. 1998 *Teaching memory strategies to persons with multiple sclerosis* USA **Pre-Post** $N_{Initial}$=10, N_{Final}=8	**Population:** Mean age=39.6yr; Mean EDSS=4.0. No further information provided. **Intervention**: MS participants took part in a memory-training program that involved computer-based teaching of imagery-based mnemonic strategies for recall of lengthy lists of words and for associating names with faces. The list-learning training involved a story that was presented with 20 words to be remembered printed in bold face. The face-name training coached the participants to associate names with either physical characteristics of pictures of people, or with the person's resemblance to an acquaintance or a celebrity. Participants were assessed on word and name recall immediately after the session. **Cognitive Outcome Measures:** Number of correct words at free recall; number of correct names after cuing; Memory questionnaires.	1. The number of words recalled at the end of the training was not significantly different compared to the scores at the end of the training. 2. The difference in the number of trials needed to successfully make a complete set of 10 face-name associations prior to training compared to after the training was not significantly different. 3. There was no significant reduction in reported difficulties with memory after training.
Plohmann et al. 1998 *Computer assisted retraining of attentional*	**Population:** Mean age=44.6yr; Gender: males=18, females=9; Disease course: RRMS=72.7%, PPMS=4.6%, SPMS=22.7%; Mean EDSS=3.8; Mean disease duration=16.6yr.	1. Significant improvements in performance for the domain's alertness and divided attention, as well as an increased performance in the go/no-go paradigm as an aspect of selective

impairments in patients with multiple sclerosis Switzerland **Pre-Post** $N_{Initial}$=22, N_{Final}=22	**Intervention:** All participants received computer-based treatment on their two most impaired attention functions using AIXTENT software. The four attention domains AIXTENT can target are: alertness, sustained attention, selective attention, and divided attention. Each participant was trained on one function at a time, each training period lasting 12 sessions over 3wks. In each treatment period, there was one attention domain trained specifically and at least one more function that was trained in a non-specific manner. Thus, participants were trained on one of their weak areas of attention for 12wks, and then on another weak area of attention for another 12 wks. Participants were assessed three times (T1, T2, T3) at 3-wk intervals before the start of the treatment, immediately after the first training period (T4), immediately after the second treatment period (T5), and twice more post-treatment at 3-wk intervals (T6, T7). **Cognitive Outcome Measures:** Test of Attentional Performance (TAP): alertness (simple, cued), divided attention, selective attention (go/no-go, incompatibility, flexibility), vigilance.[3]	attention, were achieved (p=0.018, p=0.028, p=0.028). 2. Alertness training significantly improved the incompatibility performance in selective attention (p=0.041). 3. All training programmes (alertness, divided attention, and selective attention) improved the flexibility performance (p=0.017, p=0.012, p=0.028). 4. No additional improvements were observed as a result of the second training period. 5. After the first training period, the specifically trained patients significantly improved in performance on tonic alertness, go/no-go, and incompatibility tests compared to the non-specific group (p=0.027, p=0.0495, p=0.022). 6. After the second training period (T5-T4), only the go/no-go improved in patients with specific training (p=0.04). 7. The training effects were found to remain stable after the treatment period for at least nine weeks as noted by the T6 and T7 scores.

[1]Primary Outcome Measure; [2]Secondary Outcome Measure; [3]Outcome Measure Not Specified

Summary

Table 5. Summary Table of Studies Examining Computer-based Training

	Improve	No statistical sig. difference
General Cognition/Composite Scores	• **Charvet et al. 2017** (cognitive composite) • **Charvet et al. 2015** (cognitive composite)	
Attention	• **Naeeni Davarani et al. 2020** (IVA-2) • **Pusswald et al. 2014** (TAP - auditory) • **Cerasa et al. 2013** (SCWT) • **Mattioli et al. 2010** (TEA) • **Messinis et al. 2017** • **Flachenecker et al. 2017 (**TAP – reaction time) • Orel 2014 (Leiter-3) • *Plohmann et al. 1998* (TAP – some subtests) • Rahmani et al. 2020	• **Amato et al. 2014** (VAS) • **Pusswald et al. 2014** (TAP - visual) • **Mattioli et al. 2012** (TEA) • **Hildebrandt et al. 2007** (TAP) • Filippi et al. 2012 (TEA) • Shatil et al. 2010 (N-CPC) • Mendozzi et al. 1998 (Signal Detection Task) • Hancock et al. 2015 (CPT) • Tesar et al. 2005 (DAUF)
Executive Function	• **Naeeni Davarani et al. 2020** (DKEFS) • **Arsoy et al. 2018** (SCWT) • **Cerasa et al. 2013** (SCWT) • **Mattioli et al. 2012** (WCST) • **Mattioli et al. 2010** (WCST) • **DeGiglio et al. 2015** (SCWT) • **DeGiglio et al. 2016** (SCWT) • Tesar et al. 2005 (CKV) (baseline to 3-mo f/u) • Filippi et al. 2012 (WCST)	• **Amato et al. 2014** (SCWT) • **Stuifbergen et al. 2012** (D-KEFS) • **Barbarulo et al. 2018** (SCWT) • Bonavita et al. 2015 (SCWT) • Hancock et al. 2015 (SCWT) • Gich et al. 2015 (TMT-B) • *Sastre-Garriga et al. 2011* (TMT-B)

	• Grasso et al. 2017[W] (SCWT) • Sharifi et al. 2019 (WCST) • *Barker et al. 2019* (SCWT) • Rahmani et al. 2020	
Information Processing	• **De Luca et al. 2019** (SDMT) • **Stuifbergen et al. 2018** (SDMT, PASAT – 3mo) • **Amato et al. 2014[W]** (PASAT) • **Mattioli et al. 2012** (PASAT) • **Mattioli et al. 2010** (PASAT) • Filippi et al. 2012 (PASAT) • **Bove et al. 2021[W]** (SDMT, PASAT) • **Arsoy et al. 2018** (SDMT) • **Chiaravalloti et al. 2018** (Digit Symbol, PC) • **Messinis et al. 2017** • **Campbell et al. 2016** (SDMT) • **Hildebrandt et al. 2007** (PASAT) • **Solari et al. 2004** (PASAT, SDMT) • **Messinis et al. 2020** (SDMT) • **Naeeni Davarani et al. 2020** (SDMT, PASAT) • **Pérez-Martín et al. 2017** (SDMT, PASAT) • **Barbarulo et al. 2018** (PASAT-2) • Hancock et al. 2015 (PASAT) • Vogt et al. 2009 (PASAT, FST) • *Bonavita et al. 2015* (SDMT, PASAT) • *Bonzano et al. 2020* (SDMT, PASAT) • *Barker et al. 2019* (PASAT-2) • *Fuchs et al. 2020* (SDMT) • *Fuchs et al. 2019* (SDMT) • *Covey et al. 2018* (SDMT) • *Guclu Altun et al. 2015* (PASAT, SDMT) • Gich et al. 2015 (TMT-A) • Rahmani et al. 2020	• **De Luca et al. 2019** (PASAT) • **Stuifbergen et al. 2018** (PASAT – after 6mos) • **Amato et al. 2014[W]** (SDMT, TMT) • **Mattioli et al. 2012** (SDMT) • **Mattioli et al. 2010** (SDMT) • Filippi et al. 2012 (SDMT) • **Cerasa et al. 2013** (PASAT, SDMT) • **Stuifbergen et al. 2012** (SDMT, PASAT) • **Chiaravalloti et al. 2018** (LC) • **Arsoy et al. 2018** (PASAT) • **Barbarulo et al. 2018** (PASAT-3, SDMT) • Gich et al. 2015 (SDMT, PASAT) • *Sastre-Garriga et al. 2011* (SDMT, TMT-A) • Hancock et al. 2015 (SDMT) • Vogt et al. 2009 (SDMT) • *Barker et al. 2019* (SDMT, PASAT-3)
Memory	• **Stuifbergen et al. 2018** (CVLT post study) • **Messinis et al. 2020** (GVLT, BVMT-R) • **De Luca et al. 2019** (SRT) • **Chiaravalloti et al. 2018** (CVLT-II) • **Messinis et al. 2017** • **Stuifbergen et al. 2012** (CVLT) • **Hildebrandt et al. 2007** (CVLT) • **Solari et al. 2004** (SRT, SPART, WLGT) • **Pérez-Martín et al. 2017** (SRT, SPART-DR) • **Barbarulo et al. 2018** (SPART, Digit Span) • Tesar et al. 2005[W] (VLT, NVLT) • Arian Darestani et al. 2020 (CVLT-II) • Shatil et al. 2010 (N-CPC) • Vogt et al. 2009 (CORSI, Digit Span) • Mendozzi et al. 1998 (Digit Span, CORSI, short story recall, paired associates) • *Bonavita et al. 2015* (SRT, SPART) • *Bonzano et al. 2020* (SRT, SPART, WLGT) • *Barker et al. 2019* (SRT-CLTR) • *Covey et al. 2018* (n-back) • *Guclu Altun et al. 2015* (SRT, WLGT) • Gich et al. 2015 (SPART, WLGT, LNS) • Rahmani et al. 2020 (working memory) • *Sastre-Garriga et al. 2011* (Digit Span)	• **Stuifbergen et al. 2018** (CVLT@T3&6-mo f/u, BVMT) • **De Luca et al. 2019** (WLGT, SPART) • **Campbell et al. 2016** (CVLT, BVMT) • **Amato et al. 2014** (WLGT, SPART) • **Pusswald et al. 2014** (MUSIC – verbal memory) • **Cerasa et al. 2013** (SRT, SPART, WLGT) • **Mattioli et al. 2012** (SRT, SPART) • **Mattioli et al. 2010** (SRT, SPART) • Filippi et al. 2012 (SRT, SPART) • **Arsoy et al. 2018** (SRT) • **Barbarulo et al. 2018** (SRT, WLGT) • Hancock et al. 2015 (WAIS letter number sequencing, Digit Span, BVMT) • *Bonavita et al. 2015* (WLGT) • *Barker et al. 2019* (SRT-LTS, SPART) • *Fuchs et al. 2019 (CVLT, BVMT-R)* • *Guclu Altun et al. 2015* (SPART) • Gich et al. 2015 (SRT, digit span) • Allen et al., 2019 (Memory questionnaires)

Verbal Language Skills	• **Arsoy et al. 2018** (COWAT) • **Stuifbergen et al. 2018** (COWAT – 6-mo f/u) • **Messinis et al. 2017** • **Mattioli et al. 2012** (COWAT/S) • **Mattioli et al. 2010** (COWAT) • **Pérez-Martín et al. 2017** (COWAT-F) • **Barbarulo et al. 2018** (PFV) • Arian Darestani et al. 2020 (COWAT) • Filippi et al. 2012 (COWAT/P) • Gich et al. 2015 (BNT)	• **Pusswald et al. 2014 (**MUSIC – verbal fluency) • **Mäntynen et al. 2014** (COWAT) • **Stuifbergen et al. 2012** (COWAT • **Pérez-Martín et al. 2017** (COWAT – animals) • Hancock et al. 2015 (COWAT) • *Barker et al. 2019* (COWAT) • Filippi et al. 2012 (COWAT/S) • Gich et al. 2015 (FAS)
Visuospatial skills	• **Naeeni Davarani et al. 2020** (JLO)	• **Stuifbergen et al. 2012** (JLO) • Tesar et al. 2005 (HAWIE-R) • Gich et al. 2015 (block design)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT (pre-post)

Discussion

A growing number of studies in PwMS support that computer training improves cognition on objective outcome measures evaluating the cognitive skills or domains challenged by the training. The research in computer-based cognitive rehabilitation includes variability in the training approaches, comparator groups, dose, intensity, degree of supervision, follow-up period, and baseline cognitive impairment levels. There may be commercial interest in the development of computer-based training products, introducing potential for bias in the conduct of the research.

However, cognitive domain-specific training for processing speed (7 RCTs), memory (6 RCTs), and executive function (7 RCTs) improved cognition on objective testing addressing each of these respective domains (see respective Level of Evidence statements below). The evidence was more conflicting for the verbal language and attention domains (Arian Darestani et al. 2020; Arsoy, Tuzun, and Turkoglu 2018; Filippi et al. 2012; Mäntynen et al. 2014; Flavia Mattioli et al. 2010; F. Mattioli et al. 2012; Pusswald et al. 2014; Alexa K Stuifbergen et al. 2012; A. K. Stuifbergen et al. 2018 and Amato et al. 2014; Campbell et al. 2016; Cerasa et al. 2013; Filippi et al. 2012; Flachenecker et al. 2017; Flavia Mattioli et al. 2010; F. Mattioli et al. 2012; Messinis et al. 2017; Olga 2014; A. M. Plohmann et al. 1998; Rahmani et al. 2020). No studies targeted only verbal language skill computer-based training, although some protocols included verbal language tasks. For attention training, task-specific computer training targeting reaction time specifically improved reaction time on the Test for Attentional Performance (Flachenecker et al. 2017).

Computer-based training may help to maintain current cognitive function or delay progression of cognitive impairment, even if improvements are not realized. Arsoy et al. (2018) studied a small sample of participants with a more benign MS course (EDSS≤3 ten years after MS onset) with mild CI at baseline. Participants received either no intervention or computer-based training five days a week for 50 minutes with the NOROSOFT Mental Exercise Program. The program involved training in attention, memory, reasoning, visual, and verbal tasks. The intervention group maintained stable cognitive testing scores across multiple cognitive domains, and experienced improved scores only on the Paced Auditory Serial Addition Test. However, the control group significantly worsened on the SDMT and Stroop Test over the six-month period (Arsoy, Tuzun, and Turkoglu 2018). Overall, there are more positive than negative studies supporting that PwMS with minimal CI at baseline at least maintain cognitive test scores with computer training in comparison to no treatment.

A 2019 meta-analysis of 20 RCTs similarly concluded an overall modest effect size for computer-based rehabilitation approaches benefiting cognition. However, the results for working memory, fatigue, and psychosocial and daily functioning were inconclusive. There may exist a minimum dose effect with individual variability in the response to computer cognitive training (Lampit et al. 2019). We analyzed for a possible dose effect for each cognitive domain by totaling the time spent doing computer cognitive training over the duration of each RCT. In trials where the total cognitive training hours exceeded 33 hours (n=4 RCTs), results were consistently positive for outcomes related to the verbal language domain (Arsoy, Tuzun, and Turkoglu 2018; Filippi et al. 2012; Flavia Mattioli et al. 2010; F. Mattioli et al. 2012). These positive results were observed even though the training protocols within these four trials were not specifically targeting verbal language skills. For trials with less than 33 hours of training (n= 4 RCTs), the evidence was conflicting for positive outcomes in the verbal language domain (Mäntynen et al. 2014; Barker et al. 2019; Alexa K Stuifbergen et al. 2012; Arian Darestani et al. 2020). Minimum dose effects, as well as the intensity of the training to achieve positive outcomes across cognitive domains, warrant consideration.

One study reported on brain functional reserve according to baseline white matter tract connectivity on functional MRI (Fuchs, Ziccardi, et al. 2020). Increased baseline white matter tract connectivity was associated with improvement on the Symbol Digit Modalities Test after processing speed training on the BrainHQ computer platform (Fuchs et al. 2020). In clinical practice, some patients self-report they enjoy computer-based training or gaming, while others may find the tasks frustrating. Possibly, a baseline connectivity threshold exists, where if sufficient connections are lost, improvement is more challenging to achieve. Participants with severe CI are not included in the computer-based cognitive intervention MS trials. In the moderate to severe brain injury population, computer-based cognitive training did not provide benefit for improving attention and concentration outcomes (ERABI, n.d.).

The distinction between gaming versus a non-gaming-based computer training protocol is not always clear in the literature. This distinction may be important, since patient expectations and experiences with gaming versus cognitive training paradigms may differ. Three RCTs compared no treatment to what authors describe as computer gaming (De Giglio et al. 2015; 2016; Janssen et al. 2015). The study by Janssen et al. involved a Space Fortress video game where the player shoots at a fortress while avoiding enemies, thus challenging visualspatial skills. Visuospatial memory improved compared to no treatment, yet verbal learning and memory did not (Janssen et al. 2015). Two of the RCTs included Nintendo's Brain Training video games as the intervention, and executive function and information processing speed improved compared to no treatment (De Giglio et al. 2015; 2016). In these studies, the gaming tasks had a similar focus and resemblance to the tests administered as outcome measures, supporting task-specific training effects (De Giglio et al. 2015; 2016).

In a study by Stuifbergen et al. (2018), the intervention group received luminosity training plus additional training in compensatory strategies, while the control group had unsupervised, free access to MyBrainGames (Stuifbergen et al. 2018). Interestingly, both groups improved on cognitive outcomes, with no between-group differences. Charvet et al. (2015) reported improved cognitive outcomes for an intervention group trained on luminosity in comparison to a control group receiving computer software Hoyle puzzle board games (Charvet et al. 2015). When comparing computer HQBrain training to traditional board games, Charvet et al. (2017) found similarly significantly greater improvements in cognition in the HQBrain training group (on the Neuropsychological Composite Score outcome) (Charvet et al. 2017). Computer gaming has the advantage of individualizing the level of difficulty for the participant in real time. This may be harder to achieve with board-based games or word puzzles. However, which computer training protocols are most effective for which cognitive outcomes, and how much oversight might be required to improve or maintain cognitive function, remains unclear.

Computer-based cognitive training programs relying on intact vision and hand function may not be appropriate for some PwMS, and computer cognitive skills training may not be applicable to every-day life. The RehaCom computer training program has been adapted specifically for people with visual and dexterity impairments. Computer-based training is feasible to deliver remotely in one's own home and can be combined with other compensatory or restorative strategies. The added benefit of combining computer training with non-computer-based compensatory strategies (i.e., the use of external memory aids) or restorative approaches also remains unclear (Gich et al. 2015; Perez-Martin et al. 2017; Rahmani et al. 2020; Rodgers et al. 1996; Sastre-Garriga et al. 2011). Encouragingly, there is strong evidence that computer training in processing speed, memory, and executive function improves cognitive performance on testing related to these domains. However, there is less evidence for possible carryover effects across cognitive domains (Plohmann et al. 1998) or into cognitive functioning in life activities. Virtual training or gaming platforms, covered in section 3.5 of this module, may hold even greater promise for benefiting cognition relevant to everyday function.

Conclusion

Attention

There is conflicting evidence whether computer-based cognitive rehabilitation improves attention in persons with MS (seventeen randomized controlled trials and one pre-post study; Amato et al. 2014, Campbell et al. 2016, Cerasa et al. 2013, Filippi et al. 2012, Flachenecker et al. 2017, Mattioli et al. 2010, Mattioli et al. 2012, Messinis et al. 2017, Orel 2014, Plohmann et al. 1998, Rahmani et al. 2020, and Tesar et al. 2005).

<u>RehaCom vs no treatment</u>
There is conflicting evidence whether RehaCom improves attention in persons with MS with cognitive impairment compared to no treatment (six randomized controlled trials and one prospective controlled trial; Filippi et al. 2012, Mattioli et al. 2010, Mattioli et al. 2012, Mendozzi et al. 1998, Messinis et al. 2017, Naeeni Davarni et al. 2020, and Tesar et al. 2005).

<u>Freshminder 2</u>
There is level 1b evidence that Freshminder 2 combined with counseling for compensatory strategies may improve attention in persons with MS compared to no treatment (one randomized controlled trial; Pusswald et al. 2014).

<u>VILAT-G</u>
There is level 1b evidence that VILAT-G may not improve attention in persons with MS compared to no treatment (one randomized controlled trial; Shatil et al. 2010).

<u>CogniFit 2</u>

There is level 2 evidence that CogniFit 2 may not improve attention in persons with MS compared to no treatment (one randomized controlled trial; Shatil et al. 2010).

RehaCom vs visuomotor control

There is level 1b evidence that RehaCom improves attention more than computer-based visuomotor training in persons with MS with cognitive impairment (one randomized controlled trial; Cerasa et al. 2016).

Computer-based vs pen and paper-based cog rehab training

There is level 2 evidence that ERICA attention exercises may improve attention in persons with MS with cognitive impairment compared to pen-and-paper attention exercises (one randomized controlled trial; Orel et al. 2014).

Target reaction time vs target selective attention/memory/executive function

There is level 1b evidence that computer-based cognitive rehabilitation targeting reaction time may improve reaction time more than computer-based cognitive rehabilitation targeting selective attention, working memory, and executive function in persons with MS (one randomized controlled trial; Flachenecker et al. 2017).

Attention-specific training vs non-specific cognitive rehab

There is level 1b evidence that computer-based Attention Processing Training (APT) may not improve all attention domains compared to non-specific cognitive exercises in persons with MS (one randomized controlled trial; Amato et al. 2014).

Executive Function

There is conflicting evidence whether computer-based cognitive rehabilitation improves executive function in persons with MS (sixteen randomized controlled trials and two prospective controlled trials; Amato et al. 2014, Arsoy et al. 2018, Bonavita et al. 2015, Cerasa et al. 2013, De Giglio et al. 2015, De Giglio et al. 2016, Filippi et al. 2012, Grasso et al. 2017, Hancock et al. 2015, Mäntynen et al. 2014, Mattioli et al. 2010, Mattioli et al. 2012, Naeeni Davarani et al. 2020, Rahmani et al. 2020, Sharifi et al. 2019, Stuifbergen et al. 2012, and Tesar et al. 2005).

There is level 1a evidence that computer-based cognitive rehabilitation that targets executive function improves executive function compared to no treatment (seven randomized controlled trials and one prospective controlled trial; De Giglio et al. 2015, De Giglio et al. 2016, Filippi et al. 2012, Mattioli et al. 2010, Mattioli et al. 2012, Naeeni Davarani et al. 2020, Sharifi et al. 2019, and Tesar et al. 2005).

RehaCom vs no treatment

There is level 1a evidence that computer-based cognitive rehabilitation using RehaCom modules that target executive function improves executive function for persons with MS with

cognitive impairment compared to no treatment (four randomized controlled trials; Filippi et al. 2012, Mattioli et al. 2010, Mattioli et al. 2012, and Tesar et al. 2015)

There is conflicting evidence whether using RehaCom for 8 weeks or less improves executive function for persons with MS with cognitive impairment compared to no treatment or non-specific treatment (one randomized controlled trial and one prospective controlled trial; Bonavita et al. 2015 and Tesar et al. 2015).

RehaCom vs computer-based visuomotor tasks

There is level 1b evidence that computer-based cognitive rehabilitation using RehaCom for 60 minutes per day 2 days per week for 6 weeks may improve executive function in persons with MS with cognitive impairmentcompared to computer-based visuomotor tasks (one randomized controlled trial; Cerasa et al. 2013).

MAPSS-MS (Lumosity + neuropsychonline + group therapy for compensatory strategies) vs no treatment

There is level 1b evidence that the MAPSS-MS program, which combines Lumosity for 45 minutes per day 3 times per week for 8 weeks with group therapy for compensatory strategies, may not improve executive function compared to no treatment in persons with MS with cognitive impairment (one randomized controlled trial; Stuifbergen et al. 2012).

Captain's Log vs No Treatment

There is level 2 evidence that computer-based rehabilitation using Captain's Log software for 6 weeks may improve executive function in persons with MS compared to no treatment (one prospective controlled trial; Sharifi et al. 2019).

NOROSOFT Mental Exercise Software vs no treatment

There is level 1b evidence that computer-based rehabilitation using NOROSOFT Mental Exercise Software for 24 weeks may help maintain executive function in cognitively impaired persons with MS compared to no treatment (one randomized controlled trial; Arsoy et al. 2018).

Information Processing

There is level 1a evidence that computer-based cognitive rehabilitation that specifically targets information processing speed does improve information processing speed in persons with MS compared to no treatment or non-specific cognitive rehabilitation (seven randomized controlled trials, one prospective controlled trial, and four pre-post studies; Barker et al. 2019, Bonavita et al. 2015, Chiaravalloti et al. 2018, Filippi et al. 2012, Fuchs et al. 2019, Fuchs et al. 2020, Guclu Altun et al. 2015, Mattioli et al. 2010, Mattioli et al. 2012, Messinis et al. 2017, and Messinis et al. 2020, and Rahmani et al. 2020).

RehaCom

There is level 1a evidence that computer-based cognitive rehabilitation using RehaCom that specifically targets information processing speed does improve information processing speed

in persons with MS with cognitive impairment compared to no treatment or standard MS rehabilitation (four randomized controlled trials and one prospective controlled trial; Bonavita et al. 2015, Filippi et al. 2012, Mattioli et al. 2010, Mattioli et al. 2012, Messinis et al. 2017, and Messinis et al. 2020).

Speed of Processing Training

There is level 1b evidence that computer-based cognitive rehabilitation using Speed of Processing Training may improve information processing speed in persons with MS with cognitive impairment compared to no treatment (one randomized controlled trial and three pre-post study; Barker et al. 2019, Chiaravalloti et al. 2018, Fuchs et al. 2019, and Fuchs et al. 2020).

ERICA vs traditional cognitive rehab

There is level 1b evidence that computer-based cognitive rehabilitation using ERICA software may improve visual information processing speed but not auditory information processing speed more than non-computer cognitive rehabilitation approaches in persons with MS with cognitive impairment (one randomized controlled trial; De Luca et al. 2019).

VILAT-G vs no treatment

There is level 1b evidence that computer-based cognitive rehabilitation using VILAT-G software may improve information processing speed more than no treatment in persons with MS (one randomized controlled trial; Hildebrandt et al. 2007).

Lumosity vs no treatment

There is level 1b evidence that computer-based cognitive rehabilitation using Lumosity in the MAPSS-MS program may not improve information processing speed compared to no treatment in persons with MS with cognitive impairment (one randomized controlled trial; Stuifbergen et al. 2012).

Memory

There is conflicting evidence whether computer-based cognitive rehabilitation improves memory in persons with MS (18 randomized controlled trials, 6 prospective controlled trials and 1 pre-post study; Amato et al. 2014, Arian Darestani et al. 2020, Arsoy et al. 2018, Barker et al. 2019, Bonavita et al. 2015, Bonzano et al. 2020, Bove et al. 2021, Campbell et al. 2016, Cerasa et al. 2013, Chiaravalloti et al. 2018, Covey et al. 2018, De Luca et al. 2019, Filippi et al. 2012, Fuchs et al. 2019, Hildebrandt et al. 2007, Mattioli et al. 2010, Mattioli et al. 2012, Mendozzi et al. 1998, Messinis et al. 2017, Messinis et al. 2020, Shatil et al. 2010, Solari et al. 2004, Vogt et al. 2009, and Allen et al., 2018).

Target Memory vs no treatment/nonspecific/usual care

There is level 1a evidence that computer-based cognitive rehabilitation that specifically targets memory improves memory in persons with MS compared to no treatment or their usual clinical care (six randomized controlled trials, two prospective controlled trials, and two pre-post studies; Arian Darestani et al. 2020, Bonzano et al. 2020, Covey et al. 2018, Hildebrandt et al.

2007, Janssen et al. 2015, Mendozzi et al. 1998, Messinis et al. 2017, Messinis et al. 2020, Rahmani et al. 2020, Shatil et al. 2010, and Stuifbergen et al. 2012, and Vogt et al. 2009).

<u>RehaCom vs no treatment</u>

There is level 1b evidence that computer-based cognitive rehabilitation with RehaCom targeting memory training may improve memory (two randomized controlled trials and one prospective controlled trial; Arian Darestani et al. 2020, Mendozzi et al. 1998, and Messinis et al. 2017).

<u>RehaCom vs watching natural history DVDs or nonspecific computer exercises)</u>

There is conflicting evidence whether computer-based cognitive rehabilitation with RehaCom targeting memory training improves memory in persons with MS with cognitive impairment compared to natural history DVDs or nonspecific computer exercises (two randomized controlled trials; Campbell et al. 2016 and Messinis et al. 2020).

<u>Norosoft vs no treatment</u>

There is level 1b evidence that computer-based cognitive rehabilitation using NOROSOFT may not improve memory in persons with MS (one randomized controlled trial; Arsoy et al. 2018).

<u>VILAT-G vs no treatment</u>

There is level 1b evidence that computer-based cognitive rehabilitation using VILAT-G to specifically target memory may improve memory in persons with MS (one randomized controlled trial; Hildebrandt et al. 2007).

<u>CogniFit vs no treatment</u>

There is level 2 evidence that computer-based cognitive rehabilitation using CogniFit to specifically target memory may improve memory in persons with MS (one randomized controlled trial; Hildebrandt et al. 2007).

<u>MAPSS-MS (Lumosity + neuropsychonline + group compensatory strategies) vs no treatment</u>

There is level 1b evidence that computer-based cognitive rehabilitation using Lumosity to specifically target memory combined with group compensatory strategies may improve memory in persons with MS (one randomized controlled trial; Stuifbergen et al. 2012).

<u>Lumosity + group compensatory vs MyBrainGames</u>

There is level 1b evidence that computer-based cognitive rehabilitation using Lumosity to specifically target memory combined with group compensatory strategies may not improve memory more than MyBrainGames on multiplesclerosis.com (one randomized controlled trial; Stuifbergen et al. 2018).

<u>ERICA – vs traditional cognitive rehabilitation</u>

There is level 1b evidence that computer-based cognitive rehabilitation using ERICA to specifically target memory improves spatial memory but not verbal learning and memory more than traditional cognitive rehabilitation (one randomized controlled trial; De Luca et al. 2019).

Verbal Language Skills

There is conflicting evidence whether computer-based cognitive rehabilitation improves verbal language skills in persons with MS (nine randomized controlled trials; Arian Darestani et al. 2020, Arsoy et al. 2018, Filippi et al. 2012, Mäntynen et al. 2014, Mattioli et al. 2010, Mattioli et al. 2012, Pusswald et al. 2014, Stuifbergen et al. 2012, and Stuifbergen et al. 2018).

<u>Computer-based over 33 hours vs no treatment</u>

There is level 1a evidence that computer-based cognitive rehabilitation delivered for 33 hours or longer over at least twelve weeks improves verbal language skills compared to no treatment in persons with MS with cognitive impairment (four randomized controlled trials; Arsoy et al. 2018, Filippi et al. 2012, Mattioli et al. 2010, and Mattioli et al. 2012).

<u>Computer-based less than 33 hours vs no treatment</u>

There is conflicting evidence whether computer-based cognitive rehabilitation delivered for less than 33 hours of total training is more effective than no treatment (four randomized controlled trials and one pre-post study; Barker et al. 2019, Stuifbergen et al. 2012, Mäntynen et al. 2014, Arian Darestani et al. 2020, and Pusswald et al. 2014).

<u>RehaCom 33 hours vs no treatment</u>

There is level 1a evidence that computer-based cognitive rehabilitation using RehaCom delivered for 33 hours or longer over twelve weeks improves verbal language skills compared to no treatment in persons with MS with cognitive impairment (three randomized controlled trials; Filippi et al. 2012, Mattioli et al. 2010, and Mattioli et al. 2012).

<u>NOROSOFT 100 hours vs no treatment</u>

There is level 1b evidence that computer-based cognitive rehabilitation using NOROSOFT delivered for 100 hours over twenty-four weeks maintains verbal language skills compared to no treatment in persons with MS with cognitive impairment (one randomized controlled trial; Arsoy et al. 2018).

Lay Summary

Computer cognitive training in memory improves memory in persons with MS with mild cognitive impairment compared to no treatment.

Computer cognitive training in processing speed improves processing speed in persons with MS with mild cognitive impairment compared to no treatment.

Computer cognitive training in executive function improves executive function in persons with MS with mild cognitive impairment compared to no treatment.

Computer cognitive training in attention may improve attention in persons with MS with mild cognitive impairment compared to no treatment.

There is conflicting evidence whether computer-based cognitive rehabilitation improves verbal language skills in persons with MS with minimal cognitive impairment compared to no treatment.

There is conflicting evidence whether the combination of computer-based cognitive rehabilitation with compensatory rehabilitation approaches provides added benefit for improving attention, information processing speed, executive function, spatial skills, verbal language skills, or memory in persons with MS.

3.3 Video Games

Video games are introduced together with computer rehabilitation approaches. Please see section 3.2.

Table 6. Studies Examining Video Games for Cognitive Impairment in Multiple Sclerosis

Author Year **Title** **Country** **Research Design** **PEDro** **Sample Size**	**Methods**	**Results**
De Giglio et al. 2016 *Multiple sclerosis: Changes in thalamic resting-state functional connectivity Induced by a homebased cognitive rehabilitation program* Italy **RCT** PEDro=6 $N_{Initial}$=24, N_{Final}=24	**Population:** *Intervention group (n=12):* Mean age=43.7yr; Gender: males=4, females=8; Disease course: RRMS=12; Mean EDSS=2; Mean disease duration=12.9yr. *Control group (n=12):* Mean age=40.2yr; Gender: males=6, females=6; Disease course: RRMS=12; Mean EDSS=2; Mean disease duration=13.0yr. **Intervention:** MS patients with CI were randomized to receive either a video game-based cognitive rehabilitation program or to the control condition (waitlist). The intervention group were trained on video games of memory, attention, visual-spatial processing, and calculation in 30-min sessions, 5d/wk for 8wks. The cognitive training was performed at home with Dr. Kawashima's Brain Training game. Assessments were performed at baseline (T0) and after 8wks of treatment (T1). **Cognitive Outcome Measures:** Stroop Test (SCWT); Paced Auditory Serial Addition Test (PASAT): 3 second; Symbol Digit Modalities Test (SDMT).[3]	1. The intervention group's scores significantly improved on the PASAT, SDMT, and SCWT compared to baseline (p=0.03, 0.013, and 0.02, respectively). 2. The control group's scores did not significantly change on any outcome measure. 3. A between-group change score analysis was not provided.
De Giglio et al. 2015	**Population:** *Intervention group (n=18):* Mean age=44.64yr; Gender: males=4, females=14; Disease course: RRMS=18; Mean EDSS=3.25; Mean disease duration=13.28yr.	1. Between-group comparison showed a significant improvement on SCT (F^2=0.210, p=.034 and SDMT (F^2=0.177, p=0.049) in the intervention group compared to the control group.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
A low-cost cognitive rehabilitation with a commercial video game improves sustained attention and executive functions in multiple sclerosis: a pilot study Italy **RCT** PEDro=6 $N_{Initial}$=35, N_{Final}=34	*Control group (n=17):* Mean age=42.99yr; Gender: males=5, females=12; Disease course: RRMS=17; Mean EDSS=2; Mean disease duration=11.4yr. **Intervention:** MS patients with CI were randomized to receive either an 8-wk video game-based cognitive rehabilitation (CR) program at home or to a waitlist control. The CR program used the Dr. Kawashima's Brain Training video game (DKBT; Nintendo, Japan), which has memory, attention, visuospatial processing, and calculations minigames. Assessments were performed at baseline and after treatment. **Cognitive Outcome Measures:** Stroop Test (SCWT), Paced Auditory Serial Addition Test (PASAT); Symbol Digit Modalities Test (SDMT).[3]	2. Between-group comparison showed a non-significant improvement on the PASAT (F^2=0.171, p=0.054) in the intervention group compared to the control group.
Janssen et al. 2015 *The effects of video-game training on broad cognitive transfer in multiple sclerosis: A pilot randomized controlled trial* USA **RCT** PEDro=5 $N_{Initial}$=34, N_{Final}=28	**Population:** *Training group (n=14):* Mean age=49.43yr; Gender: males=4, females=10; Disease course: RRMS=14; Mean EDSS=2.86; Mean disease duration=13.00yr. *Control group (n=14):* Mean age=44.93yr; Gender: males=3, females=11; Disease course: RRMS=14; Mean EDSS=2.68; Mean disease duration=10.93yr. **Intervention:** MS patients were randomized to the training group or a waitlist control group. Participants in the training group underwent an 8-wk hybrid-variable priority training (HVT) program using the Space Fortress video game. Outcome measures were collected at baseline and post intervention. **Cognitive Outcome Measures:** Rao's Brief Repeatable Battery (BRB) (Paced Auditory Serial Addition Test: 2,3 seconds (PASAT-2, -3); Selective Reminding Task Long-Term Storage (SRT-LTS); Selective Reminding Task Consistent Long-Term Retrieval (SRT-CLTR); 10/36 Spatial Recall Task (SPART); Oral Symbol Digit Modalities Test (SDMT); Word List Generation Task (WLGT)).[1]	1. Between-group comparison showed no significant improvement on PASAT or SDMT. 2. The control group scored significantly higher than the training group on SRT-LTS (p=0.04) and SRT-CLTR (p=0.03) post-intervention. 3. The training group scored significantly higher than controls on the SPART post-intervention (η^2=0.25, p=0.03). 4. The training group scored significantly higher than controls on immediate recall section of the SPART post-intervention (η^2=0.21, p=0.02). 5. No other significant effects of the training program were observed.

[1]Primary Outcome Measure; [3]Outcome Measure Not Specified

Discussion

Video games are discussed together with computer rehabilitation approaches. Please see section 3.2, Discussion.

Table 7. Summary Table of Studies Examining Video Games

	Executive function	Info processing	Memory

Improve	• DeGiglio et al. 2015 • DeGiglio et al. 2016	• DeGiglio et al. 2015 (SDMT) • DeGiglio et al. 2016 (SDMT, PASAT) [W]	• Janssen et al. 2015 (SPART)
No statistical sig. difference		• DeGiglio et al. 2015 (PASAT) • Janssen et al. 2015	• Janssen et al. 2015 (SRT and WLGT)

W	RCT with within-group comparison only
Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT (pre-post)

Conclusion

There is level 1b evidence that Nintendo's Brain Training video games do improve executive function and information processing speed in persons with relapsing-remitting MS (one randomized controlled trial and one randomized controlled trial with pre-post analysis; DeGiglio et al. 2015, DeGiglio et al. 2016).

There is level 2 evidence that the Space Fortress video game may improve spatial and visuospatial memory in persons with relapsing-remitting MS (one randomized controlled trial; Janssen et al. 2015).

There is level 2 evidence that the Space Fortress video game may not improve verbal learning and memory in persons with relapsing-remitting MS (one randomized controlled trial; Janssen et al. 2015).

Nintendo's Braining Training video games may improve executive function and information processing speed, and the Space Fortress video game may improve spatial memory and visuospatial memory in persons with MS.

The Space Fortress video game may not improve verbal learning and memory in persons with MS.

3.4 Virtual Reality

Virtual reality is an immersive intervention in which software simulates a different environment (Munari et al. 2020; Maggio et al. 2020).

Table 8. Studies Examining Virtual Reality for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Munari et al. 2020 *Effects of robot-assisted gait training combined with virtual reality on motor and cognitive functions in patients with multiple sclerosis: A pilot, single-blind, randomized controlled trial* Italy **RCT** PEDro=8 $N_{Initial}$=17, N_{Final}=15	**Population:** *Intervention group (n=8)*: Mean age=57yr; Sex: males=3, females=5; Disease course: RRMS=1, SPMS=7; Mean EDSS=5.4; Mean disease duration=17.7yr. *Control group (n=9)*: Mean age=51.7yr; Sex: males=4, females=5; Disease course: RRMS=2, SPMS=7; Mean EDSS=5; Mean disease duration=13.9yr. **Intervention:** Following randomization, both groups received individualized 40min/d session, 2d/wk for 6wks. The robot-assisted gait training + virtual reality (RAGT+VR) intervention group used a G-EO robotics system with three degrees of freedom. The body weight protocol was gradually reduced each week from 30% to 10%. Participants were also exposed to immersive VR while conducting the robotic gait training. Prior to training, patients were encouraged to focus on the scenario at hand. The control group received the gait training without the VR protocol (RAGT). Outcome measures were collected at baseline, after the treatment and at 1-mo f/u. **Cognitive Outcome Measures:** Paced Auditory Serial Addition Test (PASAT)[1]; Phonemic Fluency Test (PFT)[2]; Rivermead Behavioural Memory Test - Third Edition (RBMT-3); The Novel Task: Immediate and Delayed Recall (NT-IR)[2]; Wechsler Adult Intelligence Scale - Revised (WAIS-R): Digit Symbol.[2]	1. There were no significant differences between groups for any cognitive outcomes. 2. Significant improvements were seen on within-group comparison on the PFT in the RAGT+VR intervention group after intervention (effect size: 0.81, p=0.012; Z: -2.521) and at f/u (effect size: 0.57, p=0.012; Z: -2.521). 3. Significant improvements were seen on within-group comparison on the NT-IR in the RAGT+VR intervention group after intervention (effect size: 0.37, p=0.012; Z: -2.521) and at f/u (effect size: 0.49, p=0.012; Z:-2.521, p=0.012; Z:-2.521).
Maggio et al. 2020 *Do patients with multiple sclerosis benefit from semi-immersive virtual reality? A randomized clinical trial on cognitive and motor outcomes* Italy **RCT** PEDro=7 $N_{Initial}$=60, N_{Final}=60	**Population:** *Intervention group (n=30)*: Mean age=51.9yr; Sex: males=18, females=12; Disease course: RRMS, SPMS; Severity: unspecified; Disease duration: unspecified. *Control group (n=30)*: Mean age=48.2yr; Sex: males=13, females=17; Disease course: RRMS, SPMS; Severity: unspecified; Disease duration: unspecified. **Intervention:** Following randomization, all participants completed 3, 60-min sessions/wk of cognitive rehabilitation training for 8wks. The intervention group completed cognitive rehabilitation in a semi-immersive VR system called BTS-Nirvana. The intervention included ecological scenarios that simulate real life. The control group received traditional face-to-face rehabilitation training. Outcome measures were collected at baseline and at the end of the intervention.	1. Between-group analysis revealed statistically significant improvements on the MoCA (n^2: 0.22, p=0.00), ROCF copy (n^2: 0.88, p=0.00), ROCF immediate recall (n^2: 0.96, p=0.00), ROCF delayed recall (n^2: 0.20, p=0.00), SPART (n^2:0.73, p=0.00), PASAT3 (n^2:0.08, p=0.00) and PASAT2 (n^2:0.39, p=0.00). 2. The experimental group showed significant improvements on all cognitive measures (p=0.00). 3. The control group showed significant improvements on the MoCA (p=0.00), ROCF delayed recall (p=0.00) and PASAT3 (p=0.001). 4. Participants had to be mild to moderately cognitively impaired to be included in the study.

	Cognitive Outcome Measures: Montreal Cognitive Assessment (MoCA); 10/36 Spatial Recall Test (SPART); Rey-Osterrieth Complex Figure Test (ROCF); Paced Auditory Serial Attention Test (PASAT).[3]	

[1]Primary Outcome Measure; [2]Secondary Outcome Measure; [3]Outcome Measure Not Specified

Table 9. Summary Table of Studies Examining Virtual Reality

	Info processing	Memory	Verbal language skills
Improve	• **Maggio et al. 2020** (PASAT)	• **Maggio et al. 2020** (ROCF and SPART)	
No statistical sig. difference	• **Munari et al. 2020** (Digit Symbol, PASAT)	• **Munari et al. 2020** (Rivermead – spatial memory)	• **Munari et al. 2020** (PFT)

Bold	RCT PEDro $\geq$ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT (pre-post)

Discussion

Two randomized controlled trials evaluated cognitive outcomes involving a virtual reality intervention. Munari et al. (2020) investigated the effects of robot-assisted gait training with and without virtual reality. All participants received six weeks of biweekly rehabilitation sessions with a robot assisted body weight support device (a G-EO System; Reha Technology, Olten, Switzerland). Those in the virtual reality group experienced a simulation walking in a natural park on a high definition 2D video screen. Maggio et al. (2020) compared a semi-immersive virtual reality cognitive rehabilitation platform (BTS-Nirvana) to in-person cognitive rehabilitation program involving cognitive exercises with pen and pencil. The virtual reality BTS-N system allows participants to perform cognitive exercises while interacting with real-life virtual scenarios with audio-visual stimuli. Both groups received a total of 24 60-minute cognitive rehabilitation sessions over 8 weeks as well as some physical strengthening and gait training exercises.

Outcome measures were collected at baseline and following the intervention for both studies, and Munari et al. (2020) include another post intervention follow up at 1 month. The smaller study by Munari et al. (2020) (n=15) did not find statistically significant between-group differences on the cognitive outcomes at any time points. However, they do report a within-group improvement in the VR intervention group on verbal fluency and immediate recall compared to baseline, both after the intervention and sustained at the 1-month follow-up with moderate to large effect sizes. Munari et al. (2020) also report significant improvement in the two-minute walk test in favor of the virtual reality intervention. The larger study by Maggio et al. (2020) (n=60) did find statistically significant between-group differences on general cognition as measured by the Montreal Cognitive Assessment and on the visual spatial memory, spatial memory, and processing speed outcomes. They also report significant within-group pre-post improvements on all the cognitive outcomes, including the mobility outcomes.

In the Maggio et al. (2020) study, participants had mild to moderate cognitive impairment at baseline and by comparison, in the Munari et al. (2020) study, mean baseline Paced Auditory Serial Attention Test scores were less impaired according to visual inspection of the data. In the smaller Munari et al. (2020) study, the mean baseline Mini-Mental State Examination was 28 and the mean EDSS score was 5. Overall, the results from both studies support that virtual reality rehabilitation settings were feasible in patients with mild to moderate cognitive impairment and restricted mobility.

Munari et al. (2020) suggest that a virtual reality platform "provides an enriched opportunity for repetitive practice, feedback information, and motivation for endurance practice, thus promoting cognitive stimulus (visual, auditory, and somato-sensory input) and motor learning" (Munari et al. 2020, p. 158). The choice of the virtual environment may also be relevant since mindfulness and meditation interventions may influence cognitive testing results related to processing speed (See sections 3.14 for Mindfulness and 3.15 for Meditation). The small Munari et al. (2020) study may not have been powered to detect change in cognitive outcomes. However, the 2-minute walk test showed more improvements in the intervention group walking in a virtual park compared to the control group. Exploring the short-term and longer-term impact of different virtual reality settings (i.e., relaxing settings, busy real-life settings) on cognitive testing and cognitive function in simulated life situations would be of interest.

Conclusion

There is level 1b evidence that cognitive rehabilitation in the BTS-Nirvana Virtual Reality environment may improve information processing speed and memory more than traditional cognitive rehabilitation in persons with MS (one randomized control larger trial; Maggio et al. 2020).

There is level 1b evidence that robot-assisted gait training in a virtual reality environment may not improve information processing speed, memory, or verbal language skills more than robot-assisted gait training (one randomized controlled small trial; Munari et al. 2020).

Cognitive rehabilitation carried out in virtual reality may improve information processing and memory in persons with MS.

Robot-assisted gait training in a virtual reality environment may not improve information processing speed, memory, or verbal language skills more than standard robot-assisted gait training.

3.5 Visual Training

Shalmoni and Kalron (2020) describe strobic visual training as an intervention that involves intermittently taking away visual input to encourage participants to reduce reliance on online visual training with the goal of improving visual-motor control.

Table 10. Studies Examining Visual Training for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Shalmoni and Kalron 2020 *The immediate effect of stroboscopic visual training on information-processing time in people with multiple sclerosis: an exploratory study* Israel **Crossover RCT** PEDro=6 $N_{Initial}$=26, N_{Final}=26	**Population:** Mean age=47.9yr; Sex: males=10, females=16; Disease course: RRMS=17, PPMS=9; Median EDSS=4.5; Mean disease duration=9.3yr. **Intervention:** Initially, participants were randomly allocated to one session of the control or the stroboscopic visual training (SVT) intervention. Each session type was kept as similar as possible including session time and exercise type. Following a 2-wk washout period, participants were crossed over to either the control or SVT intervention. Outcome measures were collected prior to training and immediately after each session. **Cognitive Outcome Measures:** Mindstream Computerized Cognitive Test (MCCT)[1] assessing verbal and non-verbal memory, executive function, visual-spatial processing, verbal function, attention, information processing speed and motor skills.	1. There was a significant improvement in information processing speed immediately post-SVT intervention (mean pre=95.9, post=100.2, p=0.003). 2. Improvements were observed in the visual-spatial domain but did not reach statistical significance (mean pre=103.1, post=106.1, p=0.080). 3. No improvements were observed pre-post on memory, executive function, attention, verbal function, motor skills or global cognitive score following the SVT and control sessions.

[1]Primary outcome measure

Table 11. Summary Table of Studies Examining Visual Training

	Info processing	Memory	Executive Function	Verbal language skills	Global Cog Scores
Improve	• Shalmoni and Kalron 2020 (MCCT)				
No statistical sig. difference		• Shalmoni and Kalron 2020 (MCCT)	• Shalmoni and Kalron 2020 (MCCT)	• Shalmoni and Kalron 2020 (MCCT)	• Shalmoni and Kalron 2020 (MCCT)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT (pre-post)

Discussion

One crossover RCT investigated the immediate effect of strobic visual training on cognition, gait, and static balance (Shalmoni and Kalron 2020). Strobic visual glasses were worn while conducting the exercises for the intervention condition and non-strobic glasses were worn for the control condition. The 40- to 50-minute set of exercises for each condition included different drills with a ball: ball catch, wall ball, head turn and catch, and turn and catch. Cognitive performance was evaluated through a computerized software program assessing different cognitive domains (Mindstreams®, NeuroTrax Corp., NY). Cognitive testing occurred pre- and immediately post-training for each condition with a two-week washout in between conditions. Only information processing speed significantly improved immediately post-strobic visual training while non-significant improvements were reported for the visuospatial outcome measures.

These preliminary findings for the effects of strobic visual training on processing speed is encouraging, especially given that processing speed is frequently affected in MS. Shalmoni and Kalron (2020) note their findings agree with previous studies in athletes whereby some perceptual abilities were enhanced with strobic visual training. Further research in PwMS could include the Symbol Digit Modalities Test to assess processing speed since this measure is validated in the MS population.

Conclusion

There is level 1b evidence that strobic visual training may improve information processing speed but not memory, executive function, attention, verbal function, or global cognitive scores (one crossover RCT study; Shalmoni and Kalron, 2020).

Strobic visual training may improve processing speed, but not other cognitive domains in persons with MS.

3.6 EEG Neurofeedback

Neurofeedback through EEG provides participants real-time visual feedback of their brain activity patterns. The neurofeedback approach described by Kober et al. (2019) requires EEG headwear, a portable 10-channel EEG amplifier (NeXus-10 MKII, Mind Media B.V.), and a laptop with the BioTrace + software. The participant can watch on the laptop their own brain activity depicted by vertically moving bars presented on the screen while wearing the EEG headwear. Kober et al. (2019) propose that upregulating the EEG sensorimotor rhythm (SMR, 12–15 Hz) leads to cognitive improvements by way of reducing sensorimotor interferences. They report this approach has been trialed with success in healthy controls, as well as stroke and acquired brain injury research settings (Kober et al. 2019).

Table 12. Studies Examining Neurofeedback for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Kober et al. 2019 *Self-regulation of brain activity and its effect on cognitive function in patients with multiple sclerosis – First insights from an interventional study using neurofeedback* Austria	**Population:** Mean age=38.9yr; Sex: males=7, females=7; Disease course: RRMS=13, SPMS=1; Median EDSS=2.3; Mean disease duration=9.0yr. *Responder group* (n=7): Mean age=36.9yr; Sex: males=3, females=4; Disease course: RRMS=6, SPMS=1; Median EDSS=3.0; Mean disease duration=13.4yr. *Non-responder group* (n=7): Mean age=41.0yr; Sex: males=4, females=3; Disease course: RRMS=7; Median EDSS=2.0; Mean disease duration=7.2yr. **Intervention:** The intervention involved 10 at-home, neurofeedback training sessions in a 3-	1. The responder group was determined by a pre- to post-test different of >4.92 points on the overall score on BRB-N. 2. Following the intervention, the responder group showed a significant improvement in verbal long term memory (SRT) (mean pre: 43.31 vs. post: 56.06), visual-spatial long-term memory (SPART) (mean pre: 47.57 vs. post: 56.86), executive functions (WLG) (mean pre: 46.53 vs. post: 53.43), long-term memory (mean pre:43.96 vs. post: 58.63), executive function (mean pre: 46.53 vs. post: 53.43), and overall

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Pre-post $N_{Initial}$=14, N_{Final}=14	4-wk period using a tele-rehabilitation system. This system consisted of an EEG headset, EEG amplified, laptop, a server to encrypt data, and a therapist system to monitor data. The first session was a baseline run. During the subsequent sessions, participants received visual feedback of their sensorimotor rhythm, and the aim was to increase the height of the middle bar while keeping the outer two bars constant. If participants were successful in increasing the height of the bar, they were rewarded with points. Outcome measures were collected at baseline and post intervention. **Cognitive Outcome Measures:** Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (10/36 Spatial Recall Test (10/36; 10/36-SPART; SPART); Word List Generation Test (WLGT); Selective Reminding Test (SRT); Symbol Digit Modalities Test (SDMT)).[1]	BRB-N scores (mean pre: 44.43 vs. post: 55.24). 3. Following binomial experiment, it was determined that the increase in BRB-N overall scores was not a product of random chance (biominal probability p=0.0002).

[1]Primary outcome measure

Table 13. Summary Table of Studies Examining EEG Neurofeedback

	Memory	Executive Function
Improve	• *Kober et al., 2020* (SRT, SPART)	• *Kober et al., 2020* (WLG)
No statistical sig. difference		

Bold	RCT PEDro > 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT (pre-post)

Discussion

One pre-post test study utilizing a neurofeedback approach evaluated objective cognitive outcomes (Kober et al. 2019). The intervention spanned 3-4 weeks and used a tele-rehabilitation system to conduct 10 at-home sessions of neurofeedback with the goal of upregulating the sensory motor rhythm. Participants were provided with the appropriate equipment, including an EEG headset. The goal of the sessions was to increase the height of the sensory motor rhythm power bar on the screen, but not the theta power (4–7 Hz), or beta power (21–35 Hz) power bars. A reward was given if the participant was successful. The biofeedback training was remotely monitored by a therapist available by chat. Responders on the cognitive outcomes were described as those who improved by a critical difference value defined by the smallest difference between the pre and post measurements of a single person, accounting for random fluctuations. Further, a post-hoc binomial statistical analysis concluded that the seven out of fourteen people who met the responder criteria after training was higher than would be predicted by chance alone (p=0.0002). The responder group improved on verbal long term memory, visual-spatial long-term memory, long term memory, executive function outcomes, and overall BRB-N scores. The result of this preliminary study highlights that upregulation of sensory motor rhythm through visual feedback may improve cognitive function in some PwMS, but there are individual differences in response to the training.

Conclusion

There is level 4 evidence that neurofeedback training may improve long-term memory and executive function (one pre-post study; Kober et al., 2019).

Neurofeedback training may improve long-term memory and executive function in persons with MS.

3.7 Robotics

Robotic gait devices may be utilized for gait training in rehabilitation. This section includes a study using a robotic gait device as the independent variable. Gait training without robotic devices is discussed separately in section 3.26.8 of this module. Robotic gait devices may require additional cognitive effort and skills to don and use the device compared to walking without robotic devices. However, robotic-powered gait devices may also help reduce the cognitive and physical effort to walk for people with significant walking impairments.

Table 14. Studies Examining Robotics for Cognitive Impairment in Multiple Sclerosis

Author Year **Title** **Country** **Research Design** **PEDro** **Sample Size**	**Methods**	**Results**
Androwis et al. 2019 *Mobility and Cognitive Improvements Resulted from Overground Robotic Exoskeleton Gait-Training in Persons with MS* USA **RCT** PEDro=5 $N_{Initial}$=4, N_{Final}=4	**Population:** Mean age =50yr; Sex: males=1, females=3; Disease course: RRMS; Severity: unspecified; Disease duration: unspecified. **Intervention:** Following randomization, the robotic exoskeleton group underwent 8, 1-hr gait training sessions over 4wks. Therapists could control the angle of the hip and knee joints along with passive sprung ankle joint. Data collected included step count, distance walked, walk time, up-time, and level of resistance. The control group received conventional outpatient gait therapy that involved active overground walking training at the same frequency. **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT).[3]	1. Both participants in the robotics group showed improvement on their SDMT score. One participant improved by 131% while the other improved by 29%. 2. The SDMT score for participants of the control group declined.

[3]Primary outcome not specified

Table 15. Summary Table of Studies Examining Robotics

	Information Processing
Improve	
No statistical sig. difference	• Androwis et al., 2019 (SDMT)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT (pre-post)

Discussion

Androwis et al. (2019) investigated the effects of an exoskeleton overground gait-training program on ambulation and processing speed. Four participants were randomized to gait training either with an exoskeleton robotic device (n=2) or without the device (n=2). Both groups received eight one-hour gait-training sessions over four weeks. The exoskeleton robotic design provided two degrees of freedom at the hip and knee joints and a passive spring ankle joint. The design allowed powered control of the hip and knee joints through the walking motion. The Symbol Digit Modalities Test and walking outcomes were collected at baseline and following the four-week intervention period. There was improvement on the Symbol Digit Modalities Test for the two participants in the intervention group, with one participant improving their score by 131%. The Symbol Digit Modalities Test scores worsened post gait training for the two participants in the control group. This worsening of the Symbol Digit Modalities Test in the control gait-training group is inconsistent with other non-robotic gait-training research; Sandroff et al. (2016) report improvement in the Symbol Digit Modalities Test scores post gait training. In the small RCT by Androwis et al. (2019), data collection was not blinded, and the study involved a very small sample size.

Conclusion

There is level 1b evidence that robotics may not improve any measure of cognition more than gait training in persons with MS (one <u>very small</u> randomized controlled trial; Munari et al. 2020).

Robotic-assisted gait training may not improve cognitive impairment more than gait training alone in persons with MS.

3.8 Spaced Learning and Retrieval Practice

Spaced learning approaches involve temporal dispersion of learning over time. For example, information is reviewed multiple times at different time points rather than “cramming,” in which information is reviewed multiple times in the same sitting.

Retrieval practice involves testing or quizzing oneself on the materials to be learned. Retrieval practice has robust effects in healthy populations for improving memory in comparison to other learning approaches (Karpicke and Roediger 2008).

Table 16. Studies Examining Spaced Learning for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Sumowski et al. 2013 *Retrieval practice is a robust memory aid for memory-impaired Persons with MS* USA **Pre-Post** $N_{Initial}$=12, N_{Final}=12	**Population:** Mean age=49.42yr; Gender: males=0, females=12; Disease course: RRMS=10, SPMS=2; Disease severity: Unspecified; Mean disease duration=15.67yr. **Intervention:** MS patients with severe memory impairment received memory retrieval practice to aid with recall of verbal paired associates under 3 learning conditions: massed restudy (MR), spaced restudy (SR), or retrieval practice (RP). Verbal paired associate (VPA) recall was tested after a short delay (30min) or a long delay (1wk). **Cognitive Outcome Measures:** Verbal Paired Associates (VPA) recall.[1]	1. Patients recalled 72.9% of VPA studied through RP, compared to only 15.6% through MR ($p<1^{E-6}$) and 27.1% through SR ($p<1^{E-4}$). 2. Significantly better VPA recall was observed under the SR condition relative to MR (p=0.03). 3. Recall under RP was significantly greater relative to MR and SR after a long delay ($p<1e^{-4}$). 4. Patients recalled 24.0% of verbal paired associates studied through RP, compared to only 1.0% through MR (p<0.001) and 4.2% through SR (p=0.004). MR and SR did not significantly differ from each other.
Sumowski, Chiaravalloti, and DeLuca 2010 *Retrieval practice improves memory in multiple sclerosis: clinical application of the testing effect* USA **Pre-Post** $N_{Initial}$=48, N_{Final}=48	**Population:** *MS population (n=32):* Mean age=48.0yr; Gender: males=3, females=29; Disease course: RRMS=21, SPMS=6, PPMS=4, PRMS=1; Disease severity: Unspecified; Mean disease duration=12.8yr. *Healthy controls (n=16):* Mean age=47.6yr; Gender: males=1, females=15. **Intervention:** MS patients and healthy controls (HC) received memory retrieval practice where subjects studied 48 verbal paired associates (VPA) in 3 different learning conditions: massed restudy (MR), spaced restudy (SR), and spaced testing (ST). In the MR condition, the initial VPA was immediately followed by two restudy trials. For the SR condition, initial VPA presentation was followed by 3 filler trials (other VPAs), a restudy trial, 6 filler trials, and a second restudy trial. The variation in the schedule of presentation was to isolate the effect of spaced learning on memory. For the ST condition, initial VPA presentation was followed by 3 filler trials, a test trial, 6 filler trials, and a second test trial. A subgroup analysis was conducted within MS subjects with and without memory impairment. **Cognitive Outcome Measures:** Verbal Paired Associates (VPA) correct responses.[1]	1. Both groups performed significantly better on delayed VPA recall in the ST condition compared to the SR and MR conditions (η_p^2=0.54, p<0.001). 2. No significant differences between the MS and HC groups were observed in correct responses during the first or second ST trials, indicating that both groups performed the retrieval practice technique equally well. 3. In the MS group, a significant advantage was observed for VPAs learned through ST relative to SR (p<0.001), SR relative to MR (p<0.001), and ST relative to MR (p<0.001). 4. In the HC group, mnemonic advantages were observed for ST relative to SR (p<0.05), SR relative to MR (p<0.01), and ST relative to MR (p<0.001). 5. Significant advantages were observed within the MS memory-impaired group for VPAs learned through ST relative to SR (p<0.05), ST relative to MR (P<0.001), and for SR relative to MR (p<0.001). 6. Significant advantages were observed within the MS memory-intact group for VPAs learned through ST relative to SR (p<0.01), ST relative to MR (P<0.001), and for SR relative to MR (p<0.05). 7. ST was the learning strategy that produced the best (or tied for the best) recall performance in 90% of all subjects (88% in the MS memory-impaired group, 94% in MS memory-intact group).

Goverover et al. 2009 *A functional application of the spacing effect to improve learning and memory in persons with multiple sclerosis* USA **PCT** $N_{Initial}$=38, N_{Final}=38	**Population:** *MS participants (n=20):* Mean age=48.4yr; Gender: males=4, females=16; Disease course: RRMS=13, PPMS=3, SPMS=4; Disease severity: Unspecified; Mean disease duration=10.6yr. *Healthy controls (n=18):* Mean age=41.4yr; Gender: males=6, females=12. **Intervention:** Participants' performance on the acquisition of everyday functional tasks was assessed under two conditions: spaced learning trials (trials distributed over time) and massed learning trials (consecutive learning trials). Tasks in the spaced condition were presented to the participants three times with 5-min breaks between each trial. Tasks in the massed condition were presented three consecutive times. Tasks presented included route learning tasks and paragraph learning tasks. Assessments were performed immediately and 30min following the learning task trials. **Cognitive Outcome Measures:** Number of elements remembered from learning tasks.[3]	1. The mean number of elements remembered under the spaced condition was significantly higher than those under the massed condition collapsed across group (both MS and controls) and time (p<0.05) for paragraph learning tasks. 2. The benefit received under the spaced condition for paragraph learning tasks did not significantly differ between MS patients and the control group. 3. Immediate recall was significantly greater than delayed recall across the entire sample (p<0.001) for paragraph learning tasks. 4. There were no significant differences in recall between spaced and massed learning conditions at either the immediate or 30-min assessment for route learning for MS patients or healthy controls. 5. While recall was significantly greater at immediate assessment compared with after 30min (p<0.01) for the route learning task, no significant effect of spaced or massed learning condition on recall over time was observed.

[1]Primary outcome measure, [3]Primary outcome not specified

Table 17. Summary Table of Studies Examining Spaced Learning

	Memory
Improve	• *Sumowski et al. 2013 (VPA)* • *Sumowski et al. 2010 (VPA)* • Goverover et al. 2009
No statistical sig. difference	

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT (pre-post)

Discussion

Three non-RCT study designs investigated spaced learning approaches in particular against other learning strategies for improving memory. Sumowski et al. (2013; 2010) also compared the effects of retrieval practice with spaced or mass learning in two studies with within-subject designs. The results support that for optimizing memory, retrieval practice is superior to spaced learning, which in turn is superior to mass learning. Similarly, the results of the Goverover et al. (2009) study support the superiority of spaced learning over mass learning for improving memory. The first study by Sumowski et al. (2010) included 32 MS subjects and 16 age-matched healthy controls with comparable baseline IQ according to the Wechsler Test of Adult Reading. The second study followed the same within-subject design and experimental protocol, evaluating an independent sample of 12 participants with MS with severe memory impairment at baseline (Sumowski et al. 2013). Severe memory impairment was defined as scoring less than or equal to the second percentile on delayed recall of the Hopkins Verbal Learning Test, Revised. Retrieval practice improved on the short- and long-term recall of paired word associations for all MS participants in both trials, and with moderate to large effect sizes at the group level.

However, as the authors point out, retrieval practice will only improve memory relevant to everyday life activities if PwMS use the technique. Sumowski et al. (2013) provide the following example:

> Patients wishing to learn information in a newspaper article, training manual, or textbook may engage in intermittent self-quizzing throughout their reading (i.e., after each paragraph or page). This act of retrieval practice will result in greater subsequent memory than rereading the information multiple times. (p. 1945)

The simplicity of self-quizzing and its robust effect on memory suggest this approach could be applied in practice for PwMS.

Conclusion

There is level 2 evidence that spaced learning improves memory compared to mass learning (one prospective controlled trial and two pre-post studies; Goverover et al. 2009, Sumowski et al. 2010, and Sumowski et al. 2013).

There is level 2 evidence that retrieval practice improves memory with mild or advanced cognitive impairment to a greater extent than spaced learning or mass learning approaches (two pre-post studies; Sumowski et al. 2010 and Sumowski et al. 2013).

Spaced learning improves memory more than mass learning.

Retrieval practice learning improves memory more than spaced or mass learning in persons with MS with mild or severe cognitive impairment at baseline.

3.9 Cue Salience

Prospective memory challenges are common in PwMS, and affect daily functioning (i.e., remembering to do an intended task such as take a medication or attend an appointment). Prospective memory impairments (forgetfulness) may negatively affect quality of life. Cue salience is a technique proposed to help with prospective memory. Van Benthem et al. (2015) explains cue salience as follows:

> Memory cues have features that render them hypothetically more likely (high-salience) or less likely (low-salience) to act as signals for the prospective memory task. Greater salience or prominence of the cue is associated with better prospective remembering. For example, spatially displacing a letter cue (e.g., a b c) within a string of letters improved prospective memory. Although all letters were located within the field of view, the slight displacement of

> the letter cue appeared to increase its salience, as compared to conditions where the letter cue was not displaced. (Van Benthem et al. 2015, p.367)

The term prospective memory refers to the ability to remember to carry out a future intended action at the appropriate time (McDaniel and Einstein 2007). This type of memory is clearly important in day-to-day life, from tasks as simple as taking one's medication on time, to as critical as being able pick up one's child from an activity at the right time. Prospective memory also requires intact higher executive function, such as developing strategies to ensure these actions are carried out at the appropriate time and place (McDaniel and Einstein 2007).

Table 18. Studies Examining Cue Salience for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Dagenais et al. 2016 *Prospective memory in multiple sclerosis: The impact of cue distinctiveness and executive functioning* Canada **Pre-Post** $N_{Initial}$=57, N_{Final}=57	**Population:** *MS Participants (n=39):* Mean age=45yr; Gender: males=8, females=31; Disease course: RRMS=27, PPMS=5, SPMS=5, clinically isolated syndrome=2; Median EDSS=2.5; Mean disease duration=12.0yr. *Healthy Controls (n=18):* Mean age=39.61yr; Gender: males=6, females=12. **Intervention:** MS participants were assessed on a prospective memory task that varied the cue salience (text bolding of cue words). MS participants were categorized based on their executive functioning (high-, low-executive) as measured by an executive function battery of tests. **Cognitive Outcome Measures:** Prospective Memory Task (PM)[3].	1. Both high- and low-executive MS participants improved significantly on PM score in the salient condition compared to the non-salient condition (p=0.009, p=0.007 respectively). 2. The high- and low- executive MS groups differed significantly on PM scores under the non-salient cue condition (p=0.028), but no significant difference was observed under the salient cue condition (p=0.07). 3. The high-executive MS participants did not significantly differ on PM score compared to healthy controls on either salience condition.

[3]Primary outcome not specified

Table 19. Summary Table of Studies Examining Cue Salience

	Memory
Improve	• *Dagenais et al. 2013 (PM)*
No statistical sig. difference	

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT (pre-post)

Discussion

In one pre-post study, the authors aimed to determine whether using cue salience, a technique in which cue words are bolded (salient) while non-important words are not bolded (non-salient), could improve performance on a modified Prospective Memory Task (Dagenais et al. 2016). It is important to note that there was no baseline measurement, meaning there was no measure of prospective memory without cue salience done for comparison after using cue salience task. Thus, there was no true intervention in this study; instead, the authors simply compared whether PwMS respond to cue salience similarly to normal controls. The authors noted that healthy controls performed nearly perfectly on the multiple-choice questions after performing the cue salience task, while MS participants often failed to detect prospective cues. This study does confirm that prospective memory deficits are apparent in PwMS. Interestingly, it was found that PwMS with higher executive function, based on numerous tasks administered as part of a comprehensive cognitive battery, responded to the cue-salience task similarly to controls.

Conclusion

There is level 4 evidence that cue salience may improve prospective memory in both high- and low-executive functioning persons with MS (one pre-post trial; Dagenais et al. 2016).

Preliminary evidence suggests that cue salience may improve prospective memory in persons with MS.

3.10 Selective Reminding

One strategy used to assist with memory is Selective Reminding, a repetition technique (Slamecka and McElree 1983). In such techniques, it is postulated that repetition leads to better recall. In the Selective Reminding Test specifically, the stimulus items are presented, and the participant is asked to immediately recall as many items as they can. Subsequent learning trials are employed, but each time only the items that the participant did not recall on the previous trial are presented, followed by another recall trial. Learning trials persist for either a set number of trials, or until a specific threshold is reached. The benefit of this type of test is that recall, and recognition can also be tested after a delay period (retrospective memory). Selective reminding has similarities with retrieval practice techniques to enhance memory. Retrieval practice has a larger effect than spaced and mass learning techniques for improving memory in PwMS (discussed in section 3.8 of this module).

Table 20. Studies Examining Selective Reminding for Cognitive Impairment in Multiple Sclerosis

Author Year **Title** **Country** **Research Design** **PEDro** **Sample Size**	**Methods**	**Results**
McKeever et al. 2019 *Selective reminding of prospective memory in Multiple Sclerosis* USA	**Population:** *MS Selective Reminding group (n=11)*: Mean age=51.4yr; Sex: males=2, females=9; Disease course: RRMS=9, PPMS=2; Mean EDSS=5.0; Mean disease duration=9.8yr. *MS control one learning trial group (n=10)*: Mean age=48.9yr; Sex: males=2, females=8; Disease course: RRMS=7, SPMS=2, PRMS=1;	1. Between-group comparison showed MS participants in the intervention group had a significantly better SRPM score compared to the control group (43.9(3.1) vs. 17.7(10.7), d=3.4, p<0.001). 2. Between-group comparison showed healthy adults (HA) had significantly better SRPM score in the intervention group

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
RCT PEDro=6 $N_{Initial}$=43, N_{Final}=43	Mean EDSS=5.0; Mean disease duration=9.8yr. *Healthy adult Selective Reminding group (n=13):* Mean age=41.6yr; Sex: males=5, females=8; Mean EDSS=0.1. *Control Healthy adult one learning trial group (n=9):* Mean age=44.9yr; Sex: males=2, females=7; Mean EDSS=0.6. **Intervention:** Both the MS and the healthy adult groups were randomly allocated to either the selective reminding paradigm or the control one learning trial protocol. Participants completed their assigned intervention and outcome measures were completed at the end of the session. **Cognitive Outcome Measures:** Selective Reminding Prospective Memory Paradigm (SRPM)[1]	compared to the control group (d=1.08, p=0.043). 3. MS participants and healthy adults performed similarly on SRPM total scores (43.9 (3.1), 40.9 (7.2), respectively, p=0.223) when both groups received SRPM training. 4. Healthy adults in the control group significantly outperformed MS participants in the control group on SRPM total scores (MS: 17.7(10.7); HA: 29.7(12.6), p=0.039)) and MIST Time Cue score (MS: 2.3(2.1); HA: 4.6(1.5), p=0.015).
Chiaravalloti et al. 2003 *Can the repetition effect maximize learning in multiple sclerosis?* US **PCT** $N_{Initial}$=84 N_{Final}=84	**Population:** *MS participants (n=64):* Mean age=45.6yr; Gender: males=14, females=50; Disease course: RRMS=21, PPMS=18, SPMS=25; Mean EDSS=4.5; Mean disease duration=9.22yr. *Healthy controls (n=20):* Mean age=42.3yr; Gender: males=4, females=16. **Intervention:** MS participants were given a modified Selective Reminding Test (SRT), a list of 10 words to remember in a selective reminding format. The trials were repeated until the subject recalled all 10 words on two consecutive trials to a maximum of 15 trials. Subjects in each group were split independently into subgroups (low trial; high trial) based on the median number of trials required to reach 100% recall on 2 consecutive trials. Assessments were performed at 30min, 90min, and 1wk, post intervention. **Cognitive Outcome Measures:** Selective Reminding Test (SRT).[3]	1. The number of learning trials required did not significantly affect recall across the delay periods in MS participants. In fact, there was a trend that MS participants who used more learning trials had poorer recall performance than those who received fewer learning trials ($F(1,54)=3.68$, $p=0.06$). 2. Both low-trial and high-trial MS groups experienced a significant decrease in recalled words across delay periods (p<0.001). 3. The number of learning trials experienced (low- versus high-trial groups) did not significantly influence the decline in recall over time.

[1]Primary Outcome Measure; [3]Outcome Measure Not Specified

Table 21. Summary Table of Studies Examining Selective Reminding

	Memory
Improve	• **McKeever et al. 2019** (SRPM)
No statistical sig. difference	• Chiaravalloti et al. 2013 (SRT)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6

italics	Non-RCT

Discussion

McKeever (2019) evaluated memory performance after either a one-time presentation of a list of words (stimulus) or after applying the Selective Reminding paradigm (the opportunity to practice selective reminding with repeated trials). Both the healthy controls and PwMS performed significantly better (i.e., had a greater recall of presented words) after the Selective Reminding technique. Healthy controls performed better overall than PwMS on the one-time task, but there was no significant difference between the two groups in the Selective Reminding paradigm.

In the Chiaravalloti (2003) study, a similar Selective Reminding task was tested in PwMS; the Selective Reminder Test counts the number of trials to recall all words, and includes delayed recall and recognition tasks. In the healthy control group, the median number of trials to recall all words was four; for PwMS, the median was eight. All PwMS, regardless of the number of trials required to learn all the words, demonstrated a decrease in delayed recall compared to healthy controls. Interestingly, there was a trend in that PwMS who took more trials to recall all words performed worse on the recall measures compared to PwMS who took fewer trials. These findings suggest that more selective reminding trials may not be an efficient strategy for improving recall in PwMS with impaired learning. However, a limitation of this study is that a within subject comparison of the effects of a low versus a high number of selective reminding trials on delayed recall was not studied.

Conclusion

There is level 1b evidence that selective reminding tasks may improve memory in persons with MS compared to single trial encoding conditions (one randomized controlled trial; McKeever et al. 2019).

Selective reminding tasks may improve memory in persons with MS.

3.11 Self-generation Program

A self-generation learning program seeks to improve new learning based on the principal that a person is better able to remember self-generated information over provided information. The individual is trained to self-generate the information to be remembered, whether this be items important to everyday life activities or in a research setting.

Table 22. Studies Examining Self-generation Program for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Goverover et al. 2018 *A randomized controlled trial to treat impaired learning and memory in multiple sclerosis: The self-GEN trial* USA **RCT** PEDro=9 $N_{Initial}$=35, N_{Final}=35	**Population:** *Intervention group (n=19)*: Mean age=50.15yr; Sex: males=30%, females=70%; Disease course RRMS=12, PPMS=5, SPMS=2; Mean PDDS=3.8; Mean disease duration=11.1yr. *Control group (n=16)*: Mean age=48.5yr; Sex: males=20%, females=80%; Disease course: RRMS=12, PPMS=2, SPMS=2; Mean PDDS=2.9; Mean disease duration=11.4yr. **Intervention:** Following randomization, each group completed six individualized sessions over 3wks. The intervention group received the self-generation learning program (self-GEN) including four parts: in part 1, participants were asked to self-generate and remember words related to multiple presented cues; in part 2, participants were asked which list they recalled better and what helped them recall it; in part 3, the previous two parts were repeated with different stimuli; and in part 4, participants were asked to remember new words and asked how self-generation can be used. Lastly, they were instructed to summarize the activities of the session and what they thought was helpful in a journal that was taken up at the beginning of the next session. In the control group, they completed the same tasks but without the self-generated learning or the transfer instructions. Outcome measures were completed at baseline and within a wk of the last treatment. **Cognitive Outcome Measures:** Contextual Memory Test (CMT)[1]; Self-regulation Skills Interview (SRSI)[1]; Memory for Intentions Test (MIST)[1]; California Verbal Learning Test II (CVLT-II)[1]; Memory Functioning Questionnaire (MFQ)[1]; Awareness Questionnaire (AQ)[1].	1. Statistically significant improvements after controlling for baseline were observed on CMT immediate recall in the intervention group (95% confidence interval (95% CI): 14.2–16.2) compared to the control group (95% CI:10.9–13.1) ($F(2, 34)=19.6$, $p < 0.001$, with large effect size $\eta2=0.38$). 2. Statistically significant improvements after controlling for baseline were observed on CMT delayed recall scores (95% CI: 12.3–15) compared to the control group (95% CI: 9.2–12.1) ($F(2,34)=9.2$, $p=0.005$, $\eta2=0.22$). 3. Statistically significant improvements were observed on SRSI scores in the intervention group compared to the control group ($F(2,34)=3.9$, $p=0.05$, $\eta2=0.010$) after controlling for baseline performance on SRSI ($F(2,34)=16.3$, $p<0.001$). 4. Statistically significant improvements were observed on MIST in the intervention group (95% CI:38.7-43.7) compared to the control group (95% CI: 34.6-39.9) following the treatment ($F(2, 30)=4.8$, $p=0.03$, $\eta2=0.15$) and after controlling for baseline performance ($F(2, 30)=7.4$, $p < 0.05$). 5. Between-group comparison showed no difference between intervention and control groups on CVLT-II scores compared to baseline.
Chiaravalloti et al. 2019 *The application of Strategy-based Training to Enhance Memory (STEM) in multiple sclerosis: A pilot RCT* USA **RCT** PEDro=6 $N_{Initial}$=21, N_{Final}=20	**Population:** *Intervention group (n=9)*: Mean age=49.67yr; Sex: males=3, females=6; Disease course: RRMS=6, PPMS=1, SPMS=1, PRMS=1; Severity: unspecified; Mean disease duration=13.9yr. *Control group (n=11)*: Mean age=45.45yr; Sex: males=6, females=5; Disease course: RRMS=7, PPMS=1, SPMS=1; Severity: unspecified; Mean disease duration=16.2yr. **Intervention:** Following randomization, both groups received 8, one-on-one sessions over 4wks. The treatment group received the strategy-based training to enhance memory (STEM) intervention. This included discussion of the memory process, self-generation, spaced learning, and retrieval practice techniques and application to daily life. The control group	1. No significant between-group differences in change scores on the CVLT-II or the BVMT-R. 2. A non-significant, medium-large effect size was observed on the CVLT-II total learning score ($F(1,18)=1.96$, $p=.09$, one-tailed; $\eta_p^2=.11$). 3. A non-significant small treatment effect was observed on BVMT-R total learning score $F(1,18)=.13$, ns, one-tailed, $\eta_p^2=.008$).

	engaged in non-training-oriented tasks including reading a sentence and recalling target words, word association, learning and remembering names, recalling objects, learning recipes, finance management, and keeping a calendar. Both groups had the same amount of contact with the examiner. Outcome measures were collected at baseline and within 1wk following the intervention. **Cognitive Outcome Measures:** California Verbal Learning Test II (CVLT-II)[1], Brief Visuospatial Memory Test-Revised (BVMT-R)[2].	
Goverover, Chiaravalloti, and DeLuca 2014 *Task meaningfulness and degree of CI: do they affect self-generated learning in persons with multiple sclerosis?* US **Post-Test** $N_{Initial}$=70, N_{Final}=70	**Population:** *Mild-MS group (n=35):* Mean age=49.2yr; Gender: males=1, females=34; Disease course: RRMS=28, PPMS=3, SPMS=5; Severity: unspecified; Mean disease duration=134.7mo. *Severe-MS group (n=35):* Mean age=47.8yr; Gender: males=6, females=29; Disease course: RRMS=26, PPMS=4, SPMS=3; Severity: unspecified; Mean disease duration=169mo. **Intervention:** Participants learned two tasks (functional everyday tasks and laboratory tasks) under two conditions (provided and self-generated). Assessments of recall were performed immediately, at 30min, and at 1wk after initial presentation. **Cognitive Outcome Measures:** Generation Effect Task (GE): Number of items recalled from functional and laboratory tasks.[3]	1. Items learned via the self-generated condition were recalled significantly better than items learned under the provided condition (n^2=0.2, p<0.01). 2. Between-group comparison showed that the greatest benefit of self-generation was observed at the 30-min assessment (n^2=0.09, p=0.008), and this was maintained after 1wk. There was no between-group difference in immediate recall scores. 3. The effect of task, functional or laboratory, was large and significant (n^2=0.91, p<0.001). Recall of items presented during functional tasks was significantly better than recall of items presented during laboratory tasks. 4. Self-generation was more beneficial while learning items related to functional tasks than laboratory asks (significance not provided). 5. The mean number of words recalled across time declined significantly in both the generated and provided conditions (p<0.001). 6. Patients in the Severe-MS group remembered significantly fewer items than the mild-MS group across the two tasks (n^2=0.18, p<0.001). 7. Comparison between group and condition showed no significant difference in Severe-MS or Mild-MS groups; both groups benefited similarly to self-generation.
Goverover et al. 2011 *Examining the benefits of combining two learning strategies on recall of functional information in persons with multiple sclerosis* US	**Population**: *MS participants (n=20):* Mean age=47.0yr; Gender: males=2, females=18; Disease course: RRMS=15, PPMS=2, SPMS=3; Severity: unspecified; Mean disease duration=10.8yr. *Healthy controls (n=18):* Mean age=40.9yr; Gender: males=3, females=15. **Intervention**: Participants were tasked to recall names and faces, appointments, and object locations under 3 different encoding conditions: massed rehearsal, spaced learning, and combining self-generated information with spaced learning	1. Recall for names in the spaced-generated and spaced learning conditions was significantly greater than in the massed condition (p<0.001). However, there was no significant difference between the spaced learning and spaced-generation conditions. 2. Memory for object locations learned in a combined spaced-generated condition were recalled significantly better than those learned through either the spaced (p<001) or massed rehearsal conditions.

Post-Test $N_{Initial}$=38, N_{Final}=38	(spaced-generated). To control for possible order effects, the task and encoding conditions were counterbalanced across participants. Assessments were performed immediately and 30min after initial presentation. **Cognitive Outcome Measures**: Memory for names and faces; Memory for object location; Memory for appointments.[3]	3. Spaced rehearsal resulted in better memory for object locations than the massed rehearsal condition (p<0.05). 4. In the memory for appointments assessment, the combined spaced and self-generated condition resulted in significantly better recall than the spaced condition (p<0.001), and the spaced condition resulted in better recall than the massed condition (p=0.001).
Basso et al. 2008 *Self-generated learning in people with multiple sclerosis: an extension of Chiaravalloti and DeLuca 2002* US **Pre-Post** $N_{Initial}$=20, N_{Final}=20	**Population:** *MS-Memory Impaired (n=10):* Mean age=43.20yr; Gender: males=2, females=8; Disease course: RRMS=6; Mean EDSS=5.06; Mean disease duration=13.9yr. *MS-Unimpaired (n=10):* Mean age=41.50yr; Gender: males=1, females=9; Disease course: RRMS=6; Mean EDSS=3.70; Mean disease duration=6.4yr. *Healthy controls (n=17):* Mean age=46.94yr; Gender: males=5, females=12. **Intervention:** MS participants were divided into groups based on the presence of mild or average memory impairment. Participants were presented with word pairs according to the paired-associate learning task under self-generated and didactic conditions. Assessments were performed immediately and 20min after task completion. **Cognitive Outcome Measures:** Paired Associate Task: Number of words recalled and recognized: immediate and delayed recall.[3]	1. There was a significant effect of encoding condition observed when considering all groups together (p=0.05). 2. No significant difference was observed between MS groups in terms of recall enhancement due to the self-generated encoding condition. 3. No significant difference was observed in the change of recall from immediately to 20-min post-task (forgetting rate) between the encoding conditions. 4. There was no interaction observed between patient group and encoding condition, suggesting that self-generated encoded improved recall in all groups (MS and healthy).
Goverover, Chiaravalloti, and DeLuca 2008 *Self-generation to improve learning and memory of functional activities in persons with multiple sclerosis: meal preparation and managing finances* US **PCT with Pre-Post** $N_{Initial}$=38, N_{Final}=38	**Population:** *Healthy control group (n=18)*: Mean age=40.4yr; Gender: males=6, females=12. *Intervention (MS) group (n=20):* Mean age=46.1yr; Gender: males=5, females=15; Disease course: RRMS=16, PPMS=2, SPMS=2, PRMS=0; Severity: unspecified; Mean disease duration=12.1yr. **Intervention:** All participants completed two meal preparation and financial management tasks. One task in each area was presented in the provided condition, in which all instructions were provided to and read by the participants, and the other task was presented in the generated condition, in which participants were asked to generate (fill in the blank) the necessary items needed to perform each step of the task. Participants were assessed immediately following the study, at 30min, and at 1wk following initial presentation. **Cognitive Outcome Measures:** Generation Effect Task (GE): Recall of task items and step sequences from self-generation protocol[1]; Weschler Adult Intelligence Scale-Revised (WAIS-R)[2]; Symbol Digit Modalities Test (SDMT)[2]; Delis-Kaplan Executive Function System (D-KEFS), which includes the Trail Making Test (TMT), verbal fluency test, and color-word interference test[2]; Boston Naming Test (BNT)[2]; California Verbal Learning Test (CVLT).[2]	1. There was a significant benefit of self-generation over provided presentation across tasks learned for both MS and health control participants (p<0.001). 2. The MS group took significantly longer to perform the D-KEFS TMT test (p=0.002), generated significantly fewer words on the D-KEFS Verbal Fluency Test (p=0.008), and required significantly more time to complete the D-KEFS Color-Word Interference Test (p=0.04) compared to the healthy control group. 3. There was no significant difference between the MS group and the control group on all other outcome measures. Both groups benefited from the generated condition compared to the provided condition. 4. There was a significant drop in recall from 30min to 1wk (p<0.001). 5. The control group showed the greatest benefit from self-generation at immediate recall (p=0.004), while the MS group showed a trend towards a benefit obtained from self-generation at 1-wk recall (p=0.06).

O'brien et al. 2007 *An investigation of the differential effect of self-generation to improve learning and memory in multiple sclerosis and traumatic brain injury* US **Pre-Post** $N_{Initial}$=69, N_{Final}=69	**Population:** *MS participants (n=31):* Mean age=45.42yr; Gender: males=5, females=26. No further information provided. *Healthy controls (n=20):* Mean age=38.40yr; males=10, females=10. **Intervention:** MS participants performed learning and memory tasks under two conditions: self-generated and provided cues. In the generated condition 16 sentences were presented with the last word missing, as indicated by a blank line. In the provided condition an additional set of 16 complete sentences were presented in which the last word was underlined. Outcome measures were collected prior to and following the intervention. **Cognitive Outcome Measures:** Generation Effect Task (GE): recall of provided and self-generated words; Wechsler Adult Intelligence Scale-Revised (WAIS-R): Digit Span, Logical Memory I and II; Paced Auditory Serial Addition Test (PASAT); Stroop Color-Word Test (SCWT); Oral Trail Making Test-B (TMT-B); Controlled Oral Word Association Test (COWAT).[3]	1. Self-generation significantly improved recall for both groups ($F(1,47)=15.62$, $n_p^2=0.25$, $p<0.001$) compared to the provided condition. 2. Within-group comparison showed a 49% increase in recall for the MS group (provided condition: 1.84(SD:1.44) vs. self-generation condition: 2.75(SD:1.68)). 3. No significant interactions between learning condition and complex working memory, episodic memory, or executive function were observed. 4. Participants with impairments in two or more cognitive domains (complex working memory, episodic memory, executive function) recalled fewer words overall than those with no or only one domain of CI ($p<0.01$). Among those patients there was a significant effect of the generation condition ($p<0.001$).
Basso et al. 2006 *Self-generated learning in people with multiple sclerosis* US **PCT with Pre-Post** $N_{Initial}$=117, N_{Final}=117	**Population:** *Intervention (MS-MOD) group (n=12):* Mean age=47.67yr; Gender: males=1, females=11; Disease course: RRMS=4, PPMS/SPMS=3, other=5; Ambulation index=2.91; Mean disease duration: unspecified. *Intervention (MS-MILD) group (n=10):* Mean age=50.40yr; Gender: males=1, females=9; Disease course: RRMS=7, PPMS=1, other=2; Ambulation index=3.10; Mean disease duration: Unspecified. *Intervention (MS-UN) group (n=73):* Mean age=43.79yr; Gender: males=12, females=61; Disease course: RRMS=38, PPMS/SPMS=12, other=22; Ambulation index=2.47; Mean disease duration: Unspecified. *Healthy control group (n=22)*: Mean age=42.36yr; Gender: males=5, females=17. **Intervention:** Based on the California Verbal Learning Test II (CVLT-II) scores, participants were classified to the MS-Unimpaired (MS-UN), MS-Mildly Impaired (MS-MILD), and MS-Moderately Impaired (MS-MOD) groups. Participants were assigned to conditions in which either the self-generation or didactic encoding procedure was administered first. After completing both conditions, immediate free recall was measured. Twenty minutes later, delayed recall and the recognition test was administered. Subsequently, the name and face learning task, the appointment learning task, the object location learning task, and lastly a recognition test of memory for object location were assessed immediately following the test and after a delay of 20min which was allocated between every test. During the delay period, neuropsychological tests unrelated to the	1. The self-generated words, names, locations, and appointments were better remembered than the didactically presented words for all groups (all $p<0.001$). 2. There was a significant main effect on participant groups with respect to word recall, where the control group recalled more words than the three MS groups (MS-MOD, MS-MILD, MS-UN; $p<0.001$). 3. Participants also recalled fewer words during delayed recall compared to immediate recall ($p<0.001$). 4. The MS-MOD recalled fewer names than the control and the MS-UN groups ($p<0.001$). 5. The control and the MS-UN groups recalled more locations than the MS-MILD and MS-MOD groups ($p<0.001$). 6. The control group recalled more appointments than the MS-MILD and MS-MOD group ($p<0.001$).

	study were administered. **Cognitive Outcome Measures:** Paired Associate Task: free recall and recognition of paired associates, names, object location and appointments.[3]	
Chiaravalloti and DeLuca 2002 *Self-generation as a means of maximizing learning in multiple sclerosis: An application of the generation effect* US **PCT** $N_{Initial}$=48 N_{Fina}=48	**Population:** *MS participants (n=31):* Mean age=45.42yr; Gender: males=5, females=26; Disease course: unspecified; Ambulation index=2.07; Mean disease duration=127.8mo. *Healthy controls (n=17):* Mean age=41.2yr; Gender: males=6, females=11. **Intervention:** MS participants received a Generation effect protocol consisting of two types of sentence stimuli intermingled. Participants were asked to 'fill in the blank' for a missing word in a sentence, indicated by an underlined space. In some cases, the subjects filled in the space with the 'first word that comes to mind.' In the other cases the space was already filled in with a word. Later, the subjects were assessed based on the underlined words to determine if words generated by the subject were recalled at a higher rate than words provided to the subject by the examiner. Assessments were performed immediately, at 30min, and at 1wk after presentation. **Cognitive Outcome Measures:** Generation Effect Task (GE): recall and recognition of generated or provided stimuli [1]; Wechsler Adult Intelligence Scale-IV (WAIS-IV): Digit Span[1]; Paced Auditory Serial Addition Test (PASAT); Stroop Color-Word Test (SCWT) [1]; Oral Trail Making Test A, B (TMT-A, TMT-B) [1]; Wisconsin Card Sorting Test (WCST) [1]; Controlled Oral Word Association Test (COWAT) [1]; Boston Naming Test (BNT); Animal Fluency (AF)[1]; Wide Range Achievement Test-3 (WRAT-3) reading subtest; Wechsler Memory Scale-Revised (WMS-R), local memory I and II.[1]	1. Both groups exhibited significantly increased recall of self-generated words compared with examiner provided words at all time points (p<0.001, p<0.001, p<0.05, respectively) and the differences in the effect between groups were not significant. 2. A significant decrement in the number of words recalled with the passage of time was observed (p<0.001) and was equivalent in both groups (p=0.40). 3. There was a significantly greater increase in generated stimuli recalled correctly than in provided stimuli recalled correctly at the 30-min assessment than at the immediate assessment (p<0.001). 4. There was a significantly greater decline in recall of generated words compared with provided words between the 30-min and 1-wk assessments in both groups (p<0.001).

[1]Primary outcome measures, [2]Secondary outcome measures, [3]No outcome measure specified

Table 23. Summary Table of Studies Examining Self-generation Program

		Improve	No statistical sig. difference
Memory	Verbal Learning and Memory		• **Chiaravalloti et al. 2019**[T] (CVLT-II) • **Goverover et al. 2018** (CVLT-II)
	Working Memory	• **Goverover et al. 2018 (**MIST)	
	Visuospatial Memory		• **Chiaravalloti et al. 2019[T]** (BVMT-R)
	Visual Memory	• **Goverover et al. 2018 (**CMT)	

	Recall	• *Goverover et al. 2014 (GE – recall)* • *Goverover et al. 2013 (GE - recall)* • *Goverover et al. 2011 (GE- recall)* • *Basso et al. 2008 (Paired Associate Task - recall)* • *Goverover et al. 2008 (Generation Effect Task - recall)* • *O'Brien et al. 2007 (Generation Effect Task - recall)* • *Basso et al. 2006 (GE – recall)* • *Chiaravalloti & DeLuca 2002 (Generation Effect Task - recall)*	
Executive Function		• **Goverover et al. 2018 (SRSI)**	

Bold	PEDro ≥ 6
Regular	PEDro < 6
Italic	Non-RCT
T	Trend to improve

Discussion

Two higher quality RCTs (Y. Goverover et al. 2018; N. D. Chiaravalloti et al. 2019) and seven lower quality studies include self-generation learning techniques with the aim of improving learning and memory. Traditional neuropsychological memory outcomes did not reach statistical significance for a between-group difference in either of the high-quality RCTs. However, Goverover et al. (2018) include the Contextual Memory Test as the primary outcome, and Goverover et al. (2014) and others include the Generation Effect Task Recall Test in earlier studies. The results of these outcomes more directly evaluating success with the self-generation training are positive. The Contextual Memory Test evaluates immediate and delayed object recall in addition to awareness and utilization of memory strategies. The Generation Effect Task Recall test in effect evaluates the success of using the self-generation technique. After the participant self-generates items to be learned, recall of those items is evaluated immediately and in a delayed fashion. In comparison, recall is not as robust for rote items provided to participants when participants either do not receive training in self-generation or do not apply the strategy.

Encouragingly, Goverover, Chiaravalloti, and DeLuca (2014) also report that participants with severe disability are able to apply the self-generation strategy to improve learning, although their recall remained more impaired than those with less severe MS. The self-generation techniques were taught in the research settings within several or even fewer sessions by leading experts in the field. It is unclear if the same success would be realized in real-world settings by self-taught programs or if led by other health care professionals. Applying the technique also requires the participant to have time to take part in the self-generation. This may help to explain why time-sensitive or structured neuropsychological test scores did not improve, since participants may not have had opportunity to apply the self-generation strategies during the testing. This hypothesis would make the case that clinicians and PwMS should advocate for sufficient time to apply memory strategies in situations that involve new learning or testing.

In the second high-quality RCT by Chiaravalloti et al. (2019), participants in the intervention group received training in three memory strategies: self-generation, spaced learning, and retrieval practice (referred to as Strategy-based Training to Enhance Memory—STEM). The control group took part in non-training-orientated cognitive tasks. While the neuropsychological outcomes did not reach statistical significance for between-group differences in this smaller RCT, medium to large effect sizes occurred on the California

Verbal Learning Test in the STEM group. These results support allowing PwMS opportunity to learn and apply memory strategies.

Conclusion

There is level 1b evidence that Self-generation Technique improves contextual recall on tasks where the technique is applied compared to not applying the technique (one randomized controlled trial, one prospective controlled trial, and six pre-post studies; Goverover et al. 2018; 2014; 2013; 2011; and 2008; Basso et al. 2008 and 2006; O'Brien et al. 2007; Chiaravalloti & Deluca 2002).

There is level 1a evidence that teaching the Self-Generation Technique may not significantly improve verbal memory (two randomized controlled trials; Goverover et al. 2018 and Chiaravalloti et al. 2019).

There is level 1b evidence that teaching the Self-Generation Technique may not significantly improve visuospatial memory (one randomized controlled trial; Chiaravalloti et. al. 2019).

Teaching the Self-Generation Technique may improve recall on memory tasks where the technique is applied.

3.12 Story Memory

Memory—specifically, learning or immediate recall—is one of the most commonly noted impairments in PwMS (Thornton and Raz 1997). The studies in this section focus on the Story Memory technique to improve the acquisition of new information (learning). The Story Memory technique, also used for traumatic brain injury, is based on the theory that improving the quality of the memory acquisition is the best way to strengthen it. Story Memory combines two specific approaches that improve the quality of acquisition: context and imagery. A mental visual imagery technique is also reviewed separately in section 3.13 of this module.

Table 24. Studies Examining Story Memory for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Krch et al. 2019	**Population:** *Intervention group (n=10)*: Mean age=33.8yr; Sex: unspecified; Disease course: RRMS; Severity: unspecified; Mean disease duration=5.8yr.	1. Statistically significant improvements were observed in the intervention group on the HVLT-R total learning trials 1-3 (95% CI: 22.66-27.88) relative to the control group (95% CI:

Efficacy of the Spanish modified Story Memory Technique in Mexicans with multiple sclerosis: A pilot randomized controlled trial USA **RCT** PEDro=9 $N_{Initial}$=20, N_{Final}=20	*Control group (n=10)*: Mean age =39.5yr; Sex: unspecified; Disease course: RRMS; Severity: unspecified; Mean disease duration=5.4yr. **Intervention:** Following randomization, both groups received 10 sessions over 5wks. The modified Story Memory Technique (mSMT) includes training on imagery and context. Sessions 1-4 presented stories for which participants needed to complete a visual imagery memory aid. Sessions 5-8 included word lists imbedded in a story, and then participants were asked to visualize the story. Sessions 9-10 focused on application of skills to real-world settings (e.g., shopping). The control group engaged in non-training-specific tasks, including reading the same stories and answering questions, but did not learn to apply imagery and the context of the material. Outcome measures were completed at baseline and within 1wk of the treatment. **Cognitive Outcome Measures:** The Hopkins Verbal Learning Test-Revised (HVLT-R)[1]; Memory Functioning Questionnaire (MFQ).[2]	19.33-24.54) (F(1,17)=3.14, p=0.048), with a moderate-large effect size (η2p=.16). 2. Non-statistically significant improvements with a moderate effect size (η2p=.07) on the MFQ were observed in the treatment group (95% CI: 99.36-112.44) relative to the control group (95% CI: 104.26-117.34) (F(1,17)=1.25, p=0.140).
Boukrina et al. 2019 *Brain activation patterns associated with paragraph learning in persons with multiple sclerosis: The MEMREHAB trial* USA **RCT** PEDro=8 $N_{Initial}$=16, N_{Final}=16	**Population:** *Intervention group (n=6)*: Mean age=49.33yr; Sex: males=1, females=5; Disease course: RRMS=4, PRMS=1, Unknown=1; Severity: unspecified; Mean disease duration=15.7yr. *Control group (n=10)*: Mean age=46.2yr; Sex: males=4, females=6; Disease course: RRMS=7, PPMS=2, SPMS=1; Severity: unspecified; Mean disease duration=13.0yr. **Intervention:** Following randomization, both groups completed 10 treatment sessions**.** The intervention group received the modified Story Memory Technique (mSMT), which involved participants reading a story and actively recollecting as much of the story as possible followed by a series of questions on the story. They were also taught how to utilize context and imagery to encourage new learning. The control group received the same stimuli as the intervention group without the context and imagery components. During the first fMRI portion of the study, participants completed a paragraph task during sessions 1-4. This was followed by a word recognition task that included 8 words from the previous phase. Participants were presented with words for 2 seconds and instructed to indicate if the words were	1. Minimally statistically significant between-group differences were seen for the change in RBMT scores favouring the treatment group (F(1,14)=3.461, p=0.08). 2. Within-group, pre-post analysis showed a large effect size on the RBMT for improvement in the treatment group (d=1.15, p=0.25). The control group worsened (d=0.99, p=0.17). 3. No between-group differences were observed on the MAS prose memory task. 4. On the MAS, within-group comparison showed no significant change from pre- to post-treatment for either group.

	presented in the past. Outcome measures and fMRI were completed within 13d prior to the study and within 2wks following the treatment. **Cognitive Outcome Measures:** Memory Assessment Scale (MAS); Rivermead Behavioural Memory Test (RBMT).[3]	
Chiaravalloti, Moore, and DeLuca 2020 *The efficacy of the modified Story Memory Technique in progressive MS* USA **RCT** PEDro=8 $N_{Initial}$=28, N_{Final}=24	**Population:** *Intervention group (n=15)*: Mean age=55.2yr; Sex: males=4, females=11; Disease course: PPMS=3, SPMS=10, PRMS=1; Severity: unspecified; Mean disease duration=17yr. *Control group (n=13)*: Mean age=53.3yr; Sex: males=6, females=7; Disease course: PPMS=7, SPMS=6; Severity: unspecified; Mean disease duration=16yr. **Intervention:** Following randomization, both groups received 10 sessions over 5wks. The modified Story Memory Technique (mSMT) includes training on imagery and context. Sessions 1-4 presented stories for which participants needed to complete a visual imagery memory aid. Sessions 5-8 included word lists imbedded in a story, and then participants were asked to visualize the story. Sessions 9-10 focused on application of skills to real-world settings (e.g. shopping). The control group engaged in non-training specific tasks, including reading the same stories and answering questions, but did not learn to apply imagery and the context of the material. Outcome measures were gathered at baseline, within 1wk of completing treatment, and 3mos later. **Cognitive Outcome Measures:** California Verbal Learning Test II (CVLT-II)[1]; Rivermead Behavioural Memory Test (RBMT)[1]; Awareness Questionnaire (AQ)[2]; Memory Assessment Scale (MAS), Prose Memory[2]; Brief Visuospatial Memory Test–Revised (BVMT-R)[2].	1. After controlling for variance, the intervention group showed a significant improvement and medium treatment effect (Hedge's G = 0.73) on the CLVT-II at immediate follow up (95% CI: 1.22-1.93, F(1.22)=5.08, p=0.0175, one-tailed). This was maintained at 3mo f/u. 2. There was no significant difference in RBMT between the groups at immediate f/u (Hedge's G = 0.13). 3. No significant improvement in the MAS or BVMTR were observed between intervention and control groups. 4. Significant increase with a small effect size (F(1,14) = 3.67, p = 0.038, one-tailed; Hedge's G = 0.30) in awareness on the AQ post intervention in the treatment group (95% CI: 13.05-18.63) in comparison to the treatment group (95% CI: 8.37-14.79). This was maintained at 3mos.
Chiaravalloti et al. 2013 *An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial* US **RCT** PEDro=8 $N_{Initial}$=88, N_{Final}=78	**Population:** *Treatment Group (n=45)*: Mean age=48.13yr; Gender: males=11, females=34; Disease course: RRMS=33, PPMS=1, SPMS=6 PRMS=1, Unknown=4; Ambulation Index Score=2.68; Mean disease duration=170.87mo. *Control Group (n=41)*: Mean age=49.32yr; Gender: males=10, females=31; Disease course: RRMS=22, PPMS=4, SPMS=11, PRMS=0, Unknown=4; Ambulation Index Score=3.13; Mean disease duration=173.37mo. **Intervention:** The treatment group received 10 sessions of the modified Story Memory Treatment (mSMT) training	1. The treatment group demonstrated significantly more improvement (defined as a ≥10% improvement on CLVT slope) with 62% of patients showing improvement vs. 37% control group showing improvement (p=0.009). The treatment effect was maintained at 6mo f/u. 2. The treatment group performed better than the control group on the RBMT story memory delayed score on immediate f/u (d=0.372, p<0.0115). There was no difference between groups at 6mo f/u. 3. There were significantly greater improvements immediately after intervention in the treatment group compared to control

	lasting 45-60min, 2x/wk for 5wks. mSMT intervention focuses on teaching imagery and context skills. In addition, the treatment group received monthly booster sessions after immediate follow-up after intervention, where they either received training to apply mSMT to real-world situations or placebo booster sessions where the participants read a story and answered questions. The control group met with the therapist with the same frequency as the treatment group, focusing on non-training-specific tasks. The main difference was that the control group wasn't exposed to imagery and context training. Outcome measures were collected at baseline, within 1wk following the intervention and 6mos following the intervention. **Cognitive Outcome Measures:** California Learning Verbal Test II (CLVT-II)[1]; Rivermead Behavioural Memory Test (RBMT)[1]; Subjective report of functioning; Functional Assessment of MS (FAMS); Frontal Systems Behaviour Scale (FrSBe); Wechsler Abbreviated Scale of Intelligence - Digit Span, Letter Number Sequencing; Paced Auditory Serial Addition Test (PASAT); Delis-Kaplan Executive Function System (D-KEFS).[2]	for general contentment in the FAMS (p<0.05), and for FrSBe apathy (p<0.05) and executive dysfunction (p=0.06). 4. There was a significant improvement in FAMS general contentment 6mos after intervention in the treatment vs. control (p<0.05). However, there were no significant effects on RBMT story memory or awareness questionnaire.
Chiaravalloti et al. 2012 *Increased cerebral activation after behavioral treatment for memory deficits in MS* US **RCT** PEDro=6 $N_{Initial}$=16, N_{Final}=16	**Population:** *Treatment group (n=8):* Mean age=49.25yr; Gender: males=1, females=7; Disease course: RRMS=5; Mean Ambulation Index=2.13; Mean disease duration=186.71mo. *Control group (n=8):* Mean age=46.75yr; Gender: males=1, females=7; Disease course: RRMS=6; Mean Ambulation Index=3.75; Mean disease duration=177.14mo. **Intervention:** MS patients were randomized to receive modified Story Memory Technique (mSMT) or control procedure in ten 45–60 min sessions, 2x/wk, for 5wks. Assessments were performed at baseline and follow-up. The treatment group was taught context and imagery to facilitate learning, and to improve learning and memory abilities. The control group met with the therapist and engaged in non-training specific tasks. **Cognitive Outcome Measures:** California Verbal Learning Test (CVLT) short-delay free recall.[3]	1. A significantly greater number of subjects in the treatment group showed a 10% or greater improvement on the CVLT short-delay free recall when compared with the control group (p<0.05).
Chiaravalloti et al. 2005	**Population:** Disease course: RRMS=17, PPMS=4, SPMS=7; Mean Ambulation Index=2.86; Mean disease duration=135.72mo.	1. Between-group comparison showed no significant difference between the intervention and control group in HVLT-R scores.

Treating learning impairments improves memory performance in multiple sclerosis: a randomized clinical trial US **RCT** PEDro=6 $N_{Initial}$=29, N_{Final}=28	*Intervention group (n=14):* Mean age=45.14yr; Gender: males=5, females=9; Mean Ambulation Index = 3.21; Mean disease duration=168.07mo. *Control group (n=14):* Mean age=46yr; Gender: males=6, females=8; Mean Ambulation Index = 2.43; Mean disease duration=100.21mo. **Intervention:** MS patients with learning disabilities were randomly assigned to undergo either 8 sessions of Story Memory Technique (SMT) or 8 sessions of memory exercises. Patients were also stratified according to degree of learning deficits (mild, moderate, and severe). Assessments were conducted at baseline, immediately following treatment and 5wks post treatment. **Cognitive Outcome Measures:** Hopkins Verbal Learning Test-Revised (HVLT-R); Wechsler Adult Intelligence Scale-Revised (WAIS-R): Digit span; Oral Trail Making Test A and B (TMT-A, TMT-B); Animal Fluency (AF); Controlled Oral Word Association Test (COWAT); WAIS-R: Vocabulary subtest; WAIS-R: block design subtest; Paced Auditory Serial Addition Test (PASAT); Wechsler Adult Intelligence Scale-III (WAIS-III) letter-number sequencing; Symbol Digit Modalities Test – oral version (SDMT); Memory Functioning Questionnaire (MFQ).[3]	2. When the intervention group was stratified into mild vs. moderate-severe impairment, MS participants with moderate-severe impairment had a significant improvement compared to MS participants with mild impairment on the HVLT-R between baseline and immediate f/u ($p<0.01$) and baseline and long-term f/u ($p<0.05$). 3. The experimental group reported a significant improvement in their ability to remember everyday occurrences as reported on the MFQ compared with the control group immediately following treatment ($p<0.01$) and at follow-up ($p<0.001$).
Dobryakova et al. 2014 *A pilot study examining functional brain activity 6 months after memory retraining in MS: the MEMREHAB trial* US **RCT** PEDro=2 $N_{Initial}$=8, N_{Final}=6	**Population:** *Total study sample (n=8):* Gender: males=3, females=5; Disease course: RRMS=7, PPMS=1; Severity: Unspecified. *Treatment group (n=4):* Mean Age=40yr; Mean disease duration: 137.5mo. No further information provided. *Control group (n=4):* Mean Age=46yr; Mean disease duration: 84mo. No further information provided. **Intervention:** MS patients with memory impairment were randomized to receive the modified Story Memory Technique (mSMT) rehabilitation protocol or control condition. Patients in the treatment group completed 10 sessions of mSMT, while the control group performed memory exercises at the same frequency. Assessments were performed at baseline, immediately after treatment and at 6mo follow-up. **Cognitive Outcome Measures:** California Verbal Learning Test (CVLT): Short delay free recall (SDFR).[3]	1. The treatment effect (a significant difference in CVLT-SDFR immediately following treatment compared with baseline) was maintained at long-term follow up ($p=1.0$).

[1]Primary Outcome Measure; [2]Secondary Outcome Measure; [3]Outcome Measure Not Specified

Table 25. Summary Table of Studies Examining Story Memory

	Verbal learning and Memory	Full Scale Memory
Improve	• **Krch et al. 2019** (HVLT) • **Chiaravalloti et al. 2020** (CVLT-II) • **Chiaravalloti et al. 2013** (CVLT-II, RBMT: story) • **Chiaravalloti et al. 2012** (CVLT) • Dobryakova et al. 2014 (CVLT-II)	• **Boukrina et al. 2019** (RBMT)
No statistical sig. difference	• **Chiaravalloti et al. 2005** (HVLT-R)	• **Chiaravalloti et al. 2020** (RBMT) • **Boukrina et al. 2019** (MAS)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6
italics	Non-RCT

Discussion

In a pilot study, Chiaravalloti et al. (2005) aimed to determine the effectiveness of a modified story memory technique, involving imagery and context, with respect to new learning in PwMS. A control group underwent an active control, in that they met with the same therapist as did the experimental group, controlling for professional contact. This initial small pilot study did not find a significant difference between the intervention and control group on measures of information processing speed, mood symptoms, or verbal fluency. However, there was a trend towards improvement on a measure of episodic memory (HVLT-R). Subsequent studies by this same group found the modified Story Memory Technique to be beneficial in a larger, heterogeneous sample of PwMS on measures of verbal learning and memory (Chiaravalloti et al. 2012). These benefits were sustained after one year of follow up (Dobryakova et al. 2014). Further, Chiaravalloti, Moore, and DeLuca (2020) report similar positive results when examining modified Story Memory Technique in a progressive MS cohort. A Spanish version of the modified Story Memory Technique, in a Mexican population, demonstrated similar results (Krch et al. 2019).

Conclusion

There is level 1a evidence that the modified Story Memory Technique does improve verbal learning and memory but may not improve other forms of memory (five randomized controlled trials; Chiaravalloti et al. 2020, Chiaravalloti et al. 2013, Chiaravalloti et al. 2012, Dobryakova et al. 2014, Krch et al. 2019).

The Modified Story Memory Technique does improve verbal learning and memory but does not improve other forms of memory in persons with MS

3.13 Mental Visual Imagery

Ernst et al. (2018) described a mental visual imagery program designed specifically with stepwise visualisation exercises of increasing difficulty to improve autobiographical memory relevant to everyday life. A description of autobiographical memory is cited by Tulving et al. (2002) as the "ability mentally to re-experience personal detailed events within a specific spatio-temporal context" (cited in Ernst et al. 2018, p. 1111). The mental visual imagery program included the following:

> The external visualisation of 10 verbal items to imagine and describe in as much detail as possible (e.g., shape, colour, size, etc.), with the complementary visualisation of an action made with the item (e.g., visualise a ladybird and visualise it flying away). The construction phase consisted in figuring out complex scenes, bringing into play several characters and various scenarios. (Ernst et al. 2018, p. 1115).

Table 26. Studies Examining Imagery for Cognitive Impairment in Multiple Sclerosis

Author Year **Title** **Country** **Research Design** **PEDro** **Sample Size**	**Methods**	**Results**
Ernst et al. 2016 *Functional and structural cerebral changes in key brain regions after a facilitation programme for episodic future thought in relapsing-remitting multiple sclerosis patients* France **RCT** PEDro=7 $N_{Initial}$=17, N_{Final}=17	**Population**: *Intervention group (n=10):* Mean age=38.40yr; Gender: males=4, females=6; Disease course: RRMS=10; Mean EDSS=2.45; Mean disease duration=11.10yr. *Control group (n=7):* Mean age=34.71yr; Gender: males=1, females=6; Disease course: RRMS=7; Mean EDSS=1.85; Mean disease duration=8.85yr. **Intervention:** RRMS patients were randomized to receive either a mental visual imagery (MVI)-based facilitation programme (Intervention group) or a verbal control programme (Control group). Each programme was comprised of six 2-hr sessions, 1 or 2x/wk. Assessments were performed at baseline and after treatment. **Cognitive Outcome Measures:** Autobiographical Interview for Episodic Future Thought (AI-EFT): number of internal details.[3]	1. Between-group comparison showed a significant improvement in the AI-EFT: number of internal details score in the intervention group compared to the control group after treatment (p<0.001). 2. Within-group comparison showed a significant improvement in the post-treatment AI-EFT: number of internal details for the intervention group when compared to baseline (p<0.001).
Ernst 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*	**Population:** *Intervention (n=17):* Mean age=42yr; Gender: males=4, females=13; Disease course: RRMS=17; Mean EDSS=2.68; Mean disease duration=10.97yr. *Verbal control (n=10):* Mean age=37.4yr; Gender: males=1, females=9; Disease course: RRMS=10; Mean EDSS=2.45; Mean disease duration=10.60yr. *Stability control (n=13):* Mean age=40yr; Gender: males=4, females=9; Disease course: RRMS=13; Mean EDSS=2.77; Mean disease duration=11.85yr. **Intervention:** RRMS patients were randomized to three groups: the mental visual imagery	1. Between group comparison showed a significant improvement on AM and EFT mean total scores after treatment for the intervention group compared to the verbal group (p=0.001) and stability groups (p<0.001). 2. Within group comparison showed a significant improvement for the intervention and verbal control groups in AM mean total rating after treatment compared with baseline (p<0.001; p=0.03 respectively). No significant change was observed for the stability group.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
France **RCT** PEDro=7 $N_{Initial}$=40, N_{Final}=37	(MVI)-based facilitation programme, the verbal control group (sham verbal programme) or the stability group who received no intervention. The MVI programme consisted of mental visualization exercises over 6 2-hr sessions, 1 or 2x/wk. The verbal control program consisted of a narrative-oriented control programme with the same frequency and number of sessions. Assessments were conducted at baseline and 6mos after treatment. **Cognitive Outcome Measures:** Autobiographical Interview (AI); Autobiographical Memory (AM); Episodic Future Thinking (EFT) components: number of internal details recalled, number of external details recalled, mean total rating.[3]	3. No significant difference was found between the verbal control and the stability group in terms of mean number of internal details remembered post-treatment in the EFT condition. 4. Within-group comparison showed the stability group had no significant change in AM or EFT scores. 5. No significant changes in number of details remembered (internal or external) was observed within the verbal control group.
Ernst et al. 2018 *Benefits from an autobiographical memory facilitation programme in relapsing-remitting multiple sclerosis patients: a clinical and neuroimaging study* France **RCT** PEDro=6 $N_{Initial}$=20, N_{Final}=20	**Population**: *Intervention group (n=10):* Mean age=38.40yr; Gender: males=4, females=6; Disease course: RRMS; Mean EDSS=2.45; Mean disease duration=11.10yr. *Control group (n=10):* Mean age=37.4yr; Gender: males=1, females=9; Disease course: RRMS; Mean EDSS=2.45; Mean disease duration=10.60yr. **Intervention**: RRMS patients were randomized to receive either a Mental Visual Imagery (MVI)-based facilitation program (Intervention Group) or a verbal control program (Control Group). Each programme was comprised of six 2-hr sessions, 1 or 2x/wk. Cognitive outcomes and fMRI assessments were performed at baseline and after treatment. **Cognitive Outcome Measures**: Autobiographical Interview (AI).[3]	1. Between-group comparison showed a significant improvement in the number of internal details recalled during the AI for the intervention group compared to the control group (p<0.03) compared to baseline. 2. Within-group comparisons showed a significant increase in the number of internal details recalled by the intervention group (p<0.001) but not the control group (p=0.29) compared to baseline. 3. A significant positive correlation between improvement in AI score and increased grey matter volume in the left parahippocampal gyrus was observed for the intervention group (r=0.968) but not the control group (r=0.155). 4. Results from fMRI neuroimaging showed significant changes in neural activity, functional connectivity, and grey matter volume.
Ernst et al. 2013 *Autobiographical memory in multiple sclerosis patients: assessment and cognitive facilitation* France **PCT with Pre-Post** $N_{Initial}$=60, N_{Final}=60	**Population:** *Intervention (MS) group (n=25):* Mean age=42.96yr; Gender: males=4, females=21; Disease course: RRMS=100%; Mean EDSS=1.77; Mean disease duration=8.85yr. *Healthy control (HC) group (n=35)*: Mean age=42.17yr; Gender: males=6, females=29. **Intervention:** The MS participants were assessed for cognitive functioning and impairment in autobiographical memory (AbM). Of the 25 participants, 10 were included in a mental visual imagery (MVI) subgroup that was constructed to alleviate	1. There was a significant improvement in the MCT global scores in the MS group from pre-treatment to post-treatment (p<0.001). 2. MS patients had significantly poorer MCT scores than healthy controls pre-treatment (p<0.001), but post-treatment had similar scores to healthy controls (p=0.436). 3. The MS group revealed significantly lower scores for the 0-9 and 10-19yr compared to the 20-Current life period (p< 0.001).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	AbM retrieval difficulties. The control group was also assessed on AbM performance, and 10 of the 35 participants were included in the facilitation group which also underwent assessment twice within a month interval between the two sessions. **Cognitive Outcome Measures:** Cue-word Modified Crovitz test (MCT); Autobiographical Memory Interview (AMI).[3]	4. AMI personal semantics scores were not found to differ significantly between the MS group and the control group.
Ernst et al. 2012 *Induced brain plasticity after a facilitation programme for autobiographical memory in multiple sclerosis: a preliminary study* France **Pre-Post** $N_{Initial}$=23, N_{Final}=23	**Population:** *MS experimental group (n=4):* Mean age=37.25yr; Gender: males=1, females=3; Disease course: RRMS=4; Median EDSS=1.5; Mean disease duration=15yr. *MS control group (n=4):* Mean age=39.75yr; Gender: males=2, females=2; Disease course: RRMS=4; Median EDSS=2.5; Mean disease duration=13.5yr. *Healthy controls (n=15):* Mean age: unspecified; Gender: unspecified. **Intervention:** RRMS patients received the Autobiographical Memory Facilitation Programme cognitive-based training using mental visual imagery (MVI). The programme consisted of 2-hr sessions/wk for at least 6wks. Assessments were performed at baseline and 2mos later. **Cognitive Outcome Measures:** Autobiographical Interview (AI) memory assessment: free recall (mean number of internal details, mean total rating), specific probes (mean number of internal details, mean total rating).[3]	1. The experimental group showed a significant improvement compared with the MS control group for the AI free recall phase (mean number of internal detail: p=0.02; mean total rating: p=0.02). 2. The experimental group showed a significant difference compared with the MS control group for the AI specific probe phase (mean number of internal detail: p=0.02; mean total rating: p=0.00). 3. The experimental group showed a significant increase for the AI specific probe phase (mean number of internal detail: p=0.02; mean total rating: p=0.00) following treatment. 4. The experimental group showed a significant increase for the AI free recall phase (mean number of internal detail: p=0.02; mean total rating: p=0.00) following treatment. 5. The MS control group showed no significant improvement in either of the AI free recall or specific probe phases.

[3]Outcome Measure Not Specified

Table 27. Summary Table of Studies Examining Imagery

	Memory
Improve	• **Ernst et al. 2018** • **Ernst et al. 2016** • **Ernst et al. 2015** • Ernst et al. 2013 • Ernst et al. 2012
No statistical sig. difference	

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6
italics	Non-RCT

Discussion

Three RCTs and two pre-post studies, all by the same lead author, investigated a mental imagery learning program for improving memory. The chosen outcome in these studies is the Autobiographical interview memory assessment for which higher scores where consistently achieved in the intervention groups. To score the Autobiographical Interview, the researcher conducts an interview with the participant to assess recall by counting the number of internal details recalled without probing, and with specific probes provided. The Autobiographical Interview is conducted with no time constraints on the individual. Ernst et al. do not include other cognitive outcomes; therefore, it is unclear how the imagery technique might transfer to objective memory function on other testing. However, on MRI they report a significant and large correlation between improvement on the Autobiographical Interview and increased grey matter volume in the left parahippocampal gyrus only observed in the intervention group (r=0.968) (Ernst et al. 2018), and on fMRI they report significant changes in functional connectivity (Ernst et al. 2016).

A person may engage in mental visual imagery even if not overtly instructed to do so when practising other strategies aimed to enhance cognitive functioning. Variations of different mental imaging strategies were also explicitly included in combination with other memory strategies, and objective memory outcomes improved in participants with MS (see section 3.1; (Kardiasmenos et al. 2008; Rodgers et al. 1996). In the case of the intervention described by Ernst et al., the training involved a minimum of six sessions lasting two hours led by experts in the field, specifically targeting mental visual imagery training. It remains unclear which strategies can be most efficiently and feasibly applied in PwMS to improve objective cognitive function relevant to everyday life. Ernst et al. propose that the Autobiographical Interview provides an objective assessment of memory function in everyday life, and scores improve after mental imagery training.

Conclusion

There is level 1a evidence that mental visual imagery training improves memory on an autobiographical memory interview assessment compared to sham verbal training or no intervention in relapsing-remitting MS. Other objective memory and cognitive outcomes are not reported (three randomized controlled trials and two pre-post studies; Ernst et al. 2018, Ernst et al. 2016, Ernst et al. 2015, Ernst et al. 2013, and Ernst et al. 2012).

Mental visual imagery training may improve memory in persons with relapsing-remitting MS on an autobiographical memory interview assessment; other objective memory and cognitive outcomes are not reported.

3.14 Mindfulness

Mindfulness-based interventions (MBIs) derive from ancient meditation techniques, secularized and manualized for use in healthcare (Kabat-Zinn 1990). The index MBI is mindfulness-based stress reduction (MBSR), originally designed to help people with long-term conditions cope with chronic pain and stress (Kabat-Zinn 1982). A derivative, mindfulness-based cognitive therapy (MBCT) was specifically developed as a preventative treatment for recurrent depression (Segal, Williams, and Teasdale 2002). Both MBSR and MBCT have high-quality meta-analytic evidence for effectiveness, mainly in the treatment of anxiety and recurrent depression (Fjorback et al. 2011) and also somatization (Lakhan and Schofield 2013). In non-MS populations, meta-analyses support improvements in working memory, autobiographical memory, cognitive flexibility, and meta-awareness (Lao, Kissane, and Meadows 2016). How MBIs work is incompletely understood; in systematic reviews and meta-analyses, MBI practice in general populations is associated with complex patterns of functional and structural plasticity (Young et al. 2018), improvements in stress biomarkers (Pascoe et al. 2017), immune profile, and cellular aging (Black and Slavich 2016). Mediators of improvements in anxiety and depression appear to derive from enhanced mindfulness, cognitive and emotional regulation (Gu et al. 2015), and greater amount of home practice (Parsons et al. 2017). In PwMS, meta-analyses of RCTs confirm MBI effectiveness in treating symptoms of stress, anxiety, depression (Robert Simpson et al. 2019), and fatigue (Robert Simpson et al. 2020), all of which are common factors known to confound assessment of cognition in this population (Nancy D Chiaravalloti and DeLuca 2008).

Table 28. Studies Examining Mindfulness for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	**Methods**	**Results**
Senders et al. 2019 *Impact of mindfulness-based stress reduction for people with multiple sclerosis at 8 weeks and 12 months: A randomized clinical trial* USA **RCT** PEDro=8 $N_{Initial}$=67, N_{Final}=62	**Population:** *Intervention group (n=33):* Mean age=53.24yr; Sex: males=5, females=28; Disease course: RRMS=24, PPMS=2, SPMS=7; Mean EDSS=4.48; Mean disease duration=14.61yr. *Control group (n=29)*: Mean age=52.59yr; Sex: males=9, females=20; Disease course: RRMS=17, PPMS=2, SPMS=8, Unknown=2; Mean/Median EDSS=4.72; Mean disease duration=17.93yr. **Intervention:** Following randomization, both groups received 8 weekly, 2-hr classes and a 6-hr retreat at wk 6. MBSR group followed Kabat-Zinn protocol and were taught to bring mindfulness into their day through meditation, movement, eating, and interpersonal interactions. Gentle yoga, breath work and body scans were taught to facilitate mindfulness. MBSR participants were encouraged to practice for 45mins daily. The comparator education group classes focused on National MS Society pamphlets covering a variety of topics including medications, supplements, fatigue, pain, etc. Outcome measures were collected at baseline, 4wks, immediately post intervention, and at 4, 8, and 12mos post intervention. **Cognitive Outcome Measures:** Paced Auditory Serial Addition Test (PASAT)[2].	1. There were no significant between-group differences on the PASAT immediately post intervention (d=0.03, p=0.59) and at 12mos (d=0.12, p=0.59). 2. Both groups improved in PASAT scores immediately post intervention compared to baseline (MBSR group d=0.56, CI 95% 0.15, 0.96; control group d=0.44, CI 95% 0.04, 0.83), but this was not maintained at 12mos.
Manglani et al. 2020	**Population:** *Adaptive Cognitive Training (aCT) (n=20):* Mean age=44.8yr; Sex: males=4, females=16; Disease course: unspecified;	1. Between groups, there was a significant improvement in processing speed (SDMT) in the MBT group compared to aCT and

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Effects of 4-Week Mindfulness Training Versus Adaptive Cognitive Training on Processing Speed and Working Memory in Multiple Sclerosis USA **RCT** PEDro=6 $N_{Initial}$=135, N_{Final}=61	Mean/Median EDSS=4.40; Mean disease duration=12.3yr. *Mindfulness-Based Training (MBT) (n=20):* Mean age=46.5yr; Sex: males=4, females=16; Disease course: unspecified; Mean EDSS=4.63; Mean disease duration=10.1yr. *Waitlist Control (n=21):* Mean age=46.0yr; Sex: males=6, females=15; Disease course: unspecified; Mean EDSS=4.02; Mean disease duration=11.3yr. **Intervention:** MBT and aCT groups attended weekly 2-hr training sessions for 4wks. The adaptive cognitive training focused on attention, information processing speed, executive function, and working memory. It was supervised and included instruction and group discussions. Training occurred using computer games on the Poist Science BrainHQ website. The MBT group was modeled after the Mindfulness Based Stress Reduction Program. This program aims to develop breath and body awareness and meditation practices that develop sustained attention. This was supplemented by 40-min sessions at home practiced for the other 6d of the week. Outcome measures were collected at baseline and following the intervention. **Cognitive Outcome Measures:** Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (10/36 Spatial Recall Test (10/36; 10/36-SPART; SPART), Word List Generation Test (WLGT); Selective Reminding Test (SRT); Symbol Digit Modalities Test (SDMT)[1]; Paced Auditory Serial Addition Test (PASAT))[1].	control groups ($F(2, 48.3)=3.98$, $p=0.025$, $\eta_p^2=0.14$) 2. No other between-group differences on any other cognitive outcome measures.
De la Torre et al. 2020 *Neurocognitive and emotional status after one year of mindfulness-based intervention in patients with relapsing-remitting multiple sclerosis* Spain **RCT** PEDro=4 $N_{Initial}$=60, N_{Final}=60	**Population:** *Intervention (n=30)***:** Mean age=44.3yr; Sex: males=8, females=22; Disease course: RRMS; Severity: unspecified; Disease duration: unspecified. *Control (n=30):* Mean age=48.8yr; Sex: males=12, females=18; Disease course: RRMS; Severity: unspecified; Disease duration: unspecified. **Intervention:** The intervention group received 8wks of Mindfulness-Based Cognitive Therapy for Depression, a modified MBSR program. MBSR consisted of weekly in-person sessions and daily at-home practice. Control group did not receive the MBSR but continued pharmacological treatment. Both groups completed outcome measures prior to commencement of the study and 1yr later.	1. Significant improvement pre-post in the intervention group on the WATT (p=<0.001), WLT (p=<0.001), SDMT (p=<0.001), COWAT (p=<0.001) and PASAT-3 (p=<0.001). 2. Significant improvements in the control group pre-post on the WATT (p=0.001). 3. No clear between-group difference comparisons provided. 4. Participants in the study did not have serious cognitive deterioration.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	Cognitive Outcome Measures: Wechsler Memory Scale-III (WMS-III) including 6 subtests: Wechsler Attention (WATT), Wechsler Long Term Memory (WLT), Wechsler Short Term Memory (WST), Wechsler Recognition (WREC), Wechsler Learning (WLEARN), Wechsler Animals (ANIM); Symbol Digit Modalities Test (SDMT); Controlled Oral Word Association Test (COWAT); Paced Auditory Serial Addition Test-3 (PASAT-3)[3].	
Blankespoor et al. 2017 *The Effectiveness of Mindfulness-Based Stress Reduction on Psychological Distress and Cognitive Functioning in Patients with Multiple Sclerosis: A Pilot Study* Netherlands **Pre-Post** $N_{Initial}$=31, N_{Final}=16	**Population:** Mean age=55.19yr; Sex: males=4, females=12; Disease course: RRMS=5, PPMS=4, SPMS=7; Severity: unspecified; Disease duration: unspecified. **Intervention:** Group mindfulness training program lasting 8wks with 2.5-hr sessions 1x/wk consisting of meditation practice, didactic teaching, and experience sharing. This also included a 6-hr silence day and take-home exercises. Outcome measures were collected 1wk prior to intervention and 2wks following the end of the intervention. **Cognitive Outcome Measures:** Multifactorial Meta Memory Questionnaire (MMQ)[1]; Rey Auditory Verbal Learning Test (RAVLT)[1]; Location Learning Task (LLT)[1]; Paced Auditory Serial Addition Test (PASAT)[1]; Wechsler Adult Intelligence Scale-III (WAIS-III): Digit Span, Letter-number sequencing test.[1]	1. There were non-significant changes pre-post for all cognitive outcomes except for a significant improvement on the LLT (p=0.042, d=0.45; CI 95% 0.65, 3.11). 2. At baseline, the study sample was not considered cognitively impaired compared to standardized population means.

[1]Primary Outcome Measure; [2]Secondary Outcome Measure; [3]Outcome Measure Not Specified

Table 29. Summary Table of Studies Examining Mindfulness

	Attention	Executive Function	Info Processing speed	Memory	Verbal skills
Improve	• De la Torre et al. 2020[W] (WATT)		• **Manglani et al. 2020** (SDMT) • De la Torre et al. 2020[W] (PASAT)	• De la Torre et al. 2020[W] (WLT) • *Blankespoor et al. 2017* (LLT)	• De la Torre et al. 2020[W] (COWAT)
No statistical sig. difference		• *Blankespoor et al. 2017* (WAIS-III Letter number sequencing)	• **Manglani et al. 2020** (PASAT) • **Senders et al. 2018** (PASAT) • *Blankespoor et al. 2017* (PASAT)	• **Manglani et al. 2020** (WLG, SPART, SRT) • *Blankespoor et al. 2017* (RAVLT, WAIS-III - Digit Span)	

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT
W	RCT reporting within group (pre-post) results

Discussion

Four studies of variable quality met the inclusion criteria for mindfulness interventions. Objective cognitive improvements were found in the cognitive domains of attention (De la Torre et al. 2020) and visual information processing (Manglani et al. 2020). In non- MS populations, adherence with mindfulness treatment is less than optimal (~60%) (Robert Simpson et al. 2019), which may also be a limitation of the research in MS populations. Manglani et. al (2020) reported positive results on the Symbol Digit Modalities Test after only four weeks of a mindfulness-based intervention; however, a significant portion of the sample was not included in the final analysis. De la Torre et al. (2020) reported improved attention at the one-year follow-up in the mindfulness intervention group receiving 8 weeks of treatment. While the follow-up was complete and prolonged in comparison to other studies, a limitation is that the authors do not provide an analysis in comparison to the control group. This study therefore provides only lower quality pre-post results. When considering acceptability, accessibility, and implementation of mindfulness-based interventions, teachers appear to have a key role in helping PwMS make sense of the practices. Similarly, flexible group programming, either face-to-face or live online, with content tailored for enhanced relevance toward common MS symptoms and shortened meditation practices seem best suited to this population. Steps to improve adherence include recommendation by an MS clinician and email reminders. Post-course booster sessions may be necessary to sustain beneficial effects in the long term (Robert Simpson et al. 2021). Studies including only self-reported cognitive outcomes did not meet the inclusion criteria for this module (Hoogerwerf et al. 2017; R. Simpson, Mair, and Mercer 2017). Self-reported improvements in cognitive functioning are importantly positive findings associated with mindfulness-based interventions.

Conclusion

There is level 1a evidence that mindfulness-based cognitive therapies may not improve auditory information processing speed (two randomized controlled trials and one pre-post study; Manglani et al. 2020, Senders et al. 2018, and Blankespoor et al. 2017).

There is level 1b evidence that mindfulness-based cognitive therapies may improve visual information processing speed in persons with MS (one random trial; Manglani et al., 2020).

There is conflicting evidence whether mindfulness-based cognitive therapies improve memory in persons with MS (two randomized controlled trials and one pre-post study; Blankespoor et al. 2017, De la Torre et al. 2020, and Manglani et al. 2020).

There is level 2 evidence that mindfulness-based cognitive therapies may improve attention and verbal skills in relapsing-remitting MS (one randomized controlled trial reporting pre-post results; De la Torre et al. 2020).

There is level 4 evidence that mindfulness-based cognitive therapies may not improve executive function (one pre-post study; Blankespoor et al. 2017).

Preliminary evidence supports that mindfulness-based cognitive therapies may improve attention and verbal skills in persons with MS.

There is conflicting evidence whether mindfulness-based cognitive therapies improve memory in persons with MS.

Mindfulness-based cognitive therapies do not improve auditory processing speed but may improve visual processing speed in persons with MS.

Preliminary evidence suggests that mindfulness-based cognitive therapies may not improve executive function in persons with MS.

3.15 Meditation

Meditation is an umbrella term frequently used to describe a wide-ranging set of mental training techniques with varying purposes, which are commonly used to cultivate specific states of consciousness (e.g., equanimity), or compassion (Nash and Newberg 2013). Theorists separate meditation into two broad categories: focused attention and open monitoring. Meditation practices can be internally focused, externally focused, or both. Perhaps unsurprisingly, diverse meditation practices are associated with different neural activation patterns (Tomasino, Chiesa, and Fabbro 2014) and training is associated with functional and structural neuroplasticity (Fox et al. 2016) in key neural networks associated with the regulation of attention and emotion. Physical, psychological, and emotional effects differ too, though common outcome measures feature repeatedly across diverse meditation styles, such as effects on stress, anxiety, and depression (Sedlmeier et al. 2012). Meditation effects on cognitive functioning have also been investigated in PwMS.

Table 30. Studies Examining Meditation for Cognitive Impairment in Multiple Sclerosis

Author Year **Title** **Country** **Research Design** **PEDro** **Sample Size**	**Methods**	**Results**
Bhargav et al. 2016 *Immediate effect of two yoga-based relaxation techniques on cognitive*	**Population:** Age range=20-65yr; Sex: males=5, females=13; Disease course: RRMS; Mean/Median EDSS=≤ 6.5; Mean disease duration=18.16yr. **Intervention:** The intervention group received the cyclic meditation and was compared to the control group receiving supine rest	1. Between-group comparisons showed significant improvement in the cyclic meditation group on TMT-A scores (p=<0.01) and forward digit span of the WMS-R (p=<0.01). 2. In the cyclic meditation group, there were pre-post improvements on the TMT-A (ES= 0.47, p=<0.001), TMT-B (ES= 0.21,

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
functions in patients suffering from relapsing remitting multiple sclerosis: A comparative study Germany **Crossover RCT** PEDro=4 $N_{Initial}$=27, N_{Final}=18	(shavasana). Assessment was performed before and immediately after a 30-min session. **Cognitive Outcome Measures:** Trail making Test A and B (TMT-A and B)[1]; Digit Symbol Substitution Test (DSST); Auditory Verbal Learning Test (AVLT)[2]; Wechsler Memory Scale-Revised (WMS-R)[2].	p=0.009), DSST correct (ES=0.20, p=<0.001), forward digit span of WMS-R (ES= 0.42, p=<0.05), and AVLT trials 1-4 with List B scores (ES≤0.83, p=<0.05). 3. In the active supine rest control group, there were pre-post improvements on DSST total score (d=0.2, p=<0.001), and AVLT trials 1-5, immediate and delayed recall (d≤1.26, p=<0.05).
Anagnostouli et al. 2019 *A novel cognitive-behavioral stress management method for multiple sclerosis. A brief report of an observational study* Greece **PCT** $N_{Initial}$=148, N_{Final}=128	**Population:** *Intervention group (n=86)*: Mean age=44.3yr; Sex: males=21, females=65; RRMS=80, unspecified=6; Mean EDSS=2.9; Mean disease duration=11.4yr. *Control group (n=62)*: Mean age=42.8yr; Sex: males=17, females=45; Disease course: RRMS; Mean EDSS=2.7; Mean disease duration=9.8yr. **Intervention:** Pythagorean self-awareness intervention (PSAI) was taught by health professionals during 1-hr weekly sessions. Participants diarized 2x/d PSAI practice. The practice included reflection on diet, physical exercise, sleep, interpersonal contacts, and goal setting for the next day. Participants who declined the PSAI intervention comprised the standard care control group. Outcome measures were collected at baseline and at 8-wk follow-up. **Cognitive Outcome Measures:** Brief International Cognitive Assessment for Multiple Sclerosis (BiCAMS) (Symbol Digit Modalities Test (SDMT); Brief Visuospatial Memory Test-Revised (BVMT-R); California Verbal Learning Test II (CVLT-II))[3].	1. Statistically significant improvements occurred in the PSAI group compared to the control group for cognitive processing speed (SDMT) (Number-needed-to-treat=10) and with verbal memory (CVLT-II) (Number-needed-to-treat=21). 2. Participants in the PSAI were more likely to have higher levels of tertiary education, longer disease duration, higher baseline cognitive score, and psychological distress. 3. To account for the non-randomized design, a propensity scoring approach and logistic regression was used to compare between-group differences (PSAI vs. Control). The regression model included education, duration of disease, composite cognitive score, and psychological distress. 4. Numbers-needed-to-treat were calculated using a clinically meaningful change of 1.65 SD.

[1]Primary Outcome Measure; [2]Secondary Outcome Measure; [3]Outcome Measure Not Specified

Table 31. Summary Table of Studies Examining Meditation

	Executive Function	Information Processing Speed	Memory
Improve	• Bhargav et al. 2016[W] (TMT-B)	• Bhargav et al. 2016 (TMT-A) • Anagnostouli et al. 2019 (SDMT)	• Bhargav et al. 2016 (Forward Digit Span) • Anagnostouli et al. 2019 (CVLT)
No statistical sig. difference	• Bhargav et al. 2016 (TMT-B)	• Bhargav et al. 2016 (Digit Symbol Substitution Test)	• Bhargav et al. 2016 (AVLT, Backwards Digit Span) • Anagnostouli et al. 2019 (BVMT)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT

italics	Non-RCT
W	RCT with within group comparison only

Discussion

Mind-body medicine (Senders et al. 2012), meditation specifically, is widely used by PwMS (O'Donnell et al. 2020). In cross-sectional surveys (Levin, Hadgkiss, Weiland, Marck, et al. 2014), better quality of life and lower scores for depressive symptoms are reported. Which meditation style is best for PwMS remains unclear (Levin et al. 2014), given the heterogeneity between interventions. Mindfulness-based interventions have the strongest evidence of benefit, and in PwMS can help with stress, anxiety, depression (Simpson et al. 2019), and fatigue (Simpson et al. 2020). In older adults without MS, differences in how meditation programmes are delivered makes interpretation of results challenging, but in general, dose appears to moderate beneficial outcomes, with threshold parameters for frequency and duration reported in meta-analysis (Chan et al. 2019). Also in meta-analysis, among primary care populations, meditation practice is associated with improvements in stress, anxiety, depression, and pain, where the most robust effects are derived from Mindfulness-based interventions (Goyal et al. 2014).

The two studies (Bhargav et al. 2016; Anagnostouli et al. 2019) describing meditation interventions in PwMS and reporting objective cognitive outcomes are both low quality studies. Each study applied different meditation interventions, enrolling participants with relapsing-remitting MS. While both studies report improved processing speed on at least one processing speed outcome, it is unclear how changes in mood or fatigue may have contributed to these findings. The threshold intensity of meditation practice required to observe benefit is unclear. The study by Bhargav et al. (2016) involved an active control group where participants practiced the Shavasana position. The control group also improved pre-post after Shavasana on two of the cognitive outcomes, although greater improvements for other outcomes were observed in the intervention group.

Conclusion

There is level 2 evidence that meditation may not improve executive function in persons with relapsing-remitting MS (one randomized controlled trial; Bhargav et al., 2016).

There is level 2 evidence that meditation may improve information processing speed in persons with relapsing-remitting MS (one randomized controlled trial and one prospective controlled trial; Bhargav et al., 2016, Anagnostouli et al., 2019).

There is conflicting evidence whether meditation may improve memory in persons with relapsing-remitting MS (one randomized controlled trial and one prospective controlled trial; Bhargav et al., 2016, Anagnostouli et al., 2019).

Preliminary evidence supports that meditation may improve information processing speed in persons with relapsing-remitting MS.

There is conflicting evidence whether meditation improves memory in persons with relapsing-remitting MS.

3.16 Psychotherapy

Psychotherapy involves a variety of approaches which focus on understanding and identifying emotions important to psychological health and well-being. Psychotherapy and behavioural techniques are common approaches for the management of mood disorders in the general population as well as PwMS. These approaches have also been studied as potential interventions for CI in PwMS.

Table 32. Studies Examining Psychotherapy for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	**Methods**	**Results**
Abdolghaderi et al. 2019 *Comparing the Effect of Positive Psychotherapy and Dialectical Behavior Therapy on Memory and Attention in Multiple Sclerosis Patients* Iran **RCT** PEDro=5 $N_{Initial}$=45, N_{Final}=40	**Population:** *Dialectical Behaviour Therapy (DBT) Group:* Mean age=35.17yr. *Cognitive Behavioural Therapy (CBT) Group*: Mean age=36.58yr. *Control:* Mean age=34.75yr. No further information provided. **Intervention:** Intervention groups completed 8 weekly individual sessions. The DBT group received "acceptance and patient-centered empathy with cognitive behavioural problem-solving and training of social skills" (Abdolghaderi et al. 2019, p. 3). The CBT group focused on accepting weaknesses and modifying thought processes. The control group received no intervention. Outcome measures were collected at baseline and following the interventions. **Cognitive Outcome Measures:** Wechsler Memory Scale (WMS); Stroop Attention Scale (SAS)[3]	1. There was a significant improvement in memory in both experimental groups compared to the control group (f=6.48, p=<0.05). 2. Post intervention, memory improved in the DBT and CBT groups (p=<0.001) compared to baseline. There were no significant differences in the memory improvements between these two groups. 3. There were no between-group or within-group improvements for attention.
Bilgi et al. 2015 *Evaluation of the effects of group psychotherapy on cognitive function in patients with multiple sclerosis with cognitive dysfunction and depression*	**Population:** *MS patients receiving psychotherapy (n=15):* Mean age=41.67yr; Gender: males=3, females=12; Disease course: Unspecified; Mean EDSS=2.90; Mean disease duration=8.60yr. **Intervention:** MS patients with both depression and CI received six 45-min sessions of group psychotherapy 2x/mo for 3mos. CI was defined as scores lower than the normative 5th percentile on at least two of the BRB tests. Psychotherapy focused on consciousness-raising, coping strategies,	1. A significant improvement was measured in the PASAT score of patients who received psychotherapy compared to baseline (pre:24.00, post:50.20, p<0.05). No differences for the other cognitive outcomes reached significance. 2. A significant improvement on the BDI occurred compared to baseline (pre:25.2, post:19.60, p<0.05).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Turkey **Pre-Post** $N_{Initial}$=108, N_{Final}=108	empathy for self and others, depression management skills, cognitive exercises to be performed at home, and hopefulness. Assessments were performed at baseline and after 3mos of therapy. **Cognitive Outcome Measures:** Brief Repeatable Battery of Neuropsychological Tests (BRB) (10-36 Spatial Recall Test (SPART 10/36); Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT); Word List Generation Test (WLGT); Selective Reminding Test: total learning, delayed recall (SRT)); Beck Depression Index (BDI)[3]	

[3]Outcome Measure Not Specified

Table 33. Summary Table of Studies Examining Psychotherapy

	Attention	Information Processing Speed	Memory
Improve		• *Bilgi et al. 2015* (PASAT)	• Abdolghaddri et al. 2019 (WMS)
No statistical sig. difference	• Abdolghaddri et al. 2019 (STROOP)	• *Bilgi et al. 2015* (SDMT)	• *Bilgi et al. 2015* (WLG, SRT, SPART)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

Psychotherapy comprises a diverse array of interventions designed to alleviate mental distress through dialogue between patients and therapists (American Psychiatric Association, n.d.). Various types of psychotherapy have been developed, including psychoanalysis, psychodynamic therapy, cognitive behavioural therapy, dialectical behaviour therapy, interpersonal therapy, and supportive therapy. Psychotherapy can be delivered on a one-to-one basis, or in a group setting. Across different types of psychotherapy, many elements are shared such as a focus on describing thought content and emotional experience and therapeutic emphasis placed on relaxation. Furthermore, 'common factors' influence treatment outcomes, such as expectancy, goal consensus and collaboration, therapist empathy and authenticity, therapeutic alliance, positive regard, social desirability, and group effects (Wampold 2015). Factors specific to individual therapies also influence treatment outcomes, such as specific 'ingredients,' duration, intensity, and protocol adherence.

In terms of impact on cognitive functioning, psychotherapy is consistently associated with functional and structural plasticity in domains relating to cognitive and emotional re-appraisal (Weingarten and Strauman 2015). Such findings have been observed with dialectical behaviour therapy in people with borderline personality disorder (Schnell and Herpertz 2007). Cognitive behavioural therapy has well-described beneficial effects among PwMS, including improving symptoms of depression (Fiest et al. 2016), stress (Reynard, Sullivan, and Rae-Grant 2014), and fatigue (Phyo et al. 2018). Cognitive behavioural therapy may also have favourable effects on neuro-inflammation in PwMS (Phyo et al. 2018), but this does not necessarily correlate with any beneficial effects on functional outcomes (Burns et al. 2014). All in, any beneficial effects of psychotherapy on cognitive functioning in PwMS may relate more directly to improvements in well-known moderators, such as stress, anxiety, depression, and fatigue. Two studies included psychotherapy intervention one of which was an RCT (Abdolghaddri et al. 2019). The RCT reported improvements in memory in both the cognitive behavioural intervention group and the dialectical behavioural therapy group but not in the control group. These results support that different psychotherapy approaches may be effective at improving memory. The second pre-post study that delivered non-specific psychotherapy reported an improvement in only processing speed despite the inclusion of a battery of cognitive outcome measures which included memory outcomes (Biligi et al. 2015). In the pre-post study, a significant improvement was also observed on the Beck Depression Inventory. Future studies assessing the impact of psychotherapy on cognitive functioning in PwMS will thus need to control for confounding variables such as mood in their analyses.

Conclusion

There is level 2 evidence that eight weeks of cognitive behavioural therapy or dialectical behavioural therapy may improve memory in persons with MS (one randomized controlled trial; Abdolghaddri et al. 2019).

There is level 2 evidence that eight weeks of cognitive behavioural therapy or dialectical behavioural therapy may not improve attention in persons with MS (one randomized controlled trial; Abdolghaddri et al. 2019).

There is level 4 evidence that group psychotherapy may improve auditory information processing speed but not visual information processing speed in persons with MS who have depression and CI (one pre-post trial; Bilgi et al. 2015).

Preliminary evidence supports that psychotherapy may improve memory but not attention in persons with MS.

Preliminary evidence suggests that psychotherapy may improve auditory information processing speed but not visual information processing speed in persons with MS.

3.17 Social Cognitive Theory Education

Social Cognitive Theory is an effective and widely used theory informing behavioural interventions for promoting health behavior (Bandura 2004), including increasing physical activity in people with MS (Robert W Motl, Pekmezi, and Wingo 2018). Social cognitive theory according to Bandura (2004) “posits a multifaceted causal structure in which self-efficacy beliefs operate together with goals, outcome expectations, and perceived environmental impediments and facilitators in the regulation of human motivation, behavior, and well-being" (Bandura 2004, p. 1). Cognitive rehabilitation approaches may include goal-directed recognition of environment facilitators and barriers for enhancing cognitive function (see section 3.1 Cognitive Rehabilitation, Mixed Non-computer Approaches). However, Coote et al. (2017) report on specifically an education program grounded in social cognitive theory as the independent variable.

Table 34. Studies Examining Social Cognitive Theory Education for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Coote 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* Ireland **RCT** PEDro=7 $N_{Initial}$=65, N_{Final}=54	**Population:** *Social Cognitive Theory Intervention group (n=32)*: Mean age=43.3yr; Sex: males=4, females=29; Disease course: RRMS=27, PPMS=1, Benign=3; Mean EDSS=3.3; Mean disease duration=6.7yr. *Attention Control group (n=33)*: Mean age=41.9yr; Sex: males=6, females=26; Disease course: RRMS=27, SPMS=1, Benign=1; Mean EDSS=3.3; Mean disease duration=7.0yr. **Intervention:** Participants in both groups received a 10wk exercise and education program. The exercise component included both aerobic and strength components and intensity was progressively increased to meet the exercise guidelines for PwMS. There were 6 group exercise classes and weekly telephone calls. For the Social Cognitive Theory group, the education covered topics such as self-efficacy, outcome expectations, and goal setting for health behaviour change. The Attention Control group covered topics such as diet, vitamin D, and sleep. Outcome measures were collected at baseline, post-intervention, and at 3- and 6-mo f/u. **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT)[2].	1. No statistically significant differences existed between groups on all secondary outcomes at any assessment point. 2. For within-group comparisons, at the 3-mo f/u the social cognitive theory intervention group had significant improvements in cognitive processing speed with a moderate to large effect size (mean SDMT change score 5.04, 95% CI: 2.51, 7.57, p<0.01; Hedges g=0.75, 95% CI: 0.24, 1.25). At the 6-mo f/u, processing speed was improved in the intervention compared to baseline with a non-significant, small-to-moderate effect size (mean SDMT change score 3.05, 95% CI: 0.81, 5.28, p<0.01; Hedges g=0.15).

[2]Secondary Outcome Measure

Table 35. Summary Table of Studies Examining Social Cognitive Theory Education

	Information Processing Speed
Improve	
no statistical sig. difference	• **Coote et al. 2017** (SDMT)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6
italics	Non-RCT

Discussion

One study by Coote et al. (2017) reported improvement on the Symbol Digit Modalities Test following a social cognitive theory-based educational intervention in ambulatory, previously sedentary PwMS. Coote et al. (2017) compared the effects of two different educational programs in a high-quality RCT in which both groups also received a 10-week aerobic and strength-training program. The intervention group received education grounded in social cognitive theory for behavior change whereby participants learned about goal setting, self-efficacy, outcomes, barriers, and benefits related to exercise (Coote et al. 2017, p. 3). The control group attention education program covered topics not directly related to exercise (i.e., diet, vaccinations, sleep, vitamins). Fatigue, mood, physical function, and cognitive function on the SDMT where assessed post intervention and at the 3- and 6-month follow-up as secondary outcomes. The study did not include other cognitive outcomes. Ideally, improved longer-term adherence with the minimum recommendations for exercise in the intervention group would be associated with larger and more sustained benefits compared to the control group. However, the a priori between-group analyses did not reach statistical significance for the Symbol Digit Modalities Test, or for the other secondary outcomes. Despite this, only the intervention group improved significantly on the Symbol Digit Modalities Test at three and six months compared to baseline. In addition, only the intervention group significantly improved on measures of depression and anxiety compared to baseline.

The encouraging pre-post results within the intervention group support that a social cognitive theory-based educational intervention improves processing speed, either through a direct relationship, or perhaps through indirect effects on mood. These results are clinically relevant and suggest that larger samples may be required to reach statistically significant between group findings on the Symbol Digit Modalities Test. This may be especially the case when the Symbol Digit Modalities Test scores are not impaired at baseline, and when there is an active comparator group compared to a wait list or non-active comparator group.

Within-group change scores in both groups also showed significant improvement at three and six months compared to baseline on fatigue, strength, physical activity, goal setting, and exercise planning outcomes. Reported separately, the intervention group experienced greater improvement on the six-minute walk test primary outcome compared to the control group (Hayes et al. 2017). The Coote et al. (2017) study protocol is feasible, consisting of six group-based exercise sessions followed by the educational component. Phone coaching interactions with the physical therapist also occurred four times over the 10 weeks. Social cognitive theory-based educational interventions guided by physiotherapist-supported exercise show promise for realizing possible benefits on processing speed.

Conclusion

There is level 1b evidence that social cognitive education combined with aerobic and strength exercise may not improve information processing more than attention control education combined with aerobic and strength exercise (one randomized controlled trial; Coote et al. 2017).

There is level 2 evidence that social cognitive education combined with aerobic and strength exercise may improve information processing speed (within-group pre-post results from one randomized controlled trial; Coote et al. 2017).

Social Cognitive Education combined with exercise may improve information processing speed, but not more than Attention Control Education combined with exercise.

3.18 Music Therapy

Music therapy is defined by the Canadian Association of Music Therapists (2020) as "[using] music purposefully within therapeutic relationships to support development, health, and well-being" (Canadian Association of Music Therapy 2020, para.1). Some studies attribute the beneficial effects of music therapy to changes in neural activation and neuroplasticity (Sihvonen et al. 2017; François et al. 2015; Thaut et al. 2014; Altenmüller et al. 2009). A systematic review reported on a wide spectrum of music-based therapies, but only a few have been explored in MS (Vinciguerra, De Stefano, and Federico 2019).

Table 36. Studies Examining Music Therapy for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Impellizzeri et al. 2020 ***An integrative cognitive rehabilitation using neurologic music therapy in multiple sclerosis: A pilot study*** **Italy** **RCT** **PEDro=7** **$N_{Initial}$=30, N_{Final}=30**	**Population:** *Intervention group (n=15)*: Mean age=51.73yr; Sex: males=9, females=6; Disease course: RRMS=8, PPMS=3, SPMS=4; Mean/Median EDSS=5; Mean disease duration=9yr. *Control group (n=15)*: Mean age=51.33yr; Sex: males=10, females=5; Disease course: RRMS=7, PPMS=4, SPMS=4; Mean/Median EDSS=4.5; Mean disease duration=10yr. **Intervention:** Following randomization, each group underwent an 8-wk rehabilitation program with 6 sessions/wk. The control group received conventional cognitive rehab (CCR) for all sessions, while the intervention group received 3 sessions of CCR and 3 sessions of neurologic music therapy (NMT)/wk. NMT techniques included Associative Mood and Memory Training and Music in Psychosocial Training and Counselling. Each session lasted 60mins. Outcome measures were collected at baseline and following the intervention. **Cognitive Outcome Measures:** Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (10/36 Spatial Recall Test (10/36; 10/36-SPART; SPART); Word List Generation Test (WLGT); Selective Reminding Test (SRT); Symbol Digit Modalities Test (SDMT))[1].	1. Between-group comparison revealed statistically significant improvements in favor of the intervention group on the SRT in long-term storage (p<0.000) and long-term retrieval (p=0.007), and delayed recall of the 10/36-SPART (p=0.001) subscales of the BRB-N.

[1]Primary Outcome Measure

Table 37. Summary Table of Studies Examining Music Therapy

	Memory
Improve	• **Impellizzeri et al. (2020)**
No statistical sig. difference	

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

This small, randomized controlled trial provides preliminary level 1b evidence that neurologic music therapy may be superior to conventional cognitive rehabilitation for people with multiple sclerosis in terms of memory, mood, and quality of life. A power calculation is not provided, and between-group differences were positive on only two of the outcomes whithin the Brief Repeatable Battery of Neuropsychological Tests. The intervention componentry in this trial goes beyond the simple addition of music, for example involving discussions guided by a therapist about feelings in response to music. Furthermore, the lack of reporting on effect sizes limits interpretation of the findings and clinical significance is unclear.

Music therapy has considerable evidence for benefit in the realm of mental health disorders (Gold et al. 2009), as well as in other acquired brain injury populations, about which a Cochrane Review in 2017 reported improvements in communication, upper limb function, gait, and quality of life (Magee et al. 2017). How music therapy works is largely unknown, though 'dose' appears to be important (Gold et al. 2009). Qualitative evidence synthesis suggests a combination of group and specific effects are at play, depending on delivery method (Solli, Rolvsjord, and Borg 2013). It should also be noted that music therapy can have adverse effects, such as an unpleasant emotional experience (Moore 2013), and for people with physical disabilities, additional steps may be required to facilitate participation (Frid 2019).

Conclusion

There is level 1b evidence that neurologic music therapy combined with cognitive rehabilitation may improve memory more than conventional cognitive rehabilitation (one randomized controlled trial; Impellizzeri et al. 2020).

Music therapy may be beneficial for improving memory in persons with MS.

3.19 Music Mnemonic

In this section, music provides a mnemonic strategy to help organize and structure information so that it might be more easily recalled (Moore et al. 2008).

Table 38. Studies Examining Music Mnemonics for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Thaut et al. 2014 *Music mnemonics aid verbal memory and induce learning - related brain plasticity in multiple sclerosis* USA **RCT** PEDro=5 $N_{Initial}$=54, N_{Final}=54	**Population:** *Total population (n=54):* Mean age=50.3yr; Gender: males=16, females=38. *Spoken group:* Mean age=53.3yr; Gender: unspecified; Disease course: RRMS; Mean EDSS=4.3; Disease duration: Unspecified. *Sung group:* Mean age=50.3yr; Gender: unspecified; Disease course: RRMS; Mean EDSS=4.9; Disease duration: Unspecified. **Intervention**: MS participants were randomized into two groups, a spoken or sung presentation of Rey's Auditory Verbal Learning Test. Assessments were performed without further presentation of the original word list (M1) after subjects heard and free-recalled a distractor list and after a 20-min non-verbal distractor task (M2). **Cognitive Outcome Measures:** Rey's Auditory Verbal Learning Test (RAVLT)[1]	1. Between-group comparison showed a significant improvement in mean percentage of recalled words for the sung group vs. spoken group (76% vs 64.7%, respectively, significance not provided). 2. A significant improvement in pair-wise word order recall was observed in the sung group relative to the spoken group after the last learning trial and at M1 and M2 ($F(1,2)=4.51$, $p=0.038$).
Moore et al. 2008 *The effectiveness of music as a mnemonic device on recognition memory for people with multiple sclerosis* USA **RCT** PEDro=4 $N_{Initial}$=38, N_{Final}=38	**Population:** *Music group (n=20):* Mean age=50.25yr; Gender: males=4, females=16; Disease course: CPMS=7, chronic stable MS=11; Mean EDSS=4.88; Disease duration: unspecified. *Spoken group (n=18):* Mean age=53.33yr; Gender: males=4, females=14; Disease course: CPMS=4, chronic stable MS=14; Mean EDSS=4.33; Disease duration: unspecified. **Intervention:** MS patients were evaluated on a recognition memory task after randomization to two learning conditions: learning through music or speech. Assessments were performed at baseline and after treatment. **Cognitive Outcome Measures:** Rey Auditory-Verbal Learning Test (RAVLT)[1]	1. No significant differences were found between the two groups on the RAVLT subscales.

[1]Primary Outcome Measure

Table 39. Summary Table of Studies Examining Music Mnemonics

	Memory
Improve	• Thaut et al. 2014 (RAVLT)
No statistical sig. difference	• Moore et al. 2008 (RAVLT)

Bold	RCT PEDro $\geq$ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

Two randomized controlled trials investigated the use of music mnemonics on cognitive impairment in persons with MS (Moore et al. 2008; Thaut et al. 2014). Moore et al. (2008) randomized participants to a music-learning condition or a speech-learning control condition. For both conditions, participants were to recall a list of 15 words from Rey's Auditory-Verbal Learning Test after a 20-minute delay. The music group heard the list of words in a song format to the tune of *Skip to My Lou*, while the control group heard the list in a spoken format. Participants in both conditions learned an intervening distracter list and then participated in a 20-minute distractor task. Finally, recall and recognition of the words from the original list were tested. There were no significant differences between the two groups in recall based on the Rey's Auditory-Verbal Learning Test.

Thaut et al. (2014) applied a very similar protocol to the Moore et al. (2008) study, except their results were positive in favor of music mnemonics. A statistically significant greater percentage of the words were recalled in the sung group in comparison to the control group on the Rey's Auditory-Verbal Learning Test after the 20-minute distractor. Thaut et al. (2014) also report a significant improvement in pair-wise word order learning in the music group at the end of the last learning trial and the two successive memory trials. In comparing these two studies, the Thault et al. (2014) was a larger trial (54 participants versus 38 in Moore et al. 2008 study). Moore et al. (2008) found a positive association between responders to music mnemonics and less cognitive impairment at baseline. They suggest that for this reason, teaching music mnemonic learning strategies earlier in the disease course may be more beneficial. Thault et al. (2014) propose that music mnemonic learning strengthens the encoding of new memories through the recruitment of a stronger oscillatory network synchronization in the prefrontal area, a hypothesis supported by EEG recordings performed during their study.

Conclusion

There is conflicting evidence whether music mnemonics improve memory compared to spoken words in persons with MS (two randomized controlled trials; Moore et al. 2008, Thaut et al. 2014).

There is conflicting evidence whether music mnemonics improves memory in persons with MS.

3.20 Occupation Based

Occupation-based interventions involve sessions that teach compensation strategies, routines, and techniques that can be weaved into a participant's occupation (Reilly and Hynes 2018).

Table 40. Studies Examining Occupation Based for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Reilly and Hynes 2018 *A Cognitive Occupation-Based Programme for People with Multiple Sclerosis: A Study to Test Feasibility and Clinical Outcomes* Ireland **Pre-post** $N_{Initial}$=12, N_{Final}=12	**Population:** Mean age=55yr; Sex: males=1, females=11; Disease course: RRMS=5, PPMS=3, unknown=4; Severity: unspecified; Mean disease duration=14.25yr. **Intervention:** The Cognitive Occupation-Based Programme for People with Multiple Sclerosis (COB-MS) program consists of eight sessions over 2wks that includes two individual and six group-based sessions. Information provided included managing demands of employment and daily life through compensatory strategies and routines and learning new techniques. Outcome measures were collected 1wk prior to the intervention, 1wk following the final session, and 8wks following the final session. **Cognitive Outcome Measures:** Goal Attainment Scale (GAS)[1], Occupational Self-Assessment-Daily Living Scales (OSA-DLS), California Verbal Learning Test II (CVLT-II)[2]; Brief Visuospatial Memory Test-Revised (BVMT-R)[2]; Symbol Digit Modality Test (SDMT)[2]; Trail Making Test (TMT-A)[2]; Behaviour Rating Inventory of Executive Function-Adult (BRIEF-A)[2]; Everyday Memory Questionnaire-Revised (EMQ-R)[2].	1. Ability to perform ADLs and IADLs according to the GAS significantly improved pre-post and was maintained at 8-wk f/u. 2. Perceived occupational competence on the OSA-DLS significantly improved pre-post and was maintained at 8-wk f/u. 3. Fewer memory difficulties in daily life were reported by participants on the EMQ-R (p=0.006). 4. There was no significant difference on perceived rating of executive function according to the BRIEF-A across the three time points. 5. Processing speed assessed by the TMT-A (mean baseline=35.92, SD=12.07, mean time 2=34.33, SD=11.51, mean time 3= 33.75, SD= 15.93) and SDMT (mean baseline=38.42, SD=8.08, mean time 2=39.83, SD=10.20, mean time 3=41.75, SD=41.75, SD=9.28) improved but was not statistically significant (p=0.368 & 0.127 respectively).

[1]Primary outcome measure, [2]Secondary outcome measure

Table 41. Summary Table of Studies Examining Occupation Based

	Executive Function	Information Processing Speed
Improve		
No statistical sig. difference	• *Reilly and Hynes 2018* (SDMT)	• *Reilly and Hynes 2018* (TMT)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT (Pre-post)

Discussion

One pre-post test study utilizing a cognitive occupation-based program included objective cognitive outcomes (Reilly and Hynes 2018). A convenience sample of PwMS participated in a 9-week intervention with the main goal of helping participants learn compensation strategies that could be incorporated into daily work. The primary outcome measure was the Goal Attainment Scale, a measure utilized in rehabilitation practice and research, allowing participants to create their own meaningful goals for the intervention (Turner-Stokes 2009). Results of the study highlighted that participants were significantly better able to perform ADLs and IADLs as measured by the Goal Attainment Scale. There were also significant improvements in perceived occupational competency and fewer daily life memory difficulties.

However, no significant improvements were observed on the objective cognitive outcomes, the Behaviour Rating Inventory of Executive Function-Adult Version, Trail Making Test, and Symbol Digit Modalities Test.

Overall, the results of this study highlight that there is value in having participants define their own goals. Goals related to improving cognitive functioning in daily life were achieved with a cognitive occupation-based program, even when objective cognitive testing outcomes did not significantly improve. Learning compensatory strategies focusing on patient identified goals in an occupational context would be feasible in practice settings. Knowing which compensatory strategies are most effective for which situations would be critical to the success of the intervention. Future research may further improve the success of occupation-based programs by understanding influencing factors such as patient self-awareness, clinician experience, and clinician training opportunities.

Conclusion

There is level 4 evidence that a Cognitive Occupation-Based Program may not improve processing speed or executive function; however, ADLs and IADLs and occupational competence may improve by self-report (one pre-post study; Reilly et al., 2018).

Cognitive Occupation-Based Programme for People with Multiple Sclerosis (COB-MS) may not improve processing speed or executive function, but self-reported performance on ADLs, IADLs and occupational competence may improve.

3.21 Action Observation

Action observation training aims to address hand motor deficit in PwMS. This intervention typically involves watching a motor task that utilizes the involved limb (Rocca et al. 2019).

Table 42. Studies Examining Action Observation for Cognitive Impairment in Multiple Sclerosis

Author Year **Title** **Country** **Research Design** **PEDro** **Sample Size**	**Methods**	**Results**
Rocca et al. 2019 *Functional and structural plasticity following action observation training in multiple sclerosis* Italy	**Population:** *Intervention group: healthy control-action observation training (HC-AOT) (n=23)*: Mean age=45.9yr; Sex: males=12, females=11. *Intervention group: MS-AOT (n=20)*: Mean age =50.4yr; Sex: males=9, females=11; Disease course: unspecified; Median EDSS=6.5; Mean disease duration=18yr. *Control group: healthy control-control (HC-control) (n=23)*: Mean age=47.0yr; Sex: males=7, females=16.	1. Statistically significant within-group improvements were noted in all groups on the PASAT (HC-AOT: baseline: 0.11±0.85, wk 2: 0.49±1.05 p=0.006; HC-control: baseline: -0.21±1.02, wk 2: 0.33±0.75, p=0.0002; MS-AOT: baseline: -0.85±1.58, wk 2: -0.21±1.65, p=0.001; MS-Control: baseline: -0.68±1.41, wk 2: 0.06±1.35, p=0.0001). Between-group

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
RCT PEDro=7 $N_{Initial}$=87, N_{Final}=87	*Control group: MS-Control (n=21)*: Mean age=51.5yr; Sex: males=6, females=15; Disease course: unspecified; Median EDSS=6.0; Mean disease duration=16yr. **Intervention:** Following randomization, all groups received daily, 40-min sessions over 2wks of upper limb rehabilitation. The rehab sessions consisted of 10-min right upper limb passive mobilization, watching three videos, and execution of right-hand daily-life activities. The intervention groups viewed videos of daily-life right-hand and arm action while the control groups watched inanimate landscapes. Both MS participants and healthy controls received the same training with the video content being the only difference. MS participants also received daily standard rehabilitation sessions. Outcome and MRI measures were collected at baseline and following the intervention at 2wks. **Cognitive Outcome Measures:** Paced Auditory Serial Additional Test (PASAT)[3].	differences in PASAT outcomes not reported.

[3]Primary outcome measure unspecified

Table 43. Summary Table of Studies Examining Action Observation

	Attention	Information Processing Speed	Memory
Improve		• **Rocca et al. 2019** (PASAT)	
No statistical sig. difference			

Bold	RCT PEDro > 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

One randomized controlled trial investigated 2 weeks of action observation training combined with standard rehabilitation to assess whether this intervention improves hand function in right-handed individuals with MS and healthy controls (Rocca et al. 2019). Exploratory outcomes included advanced MRI analysis techniques and auditory processing speed on the Paced Auditory Serial Addition Test. Those in the intervention group watched videos of daily life using right-hand and arm actions and those in the control group watched inanimate landscapes. There were statistically significant improvements on the mean PASAT z scores between baseline and 2 weeks in all the groups. Improvements across all groups may relate to practice effects observed on the PASAT. However, in the MS action observation group, the mean PASAT z score improved by approximately 1 standard deviation. In comparison, smaller improvements were observed in the other groups. Between-group statistical analyses and effect size data were not provided, and authors state in the discussion that no specific effect of action observation was observed on the PASAT (Rocca et al. 2019, p. 1484). From this preliminary study, it remains unclear if there is an additional benefit from action observation compared to standard rehabilitation training for improving processing speed. One advantage of this approach is that watching videos would be highly feasible to implement if effective.

Conclusion

There is level 4 evidence that watching daily life hand movements (action observation) may improve auditory processing speed in persons with MS receiving an upper-limb rehabilitation program (pre-post data in one randomized controlled study; Rocca et al., 2019).

There is preliminary evidence that action observation training added to an upper-limb rehabilitation program may improve auditory processing speed in persons with MS.

3.22 Cooling

Persons living with MS may experience a transient worsening of MS symptoms when the body temperature is elevated, a phenomenon first described by Wilhelm Uhthoff (Selhorst and Saul 1995). Exposure to heat, including temperature elevation with exercise, may temporarily worsen visual function and physical function in persons with MS with heat sensitivity. Cooling approaches include wearing a cooling vest, lowering the room temperature, submersion in cool water, etc.

Table 44. Studies Examining Cooling for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Schwid et al. 2003 *A randomized controlled study of the acute and chronic effects of cooling therapy for MS* USA **RCT Crossover** PEDro=8 $N_{Initial}$=84, N_{Final}=84	**Population:** Mean age=48.1yr; Gender: males=32, females=52; Disease course: Stable or relapsing=74, Progressive MS=6; Mean EDSS=3.3; Mean disease duration: Unspecified. **Intervention:** MS participants were randomized to receive a single session of low-dose or high-dose cooling therapy acutely (single 60-min session). After 1wk, the groups crossed over and received the alternate acute treatment. One week later, patients were randomized a second time to either high-dose or no cooling therapy chronically (1 hr/d for 4wks). After a 1-wk washout period, the patients underwent the alternate condition for another 4wks. Cooling was performed with a liquid cooling garment (LCG). Assessments were performed at baseline and after cooling sessions.	1. Cooling did not produce a significant acute effect in PASAT scores in either condition (high-dose cooling, p=0.76; low-dose cooling, p=0.38) or between conditions (p=0.61). 2. Cooling did not produce a significant chronic effect in PASAT scores in either condition (home high-dose cooling, p=0.19; no cooling, p=0.35) or between conditions (p=0.18).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	Cognitive Outcome Measures: Paced Auditory Serial Addition Test (PASAT).[3]	
Gonzales et al. 2017 *Effects of a Training Program Involving Body Cooling on Physical and Cognitive Capacities and Quality of Life in Multiple Sclerosis Patients: A Pilot Study* France **RCT** PEDro=6 $N_{Initial}$=18, N_{Final}=18	**Population: Population:** *Intervention group (n=9)*: Mean age=50.04yr; Sex: males=3, females=6; PPMS=40%, SPMS=60%; Mean EDSS=5.06; Mean disease duration=9.3yr. *Control group (n=9)*: Mean age=49.12yr; Sex: males=3, females=6; PPMS=40%, SPMS=60%; Mean EDSS=5.11; Mean disease duration= 10.2yr. **Intervention:** Following stratified randomization, both groups completed a 7-wk exercise program including Nordic walking, cycle ergometers, range of motion exercises, and exercises with a ball to moderate intensity. During training, the intervention group wore a cooling vest while the control group wore a cotton t-shirt. Outcome measures were collected 1d before and 1d after the training program. **Cognitive Outcome Measures:** Trail Making Test-A (TMT-A), Trail Making Test-B (TMT-B); Isaacs Set Test (IST).[3]	1. Between-group comparison showed significant improved on TMT-A scores for the intervention group compared to the control group (p<0.05). There were no significant between-group differences in change scores on the TMT-B, and cognitive scores on the TMT-B were worse at baseline for the intervention group. On the TMT-B, only the control group improved significantly (control group mean pre=182, post=169.8, p<0.05; intervention group mean pre=94.4, post=85.5, p>0.05). 2. Between-group comparison showed a significant improvement on IST scores for the intervention group compared to control group (p<0.05). 3. Participants in the intervention group demonstrated statistically significant improved performance on the TMT-A (mean pre=49.0, post=38.4, p<0.05).
Geisler et al. 1996 *Cooling and Multiple Sclerosis: Cognitive and Sensory Effects* USA **Pre-Post** $N_{Initial}$=16, N_{Final}=16	**Population:** *MS Participants (n=8):* Mean age=43yr; Disease course: RRMS=8; No further information provided. *Healthy controls (n=8):* Mean age=27.4yr; Gender: unspecified. **Intervention:** Heat-sensitive MS participants and healthy controls underwent 2hrs of cooling on one day and 2hrs of sham cooling on another day. Cooling involved lowering the core body temperature by one degree or more with the use of a cooling jacket. Assessments were performed in the normal and cooled states. **Cognitive Outcome Measures:** Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span; Paced Auditory Serial Addition Test: 3-, 2-second (PASAT-3, -2); Symbol Digit Modalities Test (SDMT); Trail Making Test A, B (TMT-A, -B); Stroop Test (SCWT); Boston Naming Test (BNT); Complex Figure Test (CFT): immediate recall, delayed recall; Selective Reminding Test (SRT); Controlled Oral Word Association Test (COWAT).[3]	1. CFT immediate and delayed recall scores significantly worsened in both groups under the cooling condition (p<0.05; p<0.005, respectively). 2. No other outcome measures showed significant changes under the cooling condition.

[3]Outcome Measure Not Specified

Table 45. Summary Table of Studies Examining Cooling

	Executive Function	Information Processing	Memory	Verbal Fluency

Improve		• **Gonzales et al. 2017** (TMT-A)		• **Gonzales et al. 2013** (IST)
No statistical sig. difference	• **Gonzales et al. 2013** (TMT-B)	• **Schwid et al. 2013** (PASAT)		
Worsen			• Geisler et al. 1996 (CFT)	

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6
italics	Non-RCT

Discussion

Three studies report conflicting results on cooling interventions and their effect on cognitive symptoms. All three studies apply diferent methods in terms of the timing and degree of cooling in association with the timing of the cognitive testing. In the Gonzales et al. (2017) study, processing speed and verbal fluency improved with cooling, while executive function did not. Baseline cognitive scores in the control and intervention groups are not matched in the Gonzales et al (2017) study; therefore, the results are difficult to interpret. In the study by Geilser et al. (1996), memory testing conducted while the body temperature was one degree below the normal resting body temperature was associated with worsening memory scores in both the healthy control and MS groups. For both healthy controls and people with MS, a normal body temperature may be important for optimal cognitive performance. Clinically, these findings would support that cooling below normal resting temperatures may not improve cognitive performance. In addition, trying to complete challenging cognitive tasks while the body temperature is elevated (i.e., immediately after rigorous exercise) might not be advisable for optimal cognitive performance.

Conclusion

There is conflicting evidence whether cooling may improve information processing in persons with MS (two randomized controlled trials; Gonzales et al. 2017; Schwid et al. 2013).

There is level 1b evidence that a walking, cycling, and ROM exercise program while wearing a cooling garment may improve verbal fluency compared to the same exercise program without a cooling garment in persons with MS (one randomized controlled trial; Gonzales et al. 2017).

There is level 4 evidence that memory is worse when the body temperature is lowered by one degree Celsius compared to a resting control temperature in persons with MS (one pre-post study; Geisler et al. 1996).

An exercise program with a cooling garment may improve verbal fluency in persons with MS.

There is conflicting evidence whether cooling garments improve information processing in persons with MS.

Preliminary evidence suggests that cooling below the resting normal temperature may worsen memory in persons with MS.

3.23 Art

Art therapy is a complex intervention that has been studied in other patient populations to help with cognition, mood symptoms, or quality of life.

Table 46. Studies Examining Art for Cognitive Impairment in Multiple Sclerosis

Author Year **Title** **Country** **Research Design** **PEDro** **Sample Size**	**Methods**	**Results**
Van Geel et al. 2020 *Effects of a 10-week multimodal dance and art intervention program leading to a public performance in persons with multiple sclerosis - A controlled pilot-trial* Belgium **Pre-post** $N_{Initial}$=18, N_{Final}=17	**Population:** *Dance group (n=7)*: Age range=29-52yr; Sex: males=0, females=7; Disease course: RRMS; Severity: unspecified; Disease duration range=3-21yr. *Art group (n=10)*: Age range=40-65yr; Sex: males=1, females=9; Disease course: RRMS; Severity: unspecified; Disease duration range=6-21yr. **Intervention:** Participants were allocated to groups based on preference. Both groups had 90-min sessions, 2x/wk over 10wks. The dance group received choreo-based dance therapy. The sessions included a 10-min warm up, 70-min training, and 10-min cooldown. The training included three choreographies of increasing difficulty. The art group included poem recitation, creating paintings, photography, and videography. The main goal for both groups was to work toward presenting their performance and work at an exhibition for an audience after the intervention. Outcome measures were collected at baseline and within 2wks after the live performance. **Cognitive Outcome Measures:** Modified Fatigue Impact Scale (MFIS)[1]; Symbol Digits Modalities Test (SDMT)[2]; Paced Auditory Serial Addition Test (PASAT) [2]; Dual Task: Word List Generation (WLG) and subtraction[2].	1. There was statistically significant improvement in the number of correct answers for the SDMT in the art group (median pre: 53, post: 61, p=0.036) but not the dance group (median pre: 64, post: 65, p=0.917). 2. A trend towards improvement on the PASAT was observed in the dance group (median pre: 49, post: 55, p=0.068) and art group (median pre: 49, median post: 53, p=0.085). 3. Both art and dance groups showed significant improvements on Dual Task: WLG correct answers (dance pre: 11, post: 15, p=0.028; art pre: 11, art post: 15, p=0.017).

[1]Primary Outcome Measure; [2]Secondary Outcome Measure

Table 47. Summary Table of Studies Examining Art

	Visual Information Processing	Auditory Information Processing	Memory

Improve	• *Van Geel et al. 2020* (SDMT)		• *Van Geel et al. 2020* (Dual Task + WLG)
No statistical sig. difference		• *Van Geel et al. 2020* (PASAT)	

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

This small-scale pilot study provides level 4 evidence that people with relapsing-remitting multiple sclerosis (RRMS) may benefit from art therapy, with statistically significant improvements noted in information processing speed and dual task performance. Non-randomized study design and a lack of participant blinding (with intervention group allocation based on individual preference) indicates an elevated risk of bias, whilst poor reporting of participant sociodemographic and clinical characteristics limits the interpretation and thus relevance of findings. In non-MS populations, art therapy has been associated with improvements in anxiety (Abbing et al. 2018), mood and cognition (Masika, Yu, and Li 2020), and quality of life (Emblad and Mukaetova-Ladinska 2021). Art therapy is a heterogenous, complex intervention (Masika, Yu, and Li 2020); arguably, standardization is counter to the philosophy of art, which is problematic when seeking to test an art-based intervention under trial conditions. Qualitative systematic review evidence highlights that art therapy appears to be acceptable to many but needs careful application and tailoring to make it accessible in the context of physical illness (Scope, Uttley, and Sutton 2017). Further, adaptations are likely required in the context of physical and cognitive impairment (Luzzatto et al. 2017).

Conclusion

There is level 4 evidence that team-based artistic therapy, consisting of photography, painting, poetry, and videography, may improve visual information processing speed and memory but not auditory information processing speed in relapsing-remitting MS (one pre-post study; Van Geel et al. 2020).

Preliminary evidence suggests that team-based artistic therapy may improve visual information processing speed and memory but may not improve auditory information processing speed in relapsing-remitting MS.

3.24 Diet

Different diets or dietary behaviors have long been associated with worsening or improved disability outcomes in MS (Murray 2005). However, there is little research exploring cognitive outcomes in relation to diet specifically and systematic evaluation of dietary interventions is challenging. In a large cross-sectional study, a healthy lifestyle composite measure, including a healthier diet and healthy weight, was associated with significantly lower odds of cognitive impairment (0.67; 95% CI 0.55-0.79) (Fitzgerald et al.

2018). In the Fitzgerald et al. 2018 study, patients provided self-report cognitive symptoms through participation in the North American Research Committee on MS (NARCOMS) Registry (https://www.narcoms.org/).

Table 48. Studies Examining Diet for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Lee et al. 2017 *A Multimodal, Nonpharmacologic Intervention Improves Mood and Cognitive Function in People with Multiple Sclerosis* USA **Pre-Post** $N_{Initial}$=21, N_{Final}=19	**Population:** Mean age=51yr; Sex: males=5, females=14; Disease course: PPMS=2, SPMS=17; Mean EDSS=6.2; Mean disease duration=13.6yr. **Intervention:** For each participant the intervention included a modified paleolithic diet, exercises (stretching exercises, strengthening exercises), neuromuscular electrical stimulation, and stress management (meditation and self-massage). Daily home logs were kept recording the dosage of each aspect of the intervention. Outcome measures were collected at baseline and at 3, 6, 9, and 12mos after the start of the multimodal intervention. **Cognitive Outcome Measures:** Cognitive Stability Index (CSI); Cognitive Screening Test (CST); Delis-Kaplan Executive Function System (D-KEFS); Wechsler Adult Intelligence Scale-III (WAIS-III): Matrix Reasoning; WAIS-III: Similarities; Wechsler Test of Adult Reading (WTAR)[3].	1. Significant improvement in almost all the cognitive outcomes were observed at 12mos but not yet at 3mos. From 3mos to 12mos, following repeated measures and mean difference analysis, significant improvements were seen on D-KEFS language (ps=0.002 to 0.02), D-KEFS switch (ps=0.002 to 0.05), WAIS-III: Similarities (ps= 0.02 to 0.04), and WAIS-III: Matrix Reasoning (ps=0.002 to 0.003). 2. At 12mos, improvements in cognitive outcomes were significantly more associated with the diet intake compared to the dosage of stress and exercise interventions.

[3] Primary Outcome Measure Not Specified

Table 49. Summary Table of Studies Examining Diet

	Executive Function
Improve	• *Lee et al. 2017* (DKEFS, WAIS-Similarities, Matrix Reasoning)
No statistical sig. difference	

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

This small pre-post feasibility study provides level 4 evidence that a modified paleolithic diet, as part of a multimodal intervention including electrical stimulation, exercise, and stress management, is associated with significant pre-12-month follow-up improvements in memory/learning, attention, language, complex verbal fluency, and verbal and visual reasoning, but not cognitive processing/response speed. Although the authors performed multiple correlation analyses, the complexity of the intervention makes it difficult to pick apart direct effects, and it seems likely that the interventions' components interact to produce observed effects (Gardner, de Bruijn, and Lally 2011). The rationale for a direct impact of diet on cognitive function in PwMS is largely theoretical, though the potential for indirect effects is logical in that nutrition has a fundamental role in the building blocks of neural substrate and functioning (Benau et al. 2021), malnutrition is linked with increased risk for neural decline and dementia (Bianchi, Herrera, and Laura 2021), and the Mediterranean diet has well-described beneficial impact on metabolic markers of inflammation and cardiovascular risk (Papadaki, Nolen-Doerr, and Mantzoros 2020). A useful feasibility finding from this study is that participants reported >94% adherence to the dietary intervention, suggesting the diet is acceptable and sustainable in this context. A limitation with pre-post assessment such as in this study is the potential for observed effects to be unrelated, or only partially related to the intervention components, with the potential for a Hawthorne effect (Sedgwick and Greenwood 2015).

Conclusion

There is level 4 evidence that a modified paleolithic diet combined with electrical stimulation, exercise, and stress management may improve executive functioning (one pre-post study; Lee et al. 2017).

Preliminary evidence suggests that a modified paleolithic diet combined with electrical stimulation, exercise, and stress management may improve executive functioning in persons with MS.

3.25 Cognitive-Motor Dual-Task Training

Dual-task training involves simultaneously performing a cognitive task and a motor task together—for example, walking on the treadmill while counting backwards. The difficulty and the duration of the cognitive and the motor tasks performed together may vary. Studies comparing cognitive dual-task motor training to an active motor training control condition are included in this section. Cognitive dual-task balance training as an exercise intervention compared to a sedentary control condition is covered in the exercise section 3.26.6.

Table 50. Studies Examining Cognitive-Motor Dual Task Training for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Jonsdottir et al. 2018 *Intensive Multimodal Training to Improve Gait Resistance, Mobility, Balance and Cognitive Function in Persons With*	**Population:** *Intervention group (n=26)*: Mean age=51.4yr; Sex: males=9, females=17; Disease course: RRMS=22, PPMS=2, SPMS=2; Mean EDSS=5.5; Mean disease duration=16.3yr. *Control group (n=12)*: Mean age=56.7yr; Sex: males=1, females=11; Disease course: RRMS=7, PPMS=2, SPMS=3; Mean/Median EDSS=5.6; Mean disease duration=21.4yr.	1. Between-group comparison showed no significant difference between intervention and control groups. 2. A statistically and clinically significant improvements was observed on the FAB in the intervention group by almost two points (pre: 14.8, post: 16.2, p=0.002). 3. Only 10 intervention and 4 control group participants exhibited cognitive

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Multiple Sclerosis: A Pilot Randomized Controlled Trial Italy **RCT** PEDro=8 $N_{Initial}$=42, N_{Final}=38	**Intervention:** Participants in both groups received 15-20, 30-min sessions, 4-5x/wk for four weeks delivered by experienced physical therapists. The intervention group received treadmill dual-task training that was aimed at improving participant resistance, walking velocity, balance, and cognitive function. Each session consisted of an aerobic phase, a dual-task phase composed of motor and cognitive activities, and another aerobic phase. The intensity of the sessions was adjusted as the intervention sessions progressed. The control group received strength training aimed at strengthening muscles involved in walking. Exercise intensity was adjusted as the intervention progressed. Outcome measures were collected at baseline and following the 4-wk intervention. **Cognitive Outcome Measures:** Frontal Assessment Battery (FAB).[2]	deficits at baseline. In these participants, the intervention group improved by 4 points and the control group improved by 2.5 points, indicating that both training modes are beneficial.
Veldkamp et al. 2019 *Structured Cognitive-Motor Dual Task Training Compared to Single Mobility Training in Persons with Multiple Sclerosis, a Multicenter RCT* Belgium, Italy, Israel **RCT** PEDro=7 $N_{Initial}$=47, N_{Final}=40	**Population:** *Intervention group (n=20)*: Mean age =51.4yr; Sex: males=8, females=12; Disease course: RRMS=13, PPMS=3, SPMS=4; Mean EDSS=3.4; Mean disease duration=9.6yr. *Control group (n=20)*: Mean age =53.4yr; Sex: males=9, females=11; Disease course: RRMS=13, PPMS=4, SPMS=3; Mean EDSS=3.7; Mean disease duration=11.4yr. **Intervention:** Following stratified randomization, both groups took part in an 8-wk program with 20 sessions. The intervention group completed the dual-task training protocol that consisted of exercises such as walking or stepping on the spot while completing 11 different cognitive tasks ranging in difficulty. The control group completed the single mobility training protocol which consisted of 21 different gait and dynamic balance exercises. Outcome measures were collected at baseline, after the intervention and at 4-wk f/u. **Cognitive Outcome Measures**: Dual Task Cost (DTC)[1]; Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (10/36-Spatial Recall Test (SPART),[2] Word List Generation Test (WLGT),[2] Selective Reminding Test (SRT),[2] Paced Auditory Serial Addition Test (PASAT),[2] Symbol Digit Modalities Test (SDMT)).[2]	1. Between-group comparison showed no significant difference in DTC performance between intervention and control groups. 2. No between-group differences on any of the five components of the BRB-N. 3. Both groups improved (significant main effect for time) on the PASAT (3 second version) (baseline control: 46.9 ± 9.8, intervention: 42.2± 12.8, post control: 49.4± 7.7, intervention: 47.4± 12.0, f/u control: 49.2± 12.4, intervention: 48.2±12.4; p<0.001). 4. Both groups improved (significant main effect for time) on the SDMT (baseline control: 44.7±12.2, intervention: 46.8± 11.6, post control: 48.2± 10.5, intervention:48.8± 14.7, f/u control: 45.5± 10.3, intervention: 46.0± 14.7; p=0.023). These improvements were not maintained at f/u.
Sosnoff et al. 2017	**Population:** *Intervention group (n=13)*: Mean age =48.3yr; Sex: males=8, females=5; Disease	1. No differences were observed between groups in cognitive task performance on

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Dual task training in persons with Multiple Sclerosis: a feasibility randomized controlled trial USA **RCT** PEDro=7 $N_{Initial}$=20, N_{Final}=14	course: RRMS=7; Median EDSS=1.75; Mean disease duration=11.9yr. *Control group (n=6)*: Mean age =56.8yr; Sex: males=1, females=5; Disease course: RRMS=5, PPMS=1; Median EDSS=2.5; Mean disease duration=11.7yr. **Intervention:** Following randomization, participants took part in one of two, 12-wk interventions. The intervention group took part in dual-task training, which involves balance and gait training while simultaneously performing a cognitive task for half the session. The control group only completed the balance and gait training. Intensity was personalized to the participant's abilities. Outcome measures were collected at baseline and within 1wk following the end of the intervention. **Cognitive Outcome Measures:** Brief International Cognitive Assessment for MS (BiCAMS)[1] (California Verbal Learning Test II (CVLT-II), Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test-Revised (BVMT-R)).	either seated letters (F(1,13)=0.04; p=.85; η2=.004) or serial sevens (F(1,13)=1.5; p=.25; η2=.12) following the intervention when controlling for baseline values. 2. No differences were observed between group performance on SDMT (F(1,13)=0.6; p=0.47; η2=.05) and CVLT-II (F(1,13)=0.23; p=0.64; η2=.02) following the intervention when controlling for baseline values. 3. A positive trend was observed in the intervention group on the BVMT-R (F(1,13)=3.3; p=0.10; η2=0.23) following the intervention when controlling for baseline values.

[1]Primary Outcome Measure; [2]Secondary Outcome Measure

Table 51. Summary Table of Studies Examining Cognitive-Motor Dual Task Training

	Executive Function	Attention	Info processing	Memory
Improve				
No statistical sig. difference	• **Jonsdottir et al. 2018** (FAB)	• **Veldkamp et al. 2019** (DTC)	• **Sosnoff et al. 2017** (SDMT) • **Veldkamp et al. 2019** (SDMT, PASAT)	• **Sosnoff et al. 2017** (CVLT, BVMT) • **Veldkamp et al. 2019** (SPART, SRT, WLG)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6
italics	Non-RCT

Discussion

In everyday life, carrying out motor and cognitive tasks simultaneously may be required. Three higher quality RCTs evaluated the effects of dual-task training protocols (cognitive task + physical training) compared to physical training alone. On testing of cognition outcomes alone (while not dual tasking), no statistically significant between-group differences were observed in any of the studies. Within-group analysis pre-post training in both the intervention and control groups for all three studies showed iether significant improvement or a trend towards improvement on the cognitive outcomes alone. Together, these results support that combining a cognitive task with motor training does not provide additional benefit on cognition testing when the cognitive testing occurs independent of the motor task. Not surprisingly, dual-task training did improve performance on dual-task outcomes for the intervention group (Veldkamp et al. 2019). Importantly, all three studies included in this section had active comparator groups involving strength training or gait and balance training. In comparison, Felippe et al. (2019) investigated specifically a balance exercise dual-task training protocol compared to a non-active control group and report significant improvement on executive function outcomes in favor of the dual-task intervention (See section 3.26.6). Dual-task training may have real-world relevance if improvements were transferable to dual-task activities in real-world setting (i.e., if cooking a meal was easier after dual task cognitive-motor training).

Conclusion

There is level 1a evidence that dual-task training does not improve information processing speed or memory more than balance or gait training alone (two randomized controlled trials; Sosnoff et al. 2007; Veldkamp et al. 2019).

There is level 1b evidence that dual-task training does not improve attention more than gait training alone (one randomized controlled trial; Veldkamp et al. 2019).

There is level 1b evidence that dual-task training does not improve executive function more than strength training (one randomized controlled trial; Jonsdottir et al. 2018).

Dual-Task Training combined with gait training may not improve attention, memory, or information processing speed more than gait training alone in persons with MS.

Dual-Task Training may not improve executive function more than strength training in persons with MS.

3.26 Exercise Training

Exercise training may include many different types of exercise modalities, frequencies, and intensities. The literature on the effects of exercise training on cognition in MS continues to be an area of high research interest at the time of this module preparation. Importantly, in the dementia literature, exercise interventions may delay memory decline or improve cognition. Exercise interventions in early dementia (where there exists minimal CI at baseline) may be most effective for delaying cognitive decline (Cui et al. 2018; Du et al. 2018).

3.26.1 Aerobic and Strength Training

Previous studies have supported an association between exercise participation and improved cognitive performance in persons with MS (Robert W. Motl and Sandroff 2018; Angevaren et al. 2008; Engeroff, Ingmann, and Banzer 2018). Exercise guidelines recommend moderate-intensity aerobic exercises for 30 minutes and resistance training twice per week for people with mild and moderate MS (Latimer-Cheung et al. 2013). For people with moderate and severe MS, “as the disease progresses and engaging in exercise and physical activity becomes more challenging, referrals to specialists are essential for ensuring that patients' exercise and physical activity strategies are individualized to best meet their needs" (Rosalind Kalb et al. 2020, p.1461).

Table 52. Studies Examining Aerobics and Strength for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Coghe et al. 2018 *Fatigue, as measured using the Modified Fatigue Impact Scale, is a predictor of processing speed improvement induced by exercise in patients with multiple sclerosis: data from a randomized controlled trial* Italy **RCT** PEDro=6 $N_{Initial}$=30, N_{Final}=30	**Population:** *Intervention group (n=11)*: Mean age=47.54yr; Sex: males=6, females=5; Disease course: RRMS; Mean EDSS=3.68; Disease duration: unspecified. *Control group (n=11)*: Mean age=43.37yr; Sex: males=6, females=5; Disease course: RRMS; Mean EDSS=3; Disease duration: unspecified. **Intervention:** Following randomization, the intervention group took part in a supervised, 24-wk program that included 3x60-min sessions/wk of aerobic and strength training sessions. Aerobic training involved cycle ergometer and gait training, and the strength training included exercises targeting upper limbs, lower limbs, and trunk. The control group could not be participating in any systematic physical activity or rehabilitation program. Outcome measures were collected at baseline, following the 6-mo intervention, and 6mo after completion. **Cognitive Outcome Measures:** Brief International Cognitive Assessment in MS (BICAMS)[3] (Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test-Revised (BVMT-R), Rey Auditory Verbal Learning Test (RAVLT)); Attention Network Test-Interaction (ANT-I); California Verbal Learning Test II (CVLT-II)[3]; Brief Visual Memory Test-Revised (BVMT-R).[3]	1. No statistically significant between-group changes on the cognitive outcomes reported. 2. For the intervention group only, Wilcoxon test revealed significant improvements on the SDMT from baseline to end of the study (p=0.008) and from baseline to f/u 24wks after completion (p=0.013). 3. A statistically significant Spearman's test revealed a relationship between fatigue measures at baseline and change in SDMT scores (Rho=0.784, p<0.004). 4. Verbal learning and visual memory domains were not significantly improved following the intervention. 5. Worse fatigue scores at baseline were predictive of a greater improvement in SDMT change scores on linear regression analysis (R^2: 0.65, SDMT T change score increase by 0.3 for each 1 unit increase on the MFIS fatigue measure at baseline). 6. There were no between-group differences reported at baseline for cognitive scores (SDMT mean intervention group= 39.47, SD:12.63, control group=41.81, SD:10.22, p=0.622).
Sandroff et al. 2017 *Multimodal exercise training in multiple sclerosis: A randomized controlled trial in persons with substantial mobility disability* USA **RCT** PEDro=5 $N_{Initial}$=83, N_{Final}=62	**Population:** *Intervention group (n=43)*: Mean age=49.8yr; Sex: males=7, females=36; Disease course unspecified; Mean PDDS=4.0; Disease duration: unspecified. *Control group (n=40)*: Mean age=51.2yr; Sex: males=5, females=35; Disease course unspecified; Mean PDDS=3.0; Disease duration: unspecified. **Intervention:** Participants in the intervention group completed 3, 30-60-min supervised sessions/wk over 24wks. Participants spent equal time in every session on aerobic exercise, lower-extremity resistance, and balance training. The control group completed stretching and toning activities at the same frequency as the intervention group. Exercises	1. There were no significant between-group differences on cognitive outcomes. There was an overall (multivariate) non-statistically significant time by group interaction favoring the intervention group on cognitive processing speed ((F(4,78) =1.96, 2, p =0.11). 2. For the intervention group, small-to-moderate significant improvements occurred on the PASAT (F(2162)=4.67, p=0.01). 3. Participants in the intervention group demonstrated a 3-point increase in PASAT scores (+7.5%) while those in the control group demonstrated a 1.5-point decrease (-3.8%).

	were progressed through the course of the intervention for both groups. Outcome measures were collected at baseline, mid-point, and following the 6-mo intervention. **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT).[3]	4. No significant changes on the SDMT for either group over time (baseline SDMT Intervention group= 46.9, SD= 11.1; control group=46.2, SD=13.2).
Sandroff et al. 2019 *Response heterogeneity in fitness, mobility and cognition with exercise-training in MS* USA **RCT** PEDro=4 $N_{Initial}$=83, N_{Final}=32	**Population:** Mean age=49.8yr; Sex: males=7, females=25; Disease course unspecified; Median PDDS=4.0; Disease duration: unspecified. **Intervention:** The participants in the intervention group completed 3, therapist-lead training sessions/wk over 24wks. Sessions lasted between 30 and 60mins. Exercises focused on aerobic, balance and lower-extremity resistance training. The control group completed a stretching and toning program at the same frequency and duration. Outcome measures were collected at baseline and after the 6-mo intervention. **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT).[3]	1. Statistically significant improvements in cognitive processing speed were reported on the SDMT in a subgroup analysis of the original trial results exploring response heterogeneity for n=32 participants in the intervention group (t= -3.12, p<0.01, ~10% improvement) and PASAT raw score (t= -2.93, p=0.01, ~18% improvement; baseline intervention group mean SDMT score 45.8 SD 11.3; f/u score 48.8 SD 9.1 p=0.01). 2. Negative overall trial between-group results were published separately (Sandroff et al. 2017). 3. Low baseline aerobic fitness, slow walking speed, and slow cognitive processing speed at baseline were associated with greater exercise-related improvements in these respective outcomes.
Sangelaji et al. 2015 *The effect of exercise therapy on cognitive functions in multiple sclerosis patients: A pilot study* Iran **Pre-Post** $N_{Initial}$=21, N_{Final}=17	**Population:** Mean age=37.1yr; Gender: males=3, females=14; Disease course: RRMS=15, SPMS=2; Mean EDSS=2.35; Mean disease duration: Unspecified. **Intervention:** Patients participated in 3 sessions/wk for an average number of 22.5 exercise sessions. The intervention consisted of aerobic exercise, balance, and resistance exercises. Outcome measures were completed prior to and following the intervention. **Cognitive Outcome Measures:** Selective Reminding Test (SRT): short term, long term; 10/36 Spatial Recall Test (10/36); Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT)-3, -2 min; Word List Generation Test (WLGT).[3]	1. A significant improvement was observed in SRT long term retrieval (pre:42.94, post:54.65, p<0.001) scores. 2. A significant mean change in SDMT score was observed from baseline to post-treatment (pre:26.35, post: 29.76, p=0.028). 3. The average PASAT-3 score showed a significant improvement after treatment (change score: 7.54, p=0.047). 4. No significant effects of treatment were observed on PASAT-2, 10/36, and WLG scores.

[3]Outcome Measure Not Specified

Table 53. Summary Table of Studies Examining Aerobics and Strength

	Improve	No statistical sig. difference
Information Processing	• Sandroff et al. 2019 ⛨ (SDMT, PASAT) • *Sangelaji et al. 2015 (SDMT)*	• **Coghe et al. 2018** 〰 (SDMT) • Sandroff et al. 2017 ⛨ (SDMT, PASAT)
Attention		• **Coghe et al. 2018** 〰 (ANT)
Memory	• *Sangelaji et al. 2015 (SRT)*	• **Coghe et al. 2018** 〰 (BVMTR, RAVLT, CVLT) • *Sangelaji et al. 2015 (SPART, WLG)*

Note: Sandroff et al. 2019 is a sub-group analysis of Sandroff et al. 2017 study participants

⛨	EDSS ≥ 5 or PDSS ≥ 3
↗	Progressive MS
﹏	Relapse-Remitting MS
Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6
italics	Non-RCT

Discussion

A limitation of the research investigating aerobic and strength training is that cognition was generally not impaired at baseline. A post hoc analysis of the RCT by Sandroff et al. (2017) supports a response heterogeneity in that participants with lower baseline cognitive processing speeds may be more likely to improve on cognitive outcomes after an exercise intervention (Sandroff et al. 2019). The pre-post study by Sangelaji et al. (2015) did include participants where the mean processing speed score on the Symbol Digit Modalities Test was impaired at baseline. Scores on the Symbol Digit Modalities Test in this study significantly improved post intervention by almost 4 points—which may be approaching a clinically meaningful change score. Results of this same study also report statistically significant improved scores on a memory test and on the Paced Auditory Serial Addition Test (PASAT)-3 (where new digits to add are presented every 3 seconds). However, scores did not improve signficantly on the PASAT-2 (digits presented every 2 seconds), a spatial memory test or a word list generation test.

A second limitation with all of the aerobic and strength training interventional studies is the short duration of the trials, with no intervention lasting longer than 24 weeks, and no follow-up after 6 months. None of the studies report adverse effects with the exercise interventions. The possible protective effects of adherence with a mixed strength and aerobic training program on cognitive decline in the longer-term specific to the MS population warrants further study.

Conclusion

There is level 1b evidence that aerobic and strength training combined may not improve information processing speed in persons with MS at six-month follow-up (two randomized controlled trials; Coghe et al. 2018. Sandroff et al. 2017).

There is level 1b evidence that aerobic and strength training combined may not improve attention in persons with at six-month follow-up (one randomized controlled trial; Coghe et al. 2018).

There is level 1b evidence that aerobic and strength training combined may not improve memory in persons with MS (one randomized controlled trial and one pre-post study; Coghe et al. 2018, Sangelaji et al. 2015).

Aerobic and strength training combined may not improve information processing speed, attention, or memory after short-term follow-up in MS.
Long-term effects and response heterogeneity warrant further study.

3.26.2 Cycling

Due to balance impairment, muscle spasticity, and weakness, it may become difficult for some PwMS to safely ride a non-stationary classic bicycle. A variety of cycling adaptations for PwMS may allow cycling training. Types of accessible cycling options may include recumbent bicycles, tricycles, e-bikes, and hand-cycle ergometers.

Table 54. Studies Examining Cycling for Cognitive Impairment in Multiple Sclerosis

Author Year **Title** **Country** **Research Design** **PEDro** **Sample Size**	**Methods**	**Results**
Baquet et al. 2018 *Short-term interval aerobic exercise training does not improve memory functioning in relapsing-remitting multiple sclerosis—a randomized controlled trial* Germany **RCT** PEDro=7 $N_{Initial}$=68, N_{Final}=57	**Population:** *Intervention group (n=34)*: Mean age=38.2yr; Sex: males=13, females=21; Disease course: RRMS; Mean EDSS=1.7; Mean disease duration=8.1yr. *Control group (n=34)*: Mean age=39.6yr; Sex: males=9, females=25; Disease course: RRMS; Mean EDSS=1.8; Mean disease duration=9.1yr. **Intervention:** Participants were randomized to the intervention group or a waitlist control group. Following randomization, the intervention group completed individualized, physiotherapist-supervised, 12wks of bicycle ergometer-based aerobic exercise consisting of 2-3 sessions/wk. Each participant received a pre-definedtraining session schedule. Following the 12-wk intervention, participants in the control group were invited to complete the training and the intervention group was invited to continue training. Outcome measures were collected at baseline, after the intervention, and at the end of the extension phase. **Cognitive Outcome Measures:** Verbal Learning and Memory Test (VLMT)[1]; Symbol Digit Modalities Test (SDMT)[2]; Paced Auditory Serial Addition Test (PASAT)[2]; Brief Visuospatial Memory Test-Revised (BVMT-R)[2]; Corsi Block-tapping Task (CORSI)[2]; Regensburger Verbal Fluency Test (RVWT).[2]	1.No statistically significant improvements were detected on any of the cognitive outcomes (Effect size for VLMT 1-5: <0.01, VLMT 5-7: 0.01, SDMT: 0.03, BVMT-R: <0.01, PASAT: 0.03). 2. The study sample was minimally cognitively impaired at baseline only on the PASAT (mean intervention group=46, SD: 10.7; mean control group=49.8, SD: 8.8).
Briken et al. 2014 *Effects of exercise on fitness and cognition in progressive MS: A*	**Population**: *Arm ergometry group (n=10)*: Mean age=49.1yr; Gender: males=5, females=5; Disease course: SPMS=8, PPMS=2; Mean EDSS=5.2; Mean disease duration=17.1yr. *Rowing group (n=11)*: Mean age=50.9yr; Gender: males=4, females=7; Disease course:	1. All exercise groups significantly improved on VLMT scores (p=0.011). Improvements were significant compared to the control group for all three exercise groups (arm ergometry: p=0.007; rowing group: p=0.001; bicycle group: p=0.009). 2. For VLMT delayed recall, all exercise groups showed significant improvements

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
randomized, controlled pilot trial Germany **RCT** PEDro=7 $N_{Initial}$=47, N_{Final}=42	SPMS=7, PPMS=4; Mean EDSS=4.7; Mean disease duration=14.1yr. *Bicycle ergometry group (n=11)*: Mean age=48.8yr; Gender: males=5, females=6; Disease course: SPMS=8, PPMS=3; Mean EDSS=5.0; Mean disease duration=13.3yr. *Control group (n=10)*: Mean age=50.4yr; Gender: males=4, females=6; Disease course: SPMS=8, PPMS=2; Mean EDSS=4.9; Mean disease duration=18.9yr. **Intervention**: Participants were randomized to arm ergometry, rowing, bicycle ergometry, or a waitlist control condition. Participants completed an 8-10-wk intervention period, with 2-3 sessions/wk. Outcome measures were collected at baseline and following the intervention. **Cognitive Outcome Measures**: Symbol Digit Modalities Test (SDMT)[2]; Verbal Learning and Memory Test (VLMT)[2]; Test of Attentional Performance (TAP); Leistungsprüfsystem (LPS)[2]; Regensburger test of word fluency (RWT).[2]	when compared to the control group (arm ergometry: p=0.004; rowing group: p<0.001; bicycle group: p<0.001). 3. The bicycle ergometry showed significant improvements compared to controls on the TAP subtest “tonic alertness” (p=0.005). 4. The arm and bicycle ergometry groups showed significant improvements compared to controls on the TAP subtest “shift of attention” (p=0.026, p=0.002). 5. No significant effects were found for the remaining two TAP subtests, RWT, LPS, or SDMT (p>0.05). 6. Perceived exercise intensity was moderate (mean Borg score: 4.6).
Oken et al. 2004 *Randomized controlled trial of yoga and exercise in multiple sclerosis* US **RCT** PEDro=6 $N_{Initial}$=69, N_{Final}=57	**Population**: *Control group (n=20):* Mean age=48.4yr; Gender: males=0, females=20; Disease course: Unspecified; Mean EDSS=3.1; Mean disease duration: Unspecified. *Intervention (Yoga) group (n=22):* Mean age=49.8yr; Gender: males=20, females=2; Disease course: Unspecified; Mean EDSS=3.2; Mean disease duration: Unspecified. *Intervention (Bicycling) group (n=15):* Mean age=48.8yr; Gender: males=2, females=13; Disease course: Unspecified; Mean EDSS=2.9; Mean disease duration: Unspecified. **Intervention**: Participants were randomized to one of three groups: Yoga class, exercise class (bicycling), or waitlist control group. The classes were provided weekly for 6mos. Participants were assessed at baseline and at the end of the 6-mo period. **Cognitive Outcome Measures**: Stroop color and word test (SCWT)[1]; Cambridge Neurophysiological Test Automated Battery (CANTAB)–attentional shifting[2]; Paced Auditory Serial Addition Test (PASAT)[2]; Stanford sleepiness scale (SSS); State-trait anxiety inventory (STAI).	1. There was no significant difference between the three groups (yoga, exercise, control) at the end of the 6-mo period on any of the cognitive function or alertness measures. 2. Both yoga and exercise groups had a significant improvement in general fatigue compared to control (p<0.01 for both).
Sandroff et al. 2015	**Population:** Mean age=44.2yr; Gender: males=1, females=23; Disease course: RRMS; Mean EDSS=3.0; Mean disease duration=9.6yr.	1. A significant condition*time effect was observed for the cycling condition compared to quiet rest in reaction time measures (η_p^2=0.35, p<0.01).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Acute effects of walking, cycling, and yoga exercise on cognition in persons with relapsing-remitting multiple sclerosis without impaired cognitive processing speed USA **RCT Crossover** PEDro=5 $N_{Initial}$=24, N_{Final}=24	**Intervention:** MS patients underwent 4 experimental conditions consisting of 20min of moderate-intensity treadmill walking exercise, moderate-intensity cycle ergometer exercise, guided yoga, and quiet rest in a randomized, counterbalanced order. Outcome measures were collected at baseline and within 5min of completion of each experimental condition. **Cognitive Outcome Measures:** Modified-Flanker Task (FT): reaction time (RT), congruent trials, incongruent trials.[1]	2. Cycle ergometry was associated with a greater pre-to-post reduction than control in reaction time (p=0.01) but not accuracy (p=0.29). 3. Significant effects of congruency were observed in all three exercise conditions (all p<0.01).
Bahmani et al. 2019 *In Patients with Multiple Sclerosis, Both Objective and Subjective Sleep, Depression, Fatigue, and Paresthesia Improved After 3 Weeks of Regular Exercise* Switzerland **Pre-post** $N_{Initial}$=51, N_{Final}=46	**Population:** Mean age=50.74yr; Sex: males=10, females=36; Disease course unspecified; Mean EDSS=5.3; Disease duration: unspecified. **Intervention:** Participants were patients at an inpatient rehabilitation centre. The intervention involved 5, 30-min sessions/wk for 3wks. The exercise program was a cycling program at 60rpm at the lactate threshold (75% of HR_{max} or 65% of VO_2peak). The participants' regular rehabilitation program was continued simultaneously. Outcome and EEG measures were collected at baseline and following the intervention. **Cognitive Outcome Measures:** Montreal Cognitive Assessment (MoCA)[2]; Symbol Digit Modality Test (SDMT).[2]	1. Statistically significant improvements from pre- to post-intervention were observed on the SDMT (mean baseline: 33.81, mean post: 36.51, p=0.03) and the MoCA sum (mean baseline: 26.16, mean post: 27.15, p=0.01).
Barry et al. 2018 *Impact of short-term cycle ergometer training on quality of life, cognition, and depressive symptomatology in multiple sclerosis patients: a pilot study* Ireland **Pre-post** $N_{Initial}$=20, N_{Final}=19	**Population:** *Multiple sclerosis group (n=9)*: Mean age=35.33yr; Sex: males=1, females=8; Disease course: RRMS; Mean EDSS=2.17; Mean disease duration=5.8yr. *Healthy control group (n=10)*: Mean age=36yr; Sex: males=2, females=8. **Intervention:** All participants completed an 8-wk cycle ergometer, therapist-supervised program, consisting of 2 sessions/wk lasting 30min each at 65-75% age-predicted max heart rate. Outcome measures were collected at baseline and following the 8-wk training intervention. **Cognitive Outcome Measures:** Cambridge Neuropsychological Test Automated Battery (CANTAB)[3]: includes a motor screening, a mood rating scale, test of hippocampal-independent visuospatial memory, sustained attention, and executive function/cognitive flexibility.	1. Participants with MS trended towards improvement from pre-post for rapid visual information processing mean latency (pre: 419.3 vs. post: 392.4) and on rapid visual information processing total hits (pre: 31.3 vs. post: 36.9), mean correct latency (pre: 670.3 vs. post: 595.2ms), switch cost latency (pre: 335.5ms vs. post: 212.3ms), and visuospatial memory/paired associates learning total scores (pre: 17.11 vs. post: 9.63). 2. At baseline, participants with MS compared to the healthy controls had slower mean latency of rapid visual information processing (MS: 419.3 vs. control: 353.1, p<0.05), reduction in total rapid visual information processing hits (MS: 31.3 vs. control: 41.9, p<0.01), increased stimuli response time (MS: 670.3ms vs. control: 526.5ms, p<0.01),

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
		longer switch cost latency (MS: 335.5ms vs. control: 210.3ms).
Swank, Thompson, and Medley 2013 *Aerobic exercise in people with multiple sclerosis: its feasibility and secondary benefits* USA **Pre-Post** $N_{Initial}$=9, N_{Final}=6	**Population:** Mean age=42.7yr; Gender: males=2, females=7; Disease course: RRMS; Mean EDSS=3; Mean disease duration=3.2yr. **Intervention:** MS patients performed a period of aerobic exercise followed by a period of unstructured physical activity. Aerobic exercise was performed for 30min (upper and lower body ergometry and treadmill ambulation) 2x/wk for 8wks. Assessments were performed at baseline (S1), post intervention (S18), and after 3mos of self-directed exercise (S19). Eight patients completed assessment at S18 and 6 completed S19 assessment. **Cognitive Outcome Measures:** Paced Auditory Serial Addition Test 3 second (PASAT-3); Symbol Digit Modalities Test (SDMT); California Verbal Learning Test II (CVLT-II).[3]	1. No significant changes over time were observed in any cognitive outcome measures.

[1]Primary Outcome Measure; [2]Secondary Outcome Measure; [3]Outcome Measure Not Specified

Table 55. Summary Table of Studies Examining Cycling

	Information Processing	Attention	Memory	Executive Function	Verbal Fluency
Improve	• *Bahmani et al. 2019* ⛨ (SDMT)	• **Briken et al. 2014** ⛨↗ (TAP)	• **Briken et al. 2014** ⛨↗ (VLMT)	• Sandroff et al. 2015 〰 (flanker task)	
No statistical sig. difference	• **Baquet et al. 2018** 〰 (PASAT) • **Briken et al. 2014** ⛨↗ (SDMT) • **Oken et al. 2004** (PASAT) • *Barry et al. 2018* 〰 (CANTAB) • *Swank et al. 2013* (PASAT, SDMT)	• **Oken et al. 2004** (CANTAB) • *Barry et al. 2018* 〰	• **Baquet et al. (2018)** 〰 (VLMT, BVMT, RVWT, CORSI) • *Barry et al. 2018* 〰 • *Swank et al. 2013* 〰 (CVLT)	• **Briken et al. 2014** ⛨↗ (LPS) • **Oken et al. 2004** (Stroop)	• **Briken et al. 2014** ⛨↗ (RTW)

⛨	EDSS $\geq$ 5 or PDSS $\geq$ 3
↗	Progressive MS
〰	Relapse-Remitting MS
Bold	PEDro $\geq$ 6
Regular	PEDro < 6
Italic	Non-RCT

Discussion

There is conflicting evidence for the effect of a cycling intervention on cognitive outcomes between studies and across the cognitive domains. Possible moderating factors, with respect to the response to cycling exercise interventions on cognitive outcomes, may include timing of the cognitive testing in relation to the exercise, intensity of the exercise, MS disease course, degree of CI at baseline, physical deconditioning at baseline, and tolerance for the exercise intervention. Overall, there are more studies not supporting a benefit on cognition; however, most studies include people with RRMS without significant CI at baseline. Interestingly, in the protocol by Sandroff et al. (2015), RRMS participants without CI at baseline, when tested within five minutes of completing their exercise, improved on reaction time cognitive testing. Participants with progressive MS in the Briken et al. (2014) study also improved on reaction time testing (Test of Attentional Performance), but no improvement was observed in the domains of executive function, processing speed, or verbal fluency. In the Briken et al. (2014) study, the exact timing of the cognitive testing in relation to the exercise is not clear. It is possible that there are immediate effects of exercise on reaction time. Mechanisms for the improvement observed in reaction time post cycling exercise may include increased arousal and decreased symptoms of spasticity, which may temporarily affect performance on cognitive-motor reaction time-based tasks. Clinically, PwMS may wish to consider the timing of daily cognitive reaction time-based tasks in relation to their exercise routines.

Future research should include the exact timing of the exercise in relation to the cognitive testing, and details about the intensity of the training. Seated cycling may offer a safe exercise intervention for people at higher risk for falls if they transfer to a stationary bike. A cycle ergometer setup may be accessible from a wheelchair. Briken et al. (2014) report improved reaction time in participants with progressive MS even with a low-intensity cycling intervention. It is not clear if there may be additional benefits to cognition associated with higher intensity cycling training; this is perhaps dependent on baseline function and individual training responses (See also section 3.26.4 for high- versus moderate-intensity cycling training).

Conclusion

There is level 1b evidence that cycling may improve memory for persons with progressive MS (one randomized controlled trial; Briken et al. 2014).

There is level 1a evidence that cycling does not improve information processing speed compared to waitlist control in persons with MS (three randomized controlled trials; Baquet et al. 2018, Briken et al. 2014, and Oken et al. 2004).

There is level 1a evidence that cycling does not improve executive function for persons with MS (two randomized controlled trials; Briken et al. 2014, Oken et al. 2004).

There is level 1b evidence that cycling may not improve memory for persons with relapsing-remitting MS (one randomized controlled trial and two pre-post studies; Baquet et al. 2018, Barry et al. 2018, and Swank et al. 2013).

There is level 1b evidence that cycling may not improve verbal fluency for persons with progressive MS (one randomized controlled trial; Briken et al. 2014).

There is conflicting evidence whether cycling improves attention in persons with MS (two randomized controlled trials; Briken et al. 2014 and Oken et al. 2004).

There is conflicting evidence whether cycling improves cognition in persons with MS, with positive results for improving memory in persons with progressive MS.

3.26.3 Running

People with multiple sclerosis may require adapted exercise therapy programs. A progressive start-to-run program in ambulatory PwMS included cognitive outcomes (Feys et al. 2019).

Table 56. Studies Examining Running for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	**Methods**	**Results**
Feys 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* Belgium **RCT** PEDro=4 $N_{Initial}$=42, N_{Final}=35	**Population:** *Intervention group (n=21)*: Mean age=36.6yr; Sex: males=1, females=20; Disease course unspecified; Severity: unspecified; Mean disease duration=8.1yr. *Control group (n=21)*: Mean age=44.4yr; Sex: males=3, females=18; Disease course unspecified; Severity: unspecified; Mean disease duration=9.2yr. **Intervention:** The participants in the intervention group were involved in a 12-wk start-to-run program. Participants trained 3x/wk and received an individualised training schedule. Training was designed for the goal of running 5km non-stop at 12wks. Participants also wore an activity tracker that required weekly upload. Group training sessions were organized at week 4 and 8 and were supervised by the researcher and master students. These sessions included education elements, individual knowledge acquisition, social interactions, etc. The control group was a waitlist control group that was offered a training program following the end of the study timeline. Both groups had the goal to run a public 5-km race. Outcome and MRI measures were collected at baseline and at 12wks. **Cognitive Outcomes/Outcome Measures:** Brief Repeatable Battery of Neuropsychological Tests (BRB-N)[2] (10/36 Spatial Recall Test (10/36;10/36-SPART; SPART); Word List	1. Significant group*time effects following post hoc analysis were observed in the intervention group on the SPART (mean baseline: 43.1 vs. mean 12wks: 48.0, p<0.05). At baseline, half of participants in the intervention group (n=9) scored below the 10th percentile score for age and educational adjusted norms compared to four subjects after the training. 2. No other cognitive tests were significant for between-group differences; however, changes on cognitive outcome scores trended towards larger improvements for the intervention group. 3. On MRI outcomes, there was a significant group*time interaction with post-hoc tests showing an increased volume of the left pallidum in the EXP group. There was not significant change in the structural connectivity outcomes for either group.

	Generation Test (WLGT), Selective Reminding Test (SRT); Digit Symbol Substitution Test (DSST)); Paced Auditory Serial Addition Test (PASAT).[2]	
Huiskamp et al. 2020 *A pilot study of the effects of running training on visuospatial memory in MS: A stronger functional embedding of the hippocampus in the default-mode network?* Netherlands **RCT** PEDro=3 $N_{Initial}$=29, N_{Final}=29	**Population:** *Intervention group (n=15)*: Mean age=38.1yr; Sex: males=0, females=15; Disease course unspecified; Severity: unspecified; Mean disease duration=9.9yr. *Control group (n=14)*: Mean age=44.7yr; Sex: males=1, females=13; Disease course unspecified; Severity: unspecified; Mean disease duration=8.8yr. **Intervention:** The participants in the intervention group completed a 12-wk, community based, start-to-run program, including sessions 3x/wk. The goal was to run a 5-km run. The control group consisted of a waitlist control. Outcome and fMRI measures were collected at baseline and following the intervention. **Cognitive Outcome Measures:** 10/36 Spatial Recall Test (SPART); Selective Reminding Test (SRT).[3]	1. Statistically significant group*time interaction effect (F(1,27)=5.82, p=0.023) were observed on the SPART. 2. There was no group*time interaction on the SRT. 3. Statistically significant improvements were observed on visuospatial memory from pre- to post-test in the intervention group (change score=4.6, p=0.045). 4. On functional MRI, an improvement in the SPART in the intervention group was associated with an increase in functional connectivity of the hippocampus with the default mode network (r=0.62, p=0.032, corrected for age).

[2]Secondary Outcome Measure; [3]Outcome Measure Not Specified

Table 57. Summary Table of Studies Examining Running

		Memory	
	Information Processing Speed	Spatial Memory	Verbal Learning and Memory
Improve		• Feys et al. 2019 (SPART) • Huiskamp et al. 2020 (SPART)	
No statistical sig. difference	• Feys et al. 2019 (DSST and PASAT)		• Feys et al. 2019 (SRT and WLG) • Huiskamp et al. 2020 (SRT)

Bold	PEDro $\geq$ 6
Regular	PEDro < 6
Italic	Non-RCT

Discussion

The Huiskamp et al. (2020) reports a subsample from the larger RCT by Feys et al. (2019) comparing a 12-week running program to a wait list control group. Therefore, these two manuscripts report overlapping samples of participants with MS. The interventional running group also received education, socialization, and individualized coaching, with the goal of running 5 kilometres at the end of the 12 weeks. In the original RCT by Fey et. al. (2019), primary outcomes included aerobic capacity and functional outcomes, while secondary outcomes included cognition and MRI brain volume and structural connectivity. The trial was positive in favor or the running group for improvement in VO_2max, functional mobility, visual spatial memory, and increased volume of the pallidum on MRI. The manuscript by Huiskamp et al. (2020) elaborates on the fMRI outcomes through which researchers sought to explore the effects of running exercise on resting functional connectivity of the hippocampus, and on the default-mode network (DMN) on fMRI in relation to memory function. The DMN was defined as 38 cortical regions, spanning bilateral medial prefrontal areas, temporal and parietal regions, and posterior cingulate cortex.

Only the running group significantly improved post training on the 10/36 Spatial Recall Test (SPART). The SPART consists of a checkerboard with randomly placed checkers, and the participant must recall the placement of the checkers (Sousa et al. 2021). Functional connectivity of the DMN only significantly correlated with performance on the SPART in the intervention group post training (r=062; p=032) (Huiskamp et al. 2020). The mean age in intervention group, however, was over six years younger than the control group. After correcting for age, the improvement on the SPART observed in the running group was no longer statistically significant. Authors suggest that larger and longer studies exploring exercise intensity effects are warranted. The study sample included participants with a mean disease duration of approximately 10 years and a mean baseline Timed 25-Foot Walk Test of approximately 4.0 seconds (less than four seconds is normal walking speed). Participants also trained on an outdoor running track in a group setting, therefore experiencing three-dimensional visual input while training. Interestingly, participants in the running group improved on the SPART test, but not on the Selective Reminding Test, which involved recalling a list of 12 words. This trial supports the feasibility and safety of outdoor track running in people without significant walking impairment for a possible benefit on spatial memory.

Conclusion

There is level 2 evidence that running may improve spatial memory but not verbal learning and memory or information processing speed in persons with MS (two randomized controlled studies; Feyst et al. 2019; Huiskamp et al. 2020).

Preliminary evidence supports that running may improve spatial memory but not verbal learning and memory or information processing speed in persons with MS.

3.26.4 High-Intensity Aerobic Interval Training

High-intensity interval training (HIIT) typically involves short periods of maximal effort alternating with short rest periods. HIIT protocols may vary in their activation of anaerobic or aerobic pathways.

Table 58. Studies Examining High-Intensity Interval Training for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Zimmer et al. 2018 *High-intensity interval exercise improves cognitive performance and reduces matrixmetalloproteinases-2 serum levels in persons*	**Population:** *Intervention group (n=27)*: Mean age=51yr; Sex: males=7, females=20; Disease course: RRMS=14, SPMS=13; Mean EDSS=4.27; Mean disease duration=11.98yr. *Control group (n=30)*: Mean age=48yr; Sex: males=12, females=18; Disease course: RRMS=16, SPMS=14; Mean EDSS=4.37; Mean disease duration=13.3yr. **Intervention:** Participants in the high-intensity interval training group completed 3	1. Statistically significant time x group effects were observed in favor of the HIIT group for improved verbal memory following training (p=0.034). All other between-group cognitive testing outcome comparisons were not significant. 2. In both groups, statistically significant improvements over time were observed on processing speed on the SDMT

with multiple sclerosis: A randomized controlled trial Germany **RCT** PEDro=8 $N_{Initial}$=61, N_{Final}=57	training sessions/wk for 3wks, with sessionsconsisted of 5x3-min intervals at 90% VO_2peak. The control group completed 5 training sessions/wk for 3wks with 30min of continuous exercise at 65% VO_2peak. Outcome measures and blood samples were collected at baseline and following the 3-wk intervention. **Cognitive Outcome Measures:** Brief International Cognitive Assessment for Multiple Sclerosis (BiCAMS)[1] (California Verbal Learning Test II (CVLT-II), Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test-Revised (BVMT-R)); Trail Making Test (TMT-A, -B)[1]; Go/No Go tasks of the Test of Attention Performance (TAP).[1]	(p=0.001), cognitive flexibility/task shifting on Trail B (p <0.001), and response inhibition on the TAP (p=0.002). 3. A significant correlation existed between cognitive performance on some cognitive tests and VO_2peak at baseline: SDMT (r=0.292, p=0.027) and Verbal Learning Memory Test (r=0.281, p=0.034). 4. A significant correlation existed between cognitive performance on some cognitive test scores and VO_2peak at the end of the study: SDMT (r=0.271; p=0.042); Verbal Learning Memory Test (r=0.244, p=0.068); TMT-A (r=−0.316, p=0.017), TMT-B (r=−0.333, p=0.011) and TAP errors (r=−0.283, p=0.033). 5. There were no significant correlations between the change on VO_2peak and change in cognitive test scores over the study.

[1]Primary Outcome Measure

Table 59. Summary Table of Studies Examining High-Intensity Interval Training

	Attention	Executive Function	General Cognitive	Information Processing Speed	Memory
Improve					• **Zimmer et al. 2018** (CVLT – Verbal Memory)
No statistical sig. difference	• **Zimmer et al. 2018** (TAP)	• **Zimmer et al. 2018** (TMT-A/B)	• **Zimmer et al. 2018** (BiCAMS)	• **Zimmer et al. 2018** (SDMT)	• **Zimmer et al. 2018** (BVMT-R – Visuospatial Memory)

Bold	PEDro $\geq$ 6
Regular	PEDro < 6
Italic	Non-RCT

Discussion

Zimmer et. al (2018) conducted a high-quality RCT comparing aerobic cycling at 80%VO_2max compared to cycling at 60%VO_2max. The study was sufficiently powered to detect small to moderate effect sizes on cognitive outcomes. Secondary outcomes included VO_2peak and brain-derived neurotrophic factor, serotonin, and matrix metalloproteinase (MMP) 2 and -9 serum levels. Interaction effects (time×group) showed significant differences in favor of the HIIT group only for improved verbal memory and cardiorespiratory fitness, and a decrease in serum MMP-2 levels. Both groups improved pre-post training on other cognitive outcomes. Approximately 60% of participants in both groups had cognitive impairment on the BiCAMS on one of the three tests, and SDMT mean baseline scores were ~41.5 with no between-group differences. Importantly, this study excluded participants who were on any immunosuppressant, had a history of psychological disorders or had a severe cardiorespiratory condition, or had an EDSS score greater than 6 or less than 1. Thirty-six percent of participants screened met criteria for randomization. Once randomized, only 2 participants in the HIIT group and 1 participant in the moderate-intensity training group did not complete the protocol.

The results support that, for the activated patient without comorbid psychiatric conditions or severe cardiovascular disease, prescription of HIIT is feasible and may provide additional benefit on verbal memory outcomes compared to moderate-intensity exercise. Limitations of this study include the lack of a non-exercising control group, and the absence of details on how often during the training sessions the VO_2 training targets were met for each group. VO_2peak in both groups was similar at baseline (mean: 19 to 20 mL/kg/min), and VO_2 improved to a mean of 23mL/kg/min only for the HIIT group. It is unclear if higher or lower VO_2 peaks at baseline, or if larger changes in VO_2 may affect cognitive outcomes over time; however, small to moderate correlations between increased VO_2 and improved cognitive function at single time points exist.

Conclusion

There is level 1b evidence that high-intensity aerobic cycling training may improve verbal memory compared to moderate-intensity aerobic cycling training in people with a baseline VO_2 peak of ~20mL/kg/min (one randomized controlled trial; Zimmer et al. 2018).

There is level 1b evidence that high-intensity aerobic cycling training may not improve attention, processing speed, or visual-spatial memory compared to moderate-intensity aerobic cycling training in people with a baseline VO_2 peak of ~20mL/kg/min (one randomized controlled trial; Zimmer et al. 2018).

High-intensity aerobic training may improve verbal memory compared to moderate intensity aerobic training but may not improve cognition in other cognitive domains.

3.26.5 Circuit Training

Circuit training involves performing different exercises with short rest periods in between each exercise. A set number of repetitions are completed, or circuit training may occur for prespecified amount of time.

Table 60. Studies Circuit Training for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Ozkul et al. 2020 *Effect of task-oriented circuit training on motor and cognitive performance in patients with multiple sclerosis: A single-blinded*	**Population:** *Intervention group (n=10)*: Mean age=46yr; Sex: males=4, females=6; Disease course: RRMS=6, PPMS=4; Mean EDSS=4; Mean disease duration=16yr. *Control group (n=10)*: Mean age=41.5yr; Sex: males=4, females=6; Disease course: RRMS=6, PPMS=4; Mean EDSS=3.75; Mean disease duration=13.5yr. **Intervention:** Participants in both groups completed 2 sessions/wk for 6wks. The task-	1. No statistically significant between-group comparisons occurred for any of the cognitive outcomes; however, positive effect sizes were observed for improvement on the cognitive outcomes in both groups. 2. Statistically significant improvements were observed pre-post training on the SRT in the intervention group only (effect size: 1.23, p=0.016, pre: 10, post: 11).

randomized controlled trial Turkey **RCT** PEDro=6 $N_{Initial}$=23, N_{Final}=20	oriented circuit training group participated in 10 exercises in a variety of different settings and task difficulty was increased by altering sensory input (e.g. eyes closed, soft surface, etc.). The relaxation group were taught progressive relaxation exercises and were advised to practice them 2x/wk. Outcome measures were collected at baseline and following the 6-wk intervention. **Cognitive Outcome Measures:** Brief Repeatable Battery of Neuropsychological Tests (BRB-N)[3] (10/36 Spatial Recall Test (10/36; 10/36-SPART; SPART), Word List Generation Test (WLGT), Selective Reminding Test–Long-Term (SRT), Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test-3 (PASAT-3)); Multiple Sclerosis Neuropsychological Questionnaire (MSNQ).[3]	3. No other significant changes in cognition occurred in either group.

[3]Outcome Measure Not Specified

Table 61. Summary Table of Studies Examining Circuit Training

	General Cognitive	Information Processing Speed	Memory
Improve			
No statistical sig. difference	• **Ozkul et al. 2020** (BRB-N)	• **Ozkul et al. 2020** (SDMT, PASAT-3)	• **Ozkul et al. 2020** (SPART, WLG, SRT)

Bold	PEDro ≥ 6
Regular	PEDro < 6
Italic	Non-RCT

Discussion

One RCT by Ozkul et al. (2020) includes the Brief Repeatable Battery of Neuropsychological Tests as a tertiary cognitive outcome following a circuit training intervention. Significant improvement occurred pre-post training only in the circuit-training group on the Selective Reminding Test Long-Term, evaluating verbal and long-term memory. The control group received instruction to complete twice-a-week isometric muscle contraction and relaxation exercises while lying down (Jacobson's progressive relaxation exercises). The participants in the intervention group performed twice-a-week exercises involving 10 different motor tasks, each one for four minutes, with two minutes rest in between. Aerobic exercise intensity while circuit training is not provided. Balance was progressively challenged by alterations in the sensory input during the motor task by doing some tasks with eyes closed, while wearing sunglasses, while turning the head at the same time, or while standing on a softer surface. The study was powered to assess balance and walking outcomes, which significantly improved in favor of circuit training.

Ozkul et al. (2020) hypothesize why only memory improved significantly in the circuit training group, citing other work. Verbal memory tasks activate the premotor and supplementary motor cortex, and therefore motor training may be more likely to improve performance in verbal memory relative to other cognitive domains (Chein and Fiez 2001). Aerobic exercise is associated with increased hippocampal volume and improved performance on memory tasks in MS (Leavitt et al. 2014). There is the possibility of a spurious positive finding in the Ozkul et al. (2020) study for the Selective Reminding Test–Long-Term recall outcome—which was one of the eight different sub-tests of the Brief Repeatable Battery of

Neuropsychological Tests. The Selective Reminding Test–Short-Term recall did not reach statistical significance for improvement in either group pre-post training, although effect sizes were larger in the circuit training group (d=0.51) compared to the control group (d= 0.34). The effects of relaxation on improving cognitive function in the control group may have diminished the power to detect significant between-group differences for any of the cognitive outcomes in this study. However, others have also shown selective improvement in verbal memory with aerobic cycling in progressive MS (Briken et al. 2014), and high-intensity interval training in MS (Zimmer et al. 2018), supporting that aerobic training may have a preferential impact on verbal memory function.

Conclusion

There is level 1b evidence that circuit training may not improve memory, verbal fluency, visual processing speed, or auditory processing speed significantly more than relaxation exercises (one randomized controlled trial, Ozkul et al. 2020).

Preliminary evidence supports that circuit training may not improve memory, verbal fluency, or processing speed more than relaxation exercises in persons with MS

3.26.6 Balance Training and Dual Task

Dual-task balance training involves simultaneously performing a cognitive task and specifically a balance motor task together. The difficulty and the duration of the cognitive task and the balance task performed together may vary. However, different from motor training, the balance task challenges balance more than strength or exercise endurance.

Table 62. Studies Examining Balance Training and Dual Task for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Felippe et al. 2019 *A Controlled Clinical Trial on the Effects of Exercise on Cognition and Mobility in Adults with Multiple Sclerosis* Brazil **RCT** PEDro=7 $N_{Initial}$=28, N_{Final}=27	**Population:** *Intervention group (n=13)*: Mean age=35.0yr; Sex: males=10, females=3; Disease course: RRMS; Mean EDSS=3.0; Mean disease duration=5.0yr. *Control group (n=14)*: Mean age=38.0yr; Sex: males=9, females=5; Disease course: RRMS; Mean EDSS=2.0; Mean disease duration=8.0yr. **Intervention:** Following randomization, the participants in the exercise group attended 2, 1-hr exercise sessions/wk for 6mos while the control group maintained their basic activities. The exercise intervention included activities targeting motor and cognitive function. The motor tasks included exercises for	1. There were significant between-group differences at 6-mo f/u in favor of the intervention group on the MMSE (intervention group mean 28 (27.1-28.0) vs. control group mean 25.5 (23.0-27.0), p=0.007) and the FAB (intervention group mean 16.0 (15.9-17.4) vs. control group mean 14.5 (13.2-15.7), (p=0.006). 2. There were no significant between-group differences on the MMSE or the FAB at baseline (mean MSSE of 26 for both groups; and mean FAB 14.0 for the intervention group and 15.0 for the control group).

	coordination and balance while the cognitive tasks included dual-task training. Outcome measures were collected at baseline, 3mos, and 6mos. **Cognitive Outcome Measures:** Mini-Mental Status Examination (MMSE)[1]; Frontal Assessment Battery (FAB).[1]	3. Within-group longitudinal analysis revealed statistically significant improvement in the intervention group on the MMSE (p=0.001, η2p =.639) and FAB (p=0.001, η2p =.573) while the control group did not have any significant changes 9=0.223, η2p=0.107).

[1]Primary Outcome Measure

Table 63. Summary Table of Studies Examining Balance Training and Dual Task

	Executive Function	General Cognitive
Improve	• **Felippe et al. 2019** (FAB)	• **Felippe et al. 2019** (MMSE)
No statistical sig. difference		

Bold	PEDro $\geq$ 6
Regular	PEDro < 6
Italic	Non-RCT

Discussion

One small, high-quality RCT by Felippe et. al (2019) compared a very specific balance and cognitive training protocol to a sedentary control group. Participants were matched at baseline and fully ambulatory with a mean disease duration of less than 9 years. Results were significantly in favor of the intervention group for the two cognitive outcomes included (the Mini-Mental Satus Examination and the Frontal Assessment Battery) and the balance and dual-task outcomes. In addition, there was significant worsening for the balance outcomes and a trend towards worsening on the cognitive outcomes in the control group.

The intervention group received physiotherapist-guided, progressive balance and dual-task training. Participants completed 10-15 repetitive exercises for one hour twice a week. Exercises included using balls, rolls, dumbbells, and balance boards, as well as variable stepping exercises aimed to challenge balance and stimulate the core and upper and lower body muscle groups. While doing these exercises, participants completed cognitive tasks such as "sequencing, reasoning, attention, strategic planning, task shifting and memory" (Felippe et al. 2019, p. 99) Examples of the cognitive tasks include "defining nouns beginning with specific letters of the alphabet, circuits demanding sequential planning, recognizing, and reaching for objects with specific characteristics and naming fruits, animals, cities and countries." (Felippe et al. 2019, p. 99).

The unique aspect of this study is the targeted, combined progressive balance and cognitive dual-task training under the supervision of a physiotherapist. The results support a role for early physiotherapy intervention using progressive dual-task training in ambulatory PwMS who may not routinely use a mobility aid. This type of intervention may help improve and maintain both cognition and balance relevant to everyday mobility. A limitation of this study is that the cognitive evaluation of participants was limited to two cognitive outcomes (Mini-Mental Status Examination and Frontal Assessment Battery) and the validity of these outcomes in the MS population is not well established. A second limitation is the lack of an active control group. It is therefore unclear whether the cognitive tasks, the motor tasks, or the dual task training itself are driving the observed improvement in cognition. Cognitive-motor dual-task training in comparison to repetitive-motor or gait training alone may not provide additional benefit on cognitive outcomes (see section 3.25).

Conclusion

There is level 1b evidence that balance training combined with a dual task may improve general cognitive impairment and executive function at 6 months compared to no intervention in persons with relapsing-remitting MS (one randomized controlled trial; Felippe et al. 2019).

Balance training coupled with dual task training may improve general cognition and executive function compared to no intervention in persons with relapsing-remitting MS.

3.26.7 Dance

Dancing is considered a multimodal therapy characterized by motor, cognitive, and motor-cognitive dual-task training (Hamacher et al. 2015; 2016). Partnered dance practices such as salsa and ballroom dance may also help with providing support in balance, movement, and fall prevention for the person living with MS (Ng et al. 2020).

Table 64. Studies Examining Dance for Cognitive Impairment in Multiple Sclerosis

Author Year **Title** **Country** **Research Design** **PEDro** **Sample Size**	**Methods**	**Results**
Van Geel et al. 2020 *Effects of a 10-week multimodal dance and art intervention program leading to a public performance in persons with multiple sclerosis - A controlled pilot-trial* Belgium **Pre-post** $N_{Initial}$=18, N_{Final}=17	**Population:** *Dance group (n=7)*: Age range=29-52yr; Sex: males=0, females=7; Disease course: RRMS; Severity: unspecified; Disease duration range=3-21yr. *Art group (n=10)*: Age range=40-65yr; Sex: males=1, females=9; Disease course: RRMS; Severity: unspecified; Disease duration range=6-21yr. **Intervention:** Participants were allocated to groups based on preference. Both groups had 90-min sessions, 2x/wk over 10wks. The dance group received choreo-based dance therapy. The sessions included a 10-min warm up, 70-min training session, and 10-min cool down. The training included three choreographies of increasing difficulty. The art group included poem recitation and creating paintings, photography, and videography. The main goal for both groups was to work toward presenting their performance and work at an exhibition for an audience after the intervention. Outcome measures were collected at baseline and within 2wks after the live performance. **Cognitive Outcome Measures:** Modified Fatigue Impact Scale (MFIS)[1]; Symbol Digit Modalities Test (SDMT)[2]; Paced Auditory Serial	1. A trend towards improvement on the PASAT was observed in the dance group (median pre: 49, post: 55, p=0.068). 2. There was statistically significant improvement in number of correct answers for the SDMT in the art group (median pre: 53, post: 61, p=0.036). 3. Both art and dance groups showed significant improvements on dual task WLGT correct answers (dance pre: 11, post: 15, p=0.028; art pre: 11, post: 15, p=0.017).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	Addition Test (PASAT) [2]; Dual Task: Word List Generation Test (WLGT) and subtraction.[2]	
Ng et al. 2020 *Ballroom dance for persons with multiple sclerosis: a pilot feasibility study* USA **Pre-post** $N_{Initial}$=13, N_{Final}=13	**Population:** *Intervention group (n=7)*: Mean age=49yr; Sex: males=1, females=6; Disease course: RRMS=6, PPMS=1; PDDS=2; Disease duration: unspecified. *Control group (n=6)*: Mean age=55yr; Sex: females=6; Disease course: RRMS; PDDS=2; Disease duration: unspecified. **Intervention:** Participants were recruited from the National MS Society-Wisconsin Chapter. Individuals who could not participate due to scheduling or other commitments were placed in the control group. Dance sessions were 1hr in length and were hosted 2x/wk for 8wks, and participants were required to attend 6 of the 8wks. During the sessions, participants learned the rumba, foxtrot, waltz, and push-pull. The control group did not receive the dancing intervention but did complete all other procedures. Outcome measures were gathered 1wk before and following the intervention. **Cognitive Outcome Measures:** Paced Auditory Serial Addition Test (PASAT).[3]	1. Between-group comparison showed a significant improvement on the PASAT by the intervention group compared to the control group (p<0.05). 2. Within group-comparison showed a significant improvement in the intervention group on the PASAT (median pre: 49, post: 55, p=0.03). 3. Within-group comparison showed no improvement in the control group on the PASAT (median pre: 57, post: 48, p=0.47).

[1]Primary Outcome Measure; [2]Secondary Outcome Measure; [3]Outcome Measure Not Specified

Table 65. Summary Table of Studies Examining Dance

	Info processing
Improve	• Ng et al. 2020
No statistical sig. difference	• Van Geel et al. 2020

Bold	PEDro ≥ 6
Regular	PEDro < 6
Italic	Non-RCT

Discussion

Two non-randomized studies included secondary cognitive outcomes after a dancing intervention. Results are conflicting for significant improvement in processing speed on the Paced Auditory Serial Addition Test (PASAT). However, the study by Van Geel et al. (2020) was close to reaching statistical significance for pre-post improvements on the PASAT in the dancing intervention group. The comparator group in this study was an active control group that received art therapy. Interestingly, the art therapy group improved significantly pre-post on the Symbol Digit Modalities Test, but only trended towards improvement on the PASAT. The Symbol Digit Modalities Test challenges processing speed for symbol recognition while the PASAT involves no visual symbol recognition. It is unclear if this pattern of improvement on cognitive testing is related to the type of training with either dance or art therapy.

Outcomes assessing memory and other cognitive domains were not included. Future research could include effect size calculations for different cognitive outcomes to help inform if there are task-specific training effects. All participants in the Van Geel et al. (2020) study also put on a live performance that participants enjoyed. In contrast, in the ballroom dancing study by Ng et al., participants in the control group received no active intervention. Ng et al. provide a between-group analysis in favor of ballroom dancing on the PASAT (Ng et al. 2020). Both studies found dancing to be enjoyable, safe, and highly feasible in ambulatory participants with MS. Further research is warranted on whether dancing consistently improves cognition, and for which cognitive domains.

Conclusion

There is conflicting evidence whether dance training improves information processing speed in persons with MS (two pre-post studies; Van Geel et al. 2020; Ng et al. 2019).

There is conflicting evidence whether dance training improves information processing speed in persons with MS.

3.26.8 Walking

Walking and cognitive dysfunction are common in MS as the disease progresses (Benedict et al. 2011; Motl, Sandroff, and DeLuca 2016). People living with MS may find walking challenging, and walking limitations may significantly affect quality of life. Participating in exercise training, including treadmill walking, is associated with improved walking and cognitive function in MS (B. M. Sandroff and Motl 2020). This search identified four walking interventional studies and one-stepping interventional study which provide more insight on the reported association between walking and cognitive function.

Table 66. Studies Examining Walking for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Sandroff, Johnson, and Motl 2017 *Exercise training effects on memory and hippocampal viscoelasticity in multiple sclerosis: a novel application of magnetic resonance elastography* USA	**Population:** Mean age=43.5yr; Sex: males=0, females=8; Disease course: RRMS; Median EDSS=3.0; Disease duration: unspecified. **Intervention:** Participants in the intervention group completed 3, 15 to 40-min sessions/wk for 12wks. The intervention involved supervised treadmill walking that progressively increased the difficulty over the course of the intervention. Heart rate monitors were used to ensure precision of exercise prescription. The control group was a waitlist control. They were offered the 12-wk intervention at the end of the study. Outcome and magnetic resonance elastography (MRE)	1. Participants in the intervention group demonstrated an ~4-point increase in CVLT-II scores (d=0.34, small-to-moderate effect) while the control group demonstrated minimal change (d=0.00). 2. Participants did not have any significant learning or memory impairment (CVLT-II mean score=54.8, SD: 11.0).

RCT PEDro=6 $N_{Initial}$=8, N_{Final}=8	measures were collected at baseline and after the 12-wk intervention. **Cognitive Outcome Measures:** California Verbal Learning Test II (CVLT-II).[1]	
Sandroff et al. 2016 *Systematically developed pilot randomized controlled trial of exercise and cognition in persons with multiple sclerosis* USA **RCT** PEDro=5 $N_{Initial}$=10, N_{Final}=10	**Population:** *Exercise group (n=5):* Mean age=41.6yr; Gender: females=5; Disease course: RRMS; Median EDSS=3.0; Mean disease duration=11.4yr. *Control group (n=5):* Mean age=44.2yr; Gender: females=5; Disease course: RRMS; Median EDSS=2.5; Mean disease duration=12.2yr. **Intervention:** MS patients were randomized to the treatment group or to a waitlist control group. The treatment group received progressive treadmill walking exercise training for 12wks. Assessments were performed at baseline and after treatment. **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT); Delis-Kaplan Executive Function (D-KEFS): correct sorts, description; Modified Flanker Task (FT): reaction time (RT), interference control of reaction time (IC RT).[3]	1. No significant effects of treatment were observed for any cognitive outcome measures. 2. The intervention group had a large but nonsignificant improvement on SDMT scores (d=0.95, pre: 55.0, post: 58.2) while the control group worsened (pre: 65.2, post: 61.8).
Sandroff et al. 2015 Acute effects of walking, cycling, and yoga exercise on cognition in persons with relapsing-remitting multiple sclerosis without impaired cognitive processing speed USA **RCT Crossover** PEDro=5 $N_{Initial}$=24, N_{Final}=24	**Population:** Mean age=44.2yr; Gender: males=1, females=23; Disease course: RRMS; Mean EDSS=3.0; Mean disease duration=9.6yr. **Intervention:** MS patients underwent 4 experimental conditions consisting of 20min of moderate-intensity treadmill walking exercise, moderate-intensity cycle ergometer exercise, guided yoga, and quiet rest in a randomized, counterbalanced order. Outcome measures were collected at baseline and within 5min of completion of each experimental condition. **Cognitive Outcome Measures:** Modified-Flanker Task (FT): reaction time (RT), congruent trials, incongruent trials.[1]	1. A significant conditionxtime interaction was observed for the walking condition compared to quiet rest (η_p^2=0.27, p=0.01). 2. Treadmill walking was associated with a greater pre-to-post reduction in reaction time than control (p=0.01) but not accuracy (p=0.29). 3. Treadmill walking improved on executive function according to a pre-post reduction in cost of interfering stimuli on RT (F(1,23)=4.67, p=0.04, np^2=0.17). Pre-post test scores for the same outcome did not improve in cycle or yoga intervention group. 4. Significant effects of congruency were observed in all three exercise conditions (all p<0.01).
Van Geel et al. 2020 *Feasibility study of a 10-week community-based program using the WalkWithMe application on physical activity, walking, fatigue and cognition in persons with Multiple Sclerosis* Belgium **Pre-post**	**Population:** Median age=42.5yr; Sex: males=0, females=19; Disease course: RRMS=18, SPMS=1; Severity: unspecified; Median disease duration=7yr. **Intervention:** Participants completed a 10-wk WalkWithMe app-led intervention. Each participant performed baseline testing and met with a physical therapist at the outset of the intervention to define their goal for the intervention. The goal was defined based on the participant's answer to the question asking how long they want to be able to walk without interruptions. An individualized program was then inputted into the app. Participants completed at least 2 sessions/wk.	1. Statistically significant improvement with a large effect size was observed on the SDMT test (cohen's d=0.70; SDMT mean scores at baseline=57 range 52-60 and at 10-wk=61 range 59-68). 2. There was no significant change on the PASAT scores (mean scores for both pre and post=53). However, cognitive fatigability while completing the PASAT test was significantly decreased post intervention according to the CFI.

$N_{Initial}$=19, N_{Final}=12	Outcome measures were collected at baseline and following the 10-wk intervention. **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT)[2]; Paced Auditory Serial Addition Test (PASAT)[2], Cognitive Fatigability Index (CFI).[2]	

[1]Primary Outcome Measure; [2]Secondary Outcome Measure; [3]Outcome Measure Not Specified

Table 67. Summary Table of Studies Examining Walking

	Improve	No statistical sig. difference
Verbal learning and Memory		• **Sandroff et al. 2017** ﹏ (CVLTII)
Information Processing Speed	• *Van Geel et al. 2020* (SDMT)	• Sandroff et al. 2016 ﹏ (SDMT) • *Van Geel et al. 2020* (PASAT)
Executive Function	• Sandroff et al. 2015 (MFT)	• Sandroff et al. 2016 ﹏ (DKEFS, MFT)

﹏	Relapse-Remitting MS
Bold	RCT PEDro $\geq$ 6
Regular	RCT PEDro < 6
italics	Non-RCT

Dicussion

Information processing speed is the most impaired cognitive domain in MS. However, no studies included people with significant impairment in processing speed at baseline. Both the small RCT by Sandroff et al. (2016) and the pre-post study by Van Geel et al. (2020) included persons with mean processing speed scores that were within the normal range at baseline on the Symbol Digit Modalities Test. Despite this, after a walking intervention both studies still observed large effect sizes for improvement on the Symbol Digit Modalities Test. Only the pre-post study was sufficiently powered to reach a statistically significant change in Symbol Digit Modalities Test scores (Van Geel et al. 2020). The research is limited to small studies led by the same authors (Brian M. Sandroff et al. 2015; 2016; B. M. Sandroff, Johnson, and Motl 2017). Larger studies with longer-term follow-up in people with CI at baseline are needed to determine if walking interventions may help improve processing speed or slow the rate of decline in processing speed in PwMS over time.

From a practical perspective, walking is a low-cost intervention that is safely feasible for the majority of PwMS over the early disease course. However, PwMS may perceive their walking to be effortful both physically and cognitively even when by direct observation the gait impairments may appear invisible (Knox et al. 2020). In counselling about walking among PwMS, the increased energy cost of walking and additional measures to improve walking safety and endurance should be considered (i.e., pacing and adaptive equipment). The many health benefits associated with walking support that in PwMS, maintaining and increasing safe walking in everyday life or for exercise should be priority. The impact of walking interventions on cognition in MS remains uncertain. However, importantly, worsening on cognitive outcomes is not reported in the walking intervention arms of the trials, while worsening of cognition was observed in at least one control group (Brian M. Sandroff et al. 2016).

Conclusion

There is conflicting evidence whether walking programs may improve information processing speed in persons with MS (one randomized controlled trial and one pre-post study; Sandroff et al. 2016 and Van Geel et al. 2020).

There is conflicting evidence whether walking programs improve executive function in persons with MS (two randomized controlled trial; Sandroff et al. 2016 and Sandroff et al. 2015).

There is level 1b evidence that walking programs may not improve verbal learning and memory in persons with relapsing-remitting MS (one randomized controlled trial; Sandroff et al. 2017).

There is conflicting evidence whether walking programs improve information processing speed or executive function in persons with MS.

Walking Programs may not improve verbal learning and memory in persons with MS.

3.26.9 Stepping

Stepping interventions include step training where the natural sequence of stepping with normal overground walking is disrupted intentionally. Step training may require additional cognitive demands.

Table 68. Studies Examining Stepping for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	**Methods**	**Results**
Hoang 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* Australia **RCT** PEDro=8	**Population:** *Intervention group (n=28):* Mean age=53.4yr; Gender: males=7, females=21; Disease course: RRMS=15, PPMS=8, SPMS=5; Mean EDSS=4.1; Mean disease duration=11.6yr. *Control group (n=22):* Mean age=51.4yr; Gender: males=5, females=17; Disease course: RRMS=11, PPMS=2, SPMS=7, unknown=2; Mean EDSS=4.2; Mean disease duration=13.4yr. **Intervention:** MS patients were randomized to either the intervention or control groups. The intervention group performed step training for at least 2x/wk for 30min for 12wks. Those in the control group continued their usual physical activity. Assessments	1. No significant differences were observed between the intervention and control group in SDMT or TMT B-A tests 2. A significant difference was observed between the intervention and the control group on motor reaction timed tasks: Improvements were observed on Choice stepping reaction time (effect size 0.35, p=0.031) and the Stroop stepping test (effect size 0.42, p=0.011) in favor of the intervention group. 3. A significant difference was observed between the intervention and control group on the cognitive motor task (the TUG-Dual Task; p=0.036).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
$N_{Initial}$=50, N_{Final}=44	were performed at baseline and within 7d of the completion of the program. **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT); Trail Making Test A and B[3]; Timed Up and Go-Dual Task; Choice stepping reaction time[1]; Stroop stepping test[1].	
Sebastiao et al. 2018 *Home-based, square-stepping exercise program among older adults with multiple sclerosis: results of a feasibility randomized controlled study* USA **RCT** PEDro=6 $N_{Initial}$=26, N_{Final}=25	**Population:** *Intervention group (n=15)*: Mean age=63.8yr; Sex: males=2, females=13; Disease course: RRMS=14, SPMS=1; Median EDSS=3.75; Mean disease duration=21.9yr. *Control group (n=xx)*: Mean age=65.1yr; Sex: males=1, females=9; Disease course: RRMS=9, SPMS=1; Median EDSS=4.25; Mean disease duration=19.9yr. **Intervention:** Participants in the intervention group received a home-based, 12-wk square-stepping exercise program. Participants were provided with a mat for home-based practice, an instruction manual, a pedometer to track compliance, and a logbook to track exertion, feeling, enjoyment, and physical and mental fatigue. Session length was progressed from 10 to 30min. The control group completed a light-intensity stretching and strengthening program. Intensity was increased through the addition of more exercises. Both groups received weekly Skype calls and biweekly meetings with an exercise trainer. Outcome measures were collected at baseline and following the 12-wk period. **Cognitive Outcome Measures:** Brief International Cognitive Assessment for MS (BiCAMS)[3] (California Verbal Learning Test II (CVLT-II), Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test-Revised (BVMT-R)).	1. No statistically significant between-group differences over time were observed on the SDMT, CVLT, or the BVMT. 2. For the intervention group, there was a non-significant, small-to-moderate effect size for improvement at 12wks compared to baseline on the CVLT (d=0.40) and BVMT (d=0.34), but not for the SDMT (d=0.05). 3. At baseline, the control group had lower processing speeds on the SDMT compared to the intervention group (mean 42.1, SD 15.8 vs. mean 52.8, SD 10.7).

[1]Primary Outcome Measure; [3]Outcome Measure Not Specified

Table 69. Summary Table of Studies Examining Stepping

	Info Processing	Executive Function	Memory
Improve			
No statistical sig. difference	• **Hoang et al. 2016** (SDMT) • **Sebastiao et al. 2018** (SDMT)	• **Hoang et al. 2016** (TMT B)	• **Sebastiao et al. 2018** (CVLT, BVMT)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6
italics	Non-RCT

Discussion

Hoang et al. (2016) investigated a step exergame intervention to no intervention and Sebastiao et al. (2018) compared a mat square-stepping intervention to light-intensity stretching and strengthening. Both studies were smaller feasibility studies and neither study reports statistically significant between-group differences for the purely cognitive outcomes.

In the Hoang et al. (2016) study, the intervention group used a stepmania open-source software program to provide timed stepping rhythms synchronized to stimuli presented on a television screen. The primary outcome measures in this study were the Choice stepping reaction time and Stroop stepping test time. While these are measures of selective attention, they rely on motor-stepping function as well. Other cognitive outcomes included the Symbol Digit Modalities Test, the Trail Making Test A and B, and a dual motor-cognitive task (the Timed Up and Go Test while counting backwards from 100 by three). The Symbol Digit Modalities Test and Trail Making Tests A and B did not reach statistical significance for between-group differences; however, the results support task-specific training effects since outcomes involving stepping improved. The authors also note that participants with worse impairment at baseline were more likely to improve across multiple outcomes over the course of the study.

One of the main limitations of the Sebastiao et al. (2018) study was that participants in the control group were more cognitively impaired at baseline on the Symbol Digit Modalities Test. This limitation potentially further decreased the power for finding statistically significant between-group differences. However, importantly, effect sizes remained larger for greater improvement on the cognitive outcomes in the stepping interventional group compared to the control group.

Step training improves attention in stepping tasks and this improvement may be relevant to maintaining balance in everyday life activities. However, larger studies are needed to determine if step training significantly improves other objective cognitive outcomes.

Conclusion

There is level 1b evidence that square stepping may not improve visual spatial memory, verbal memory, or visual processing speed significantly more than a light stretching and strengthening program (one randomized controlled trial; Sebastião et al. 2018).

There is level 1b evidence that a stepping exergame program may not improve visual-spatial processing speed significantly more than usual physical activities (one randomized controlled trial; Hoang et al. 2016).

Preliminary evidence from small studies supports that stepping exercises may not improve cognitive outcomes in persons with MS compared to usual activity or light physical activity.

3.26.10 Pilates

Pilates is widely regarded as a mind-body fitness practice in which practitioners are taught to focus on breath and posture while training core muscle stability, strength, and flexibility (Wells, Kolt, and

Bialocerkowski 2012), often using specially designed resistance equipment. Pilates is increasingly used in rehabilitation programs, particularly those treating low back pain, where meta-analysis supports improvements in pain scores but not disability (Lim et al. 2011). Core theoretical principles taught in Pilates include activation of core stability musculature, concentration during exercise, control of posture and movement, precision of technique, flow or smooth transition between movements, and coordinated breath control (Wells, Kolt, and Bialocerkowski 2012). Several of these putative elements can be linked in theory with elemental cognitive processes, such as attentional control, somatosensory and interoceptive awareness, and autonomic functioning.

Table 70. Studies Examining Pilates for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	**Methods**	**Results**
Abasiyanik et al. 2020 *The effects of Clinical Pilates training on walking, balance, fall risk, respiratory, and cognitive functions in persons with multiple sclerosis: A randomized controlled trial* Turkey **RCT** PEDro=4 $N_{Initial}$=42, N_{Final}=33	**Population:** *Intervention group (n=16)*: Mean age=42.5yr; Sex: males=4, females=12; Disease course: RRMS=14, SPMS=2; Mean EDSS=3.06; Mean disease duration=12.59yr. *Control group (n=17)*: Mean age=48.24yr; Sex: males=6, females=11; Disease course: RRMS=14, SPMS=3; Mean EDSS=3.24; Mean disease duration=9.83yr. **Intervention:** Participants in both groups conducted 3 sessions/wk for 8wks. The Pilates group was offered 1 session/wk of group exercises and 2 home-exercise sessions. The first session included education on abdominal draw-in maneuver and basic Pilates principles. Each session of 55-60min included exercises in different positions and use of resistance bands and exercise balls. Difficulty was increased gradually by upgrading the resistance bands. The control group home-exercise programs focused on flexibility, strength, trunk and pelvic stability, and balance. Progression included increased repetitions, change in positions, and decrease in base support. Weekly phone calls assessed compliance. Outcome measures were collected at baseline and at the end of the intervention. **Cognitive Outcome Measures:** Brief International Cognitive Assessment for MS (BiCAMS) (California Verbal Learning Test II (CVLT-II), Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test-Revised (BVMT-R)).[1]	1. Statistically significant between-group differences were observed in favor of the intervention group for improvement on the SDMT (intervention group mean change: 6.63, control group mean change: 0.88, p=0.006), CVLT-II (intervention group mean change: 7.31, control group mean change: 1.76, p=0.001), and BVMT-R (intervention group mean change: 6, control group mean change: 2, p=0.007). 2. Within-group comparisons showed significant improvements in the intervention group on the SDMT (pre: 38.62, post: 45.25), CVLT-II (pre: 51.00, post: 58.31), and BVMT-R (pre: 22.12, post: 28.13) (all ps<0.05). 3. Within-group comparisons showed non-significant improvements in the control group on the SDMT (pre: 36.82, post: 37.71), CVLT-II (pre: 48.47, post: 50.24), and BVMT-R (pre: 21.47, post: 23.47).
Küçük et al. 2016 *Improvements in cognition, quality of life, and physical performance with*	**Population:** *Pilates group (n=11):* Mean age=47.2yr; Gender: males=4, females=7; Disease course: Unspecified; Mean EDSS=3.2; Mean disease duration=14.8yr. *Control group (n=9):* Mean age=49.7yr; Gender: males=3, females=6; Disease course: Unspecified; Mean EDSS=2.8; Mean disease duration=14.2yr.	1. Between-group comparison showed a significant improvement in PASAT scores for the intervention group compared to the control group (p<0.05). 2. Within-group comparison showed a significant improvement in PASAT and MFIS cognitive scale scores for the intervention group (p<0.05 for both).

clinical Pilates in multiple sclerosis: a randomized controlled trial Turkey **RCT** PEDro=4 $N_{Initial}$=37, N_{Final}=20	**Intervention:** MS patients were randomized to a Pilates group or an active control. The control group received a traditional exercise program including strength, balance, and coordination exercises. Both groups received 2d of exercise training/wk for 8wks and each session was 45-60min long. Assessments were performed before and after 8wks of treatment. **Cognitive Outcome Measures:** Paced Auditory Serial Addition Test (PASAT); Modified fatigue impact scale (MFIS), cognitive subscale.[3]	3. Within-group comparison showed a significant improvement in PASAT scores for the control group (p<0.05).
Kara et al. 2017 *Different types of exercise in Multiple Sclerosis: Aerobic exercise or Pilates, a single-blind clinical study* Turkey **Pre-post** $N_{Initial}$=76, N_{Final}=56	**Population:** *Aerobic exercise group (n=26)*: Mean age=43.03yr; Sex: males=9, females=17; Disease course: RRMS; Mean EDSS=3.2; Mean disease duration=12.3yr. *Pilates group (n=9)*: Mean age=49.77yr; Sex: males=3, females=6; Disease course: RRMS; Mean EDSS=2.85; Mean disease duration=14.22yr. *Healthy control group (n=21)*: Mean age=44.42yr; Sex: males=8, females=13. **Intervention:** The MS participants were assigned to either the aerobic or Pilates exercise groups, while the healthy participants were assigned to the control group. Both groups were assigned to 2 sessions/wk for 8wks that were supervised by a physical therapist. The aerobic group was educated on how to monitor their heart rate and conducted a 30-40-min session of an aerobic exercise. The Pilates group was taught key elements of the practice including breathing, focus, and body placement. Outcome measures were collected at baseline and after the intervention. **Cognitive Outcome Measures:** Multiple Sclerosis Functional Composite (MSFC) (Paced Auditory Serial Addition Test (PASAT-3).[3]	1. Following between-group comparison, statistically significant improvements were noted in the Pilates exercise group (p<0.05) compared to the aerobics group on the PASAT. 2. No significant improvements were noted in the aerobics group. 3. No other significant differences existed between groups.

[1]Primary Outcome Measure; [3]Outcome Measure Not Specified

Table 71. Summary Table of Studies Examining Pilates

	Info Processing speed	Memory
Improve	• Abasiyanik et al. 2020 (SDMT) • Küçük et al. 2016 (PASAT) • *Kara et al. 2017* (PASAT)	• Abasiyanik et al. 2020 (CVLT, BVMT-R)
No statistical sig. difference		

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

Two lower quality RCTs and one pre-post study included objective cognitive outcomes following a Pilates intervention, with improvement observed on the Paced Auditory Serial Addition Test for all three studies.

Exercise is a core part of rehabilitation programs for PwMS and has several important benefits, including possibly playing a role in preventing disability progression through disease modifying effects (Dalgas et al. 2019), symptom management (R.W. Motl and Gosney 2008), and quality of life (Lara A. Pilutti et al. 2013). A recent meta-analysis reported a null effect of exercise interventions on cognitive function (Gharakhanlou et al. 2021). Since exercise modality, duration, and intensity may vary widely, the MSBEST module has summarized different exercise interventions separately. Caution is required when generalizing findings to a given patient or exercise modality. In meta-analysis, multimodal exercise is associated with upregulation of neuroplasticity biomarkers in PwMS (Diechmann et al. 2021), as has also been observed in a single Pilates study (Eftekhari and Etemadifar 2018).

Pilates is a form of exercise widely used by people with multiple sclerosis (Sánchez-Lastra et al. 2019), who perceive it as an accessible modality. PwMS report physical, psychological, social, and functional benefits following Pilates training, perceiving these benefits to be derived from increased awareness of core musculature in functional task performance (van der Linden et al. 2014). A recent systematic review of Pilates includes 10 RCTs and suggests multiple benefits (improvements in physical functioning, balance, mobility, fatigue, and quality of life) from individual studies, but meta-analysis found only marginal benefits when compared with active comparator conditions (Sánchez-Lastra et al. 2019).

Only two RCTs met the MSBEST criteria for objective cognitive outcomes following a Pilates intervention; however, both studies included active exercise comparator groups. In both RCTs, the Paced Auditory Serial Addition Test, a measure of processing speed requiring sustained attention, improved significantly more in the Pilates group. It is feasible that Pilates may provide training in attentional control especially relevant to testing that demands sustained attention.

Conclusion

There is level 2 evidence that Pilates may improve information processing speed compared to traditional exercise programs in persons with MS (two randomized controlled trials and one pre-post study; Abasiyanik et al. 2020, Küçük et al. 2016, and Kara et al. 2017).

There is level 2 evidence that Pilates may improve memory in persons with MS compared to traditional exercise programs (one randomized controlled trial; Abasiyanik et al. 2020).

Preliminary evidence supports that Pilates may improve information processing speed and memory for persons with MS.

3.26.11 Yoga

Yoga is an ancient Indian practice incorporating breathing, physical postures, and relaxation. Yoga might be classified into different types such as Hatha and Kundalini Ashtanga, which are gentle and focus on breath and pose, and Vinyasa, which is more physical (Senders et al. 2012). Although not all yoga practices are appropriate for PwMS, yoga's focus on breath, movement, and stretching may have potential to improve self-efficacy, mental health, and quality of life for PwMS (Frank and Larimore 2015).

Table 72. Studies Examining Yoga for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Oken et al. 2004 *Randomized controlled trial of yoga and exercise in multiple sclerosis* US **RCT** PEDro=6 $N_{Initial}$=69, N_{Final}=57	**Population:** *Intervention (Yoga) group (n=22):* Mean age=49.8yr; Gender: males=20, females=2; Disease course: Unspecified; Mean EDSS=3.2; Mean disease duration: Unspecified. *Intervention (Exercise) group (n=15):* Mean age=48.8yr; Gender: males=2, females=13; Disease course: Unspecified; Mean EDSS=2.9; Mean disease duration: Unspecified. *Control group (n=20):* Mean age=48.4yr; Gender: males=0, females=20; Disease course: Unspecified; Mean EDSS=3.1; Mean disease duration: Unspecified. **Intervention:** Participants were randomized to one of three groups: yoga class, exercise class (bicycling), or waitlist control group. The classes were provided weekly for 6mos. Participants were assessed at baseline and at the end of the 6-mo period. **Cognitive Outcome Measures:** Stroop Color-Word Test (SCWT); Cambridge Neurophysiological Test Automated Battery (CANTAB); Paced Auditory Serial Addition Test (PASAT).[3]	1. There was no significant difference between the three groups (yoga, exercise, control) at the end of the 6-mo period on any of the cognitive function or alertness measures. 2. Both yoga and exercise groups had a significant improvement in general fatigue compared to control (p<0.01 for both).
Sandroff et al. 2015 Acute effects of walking, cycling, and yoga exercise on cognition in persons with relapsing-remitting multiple sclerosis without impaired cognitive processing speed USA **RCT Crossover** PEDro=5 $N_{Initial}$=24, N_{Final}=24	**Population:** Mean age=44.2yr; Gender: males=1, females=23; Disease course: RRMS; Mean EDSS=3.0; Mean disease duration=9.6yr. **Intervention:** MS patients underwent 4 experimental conditions consisting of 20min of moderate-intensity treadmill walking exercise, moderate-intensity cycle ergometer exercise, guided yoga, or quiet rest in a randomized, counterbalanced order. Outcome measures were collected at baseline and within 5min of completion of each experimental condition. **Cognitive Outcome Measures:** Modified-Flanker Task (FT) sub-scores: reaction time (RT), congruent trials, incongruent trials.[1]	1. Between-group comparison showed significant improvement in RT for the yoga group compared to the quiet rest control group (η_p^2=0.24, p=0.01). 2. Treadmill walking was associated with a greater pre-to-post reduction than control (effect of time) in RT (p=0.03). 3. Cycle ergometry was associated with a greater pre-to-post reduction than control (effect of time) in RT (p=0.01). 4. Significant effects of congruency were observed in all three exercise conditions (all p<0.01).
Velikonja et al. 2010 *Influence of sports climbing and yoga on spasticity, cognitive function, mood, and*	**Population:** *Sports Climbing group (SC; n=10)*: Median Age=42yr; Gender: Unspecified; Disease course: RRMS, PPMS, SPMS; Median EDSS=4; Disease duration: Unspecified. *Yoga group (YG; n=10)*: Median Age=41yr; Gender: Unspecified; Disease course: RRMS, PPMS, SPMS; Median EDSS=4.2; Disease duration: Unspecified.	1. Within-group comparison showed the yoga group had significantly improved Bd2T scores (pre: 151.0, post: 176.5, p=0.005). 2. Within-group comparison showed the climbing group did not significantly improve their Bd2T scores (pre: 115.0, post: 119.5, p=1.000).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
fatigue in patients with multiple sclerosis Slovenia **RCT** PEDro=5 $N_{Initial}$=20, N_{Final}=20	**Intervention:** Participants with MS were randomly assigned to sports climbing exercise or yoga exercise for 10wks. Outcomes were assessed at baseline and post treatment. **Cognitive Outcome Measures:** Tower of London Test (TOL): total number of moves (TOLtnm), total time (TOLtt); Brickenkamp d2Test (Bd2T); Neuropsychological Assessment Battery (NAB): mazes subtest.[3]	3. No significant differences in the TOL or NAB: mazes were observed in either group.

[1]Primary Outcome Measure; [3]Outcome Measure Not Specified

Table 73. Summary Table of Studies Examining Yoga

	Attention	Executive Function
Improve	• Velikonja et al. 2010[B]	• Sandroff et al. 2015[A]
No statistical sig. difference		• **Oken et al. 2004** • Velikonja et al. 2010[B]

[A] compared to rest/no exercise

[B] not a true between-group comparison (no statistical comparison between groups, but the yoga group improved, and the other group did not)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

Each of the three studies examining cognition following a yoga intervention included different cognitive outcomes. Only two of the three studies reported positive findings for only some of the cognitive outcome or subscores within these outcomes (Velikonja et al. 2010, Sandroff et al. 2015). Although yoga did not consistently improve executive function scores, yoga may help improve attention (Velikonja et al. 2010). The timing of the testing might influence results in the attention domain. Sandroff et al. (2015) report improved reaction time with testing completed within five minutes of ending the yoga session. Reaction time was evaluated as a subscore within the modified Flanker task, a test of executive function with attention components within. These three studies with a yoga intervention did not report any adverse effects. Although yoga may not provide a long-term benefit to cognition on objective testing, yoga may provide other health benefits to people living with MS. It would be rational to consider scheduling yoga exercise prior to completing daily tasks that require increased attentional demands. The studies did not include people with more advanced physical or cognitive disability. Modified seated yoga alternatives exist for people who are at risk for falls or unable to transfer independently to the floor. Modified yoga programs have not been studied for their effect on objective outcomes of attention in advanced MS.

Conclusion

There is conflicting evidence whether yoga improves executive function in persons with MS (two randomized controlled trials; Oken et al. 2004, Velikonja et al. 2010)

There is level 2 evidence that yoga may improve attention more than sports climbing in persons with MS (one randomized controlled trial; Velikonja et al. 2010)

Preliminary evidence supports that yoga may improve attention in persons with MS.

There is conflicting evidence whether yoga improves executive function in persons with MS.

3.27 Electrical or Magnetic Stimulation

3.27.1 Functional Electrical Stimulation Cycling

Functional electrical stimulation (FES) cycling is a form of exercise training in which external surface electrodes over the quadriceps, hamstrings, and gluteal muscle groups are controlled by a microprocessor and custom software to create the leg cycling movement (Pilutti et al. 2019). We include FES cycling in this section of the module since it uniquely inovles external electrical stimulation compared to other modes of exercise discussed in section 3.26.

Table 74. Studies Examining Muscle Electrical Stimulation for Cognitive Impairment in Multiple Sclerosis

Author Year **Title** **Country** **Research Design** **PEDro** **Sample Size**	**Methods**	**Results**
Pilutti et al. 2019 *Functional Electrical Stimulation Cycling Exercise in People with Multiple Sclerosis Secondary Effects on Cognition, Symptoms, and Quality of Life* USA **RCT** PEDro=5 $N_{Initial}$=11, N_{Final}=8	**Population:** *Intervention group (n=4)*: Mean age =57.3yr; Sex: males=1, females=3; Disease course: RRMS=2, PPMS=2; Median EDSS=6.25; Mean disease duration=22.3yr. *Control group (n=4)*: Mean age=48.5yr; Sex: females=4; Disease course: RRMS=2, PPMS=2; Median EDSS=6.25; Mean disease duration=20.8yr. **Intervention:** Participants were randomly allocated to the functional electrical stimulation (FES) or the passive leg cycling condition for 3 weekly sessions for 24wks. Both protocols were delivered at 50 rpm cadence, using the same training facility, equipment, and research staff. The intervention group received stimulation and active pedaling to the target cadence and prescribed heart rate as outlined by the American College of Sports Medicine and MS-specific physical activity	1. The FES cycling intervention group compared to passive cycling control group demonstrated a moderate effect size for improvement on the SDMT (d=0.53) in favor of FES cycling. 2. Between-group statistical analyses of change scores over time were not provided. 3. There was no significant difference at baseline between groups on the SDMT (Intervention FES group mean score=41.5, SD=8.8; control group mean score 42.8, SD 10.5).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	guidelines for moderate to vigorous aerobic exercise. The control group did not receive any stimulation or active pedaling. Outcome measures were collected at baseline and at the end of the program **Cognitive Outcome Measures:** Symbol Digit Modalities Test (SDMT).[2]	

[2]Secondary outcome measures

Table 75. Summary Table of Studies Examining Muscle Electrical Stimulation

	Information Processing Speed
Improve	• Pilutti et al. 2019 (SDMT)
No statistical sig. difference	

Bold	RCT PEDro > 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

Pilluti et al. (2019) reported secondary cognitive outcomes on the Symbol Digit Modalities Test from a pilot study comparing passive versus functional electrical stimulation (FES) cycling in MS. The original pilot study published elsewhere found FES cycling to be feasible and effective for improving mobility and cardiovascular fitness in ambulatory PwMS with more advanced disability (EDSS score 5.5 to 6.5) (Edwards et al. 2018). Encouragingly, those in the FES cycling group improved on the SDMT by 14.5% (a mean change score of 6 points) compared to 2.9% (a mean change score of 1.3 points) in the passive cycling group. This improvement in favor of FES cycling supports a likely clinically meaningful change. However, between-group statistical analyses are not provided due to the pilot nature of this study.

The FES cycling protocol involved a biphasic symmetrical waveform, a phase duration of 250 µs, and a pulse rate of 50 pulses per second. The FES cycle product used in this study was the RT300 cycle (Restorative Therapies Inc, Baltimore, MD). In the FES cycling group, target cycling cadence and prescribed heart rate were based on recommendations for moderate to rigorous aerobic exercise from the American College of Sports Medicine and MS-specific physical activity guidelines (American College of Sports Medicine 2013; Latimer-Cheung et al. 2013). In the passive cycling group, the cycle ergometer motor generated passive leg movement. A limitation with FES cycling in practice may be access to an FES cycling machine and staff familiar with FES cycling protocols. However, FES cycling does provide a safe platform for moderate to vigorous aerobic exercise in patients with restricted mobility, with potential for benefiting cognition in addition to other health benefits.

Conclusion

There is level 2 evidence that functional electrical stimulation cycling may improve visual processing speed compared to passive cycling in persons with MS with mobility impairments (one randomized controlled trial; Pilutti et al., 2019).

Functional electrical stimulation cycling may improve visual processing speed compared to passive cycling in persons with MS with mobility impairments.

3.27.2 High-Frequency Repetitive Transcranial Magnetic Stimulation

High-frequency repetitive transcranial magnetic stimulation (rTMS) provides ≥5 Hz of repetitive magnetic stimulation (rTMS), against the scalp, inducing the excitability of a particular cortical region (Hulst et al. 2017). Health Canada first approved rTMS for the treatment of treatment-resistant major depressive disorder (Downar, Blumberger, and Daskalakis 2016). The Canadian Stroke Best Practice Guidelines recommend that rTMS could be considered as an adjunct to upper-extremity therapy (Evidence Level A) (Canadian Best Stroke Practices, 2019), but does not provide recommendations on the use of rTMS for language or perceptual impairments following stroke.

Table 76. Studies Examining High-Frequency Repetitive Transcranial Magnetic Stimulation for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	**Methods**	**Results**
Hulst et al. 2017 *rTMS affects working memory performance, brain activation and functional connectivity in patients with multiple sclerosis* Netherlands **RCT Crossover** PEDro=7 $N_{Initial}$=30, N_{Final}=28	**Population:** *MS participants (n=17):* Mean age=43.3yr; Gender: males=7, females=10; Disease course: RRMS=13, SPMS=4; Mean EDSS=3.5; Mean disease duration=11.9yr. *Healthy controls (n=11):* Mean age=42.3yr; Gender: males=5, females=6. **Intervention:** MS patients and healthy controls underwent three experimental sessions (baseline, rTMS, sham-rTMS) including an N-back task under three load conditions: 1-back (N1), 2-back (N2), 3-back (N3), and 0-back control (N0). Assessments were performed at baseline and after rTMS or sham-rTMS. **Cognitive Outcome Measures:** N-back working memory task: accuracy, reaction time.[1]	1. In MS patients, N-back task accuracy significantly improved with-rTMS compared to baseline during the 2-back and 3-back task loads (p=0.029, p=0.015 respectively). This improvement from baseline test scores was not signficant under the sham-rTMS condition. Between-group (rTMS vs. sham-rTMS) change scores on the N-back accuracy test also did not reach statistical significance. 2. In MS patients a significant difference in N-back task reaction time was observed during rTMS compared with baseline under the 3-back condition (p=0.016). 3. No other significant differences in cognitive outcomes were observed. 4. In healthy controls, there was no significant change in N-back task accuracy between rTMS and baseline or between rTMS and sham-rTMS. On the 2-back task load, there was significant improvement after sham-rTMS compared to baseline (p=0.023). There were no significant differences in reaction time observed.

[1]Primary Outcome Measure

Table 77. Summary Table of Studies Examining High-Frequency Repetitive Transcranial Magnetic Stimulation

	Memory
Improve	
No statistical sig. difference	• **Hulst et al. 2017** (N-back)

Bold	RCT PEDro $\geq$ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

One study reported on the effects of high-frequency repetitive transcranial magnetic stimulation (rTMS) of the right dorsolateral prefrontal cortex on working memory and fMRI outcomes.(Hulst et al. 2017). Healthy controls and PwMS completed, in a random order, a visuospatial N-back working-memory task with three levels of increasing difficulty (1-back, 2-back, and 3-back) and a control condition (N0) while fMRI data was collected under the rTMS and sham-rTMS conditions. There was no statistically significant difference between the N-back scores in the rTMS and the sham-rTMS conditions. This small study may not have been sufficiently powered to detect between group differences. The authors do not include other outcome measures assessing memory or other cognitive domains. However, PwMS and the healthy controls in this study are reported to have normal cognitive function at baseline. For the PwMS, within the rTMS condition, results on the 2-back and 3-back accuracy test scores and 3-back reaction time scores significantly improved compared to the baseline scores. On fMRI, PwMS also displayed higher task-related frontal activation of the left dorsolateral prefrontal cortex compared to controls on the level 2 difficulty (2-back) of the N-back test. The increased activation in the left dorsolateral prefrontal cortex likely indicates abnormal and less-efficient brain connectivity in PwMS while performing a more difficult cognitive task. This finding of a less efficient brain activation pattern in PwMS is also supported by the work of others (Staffen et al. 2002). The increased cortical activation in the PwMS in the RCT by Hulst et al. (2017) interestingly normalized only after rTMS, but not after sham-rTMS.

A limitation of the Hulst et al. study is the strict inclusion criteria to safeguard against the risk of rTMS triggering a possible seizure in participants more susceptible to seizures. Exclusion criteria included: use of medication that lowers the seizure threshold (which presumably would indicate that participants on baclofen were excluded); and/or if participants had ≥12 cortical MS lesions. The study rTMS protocol is described as follows: 10 Hz, 110% RMT, 60 trains of 5 seconds, 25 seconds between trains, in total 3000 biphasic pulses in 30 minutes. The rTMS is individually positioned for each participant to ensure stimulation over the right dorsolateral prefrontal cortex. The sham protocol differs in intensity with a lower intensity of 80% RMT, and in positioning over a non-effective area (2 centimetres posterior to the vertex). Authors suggest that rTMS should be explored in terms of safety for PwMS with more severe cognitive impairment and extensive MS lesion load.

Conclusion

There is level 1b evidence that high-frequency repetitive transcranial magnetic stimulation (rTMS) may not significantly improve working memory compared to sham-rTMS in persons with

MS without cognitive impairment at baseline (one randomized controlled trial; Hulst et al. 2017).

Preliminary evidence from small studies supports that high frequency repetitive transcranial magnetic stimulation may not improve working memory in persons with MS.

3.27.3 Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) involves a low- intensity direct current applied through surface electrodes placed on the scalp. The current modulates the membrane polarity of the underlying neurons thought to promote cortical excitability and neuroplasticity (Mattioli et al. 2016). The Canadian Best Stroke Practices Guidelines recommend tDCS "could be considered as adjunct therapy following stroke to improve upper limb function (Level B evidence)" (Canadian Stroke Best Practices 2019, p.38). However, these guidelines do not provide recommendations concerning tDCS for the rehabilitation of language or perceptual deficits following stroke. The exact therapeutic mechanisms are not well understood.

Table 78. Studies Examining Transcranial Direct Current Stimulation for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Mattioli et al. 2016 *Neuroenhancement through cognitive training and anodal tDCS in multiple sclerosis* Italy **RCT** PEDro=8 $N_{Initial}$=20, N_{Final}=20	**Population:** *a-tDCS group (n=10):* Mean age=38.2yr; Gender: males=3, females=7; Disease course: RRMS; Mean EDSS=2.1; Mean disease duration=6.6yr. *Sham group (n=10):* Mean age=47.2yr; Gender: males=1, females=9; Disease course: RRMS; Mean EDSS=2.9; Mean disease duration=11.0yr. **Intervention:** MS patients were randomly assigned to receive cognitive training with actual or sham anodal transcranial direct current stimulation (a-tDCS). a-tDCS was applied directly over the left dorsolateral prefrontal cortex (DLPFC). The cognitive training involved combining attention training with real or sham a-tDCS for 10 daily sessions. Assessments were performed at baseline (T0), after treatment (T1), and 6mos later (T2). **Cognitive Outcome Measures:** Selective Reminding Test: long-term storage (SRT-LTS), consistent long-term retrieval (SRT-CLTR), delayed recall (SRT-D); Spatial Recall Test: delayed recall (SPART-D); Symbol Digit Modalities Test (SDMT); Paced Auditory Serial	1. Between-group analyses from T0 to T1 showed the intervention group significantly improved compared to the control group on the SDMT (d=1.15, p=0.019), WCST total errors (d=1.31, p=0.003), WCST perseverative responses (d=0.98, p=0.035), WCST perseverative errors (d=1.11, p=0.043), and WCST non-perseverative errors (d=1.29, p=0.009); there were no significant between-group differences on the SRT, SPART-D, WLGT, PASAT-2 and PASAT-d3 over this same time period. 2. Between-group analyses from T0 to T2 showed the intervention group performed significantly better than the control group on only the PASAT-2 (d=1.23, p=0.015) and WCST total errors (d=1.05, p=0.035). 3. Between-group analyses from T1 to T2 were not significantly different in any test, indicating that improvements were maintained for 6mos after the training period.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	Addition Task: 3, 2 seconds (PASAT-3, -2); Word List Generation Test (WLGT); Wisconsin Card Sorting Test (WCST): total errors, perseverative responses, perseverative errors, non-perseverative errors.[3]	
Chalah et al. 2017 *Effects of left DLPFC versus right PPC tDCS on multiple sclerosis fatigue* France **Crossover RCT Design** PEDro=6 $N_{Initial}$=12, N_{Final}=10	**Population:** Mean age=40.5yr; Sex: males=6, females=4; Disease course: RRMS=9, SPMS=1; Mean EDSS=2.3; Mean disease duration=14.0yr. **Intervention:** Participants were randomized into three anodal transcranial direct current stimulation (tDCS) blocks: active stimulation over left dorsolateral prefrontal cortex (DLPFC), active stimulation over the right posterior parietal cortex (PPC), or sham stimulation over either cortical site. Participants were then assigned to a secondary active stimulation (e.g.: DLPFC assigned to PPC) or the sham protocol. Finally, participants were then crossed over to the opposite allocation (sham or active). Each participant received five consecutive daily sessions at the same time of day. There was a 3-wk washout period before outcome measures were collected on day 1 and day 5 of the intervention. **Cognitive Outcome Measures:** Attention Network Test (ANT).[3]	1. There was no difference between active stimulation and sham treatment for any ANT parameters, including mean reaction time, mean accuracy, and efficiency of attention networks.
Charvet et al. 2018 *Remotely Supervised Transcranial Direct Current Stimulation Increases the Benefit of At-Home Cognitive Training in Multiple Sclerosis* USA **Pre-post** $N_{Initial}$=46, N_{Final}=45	**Population:** *Intervention group (n=25)*: Mean age=52.7yr; Sex: males=4, females=21; Disease course: RRMS=7, other=18; Severity: unspecified; Mean disease duration=17.7yr. *Control group (n=20)*: Mean age=51.0yr; Sex: males=7, females=13; Disease course: RRMS=15, Other=5; Severity: unspecified; Mean disease duration=15.7yr. **Intervention:** Participants were assigned to either the control group or the active intervention group. Both received 10, 20-min sessions over 2wks. The intervention group received transcranial direct current stimulation (tDCS) and cognitive training. The tDCS was an at-home, technician-guided intervention that delivered 1.5mA of stimulation while the participants completed the cognitive training. Both groups received the cognitive training program, which focused on five areas: n-back, auditory span, visual span, simple arithmetic, and match-to-sample. Outcome measures were collected at baseline and post-intervention.	1. The intervention group had significantly greater improvements on complex attention (means for intervention: 0.28, SD: 0.53, control= -0.25, SD: 0.55, p=0.01) and intra-individual variability (means for intervention=0.4, SD: 0.84, control= -0.33, SD: 0.76, p=0.01). 2. There were no between-group differences for the BiCAMS score, but both groups slightly improved (means for intervention=0.09, SD: 0.47; control=0.09, SD: 0.47, p=0.99) 3. There were no between-group differences for basic attention, but both groups improved slightly (means for intervention= -0.01, SD: 0.72, control=0.01, SD: 0.32, p=0.95). 4. Intra-individual variability on cognitive performance was non-statistically different between groups but improved in the intervention group while worsening in the control group.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	Cognitive Outcome Measures: Brief International Cognitive Assessment in MS (BiCAMS) (Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test-Revised (BVMT-R), Rey Auditory Verbal Learning Test (RAVLT)); Attention Network Test-Interaction (ANT-I); Cogstate Brief Battery.[3]	

[3]Outcome Measure Not Specified

Table 79. Summary Table of Studies Examining Transcranial Direct Current Stimulation

	Executive function	Info processing	Attention	Memory
Improve	• **Mattioli et al. 2016** (WCST) • *Charvet et al. 2018* (complex attention, composite score)	• **Mattioli et al. 2016** (SDMT)		
No statistical sig. difference		• *Charvet et al. 2018* (SDMT)	• **Chalah et al. 2017** (ANT) • *Charvet et al. 2018* (ANT-I)	• **Mattioli et al. 2016** (SRT, SPART, WLG) • *Charvet et al. 2018* (BVMT-R)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

Three studies tested the effects of transcranial direct current stimulation (tDCS) on objective cognitive outcomes. Two of the three studies report positive findings favoring treatment for some of the cognitive outcomes (Mattioli et al. 2016; Charvet et al. 2018). Interestingly, the third study by Chalah et al. (2017) does not report any significant cognitive outcomes, but does report that tDCS over the left dorsolateral prefrontal cortex is associated with improved fatigue on the Fatigue Severity Scale and the Modfied Fatigue Impact Scale physical and psychological sub-scales, but not with the Modified Fatigue Impact Scale cognitive subscore. The primary outcome in the Chalah et al. (2017) study was fatigue.

In the RCT by Mattioli et al. (2016) and the prep-post study by Charvet et al. (2018), both the intervention and sham control groups participated in cognitive rehabilitation exercises while undergoing tDCS or sham treatment, while the participants in the RCT by Chalah et al. (2017) did not. Possibly, tDCS enhances cognition on some outcome measures only when combined also with cognitive rehabilitation training.

Cognitive outcomes in both the sham and the treatment groups improved in all three studies, demonstrating the importance of having a sham control. The Mattioli et al. (2016) study report statistically significant findings for between-group differences for select cognitive outcomes (i.e., the Symbol Digit Modalities Test and Wisconsin Card Sorting Test) and Charvet et al. (2018) report significant between-group differences for only one of their cognitive outcomes evaluating complex attention. The clinical significance of the positive between-group findings favoring the tDCS treatment on these select cognitive outcomes is uncertain. Effect size calculations in future tDCS research would be informative.

Mattioli et al. (2016) suggest that cognitive training during tDCS over the left dorsolateral prefrontal cortex improves information processing speed and executive function through longer-term changes in the synaptic strength of the transmissions. Cognitive outcomes in the memory domain did not significantly improve after tDCS treatment compared to the sham treatment. However, the cognitive rehabilitation training protocols (for the two studies including cognitive exercises) did not focus specifically on memory-related training (Mattioli et al. 2016; Charvet et al. 2018).

Conclusion

There is level 1b evidence that transcranial direct current stimulation combined with cognitive training may improve executive function compared to sham treatment combined with cognitive training (one randomized controlled trial and one pre-post study; Chalah et al. 2017, Charvet et al. 2018).

There is level 1b evidence that transcranial direct current stimulation may not improve basic attention compared to sham treatment (one randomized controlled trial and one pre-post study; Chalah et al. 2017, Charvet et al. 2018).

There is level 1b evidence that transcranial direct current stimulation may not improve memory in persons with MS compared to sham treatment (one randomized controlled trial and one pre-post study; Mattioli et al. 2016; Charvet et al. 2018).

There is conflicting evidence whether transcranial direct current stimulation combined with cognitive training improves visual information processing compared to sham treatment combined with cognitive training (one randomized controlled trial and one pre-post study; Mattioli et al. 2016, Charvet et al. 2018).

Transcranial Direct Current Stimulation over the left dorsolateral prefrontal cortex may improve executive function when combined with cognitive training tasks.

3.27.4 Transcranial Random Noise Stimulation

Transcranial random noise stimulation is a form of transcranial electric stimulation that involves transmission of a randomly oscillating current in a defined threshold over the dorsolateral prefrontal cortex (Palm et al. 2016).

Table 80. Studies Examining Transcranial Random Noise Stimulation for CI in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Palm et al. 2016 *Effects of transcranial random noise stimulation (tRNS) on affect, pain, and attention in multiple sclerosis* France **RCT Crossover** PEDro=5 $N_{Initial}$=16, N_{Final}=16	**Population:** Mean age=47.4yr; Gender: males=3, females=13; Disease course: RRMS=11, SPMS=4, PPMS=1; Mean EDSS=4.2; Mean disease duration=12.5yr. **Intervention:** MS patients received two blocks of transcranial random noise stimulation (tRNS) over the dorsolateral prefrontal cortex (DLPFC) in a randomized order. The blocks were separated by a 3-wk washout period. Each block consisted of three consecutive daily sessions of either active or sham tRNS. Assessments were performed at baseline and after each tRNS block. **Cognitive Outcome Measures:** Attention Network Test (ANT); ANT subscales included: mean response time (MRT), mean accuracy (MA), alerting, orienting, executive control.[3]	1. No significant changes were observed in any of the ANT subscales after sham stimulation or tRNS.

[3]Outcome Measure Not Specified

Table 81. Summary Table of Studies Examining Transcranial Random Noise Stimulation

	Attention
Improve	
No statistical sig. difference	• Palm et al. 2016 (ANT)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

One crossover RCT investigated the effects of transcranial random noise stimulation on neuropathic pain and attention in participants with MS (Palm et al. 2016). Participants received two blocks of transcranial random noise stimulation followed by a three-week washout period. The blocks involved either active or sham transcranial random noise stimulation that were delivered over three consecutive daily sessions. The sessions using transcranial random noise stimulation involved wearing a cap with predefined localization over the dorsolateral prefrontal cortex. The stimulation intensity and duration were set for 2mA and 20-30 minutes, respectively. The sham protocol involved the software ramping up for 15 seconds before it switched off. Attention was measured at baseline and following each training block. Results of the study concluded that there were no significant changes in attention following sham or transcranial random noise stimulation. A trend for improved pain was observed in the intervention group in this small study of 16 participants. The dorsolateral prefrontal cortex has a role in pain and attention circuits, and authors suggest that protocols with longer stimulation may yield better outcomes.

Conclusion

There is level 1b evidence that transcranial random noise stimulation may not improve attention in persons with MS compared to placebo (from one randomized controlled trial; Palm et al. 2016).

Transcranial random noise stimulation may not improve attention in persons with MS.

3.27.5 Tongue Electrical Stimulation

The Portable Neuromodulation Stimulator (PoNS™) is a medical device that provides direct transcutaneous electrical stimulation to the tongue, marketed by Helius Medical Technologies. The FDA approved the device in March of 2021 through their breakthrough device program as a novel medical device (FDA 2022; 2021a). According to the FDA, the PoNS™ is be used only as an adjunct to short-term, physiotherapist-guided gait training in people with MS with mild to moderate symptoms (FDA 2021b). Prior to this, Health Canada approved the device in ￼., the PoNS™ device and corresponding training is available through authorized PoNS Therapy™ ￼clinics.ost varies from $20,000 to $30,000 CAD from site to site and includes the cost of the device ($9,500 CAD) and the cost of therapy sessions. CAD) and the cost of therapy sessions.

Data from two studies with 20 and 14 PwMS respectively (Tyler et al 2014, Leonard et. al. 2017), as well as real-world safety data, led to FDA approval of PoNS™. The participants in the RCTs received real or sham tongue stimulation, and all participants in both studies received individualized, physiotherapist-guided, in-lab training for 90 minutes twice a day for 14 days, followed by home exercise training for an additional 12 weeks. Participants treated with sham or real tongue stimulation both improved over the course of these studies on the primary outcomes: the clinician-scored Dynamic Gait Index (Chiu et al. 2006) or the Sensory Organization Tasks (Broglio et al. 2008). The Sensory Organization Tasks consist of computerized balance data captured through a force plate. There was significantly greater improvement in favour of the intervention stimulation groups on the Dynamic Gait Index for the larger of the two studies (Tyler et al. 2014) and on the Sensory Organization Tasks for the smaller study (Leonard et al. 2017). More conventional gait outcomes utilized in MS, such as the Timed-25 Foot Walk Test, were not included. Authors propose that electrical stimulation of the tongue modulates central nervous system structures controlling balance and movement (Tyler et al. 2014).

Table 82. Studies Examining Muscle Electrical Stimulation for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	**Methods**	**Results**
Leonard et al. 2017 *Noninvasive tongue stimulation combined*	**Population:** *Active group (n=7):* Mean age=47.7yr; Gender: males=3, females=4; Disease course: Unspecified; Mean EDSS=4.2; Mean disease duration=11.2yr. *Sham group (n=7):* Mean age=49.7yr; Gender: males=3, females=4; Disease course:	1. No significant between-group difference in change scores were observed for the cognitive outcomes. 2. Both groups improved on the cognitive outcomes. In both groups there was significant improvement on the Symbol

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
with intensive cognitive and physical rehabilitation induces neuroplastic changes in patients with multiple sclerosis: A multimodal neuroimaging study Canada **RCT** PEDro=4 $N_{Initial}$=14, N_{Final}=14	Unspecified; Mean EDSS=4.2; Mean disease duration=22.3yr **Intervention:** MS patients were randomized to receive either active non-invasive electrical tongue stimulation or sham stimulation. All subjects received intensive physical training for walking and balance (14wks) and concurrent working memory training on the computer-based memory training software program (COGMED) for 10 of the 14wks. Assessments were performed at baseline and after 14wks of treatment. **Cognitive Outcome Measures:** Wechsler Abbreviated Scale of Intelligence (WASI); California Verbal Learning Test II (CVLT-II); D-Kefs trails: color/word, verbal fluency; Tower of London 2nd edition; Ruff 2 and 7; Wechsler Adult Intelligence Scale-IV (WAIS-IV): letter-number sequencing, coding, and symbol search; Paced Auditory Serial Addition Test (PASAT); Cognitive function inventory for MS.[3]	Search, Colour-Word Naming and Inhibition, and Trail Making Switching (p<0.01 for all). 3. Both groups demonstrated significant improvement on COGMED scores from baseline to post-training (p>0.0001). Between-group comparisons did not reach statistical significance. 4. fMRI during a cognitive memory-based task revealed a significant increase in the Blood oxygen level dependent (BOLD) signal in the left dorsal lateral prefrontal cortex (DLPC) and rostral anterior cingulate cortex, and a similar trend on the right side in the active treatment group only. The control group showed bilateral increased premotor cortical BOLD signal.

[3]Outcome Measure Not Specified

Table 83. Summary Table of Studies Examining Muscle Electrical Stimulation

	Executive Function	Information Processing Speed	Memory
Improve			
No statistical sig. difference	• Leonard et al. 2017 (D-Kefs trails, Tower of London)	• Leonard et al. 2017 (PASAT)	• Leonard et al. 2017 (CVLT-II)

Bold	RCT PEDro ≥ 6
Regular	RCT PEDro < 6 or PCT
italics	Non-RCT

Discussion

One RCT investigated the use of non-invasive cranial nerve modulation delivered via electrical tongue stimulation combined with multi-modal training on walking and balance, as well as working memory and fMRI outcomes in individuals with moderate disability (EDSS 3-6) (Leonard et al. 2017). The portable neuromodulation stimulator device (PoNS™ version 2.2) was used in both groups to either deliver the electrical stimulation (intervention group), or sham treatment (control group).

Participants in both groups in the Leonard et al. study also completed physical therapy exercises and computer cognitive training targeting memory using the COGMED software program. Targeted computer based cognitive training may improve cognition on related cognitive testing in PwMS, with possible dose training effects (see section 3.2). In a small study of PwMS, five days a week working memory training with COGMED over five weeks improved memory on a related Color Word Interference Test (Blair et al. 2021). In the Leonard et al. PoNS™ study, the COGMED protocol included training four times per week for the final 10 weeks. The physical training involved balance and walking drills, motor-control exercises, and practicing breathing and awareness techniques. The proposed physical training dose was extremely high, totaling a target of 180 minutes daily over 14 weeks. Exercise training may also influence cognitive testing results (see section 3.26). The Leonard et al. study did not report on adherence with these extensive training programs for either the control group or the intervention group. The PoNS™ device was held between the lips and teeth, and in the intervention group, stimulation over the anterior superior tongue was increased until the participants felt "moderate intense tingling" (Leonard et al. 2017, p. 3).

There were no statistically significant differences between the intervention and sham control groups for the cognitive outcomes. The study was small (n=14), not powered to detect clinically meaningful change, and the principal investigator was not blinded. Pre-post training, some of the cognitive outcomes targeting memory improved in both groups, with a trend towards larger improvements in the intervention group. Differences on fMRI during a probed memory task were reported, with changes in the left primary motor cortex seen only in the intervention group. Authors include data from a healthy control group and a "rollover" group of PwMS in describing the fMRI results, groups not mentioned in the initial methods section of the study.

The Leonard et al. (2017) study involved a multi-modal intervention; therefore, it is difficult to make any conclusions on the possible independent effects of tongue stimulation. The follow up in the Leonard et al. (2017) study is limited to immediately post-training. Authors do not report effect sizes or the raw scores on the cognitive tests. We do not know how cognitively impaired participants were at baseline or how much improvement occurred pre-post the training protocol. Overall, the addition of tongue stimulation to a multimodal intervention provided no additional benefit compared to sham tongue stimulation for cognition.

Conclusion

There is level 2 evidence that adding non-invasive cranial nerve stimulation to the tongue in addition to COGMED training and exercise may not improve memory, executive function, or information processing speed compared to no tongue stimulation and COGMED and exercise training (one randomized controlled trial; Leonard et al. 2017).

Preliminary evidence supports that non-invasive tongue stimulation may not improve memory, executive function, or information processing speed in persons with MS.

4.0 Evidence Statement Summary

There is level 1a evidence that the following interventions may benefit cognition in MS on one ore more cognitive outcomes:

- Computer-based cognitive rehabilitation targeting executive function
- Computer-based cognitive rehabilitation targeting information processing speed

- Computer-based cognitive rehabilitation targeting memory
- Computer-based cognitive rehabilitation over 33 hr for 12 wk
- RehaCom modules targeting executive function
- RehaCom modules targeting information processing speed
- RehaCom modules over 33 hr for 12 wk
- Story memory
- Mental visual imagery on an autobiographical memory interview assessment

There is <u>level 1a</u> evidence that the following interventions <u>do not benefit</u> cognition in MS on one ore more cognitive outcomes:

- Self-generation technique
- Story memory
- Mindfulness-based
- Dual task training
  - Information processing speed
  - Memory
- Cycling
  - Information processing speed
  - Executive function

There is <u>level 1b</u> evidence that the following interventions <u>may benefit</u> cognition in MS on one ore more cognitive outcomes:

- REACTIV program
- REACTIV protocol
- French ProCog-SEP involving facilitation & reorganization trainig
- Compensatory strategies targeting attention & memory
- Freshminder 2 combined with counselling for compensatory strategies
- RehaCom
- RehaCom targeting memory
- Computer-based cognitive rehabilitation targeting reaction time
- NOROSOFT mental exercise software for 24 wk
- Speed of processing training
- ERICA software
- ERICA targeting memory
- VILAT-G
- VILAT-G targeting memory
- Lumosity targeting memory combined with group compensatory strategies

- NOROSOFT 100 hr for 24 wk
- Nintendo's Brain Training video games
- BST-Nirvana virtual reality training
  - Information processing speed
  - Memory
- Strobic visual training
- Selective reminding
- Self-generation technique
- Mindfulness-based training
- Neurologic music therapy combined with cognitive rehabilitation
- Walking, cycling, and ROM exercise while wearing cool garment
- Cycling
- High intensity interval training
  - Audio processing speed
  - Verbal memory
  - Executive function
- Balance training + dual task (6 mon)
  - General cognitive impairment
  - Executive function
- Stepping
- Transcranial direct current stimulation

There is level 1b evidence that the following interventions do not benefit cognition in MS on one ore more cognitive outcomes:

- Memory & attention rehabilitation using education & compensatory strategies
- Compensatory memory strategies
- French ProCog-SEP involving facilitation & reorganization training
- REACTIVE program
- Group cognitive training that focuses on compensatory strategies & restitution for memory & attention
- VILAT-G
- Attention processing training
- MAPSS-MS program
- Lumosity
- Lumosity targeting memory combined with group compensatory strategies
- NOROSOFT
- Robotic-assisted gait-training in a virtual reality environment
  - Information processing speed
  - Memory
  - Verbal language skills

- Strobic visual training
  - Memory
  - Executive function
  - Attention
  - Verbal function
  - Global cognitive scores
- Robotics
- Self-generation technique
- Social education cognitive + aerobic & strength
- Dual task training
  - Attention
  - Executive function
- Aerobic & strength
  - Information processing speed (6 mon)
  - Attention (6 mon)
  - Memory
- Cycling
  - Memory
  - Verbal fluency
- High intensity interval training
  - Attention
  - Visual processing speed
- Circuit training
  - Verbal learning & memory
  - Spatial memory
  - Verbal fluency
  - Visual processing speed
  - Audio processing speed
  - Neuropsychological impairment
- Walking
- Square stepping
  - Visual spatial memory
  - Verbal learning & memory
  - Visual processing speed
- Stepping
- High frequency repetitive transcranial magnetic stimulation
- Transcranial direct current stimulation
  - Attention
  - Memory
- Transcranial random noise stimulation

Level of Evidence Statements

Satements are listed from the highest to lowest levels of evidence, and in the order found in the table of contents for the categories of interventions.

Level 1a – benefits cognition in one or more cognitive domain

Computer Based Cognitive Rehabilitation Approaches

There is level 1a evidence that computer-based cognitive rehabilitation that targets executive function improves executive function compared to no treatment (from seven randomized controlled trials and one prospective controlled trial; De Giglio et al. 2015, De Giglio et al. 2016, Filippi et al. 2012, Mattioli et al. 2010, Mattioli et al. 2012, Naeeni Davarani et al. 2020, Sharifi et al. 2019, and Tesar et al. 2005).

There is level 1a evidence that computer-based cognitive rehabilitation that specifically targets information processing speed does improve information processing speed in persons with MS compared to no treatment or non-specific cognitive rehabilitation (from seven randomized controlled trials, one prospective controlled trial, and four pre-post studies; Barker et al. 2019, Bonavita et al. 2015, Chiaravalloti et al. 2018, Filippi et al. 2012, Fuchs et al. 2019, Fuchs et al. 2020, Guclu Altun et al. 2015, Mattioli et al. 2010, Mattioli et al. 2012, Messinis et al. 2017, and Messinis et al. 2020, and Rahmani et al. 2020).

There is level 1a evidence that computer-based cognitive rehabilitation that specifically targets memory improves memory in persons with MS compared to no treatment or their usual clinical care (from six randomized controlled trials, two prospective controlled trials, and two pre-post studies; Arian Darestani et al. 2020, Bonzano et al. 2020, Covey et al. 2018, Hildebrandt et al. 2007, Janssen et al. 2015, Mendozzi et al. 1998, Messinis et al. 2017, Messinis et al. 2020, Rahmani et al. 2020, Shatil et al. 2010, and Stuifbergen et al. 2012, and Vogt et al. 2009).

There is level 1a evidence that computer-based cognitive rehabilitation delivered for 33 hours or longer over at least twelve weeks improves verbal language skills compared to no treatment in persons with MS with cognitively impaired (from four randomized controlled trials; Arsoy et al. 2018, Filippi et al. 2012, Mattioli et al. 2010, and Mattioli et al. 2012).

There is level 1a evidence that computer-based cognitive rehabilitation using RehaCom modules that target executive function improves executive function for persons with MS with cognitively impaired compared to no treatment (from four randomized controlled trials; Filippi et al. 2012, Mattioli et al. 2010, Mattioli et al. 2012, and Tesar et al. 2015).

There is level 1a evidence that computer-based cognitive rehabilitation using RehaCom that specifically target information processing speed does improve information processing speed in persons with MS with cognitively impaired compared to no treatment or standard MS rehabilitation (from four randomized controlled trials and one prospective controlled trial;

Bonavita et al. 2015, Filippi et al. 2012, Mattioli et al. 2010, Mattioli et al. 2012, Messinis et al. 2017, and Messinis et al. 2020).

There is level 1a evidence that computer-based cognitive rehabilitation using RehaCom delivered for 33 hours or longer over twelve weeks improves verbal language skills compared to no treatment in persons with MS with cognitively impaired (from three randomized controlled trials; Filippi et al. 2012, Mattioli et al. 2010, and Mattioli et al. 2012).

Story Memory

There is level 1a evidence that the modified Story Memory Technique does improve verbal learning and memory in persons with MS but may not improve other forms of memory (from five randomized controlled trials; Chiaravalloti et al. 2020, Chiaravalloti et al. 2013, Chiaravalloti et al. 2012, Dobryakova et al. 2014, Krch et al. 2019).

Mental Visual Imagery

There is level 1a evidence that mental visual imagery training improves memory on an autobiographical memory interview assessment compared to sham verbal training or no intervention in relapsing-remitting MS. Other objective memory and cognitive outcomes are not reported (from three randomized controlled trials and two pre-post studies; Ernst et al. 2018, Ernst et al. 2016, Ernst et al. 2015, Ernst et al. 2013, and Ernst et al. 2012).

Level 1a – no objective benefit in one more cognitive domain

Self-generation Program

There is level 1a evidence that teaching the Self-Generation Technique may not significantly improve verbal memory (two randomized controlled trials; Goverover et al. 2018 and Chiaravalloti et al. 2019).

Mindfulness

There is level 1a evidence that mindfulness-based cognitive therapies may not improve auditory information processing speed in persons with MS (from two randomized controlled trials and one pre-post study; Manglani et al. 2020, Senders et al. 2018, and Blankespoor et al. 2017).

Cognitive-Motor Dual Task Training

There is level 1a evidence that dual task training does not improve information processing speed or memory more than balance or gait training alone (from two randomized controlled trials; Sosnoff et al. 2007; Veldkamp et al. 2019).

Cycling

There is level 1a evidence that cycling does not improve information processing speed compared to waitlist control in persons with MS (from three randomized controlled trials; Baquet et al. 2018, Briken et al. 2014, and Oken et al. 2004).

Cycling

There is level 1a evidence that cycling does not improve executive function for persons with MS (from two randomized controlled trials; Briken et al. 2014, Oken et al. 2004).

Level 1b – benefits cognition in one or more cognitive domain

Cognitive Rehabilitation, Mixed Non-computer Approaches

There is level 1b evidence that the REACTIV program, which targets attention, may improve attention more than non-specific cognitive exercises in persons with MS with cognitively impaired (from one randomized controlled trial; Lamargue et al. 2020).

There is level 1b evidence that the french ProCog-SEP involving facilitation and reorganization training improves memory in persons with MS more than non-cognitive training and discussion (from one randomized controlled trial and one prospective controlled trial; Brissart et al. 2020 and Brissart et al. 2013).

There is level 1b evidence that the REACTIV protocol may improve verbal learning and memory but not other aspects of memory in persons with MS with cognitively impaired (from one randomized controlled trial; Lamargue et al. 2020).

There is level 1b evidence that compensatory strategies targeting attention and memory may improve memory more than no treatment (Mousavi et al. 2018 and Mousavi et al. 2018b).

Computer Based Cognitive Rehabilitation Approaches

Freshminder 2

There is level 1b evidence that Freshminder 2 combined with counseling for compensatory strategies may improve attention in persons with MS compared to no treatment (from one randomized controlled trial; Pusswald et al. 2014).

RehaCom

There is level 1b evidence that RehaCom improves attention more than computer-based visuomotor training in persons with MS with cognitively impaired (from one randomized controlled trial; Cerasa et al. 2016).

There is level 1b evidence that computer-based cognitive rehabilitation using RehaCom for 60 minutes per day 2 days per week for 6 weeks may improve executive function in persons with MS with cognitively impaired compared to computer-based visuomotor tasks (from one randomized controlled trial; Cerasa et al. 2013).

There is level 1b evidence that computer-based cognitive rehabilitation with RehaCom targeting memory training may improve memory (from two randomized controlled trials and

one prospective controlled trial; Arian Darestani et al. 2020, Mendozzi et al. 1998, and Messinis et al. 2017).

Reaction time training

There is level 1b evidence that computer-based cognitive rehabilitation targeting reaction time may improve reaction time more than computer-based cognitive rehabilitation targeting selective attention, working memory, and executive function in persons with MS (from one randomized controlled trial; Flachenecker et al. 2017).

Speed of Processing Training

There is level 1b evidence that computer-based cognitive rehabilitation using Speed of Processing Training may improve information processing speed in persons with MS with cognitively impaired compared to no treatment (from one randomized controlled trial and three pre-post study; Barker et al. 2019, Chiaravalloti et al. 2018, Fuchs et al. 2019, and Fuchs et al. 2020).

NOROSOFT Mental Exercise Software

There is level 1b evidence that computer-based rehabilitation using NOROSOFT Mental Exercise Software for 24 weeks may help maintain executive function in persons with MS with cognitively impaired compared to no treatment (from one randomized controlled trial; Arsoy et al. 2018).

There is level 1b evidence that computer-based cognitive rehabilitation using NOROSOFT delivered for 100 hours over twenty-four weeks maintains verbal language skills compared to no treatment in persons with MS with cognitively impaired (from one randomized controlled trial; Arsoy et al. 2018).

VILAT-G

There is level 1b evidence that computer-based cognitive rehabilitation using VILAT-G software may improve information processing speed more than no treatment in persons with MS (from one randomized controlled trial; Hildebrandt et al. 2007).

There is level 1b evidence that computer-based cognitive rehabilitation using VILAT-G to specifically target memory may improve memory in persons with MS (from one randomized controlled trial; Hildebrandt et al. 2007).

ERICA

There is level 1b evidence that computer-based cognitive rehabilitation using ERICA to specifically target memory improves spatial memory but not verbal learning and memory more than traditional cognitive rehabilitation (from one randomized controlled trial; De Luca et al. 2019).

Lumosity

There is level 1b evidence that computer-based cognitive rehabilitation using Lumosity to specifically target memory combined with group compensatory strategies may improve memory in persons with MS (from one randomized controlled trial; Stuifbergen et al. 2012).

Video Games

There is level 1b evidence that Nintendo's Brain Training video games do improve executive function and information processing speed in persons with MS (from one randomized controlled trial and one randomized controlled trial with pre-post analysis; DeGiglio et al. 2015, DeGiglio et al. 2016).

Virtual Reality

There is level 1b evidence that cognitive rehabilitation in the BTS-Nirvana Virtual Reality environment may improve information processing speed and memory more than traditional cognitive rehabilitation in persons with MS (one randomized control larger trial; Maggio et al. 2020).

Selective Reminding

There is level 1b evidence that selective reminding tasks may improve memory in persons with MS compared to single trial encoding conditions (one randomized controlled trial; McKeever et al. 2019).

Self-generation Program

There is level 1b evidence that Self-generation Technique improves contextual recall on tasks where the technique is applied compared to not applying the technique (one randomized controlled trial, one prospective controlled trial and six pre-post studies; Goverover et al. 2018; 2014; 2013; 2011; and 2008; Basso et al. 2008 and 2006; O'Brien et al. 2007; Chiaravalloti & Deluca 2002).

Music Therapy

There is level 1b evidence that neurologic music therapy combined with cognitive rehabilitation may improve memory more than conventional cognitive rehabilitation (one randomized controlled trial; Impellizzeri et al. 2020).

Cooling

There is level 1b evidence that a walking, cycling, and ROM exercise program while wearing a cooling garment may improve verbal fluency compared to the same exercise program without a cooling garment in persons with MS (one randomized controlled trial; Gonzales et al. 2017).

Cycling

There is level 1b evidence that cycling may improve memory for patients with progressive MS (from one randomized controlled trial; Briken et al. 2014).

High Intensity Interval Training

There is level 1b evidence that high intensity aerobic cycling training may improve verbal memory compared to moderate intensity aerobic cycling training in people with a baseline VO2 peak of ~20mL/kg/min (one randomized controlled trial; Zimmer et al. 2018).

Balance Training and Dual Task

There is level 1b evidence that balance training combined with a dual task may improve general cognitive impairment and executive function at 6 months compared to no intervention (one randomized controlled trial; Felippe et al. 2019).

Transcranial Direct Current Stimulation

There is level 1b evidence that transcranial direct current stimulation combined with cognitive training may improve executive function compared to sham treatment combined with cognitive training (one randomized controlled trial and one pre-post study; Chalah et al. 2017, Charvet et al. 2018).

Level 1b – no objective benefit in one or more cognitive domain

Cognitive Rehabilitation, Mixed Non-computer Approaches

There is level 1b evidence that memory and attention rehabilitation using education and compensatory strategies may not improve attention more than sham psychoeducation in persons with MS with cognitively impaired (from one randomized controlled trial; Mani et al. 2018).

There is level 1b evidence that compensatory memory strategies may not improve memory more than restitution in persons with MS with cognitively impaired (from one randomized controlled trial; Martin et al. 2014).

There is level 1b evidence that the french ProCog-SEP program involving facilitation and reorganization training may not improve information processing speed more than non-cognitive exercises and discussion (from one randomized controlled trial, Brissart et al. 2020).

There is level 1b evidence that the REACTIV program may not improve information processing more than non-specific cognitive training and physical activity (from one randomized controlled trial; Lamargue et al. 2020).

There is level 1b evidence that group cognitive training that focuses on compensatory strategies and restitution for memory and attention may not improve information processing speed compared to usual care (defined as advice from nursing and OT) in persons with MS (from one randomized controlled trial; Lincoln et al. 2020).

Computer-Based Cognitive Rehabiliatiation Approaches

VILAT-G

There is level 1b evidence that VILAT-G may not improve attention in persons with MS compared to no treatment (from one randomized controlled trial; Shatil et al. 2010).

Attention-specific training

There is level 1b evidence that computer-based Attention Processing Training (APT) may not improve all attention domains compared to non-specific cognitive exercises in persons with MS (from one randomized controlled trial; Amato et al. 2014).

MAPSS-MS (Lumosity + neuropsychonline + group therapy for compensatory strategies)

There is level 1b evidence that the MAPSS-MS program, which combines Lumosity for 45 minutes per day 3 times per week for 8 weeks with group therapy for compensatory strategies, may not improve executive function compared to no treatment in persons with MS with cognitively impaired (from one randomized controlled trial; Stuifbergen et al. 2012).

Lumosity

There is level 1b evidence that computer-based cognitive rehabilitation using Lumosity in the MAPSS-MS program may not improve information processing speed compared to no treatment in persons with MS with cognitively impaired (from one randomized controlled trial; Stuifbergen et al. 2012).

There is level 1b evidence that computer-based cognitive rehabilitation using Lumosity to specifically target memory combined with group compensatory strategies may not improve more than MyBrainGames on multiplesclerosis.com (from one randomized controlled trial; Stuifbergen et al. 2018).

Norosoft

There is level 1b evidence that computer-based cognitive rehabilitation using NOROSOFT may not improve memory in persons with MS (from one randomized controlled trial; Arsoy et al. 2018).

Virtual Reality

There is level 1b evidence that robot-assisted gait training in a virtual reality environment may not improve information processing speed, memory, or verbal language skills more than robot-assisted gait training (one randomized controlled small trial; Munari et al. 2020).

Visual Training

There is level 1b evidence that strobic visual training may improve information processing speed but not memory, executive function, attention, verbal function, or global cognitive scores (one crossover RCT study; Shalmoni et al., 2020).

Robotics

There is level 1b evidence that robotics may not improve any measure of cognition more than gait-training in persons with MS (from one very small randomized controlled trial; Munari et al. 2020).

[Self-generation Program]

There is level 1b evidence that teaching the Self-Generation Technique may not significantly improve visuospatial memory (one randomized controlled trial; Chiaravalloti et. al. 2019).

[Mindfulness]

There is level 1b evidence that mindfulness-based cognitive therapies may improve visual information processing speed in persons with MS (from one random trial; Manglani et al., 2020).

[Social Cognitive Theory Education]

There is level 1b evidence that social cognitive education combined with aerobic and strength exercise may not improve information processing more than attention control education combined with aerobic and strength exercise (from one randomized controlled trial; Coote et al. 2017).

[Cognitive-Motor Dual Task Training]

There is level 1b evidence that dual task training does not improve attention more than gait training alone (from one randomized controlled trial; Veldkamp et al. 2019).

[Cognitive-Motor Dual Task Training]

There is level 1b evidence that dual task training does not improve executive function more than strength training (from one randomized controlled trial; Jonsdottir et al. 2018).

[Aerobic and Strength Training]

There is level 1b evidence that aerobic and strength training combined may not improve information processing speed in persons with MS at six months follow up (from two randomized controlled trials; Coghe et al. 2018. Sandroff et al. 2017).

[Aerobic and Strength Training]

There is level 1b evidence that aerobic and strength training combined may not improve attention in persons with relapsing-remitting MS at six months follow up (from one randomized controlled trial; Coghe et al. 2018).

[Aerobic and Strength Training]

There is level 1b evidence that aerobic and strength training combined may not improve memory in persons with MS (from one randomized controlled trial and one pre-post study; Coghe et al. 2018, Sangelaji et al. 2015).

[Cycling]

There is level 1b evidence that cycling may not improve memory for persons with relapsing-remitting MS (from one randomized controlled trial and two pre-post studies; Baquet et al. 2018, Barry et al. 2018, and Swank et al. 2013).

There is level 1b evidence that cycling may not improve verbal fluency for persons with progressive MS (from one randomized controlled trial; Briken et al. 2014).

High Intensity Interval Training

There is level 1b evidence that high intensity aerobic cycling training may not improve attention, processing speed or visual spatial memory compared to moderate intensity aerobic cycling training in people with a baseline V02 peak of ~20mL/kg/min (one randomized controlled trial; Zimmer et al. 2018).

Circuit Training

There is level 1b evidence that circuit training may not improve memory, verbal fluency, visual processing speed, or auditory processing speed significantly more than relaxation exercises (one randomized controlled trial, Ozkul et al. 2020).

Walking

There is level 1b evidence that walking programs may not improve verbal learning and memory in persons with relapsing-remitting MS (from one randomized controlled trial; Sandroff et al. 2017).

Stepping

There is level 1b evidence that square stepping may not improve visual spatial memory, verbal memory, or visual processing speed significantly more than a light stretching and strengthening program (one randomized controlled trial; Sebastião et al. 2018).

There is level 1b evidence that a stepping exergame program may not improve visual spatial processing speed significantly more than usual physical activities (one randomized controlled trial; Hoang et al. 2016).

High Frequency Repetitive Transcanial Magnetic Stimulation

There is level 1b evidence that high frequency repetitive transcranial magnetic stimulation (rTMS) may not significantly improve working memory compared to sham rTMS in persons with MS without cognitive impairment at baseline (from one randomized controlled trial; Hulst et al. 2017).

Transcranial Direct Current Stimulation

There is level 1b evidence that transcranial direct current stimulation may not improve basic attention compared to sham treatment (one randomized controlled trial and one pre-post study; Chalah et al. 2017, Charvet et al. 2018).

Transcranial Direct Current Stimulation

There is level 1b evidence that transcranial direct current stimulation may not improve memory in persons with MS compared to sham treatment (one randomized controlled trial and one pre-post study; Mattioli et al. 2016; Charvet et al. 2018).

Transcranial Random Noise Stimulation

There is level 1b evidence that transcranial random noise stimulation may not improve attention in persons with MS compared to placebo (from one randomized controlled trial; Palm et al. 2016).

Level 2 – benefits cognition in one or more cognitive domain

Cognitive Rehabilitation, Mixed Non-computer Approaches

There is level 2 evidence that n-back training over the course of 1 week may improve working memory compared to no treatment (from one randomized controlled trial; Aguirre et al. 2019).

There is level 2 evidence that the REHACOP protocol might improve memory compared to no treatment (from one randomized controlled trial; Rilo et al. 2013).

There is level 2 evidence that the REHACOP protocol may improve executive function more than no treatment for persons with MS (from one randomized controlled trial; Rilo et al. 2018).

There is level 2 evidence that executive functioning training using executive function textbook exercises may improve executive function more than RehaCom reaction time training or no treatment (from one prospective controlled trial; Fink et al. 2010).

There is level 2 evidence that the REHACOP protocol may improve information processing more than no treatment in persons with MS (from one randomized controlled trial; Rilo et al. 2018).

There is level 2 evidence that Tele-MIT may improve information processing more than no treatment in persons with MS (from one randomized controlled trial; Kahraman et al. 2020).

Computer Based Cognitive Rehabilitation Approaches

ERICA
There is level 2 evidence that ERICA attention exercises may improve attention in persons with MS with cognitively impaired compared to pen-and-paper attention exercises (from one randomized controlled trial; Orel et al. 2014).

CogniFit
There is level 2 evidence that computer-based cognitive rehabilitation using CogniFit to specifically target memory may improve memory in persons with MS (from one randomized controlled trial; Hildebrandt et al. 2007).

Video Games
There is level 2 evidence that the Space Fortress video game may improve spatial and visuospatial memory in persons with MS (from one randomized controlled trial; Janssen et al. 2015).

Spaced Learning

There is level 2 evidence that spaced learning improves memory compared to mass learning (one prospective controlled trial and two pre-post studies; Goverover et al. 2009, Sumowski et al. 2010 and Sumowski et al. 2013).

Spaced Learning

There is level 2 evidence that retrieval practice improves memory in persons with MS with mild or advanced cognitive impairment to a greater extent then spaced learning or mass learning approaches (two pre-post studies; Sumowski et al. 2010 and Sumowski et al. 2013).

Mindfulness

There is level 2 evidence that mindfulness-based cognitive therapies may improve attention and verbal skills in persons with MS (from one randomized controlled trial reporting pre-post results; De la Torre et al. 2020).

Meditation

There is level 2 evidence that meditation may improve information processing speed in persons with relapsing-remitting MS (from one randomized controlled trial and one prospective controlled trial; Bhargav et al., 2016, Anagnostouli et al., 2019).

Psychotherapy

There is level 2 evidence that eight weeks of cognitive behavioural therapy or dialectical behavioural therapy may improve memory in persons with MS (from one randomized controlled trial; Abdolghaddri et al. 2019).

Social Cognitive Theory Education

There is level 2 evidence that social cognitive education combined with aerobic and strength exercise may improve information processing speed (within group pre-post results from one randomized controlled trial; Coote et al. 2017).

Running

There is level 2 evidence that running may improve spatial memory but not verbal learning and memory or information processing speed in persons with MS (from two randomized controlled studies; Feyst et al. 2019; Huiskamp et al. 2020).

Pilates

There is level 2 evidence that Pilates may improve information processing speed compared to traditional exercise programs in persons with MS (from two randomized controlled trials and one pre-post study; Abasiyanik et al. 2020, Küçük et al. 2016, and Kara et al. 2017).

There is level 2 evidence that Pilates may improve memory in persons with MS compared to traditional exercise programs (from one randomized controlled trial; Abasiyanik et al. 2020).

Yoga

There is level 2 evidence that yoga may improve attention more than sports climbing in persons with MS (from one randomized controlled trial; Velikonja et al. 2010).

Functional Electrical Stimulation Cycling

There is level 2 evidence that functional electrical stimulation cycling may improve visual processing speed compared to passive cycling in persons with MS with mobility impairments (from one randomized controlled trial; Pilutti et al., 2019).

Level 2 – no objective benefit in one or more cognitive outcomes

Cognitive Rehabilitation, Mixed Non-computer Approaches

There is level 2 evidence that the REHACOP protocol may not improve attention more than no treatment for persons with MS (from one randomized controlled trial; Riloet al. 2018).

There is level 2 evidence that cognitive rehabilitation targeting executive function may not improve executive function more than normal MS rehab and physiotherapy (from one randomized controlled trial; Hanssen et al. 2016).

Computer Based Cognitive Rehabiliation Approaches

CogniFit 2

There is level 2 evidence that CogniFit 2 may not improve attention in persons with MS compared to no treatment (from one randomized controlled trial; Shatil et al. 2010).

Captain's Log

There is level 2 evidence that computer-based rehabilitation using Captain's Log software for 6 weeks may improve executive function in persons with MS compared to no treatment (from one prospective controlled trial; Sharifi et al. 2019).

Video Games

There is level 2 evidence that the Space Fortress video game may not improve verbal learning and memory in persons with MS (from one randomized controlled trial; Janssen et al. 2015).

Meditation

There is level 2 evidence that meditation may not improve executive function in persons with relapsing-remitting MS (from one randomized controlled trial; Bhargav et al., 2016).

Psychotherapy

There is level 2 evidence that eight weeks of cognitive behavioural therapy or dialectical behavioural therapy may not improve attention in persons with MS (from one randomized controlled trial; Abdolghaddri et al. 2019).

Tongue Electrical Stimulation

There is level 2 evidence that adding non-invasive cranial nerve stimulation to the tongue in addition to COGMED training and exercise may not improve memory, executive function, or information processing speed compared to no tongue stimulation and COGMED and exercise training (from one randomized controlled trial; Leonard et al. 2017).

Level 4 – benefits cognition in one or more cognitive domain

Cognitive Rehabilitation, Mixed Non-computer Approaches

There is level 4 evidence that practicing mental imagery with mnemonic memory techniques together may improve prospective memory when playing a board game in minimally cognitive impaired persons with MS more than in healthy controls (from one pre-post study; Kardiasmenos et al. 2008).

EEG Neurofeedback

There is level 4 evidence that EEG neurofeedback training may improve long-term memory and executive function (from one pre-post study; Kober et al., 2019).

Cue Salience

There is level 4 evidence that cue salience may improve prospective memory in both high- and low-executive functioning persons with MS (one pre-post trial; Dagenais et al. 2016).

Psychotherapy

There is level 4 evidence that group psychotherapy may improve auditory information processing speed but not visual information processing speed in persons with MS who have depression and CI (from one pre-post trial; Bilgi et al. 2015).

Action Observation

There is level 4 evidence that watching daily life hand movements (action observation) may improve auditory processing speed in persons with MS receiving an upper limb rehabilitation program (from pre-post data in one randomized controlled study; Rocca et al., 2019).

Art

There is level 4 evidence that team-based artistic therapy, consisting of photography, painting, poetry, and videography, may improve visual information processing speed and memory but not auditory information processing speed in persons with relapsing-remitting MS (one pre-post study; Van Geel et al. 2020).

Diet

There is level 4 evidence that a modified paleolithic diet combined with electrical stimulation, exercise, and stress management may improve executive functioning (one pre-post study; Lee et al. 2017).

Level 4 – no objective benefit in one or more cognitive domains

Mindfulness

There is level 4 evidence that mindfulness-based cognitive therapies may not improve executive function in persons with MS (from one pre-post study; Blankespoor et al. 2017).

Occupation Based

There is level 4 evidence that a Cognitive Occupation-Based Program may not improve processing speed or executive function, however ADLs and IADLs and occupational competence may improve by self-report (one pre-post study; Reilly et al., 2018).

Cooling

There is level 4 evidence that memory is worse when the body temperature is lowered by one degree Celsius compared to a resting control temperature in persons with MS (from one pre-post study; Geisler et al. 1996).

Conflicting Evidence

Cognitive Rehabilitation, Mixed Non-computer Approaches

There is conflicting evidence whether cognitive rehabilitation improves attention in persons with MS (from three randomized controlled trials and one pre-post study; Brenk et al. 2008, Lamargue et al. 2020, Mani et al. 2018, and Rilo et al. 2018).

There is conflicting evidence whether cognitive rehabilitation improves memory in persons with MS among studies with different rehabilitation interventions, comparator groups and memory outcomes (from twelve randomized controlled trials, four prospective controlled trials, and one pre-post study; Aguirre et al. 2019, Brenk et al. 2008, Brissart et al. 2013, Brissart et al. 2020, Carr et al. 2014, Fink et al. 2010, Goverover et al. 2009, Jonsson et al. 1993, Kahraman et al. 2020, Lamargue et al. 2020, Lincoln et al. 2020, Mani et al. 2018, Martin et al. 2014, Mousavi et al. 2018, , Rilo et al. 2018, Rodgers et al., 1996, and Shahpouri et al. 2019).

There is conflicting evidence whether cognitive rehabilitation improves executive function in persons with MS (from four randomized controlled trials, one prospective controlled trial, and one pre-post study; Brenk et al. 2008, Fink et al. 2010, Hanssen et al. 2016, Lincoln et al. 2002, Mani et al. 2018, and Rilo et al., 2018).

There is conflicting evidence whether memory and attention cognitive rehabilitation combined with compensatory strategies improves executive function in person with MS (from two randomized controlled trials; Lincoln et al. 2002 and Mani et al. 2018).

There is conflicting evidence whether cognitive rehabilitation improves information processing speed in persons with MS (from five randomized controlled trials, one prospective

trial study, and one pre-post study; Brissart et al. 2020, Kahraman et al. 2020, Lamargue et al. 2020, Lincoln et al. 2020, Rilo et al. 2018, Rodgers et al., 1996, and Zuber et al. 2020).

There is conflicting evidence whether cognitive rehabilitation improves verbal language skills in persons with MS (from one randomized controlled trial and one prospective controlled trial; Brissart et al. 2013 and Rilo et al. 2013).

Computer Based Cognitive Rehabilitation Approaches

There is conflicting evidence whether computer-based cognitive rehabilitation delivered for less than 33 hours of total training is more effective than no treatment (from four randomized controlled trials and one pre-post study; Barker et al. 2019, Stuifbergen et al. 2012, Mäntynen et al. 2014, Arian Darestani et al. 2020, and Pusswald et al. 2014).

There is conflicting evidence whether computer-based cognitive rehabilitation improves attention in persons with MS (from seventeen randomized controlled trials and one pre-post study; Amato et al. 2014, Campbell et al. 2016, Cerasa et al. 2013, Filippi et al. 2012, Flachenecker et al. 2017, Mattioli et al. 2010, Mattioli et al. 2012, Messinis et al. 2017, Orel 2014, Plohmann et al. 1998, Rahmani et al. 2020, and Tesar et al. 2005).

There is conflicting evidence whether computer-based cognitive rehabilitation improves executive function in persons with MS (from sixteen randomized controlled trials and two prospective controlled trials; Amato et al. 2014, Arsoy et al. 2018, Bonavita et al. 2015, Cerasa et al. 2013, De Giglio et al. 2015, De Giglio et al. 2016, Filippi et al. 2012, Grasso et al. 2017, Hancock et al. 2015, Mäntynen et al. 2014, Mattioli et al. 2010, Mattioli et al. 2012, Naeeni Davarani et al. 2020, Rahmani et al. 2020, Sharifi et al. 2019, Stuifbergen et al. 2012, and Tesar et al. 2005).

There is conflicting evidence whether computer-based cognitive rehabilitation improves memory in persons with MS (from 18 randomized controlled trials, 6 prospective controlled trials and 1 pre-post study; Amato et al. 2014, Arian Darestani et al. 2020, Arsoy et al. 2018, Barker et al. 2019, Bonavita et al. 2015, Bonzano et al. 2020, Bove et al. 2021, Campbell et al. 2016, Cerasa et al. 2013, Chiaravalloti et al. 2018, Covey et al. 2018, De Luca et al. 2019, Filippi et al. 2012, Fuchs et al. 2019, Hildebrandt et al. 2007, Mattioli et al. 2010, Mattioli et al. 2012, Mendozzi et al. 1998, Messinis et al. 2017, Messinis et al. 2020, Shatil et al. 2010, Solari et al. 2004, Vogt et al. 2009, and Allen et al., 2018).

There is conflicting evidence whether computer-based cognitive rehabilitation improves verbal language skills in persons with MS (from nine randomized controlled trials; Arian Darestani et al. 2020, Arsoy et al. 2018, Filippi et al. 2012, Mäntynen et al. 2014, Mattioli et al. 2010, Mattioli et al. 2012, Pusswald et al. 2014, Stuifbergen et al. 2012, and Stuifbergen et al. 2018).

RehaCom

There is conflicting evidence whether RehaCom improves attention in persons with MS with cognitively impaired compared to no treatment (from six randomized controlled trials and one prospective controlled trial; Filippi et al. 2012, Mattioli et al. 2010, Mattioli et al. 2012, Mendozzi et al. 1998, Messinis et al. 2017, Naeeni Davarni et al. 2020, and Tesar et al. 2005).

There is conflicting evidence whether using RehaCom for 8 weeks or less improves executive function for persons with MS with cognitively impaired compared to no treatment or non-specific treatment (from one randomized controlled trial and one prospective controlled trial; Bonavita et al. 2015 and Tesar et al. 2015).

There is conflicting evidence whether computer-based cognitive rehabilitation with RehaCom targeting memory training improves memory in persons with MS with cognitively impaired compared to natural history DVDs or nonspecific computer exercises (from two randomized controlled trials; Campbell et al. 2016 and Messinis et al. 2020).

Mindfulness

There is conflicting evidence whether mindfulness-based cognitive therapies improve memory in persons with MS (from two randomized controlled trials and one pre-post study; Blankespoor et al. 2017, De la Torre et al. 2020, and Manglani et al. 2020).

Meditation

There is conflicting evidence whether meditation may improve memory in persons with relapsing-remitting MS (from one randomized controlled trial and one prospective controlled trial; Bhargav et al., 2016, Anagnostouli et al., 2019).

Music Mnemonic

There is conflicting evidence whether music mnemonics improve memory compared to spoken words in persons with MS (from two randomized controlled trials; Moore et al. 2008, Thaut et al. 2014).

Cooling

There is conflicting evidence whether cooling may improve information processing in persons with MS (from two randomized controlled trials; Gonzales et al. 2017; Schwid et al. 2013).

Cycling

There is conflicting evidence whether cycling improves attention in persons with MS (from two randomized controlled trials; Briken et al. 2014 and Oken et al. 2004).

Dance

There is conflicting evidence whether dance training improves information processing speed in persons with MS (two pre-post studies; Van Geel et al. 2020; Ng et al. 2019).

Walking

There is conflicting evidence whether walking programs may improve information processing speed in persons with MS (from one randomized controlled trial and one pre-post study; Sandroff et al. 2016 and Van Geel et al. 2020).

Walking

There is conflicting evidence whether walking programs improve executive function in persons with MS (from two randomized controlled trial; Sandroff et al. 2016 and Sandroff et al. 2015).

Yoga

There is conflicting evidence whether yoga improves executive function in persons with MS (from two randomized controlled trials; Oken et al. 2004, Velikonja et al. 2010).

Transcranial Direct Current Stimulation

There is conflicting evidence whether transcranial direct current stimulation combined with cognitive training improves visual information processing compared to sham treatment combined with cognitive training (one randomized controlled trial and one pre-post study; Mattioli et al. 2016, Charvet et al. 2018).

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